Extended analysis of the randomised comparisons of the RECOVERY trial immunomodulatory COVID-19 treatments

Oxford Population Health
(Nuffield Department of Population Health)



Mark Campbell
Linacre College, Oxford

Thesis submitted for the degree of Doctor of Philosophy
Trinity Term 2024
Word Count: 49,670

Acknowledgements

I would like to dedicate this thesis to my family who have been my support and motivation for every moment of the last 3 years of work. To my children, Thea, Nicholas, and Ruben – you bring me joy every single day and I love learning about the world alongside you. To my wife, Lucy – thank you for supporting this journey and for so much more. You are everything anyone could ever wish for in a partner.

Thank you to my supervisors: Professor Richard Haynes, Associate Professor Natalie Staplin, Associate Professor Marion Mafham, and Professor Kenneth Baillie. You have been a constant source of guidance, belief, and common sense throughout this time. I've hugely enjoyed working with you and will be grateful for this opportunity for the rest of my life. Thank you also to the RECOVERY Chief Investigators – Professor Sir Martin Landray and Professor Sir Peter Horby - for allowing me to become involved in RECOVERY in the first place and facilitating this research at any opportunity. It has been an honour and a privilege to be involved with RECOVERY.

Thank you to the wider research teams who have been a huge and essential part of my experience and helped enormously with different challenges along the way. This includes everyone involved in the RECOVERY trial (the data linkage team, the trial management team, the clinical support team, the Vascular Overviews Group, local site staff, and many more) and colleagues at Public Health Scotland, especially my research coordinator, Susan Knight.

Last, but by no means least, thank you to all the patients who agreed to be involved in RECOVERY – without your desire to help others at a time of huge personal stress, none of this would even exist. My name is a tiny footnote in the long list of peoples' lives that you have changed for the better.

Statement of contribution to work

I conceptualised, designed, analysed and wrote this thesis. I received guidance and feedback from my supervisors and some assistance on specific elements from other members of the RECOVERY trial team during the course of the DPhil, as detailed below.

In Chapter 1, I conceptualised and wrote the content of this chapter and received feedback on written drafts from my supervisors.

In Chapter 2, I discussed the literature search strategy with a departmental information specialist and a local research team experienced in carrying out systematic reviews (the Vascular Overviews Group). I carried out the literature search, screened and categorised the results, and extracted the data for meta-analysis. I performed the meta-analysis and produced the results figures using code adapted from scripts in the departmental style provided by one of my supervisors. I wrote the content of this chapter and received feedback on written drafts from my supervisors.

In Chapter 3, I drafted the data analysis plans and received feedback from my supervisors before finalising a version that was also agreed with the RECOVERY trial Chief Investigators. Statistical methods were discussed and finalised with advice from my supervisors. The definitions and derivations of all analysis assessments were developed and performed by me, except a small number of long-term follow-up analysis assessments that were already in use for the RECOVERY trial – these are explicitly labelled in the chapter text. The raw routinely collected healthcare datasets (RCD) received from data custodians were initially processed and deidentified by the RECOVERY data linkage team into .csv files for further use. I then performed all other processing of these datasets. The information governance approval and data linkage process was led by me with oversight and support from one of my supervisors, colleagues in the RECOVERY data linkage team, the University of Oxford Research Contracts team

and colleagues at Public Health Scotland. I wrote the content of this chapter. The descriptions of the previously used analysis assessments and some of the RCD data sources were adapted from existing trial-specific documentation (referenced in the chapter). I received feedback on written drafts from my supervisors.

In Chapter 4, I designed, carried out, screened, extracted data, and performed analyses from the literature search. I constructed the clinical codelists and received input from a second departmental clinician to finalise them. I performed all analyses and produced results tables and figures of the assessment definition testing. I wrote the content of this chapter and received feedback on written drafts from my supervisors.

In Chapter 5, I performed all analyses and produced results tables and figures. The code for the subgroup analyses figures was adapted from scripts in the departmental style provided by one of my supervisors. I wrote the content of this chapter and received feedback on written drafts from my supervisors.

In Chapter 6, I performed all analyses except the standardised subgroup analysis in Section 6.3.4, which was performed by one of my supervisors using the specific capabilities of another statistical software programme (SAS), with input data provided by me. I produced all results tables and figures. The code for the subgroup analyses figures was adapted from scripts in the departmental style provided by one of my supervisors (as for Chapter 5). I wrote the content of this chapter and received feedback on written drafts from my supervisors.

In Chapter 7, I performed the meta-analysis and produced the results figures using code adapted from original scripts provided by one of my supervisors. I wrote the content of this chapter and received feedback on written drafts from my supervisors.

The thesis material has not yet been published in peer-reviewed journals - a Publication Plan can be found in the Appendix, Section D.

Table of Contents

Abstract ..... **xii**

List of Figures ..... **xiv**

List of Tables ..... **xxiii**

List of Abbreviations ..... **xxviii**

Chapter 1 Introduction **1**

1.1 Chapter Summary 1

1.2 Research Context 2

1.2.1 COVID-19 2

1.2.2 Epidemiology 2

1.2.3 Natural history 4

1.2.4 Pathophysiology 4

1.2.5 Treatment 5

1.3 Knowledge Gaps 7

1.3.1 Long-term follow-up 7

1.3.2 Potential treatment-related harms 7

1.3.3 Illness recovery 8

1.3.4 Treatment effects of corticosteroids across the disease severity spectrum 9

1.3.5 Treatment effects on biological measurements 10

1.3.6 Bridging knowledge gaps with thesis 11

1.4 Thesis Aims 13

Chapter 2 Systematic Review and Meta-analysis **15**

2.1 Chapter Summary 15

2.2 Methods 16

2.2.1 Inclusion criteria 16
2.2.2 Search strategy 17
2.2.3 Meta-analysis 19
2.2.4 Certainty of evidence 19
2.3 Results 20
2.3.1 Overview of search results 20
2.3.2 Corticosteroids compared with no corticosteroids 28
2.3.3 IL-6 RAs 32
2.3.4 JAKIs 37
2.3.5 Higher dose corticosteroids compared with lower dose corticosteroids 40
2.3.6 Summary of findings 45
2.4 Discussion 52
2.4.1 Mortality 52
2.4.2 Secondary infections 52
2.4.3 Other potential treatment-related harms 53
2.4.4 Illness recovery 54
2.4.5 Biological measurements 54
2.4.6 Corticosteroid effects across the disease severity spectrum 55
2.5 Conclusions 56
Chapter 3 Methods 57
3.1 Chapter Summary 57
3.2 Study Design and Population 58
3.3 Data Sources 61
3.3.1 RECOVERY 62
3.3.2 RCD 67

3.3.3 ISARIC4C 73
3.4 Long-term Follow-up Analysis Assessments 76
3.4.1 Primary Outcomes 78
3.4.2 Secondary Outcomes 79
3.4.3 Tertiary Outcomes 84
3.4.4 Exploratory analyses 89
3.4.5 Additional baseline characteristics 93
3.4.6 Subgroup analyses 96
3.4.7 Sensitivity analyses 97
3.5 Exploratory Analysis Assessments 99
3.5.1 Outcome selection and classification 99
3.5.2 Physiological measurements 99
3.5.3 Commonly-measured blood biomarkers 101
3.5.4 Gene expression data 103
3.5.5 Subgroup analyses 104
3.5.6 Sensitivity analyses 105
3.6 Statistical Methods 107
3.6.1 Baseline comparability of randomised groups 107
3.6.2 Analysis of time to event outcomes 108
3.6.3 Analysis of categorical outcomes 110
3.6.4 Analysis of continuous outcomes 110
3.6.5 Analysis of ordinal outcomes 110
3.6.6 Analysis of gene expression data 111
3.6.7 Subgroup analyses 112
3.6.8 Minimum detectable effect size 113

3.6.9 Multiplicity of comparisons 117
3.6.10 Missing data 117
3.6.11 Software 118
3.7 Ethics and Information Governance 119
3.7.1 Ethics 119
3.7.2 Data Linkage 119
Chapter 4 Method Development 126
4.1 Chapter Summary 126
4.2 Literature Review 128
4.2.1 Aims 128
4.2.2 Methods 128
4.2.3 Results 131
4.2.4 Discussion 153
4.2.5 Conclusions 161
4.3 Definition Development Process 162
4.3.1 Introduction 162
4.3.2 Clinical codelist development 162
4.3.3 Assessment definition testing methods 165
4.3.4 Assessment definition testing results 172
4.3.5 Discussion 186
4.3.6 Conclusions 194
Chapter 5 Long-term Follow-up Analysis Results 196
5.1 Chapter Summary 196
5.2 Data Completeness 197
5.3 Dexamethasone Randomised Comparisons 199

5.3.1 Baseline characteristics 199
5.3.2 Long-term mortality 200
5.3.3 Non-COVID infection 203
5.3.4 Other clinical benefits 208
5.3.5 Other potential treatment-related harms 210
5.3.6 Subgroup analyses 212
5.4 Tocilizumab Randomised Comparisons 216
5.4.1 Baseline characteristics 216
5.4.2 Long-term mortality 217
5.4.3 Non-COVID infection 220
5.4.4 Other clinical benefits 224
5.4.5 Other potential treatment-related harms 226
5.4.6 Subgroup analyses 227
5.5 Baricitinib Randomised Comparisons 232
5.5.1 Baseline characteristics 232
5.5.2 Long-term mortality 233
5.5.3 Non-COVID infection 236
5.5.4 Other clinical benefits 239
5.5.5 Other potential treatment-related harms 241
5.5.6 Subgroup analyses 243
5.6 Higher Dose Dexamethasone Randomised Comparisons 247
5.6.1 Baseline characteristics 247
5.6.2 Long-term mortality 248
5.6.3 Non-COVID infection 250
5.6.4 Other clinical effects 253

5.6.5 Subgroup analyses 256

Chapter 6 Exploratory Analysis Results 260

6.1 Chapter Summary 260

6.2 RECOVERY-ISARIC Representativeness 261

6.2.1 All treatment comparisons 261

6.2.2 Dexamethasone 264

6.2.3 Tocilizumab 266

6.2.4 Baricitinib 267

6.3 Exploration of the Heterogeneity of Dexamethasone Treatment Effect 270

6.3.1 Rationale 270

6.3.2 Extended respiratory support subgroups 270

6.3.3 Effect on secondary efficacy outcomes 272

6.3.4 Interactions between respiratory support and frailty subgroups 273

6.3.5 Effect on potential treatment-related harms 277

6.3.6 Clinical trajectory in the dexamethasone ‘no oxygen’ subgroup 278

6.4 Randomised Comparisons of Biological Measurements 282

6.4.1 Ordinal scale score 282

6.4.2 Commonly-measured blood biomarkers 285

6.4.3 Subgroup analyses of biological measurements 291

6.5 Randomised Comparisons of Gene Expression Data 293

6.5.1 Baseline characteristics 293

6.5.2 Differential gene expression 293

Chapter 7 Discussion 299

7.1 Chapter Summary 299

7.2 Results Overview 300

7.2.1 Mortality 300
7.2.2 Other clinical benefits 300
7.2.3 Non-COVID infection 300
7.2.4 Other potential treatment-related harms 301
7.2.5 Heterogeneity of dexamethasone treatment effect 302
7.2.6 Biological measurements 302
7.3 Application of Findings to Thesis Aims 303
7.3.1 Efficacy of immunomodulatory treatments at long-term follow-up 303
7.3.2 Safety of immunomodulatory treatments 310
7.3.3 Effect of immunomodulatory treatments on illness recovery 328
7.3.4 Exploration of the heterogeneity of corticosteroid treatment effects 330
7.3.5 Effects of immunomodulatory treatments on biological measurements 335
7.4 Strengths and Limitations 340
7.4.1 Study design 340
7.4.2 Routinely collected data sources 340
7.4.3 Performance characteristics of assessments 341
7.4.4 ISARIC4C data 343
7.4.5 Competing risks 344
7.4.6 Minimum detectable effect size 344
7.4.7 Other potential sources of error 345
7.4.8 Generalisability 345
7.5 Wider Applications and Future Directions of Research 347
7.6 Conclusions 349
References 351
Supplementary Figures and Tables 381

Supplementary Figures 381

List of Supplementary Figures 381

Supplementary Tables 408

List of Supplementary Tables 408

Abstract

Introduction: This thesis aims to evaluate and explore extended treatment effects of the COVID-19 immunomodulatory therapies that reduced short-term mortality in the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial and are being used in current clinical practice for hospitalised patients with COVID-19. These treatments are dexamethasone (a corticosteroid), tocilizumab (an interleukin-6 receptor antagonist), and baricitinib (a Janus kinase inhibitor).

Methods: An extended analysis was performed of additional efficacy, safety, and exploratory assessments, including: long-term mortality; non-COVID infection and other potential treatment-related harms; and illness recovery and long COVID. The assessments were derived from a broad range of routinely collected healthcare data (RCD) sources and a large-scale cohort study of patients hospitalised with COVID-19 (ISARIC4C). The additional data was linked at an individual participant level and the analyses were carried out within the original randomised treatment comparisons from RECOVERY.

Results: RCD was available for >96% of RECOVERY participants in the dexamethasone, tocilizumab and baricitinib treatment comparisons. In the primary efficacy outcome of 6-month all-cause mortality, each of these immunomodulatory treatments demonstrated a preserved mortality benefit at long-term follow-up. In the primary safety outcome of major non-COVID infection, there was no clear evidence of an increased risk of non-COVID infection at short- or long-term follow-up. Few other safety signals were identified, despite systematic evaluation. There was no evidence of benefit of short-term immunomodulatory treatment on functional recovery or long COVID. Exploratory analyses suggested that the heterogeneity of dexamethasone treatment effect observed in RECOVERY may be determined by a benefit-risk balance of disease severity, host vulnerability and drug dose

factors. Randomised comparisons of biological measurements produced rich data applicable to future research.

Conclusions: Dexamethasone (at a dose of 6mg/day), tocilizumab and baricitinib reduce mortality at long-term follow-up. The benefits of these treatments outweigh any possible risks and the treatments can continue to be used with greater confidence for hospitalised patients with COVID-19.

List of Figures

Figure 1-1: Weekly new COVID-19 deaths over time in the United Kingdom. 3

Figure 1-2: Effect of dexamethasone on 28-day mortality according to respiratory support at randomisation in the RECOVERY trial. 9

Figure 1-3: Overview of the concept of the thesis extended analysis. 12

Figure 2-1: Flowchart of systematic literature search. 20

Figure 2-2: Meta-analysis of 28-day all-cause mortality in randomised controlled trials of systemic corticosteroids compared with no corticosteroids in hospitalised patients with COVID-19. 28

Figure 2-3: Meta-analysis of 90-day all-cause mortality in randomised controlled trials of systemic corticosteroids compared with no corticosteroids in hospitalised patients with COVID-19. 29

Figure 2-4: Meta-analysis of secondary infections within 28 days in randomised controlled trials of systemic corticosteroids compared with no corticosteroids in hospitalised patients with COVID-19. 30

Figure 2-5: Meta-analysis of hyperglycaemia within 28 days in randomised controlled trials of systemic corticosteroids compared with no corticosteroids in hospitalised patients with COVID-19. 31

Figure 2-6: Meta-analysis of all-cause mortality within 28 days in randomised controlled trials of interleukin-6 receptor antagonists compared with usual care/placebo in hospitalised patients with COVID-19. 33

Figure 2-7: Meta-analysis of all-cause mortality within 90 days in randomised controlled trials of interleukin-6 receptor antagonists compared with usual care/placebo in hospitalised patients with COVID-19. 34

Figure 2-8: Meta-analysis of secondary infections within 28 days in randomised controlled trials of interleukin-6 receptor antagonists compared with usual care/placebo in hospitalised patients with COVID-19. 35
Figure 2-9: Meta-analysis of secondary infections within 90 days in randomised controlled trials of interleukin-6 receptor antagonists compared with usual care/placebo in hospitalised patients with COVID-19. 36
Figure 2-10: Meta-analysis of all-cause mortality within 28 days in randomised controlled trials of Janus kinase inhibitors compared with usual care/placebo in hospitalised patients with COVID-19. 37
Figure 2-11: Meta-analysis of all-cause mortality within 90 days in randomised controlled trials of Janus kinase inhibitors compared with usual care/placebo, in hospitalised patients with COVID-19. 38
Figure 2-12: Meta-analysis of secondary infections within 28 days in randomised controlled trials of Janus kinase inhibitors compared with usual care/placebo, in hospitalised patients with COVID-19. 39
Figure 2-13: Meta-analysis of all-cause mortality within 28 days in groups defined by baseline disease severity in randomised controlled trials of higher dose corticosteroids compared with lower dose corticosteroids in hospitalised patients with COVID-19. 41
Figure 2-14: Meta-analysis of all-cause mortality within 90 days in randomised controlled trials of higher dose corticosteroids compared with lower dose corticosteroids in hospitalised patients with COVID-19. 42
Figure 2-15: Meta-analysis of secondary infections within 28 days in randomised controlled trials of higher dose corticosteroids compared with lower dose corticosteroids in hospitalised patients with COVID-19. 43
Figure 2-16: Meta-analysis of hyperglycaemia within 28 days in randomised controlled trials of higher dose corticosteroids compared with lower dose corticosteroids in hospitalised patients with COVID-19. 44

Figure 3-1: Overview of the extended analysis study design. 59
Figure 3-2: Timeline of the data linkage process for the extended analysis. 120
Figure 3-3: Data flow diagram for RECOVERY-ISARIC4C data linkage between the University of Oxford and Public Health Scotland. 125
Figure 4-1: Overview of the method development process. 127
Figure 4-2: Flow diagram of method development systematic literature search. 132
Figure 4-3: Distribution of primary care frailty assessment categories across Hospital Frailty Risk Score groups. 174
Figure 4-4: Distribution of Clinical Frailty Scale scores by Hospital Frailty Risk Score group. 175
Figure 4-5: Positive predictive value of routinely collected data-derived major non-COVID infection events by diagnostic position, compared to a reference standard of RECOVERY case report form data. 179
Figure 4-6: Major non-COVID infection at 28 days in the RECOVERY baricitinib comparison by method of follow-up data collection. 184
Figure 4-7: Venn diagram of data sources of major non-COVID infection events within 28 days in the RECOVERY baricitinib comparison. 185
Figure 4-8: Venous thromboembolism at 28 days in the RECOVERY baricitinib comparison by method of follow-up data collection. 186
Figure 5-1: Flow diagram of RECOVERY participants in the thesis extended analysis by immunomodulatory treatment comparison. 198
Figure 5-2: Effect of allocation to dexamethasone on all-cause mortality in the RECOVERY dexamethasone comparison. 201
Figure 5-3: Effect of allocation to dexamethasone on 2-year mortality in the RECOVERY dexamethasone comparison. 202
Figure 5-4: All-cause mortality in all participants in the RECOVERY dexamethasone comparison, stratified by follow-up time period. 203

Figure 5-5: Effect of allocation to dexamethasone on major non-COVID infection in the RECOVERY dexamethasone comparison. 204
Figure 5-6: Major non-COVID infection in the RECOVERY dexamethasone comparison stratified by follow-up time period. 205
Figure 5-7: Effect of allocation to dexamethasone on discharge alive from hospital in the RECOVERY dexamethasone comparison. 209
Figure 5-8: Subgroup analysis of effect of allocation to dexamethasone on all-cause mortality within 6 months. 213
Figure 5-9: Subgroup analysis of effect of allocation to dexamethasone on major non-COVID infection within 28 days. 214
Figure 5-10: Subgroup analysis of effect of allocation to dexamethasone on major non-COVID infection within 6 months. 215
Figure 5-11: Effect of allocation to tocilizumab on all-cause mortality in the RECOVERY tocilizumab comparison. 218
Figure 5-12: Effect of allocation to tocilizumab on 2-year mortality in the RECOVERY tocilizumab comparison. 219
Figure 5-13: Mortality in the all participants in the RECOVERY tocilizumab comparison, stratified by follow-up time period. 220
Figure 5-14: Effect of allocation to tocilizumab on major non-COVID infection in the RECOVERY tocilizumab comparison. 221
Figure 5-15: Major non-COVID infection in the RECOVERY tocilizumab comparison stratified by follow-up time period. 222
Figure 5-16: Effect of allocation to tocilizumab on discharge alive from hospital in the RECOVERY tocilizumab comparison. 225
Figure 5-17: Subgroup analysis of effect of allocation to tocilizumab on all-cause mortality within 6 months. 229

Figure 5-18: Subgroup analysis of effect of allocation to tocilizumab on major non-COVID infection within 28 days. 230
Figure 5-19: Subgroup analysis of effect of allocation to tocilizumab on major non-COVID infection within 6 months. 231
Figure 5-20: Effect of allocation to baricitinib on all-cause mortality in the RECOVERY baricitinib comparison. 234
Figure 5-21: Effect of allocation to baricitinib on 2-year mortality in the RECOVERY baricitinib comparison. 235
Figure 5-22: All-cause mortality in all participants in the RECOVERY baricitinib comparison, stratified by follow-up time period. 236
Figure 5-23: Major non-COVID infection in the RECOVERY baricitinib comparison stratified by follow-up time period. 237
Figure 5-24: Effect of allocation to baricitinib on discharge alive from hospital in the RECOVERY baricitinib comparison. 240
Figure 5-25: Subgroup analysis of effect of allocation to baricitinib on all-cause mortality within 6 months. 244
Figure 5-26: Subgroup analysis of effect of allocation to baricitinib on major non-COVID infection within 28 days. 245
Figure 5-27: Subgroup analysis of effect of allocation to baricitinib on major non-COVID infection within 6 months. 246
Figure 5-28: Effect of allocation to higher dose dexamethasone on all-cause mortality in participants who were hypoxic but not requiring ventilatory support in the RECOVERY higher dose dexamethasone comparison. 249
Figure 5-29: Mortality in participants who were hypoxic but not requiring ventilatory support in the RECOVERY higher dose dexamethasone comparison, stratified by follow-up time period. 250

Figure 5-30: Major non-COVID infection in the completed subgroup of the RECOVERY high dose dexamethasone comparison stratified by follow-up time period. 251
Figure 5-31: Discharge alive from hospital in participants who were hypoxic but not requiring ventilatory support at randomisation in the RECOVERY higher dose dexamethasone comparison. 254
Figure 5-32: Subgroup analysis of effect of allocation to higher dose dexamethasone on all-cause mortality within 6 months. 257
Figure 5-33: Subgroup analysis of effect of allocation to higher dose dexamethasone on major non-COVID infection within 28 days. 258
Figure 5-34: Subgroup analysis of effect of allocation to higher dose dexamethasone on major non-COVID infection within 6 months. 259
Figure 6-1: Proportion of RECOVERY participants included in ISARIC4C over time. 262
Figure 6-2: Subgroup analysis of 28-day mortality in the RECOVERY dexamethasone comparison by ISARIC4C linkage status. 265
Figure 6-3: Subgroup analysis of 28-day mortality in the RECOVERY tocilizumab comparison by ISARIC4C linkage status. 267
Figure 6-4: Subgroup analysis of 28-day mortality in the RECOVERY baricitinib comparison by ISARIC4C linkage status. 269
Figure 6-5: Subgroup analysis of effect of allocation to dexamethasone on all-cause mortality within 28 days, by subgroups defined by extended respiratory support group at randomisation in the RECOVERY-ISARIC dexamethasone comparison population. 271
Figure 6-6: Subgroup analysis of effect of allocation to dexamethasone on discharge alive from hospital within 28 days in the RECOVERY dexamethasone comparison. 272
Figure 6-7: Subgroup analysis of effect of allocation to dexamethasone on invasive mechanical ventilation or death within 28 days in the RECOVERY dexamethasone comparison. 273

Figure 6-8: Subgroup analysis of 28-day mortality in the RECOVERY dexamethasone comparison after considering interactions with other key subgroups with standardisation. 277
Figure 6-9: Subgroup analysis of effect of allocation to dexamethasone on hyperglycaemia within 28 days, assessed in the RECOVERY-ISARIC dexamethasone comparison. 278
Figure 6-10: Mean modified ordinal scale score per study day according to vital status at 28 days for participants in the ‘no oxygen’ subgroup of the RECOVERY-ISARIC dexamethasone comparison population. 280
Figure 6-11: Mean C-reactive protein per study day according to vital status at 28 days for participants in the ‘no oxygen’ subgroup of the RECOVERY-ISARIC dexamethasone comparison population. 281
Figure 6-12: Daily rate of change in ordinal scale score within the first 7 days after randomisation, by treatment allocation in the RECOVERY-ISARIC dexamethasone comparison population. 283
Figure 6-13: Mean ordinal scale score per study day according to randomised allocation for participants in the dexamethasone RECOVERY-ISARIC population..... 284
Figure 6-14: Distribution of ordinal scale score at 5 days by randomised allocation in the RECOVERY-ISARIC dexamethasone comparison. 285
Figure 6-15: Daily rate of change in C-reactive protein within the first 7 days after randomisation, by treatment allocation in the RECOVERY-ISARIC dexamethasone comparison population. 286
Figure 6-16: Mean C-reactive protein per study day according to randomised allocation for participants in the RECOVERY-ISARIC dexamethasone comparison population. 287
Figure 6-17: Daily rate of change in glucose within the first 7 days after randomisation, by treatment allocation in the RECOVERY-ISARIC dexamethasone comparison population. 288

Figure 6-18: Mean glucose per study day according to randomised allocation for participants in the RECOVERY-ISARIC dexamethasone comparison population. 289
Figure 6-19: Daily rate of change in Neutrophil:lymphocyte ratio within the first 7 days after randomisation, by treatment allocation in the RECOVERY-ISARIC dexamethasone comparison population. 290
Figure 6-20: Mean Neutrophil:lymphocyte ratio per study day according to randomised allocation for participants in the RECOVERY-ISARIC dexamethasone comparison population. 291
Figure 6-21: Subgroup analyses of daily rate of change in ordinal scale score and C-reactive protein within the first 7 days after randomisation in the RECOVERY-ISARIC dexamethasone comparison population. 292
Figure 6-22: Volcano plot of differentially expressed genes at day 3 after randomisation according to dexamethasone treatment allocation. 294
Figure 6-23: Top 10 differentially expressed Gene Ontology Biological Processes terms from pathway enrichment analysis of differentially expressed genes by dexamethasone randomised treatment allocation. 296
Figure 7-1: Meta-analysis of longer-term all-cause mortality in randomised controlled trials of systemic corticosteroids compared with no corticosteroids in hospitalised patients with COVID-19, updated to include results of the extended analysis. 305
Figure 7-2: Meta-analysis of longer-term all-cause mortality in randomised controlled trials of interleukin-6 receptor antagonists compared with usual care/placebo in hospitalised patients with COVID-19, updated to include results of the extended analysis. 307
Figure 7-3: Meta-analysis of longer-term all-cause mortality in randomised controlled trials of Janus kinase inhibitors compared with usual care/placebo in hospitalised patients with COVID-19, updated to include results of the extended analysis. 309

Figure 7-4: Meta-analysis of secondary infection within 28 days in randomised controlled trials of systemic corticosteroids compared with no corticosteroids in hospitalised patients with COVID-19, updated to include results of the extended analysis. 315
Figure 7-5: Meta-analysis of secondary infection within 28 days in randomised controlled trials of interleukin-6 receptor antagonist compared with usual care/placebo in hospitalised patients with COVID-19, updated to include results of the extended analysis. 317
Figure 7-6: Meta-analysis of secondary infection at long-term follow-up in randomised controlled trials of interleukin-6 receptor antagonist compared with usual care/placebo in hospitalised patients with COVID-19, updated to include results of the extended analysis. 318

List of Tables

Table 2-1: Randomised controlled trials evaluating corticosteroids compared with no corticosteroids in hospitalised patients with COVID-19. 21

Table 2-2: Randomised controlled trials evaluating interleukin-6 receptor antagonists compared with usual care/placebo in hospitalised patients with COVID-19..... 22

Table 2-3: Randomised controlled trials evaluating Janus kinase inhibitors compared with usual care/placebo for hospitalised patients with COVID-19. 24

Table 2-4: Randomised controlled trials evaluating higher dose corticosteroids compared with lower dose corticosteroids in hospitalised patients with COVID-19. 26

Table 2-5: Summary of findings table for systematic review and meta-analysis of randomised controlled trials of corticosteroids, interleukin-6 receptor antagonists and Janus kinase inhibitors compared with usual care/placebo in hospitalised patients with COVID-19 45

Table 3-1: Summary of the data sources used for the extended analysis..... 61

Table 3-2: Details of the RECOVERY immunomodulatory treatment comparisons. 64

Table 3-3: Summary of final long-term follow-up assessments used in the thesis extended analysis..... 76

Table 3-4: Categories of diagnoses leading to death and hospital-recorded diagnoses. . 90

Table 3-5: Definition of the ordinal scale score used in the extended analysis. 100

Table 3-6: Minimum detectable effect sizes for planned study outcomes across all treatment comparisons, based on blinded data..... 114

Table 4-1: Summary of case validation studies evaluating routinely collected data-derived infection events..... 134

Table 4-2: Summary of diagnostic accuracy studies evaluating routinely collected data-derived infection events. 136

Table 4-3: Summary of case validation studies evaluating routinely collected data-derived venous thromboembolism events..... 138
Table 4-4: Summary of diagnostic accuracy studies evaluating routinely collected data-derived venous thromboembolism events. 140
Table 4-5: Summary of case validation studies evaluating routinely collected data-derived gastrointestinal complication events..... 142
Table 4-6: Summary of diagnostic accuracy study evaluating routinely collected data-derived gastrointestinal complication events. 143
Table 4-7: Summary of case validation studies evaluating routinely collected data-derived diagnoses of diabetes mellitus. 145
Table 4-8: Summary of diagnostic accuracy studies evaluating routinely collected data-derived diagnoses of diabetes mellitus. 146
Table 4-9: Summary measures of validity and diagnostic accuracy results from the systematic literature review of studies relating to thesis extended analysis outcomes... 152
Table 4-10: Summary of results of case validation of thesis routinely collected data-derived outcome events compared with a reference standard of manual medical record review. 172
Table 4-11: Prevalence of medication administration in the secondary care prescribing routinely collected dataset split by participants with the outcome of interest present or absent..... 173
Table 4-12: Diagnostic performance of different assessment definitions compared with a reference standard of the RECOVERY case report form data..... 176
Table 4-13: Diagnostic performance of different assessment definitions compared with a reference standard of the ISARIC4C case report form data. 181
Table 5-1: Baseline characteristics according to randomised treatment allocation for participants in the RECOVERY dexamethasone comparison..... 199

Table 5-2: Effect of allocation to dexamethasone on primary long-term follow-up outcomes. 200
Table 5-3: Major non-COVID infection event details by randomised treatment allocation in the RECOVERY dexamethasone comparison. 206
Table 5-4: Effect of allocation to dexamethasone on secondary and tertiary infection outcomes. 207
Table 5-5: Effect of allocation to dexamethasone on other clinical benefits. 208
Table 5-6: Effect of allocation to dexamethasone on other potential treatment-related harms. 210
Table 5-7: Baseline characteristics according to randomised treatment allocation for participants in the RECOVERY tocilizumab comparison. 216
Table 5-8: Effect of allocation to tocilizumab on primary long-term follow-up outcomes. 217
Table 5-9: Major non-COVID infection event details by randomised treatment allocation in the RECOVERY tocilizumab comparison. 223
Table 5-10: Effect of allocation to tocilizumab on secondary and tertiary infection outcomes. 224
Table 5-11: Effect of allocation to tocilizumab on other clinical benefits. 226
Table 5-12: Effect of allocation to tocilizumab on potential treatment-related harms. 227
Table 5-13: Baseline characteristics according to randomised treatment allocation for participants in the RECOVERY baricitinib comparison 232
Table 5-14: Effect of allocation to baricitinib on primary long-term follow-up outcomes. 233
Table 5-15: Major non-COVID infection event details by randomised treatment allocation in the RECOVERY baricitinib comparison. 238
Table 5-16: Effect of allocation to baricitinib on secondary and tertiary infection outcomes. 239
Table 5-17: Effect of allocation to baricitinib on other clinical benefits. 241
Table 5-18: Effect of allocation to baricitinib on potential treatment-related harms. 242

Table 5-19: Baseline characteristics according to randomised treatment allocation for participants who were hypoxic but not requiring ventilatory support at randomisation in the RECOVERY higher dose dexamethasone comparison. 247
Table 5-20: Effect of allocation to higher dose dexamethasone on primary long-term follow-up outcomes. 248
Table 5-21: Major non-COVID infection event details by randomised treatment allocation in the completed subgroup of the RECOVERY high dose dexamethasone comparison. 252
Table 5-22: Effect of allocation to higher dose dexamethasone on secondary and tertiary infection outcomes. 253
Table 5-23: Effect of allocation to higher dose dexamethasone on other clinical effects. 255
Table 6-1: Baseline characteristics and 28-day mortality according to linkage with ISARIC4C for all RECOVERY participants. 261
Table 6-2: Baseline characteristics and 28-day mortality according to linkage with ISARIC4C for RECOVERY dexamethasone comparison participants. 263
Table 6-3: Baseline characteristics according to randomised treatment group in the RECOVERY-ISARIC dexamethasone comparison population. 264
Table 6-4: Baseline characteristics according to randomised treatment group in the RECOVERY-ISARIC tocilizumab comparison population. 266
Table 6-5: Baseline characteristics according to randomised treatment group in the RECOVERY-ISARIC baricitinib comparison population. 268
Table 6-6: Baseline characteristics according to respiratory support groups in the RECOVERY dexamethasone comparison. 274
Table 6-7: Baseline characteristics according to Hospital Frailty Risk Score groups. 275
Table 6-8: Categorisation of diagnoses leading to death within 28 days in the ‘no oxygen’ subgroup of the RECOVERY dexamethasone comparison. 279

Table 6-9: Daily rate of change in biological measurements in the first 7 days after randomisation by vital status in the ‘no oxygen’ subgroup of the RECOVERY-ISARIC dexamethasone comparison population. 279
Table 6-10: Exploratory outcomes of daily rate of change in biological measurements in the first 7 days after randomisation in the RECOVERY-ISARIC dexamethasone comparison population. 283
Table 6-11: Baseline characteristics and outcomes by randomised allocation for participants in the RECOVERY-ISARIC dexamethasone comparison population with gene expression data available at day 3 of follow-up. 293
Table 6-12: Gene set enrichment analysis of dexamethasone treatment effect on gene sets of interest identified a priori. 298
Table 7-1: Summary of immunomodulatory mortality treatment effect estimates from the extended analysis, RECOVERY 28-day follow-up and thesis meta-analyses..... 304

List of Abbreviations

95% CI	95% Confidence Interval
AKI	Acute kidney injury
ALT	Alanine aminotransferase
BNF	British National Formulary
BSI	Bloodstream infection
CFS	Clinical Frailty Scale
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRP	C-reactive protein
DNA	Deoxyribonucleic acid
DVT	Deep vein thrombosis
eDRIS	Electronic Data Research and Innovation Service
EDTA	Ethylenediaminetetraacetic acid
eFI	Electronic Frailty Index
EPMA	Electronic Prescribing and Medicines Administration
FiO_2	Fraction of inspired oxygen
GDPPR	General Practice Extraction Service Data for Pandemic Planning and Research
GI	Gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development and Evaluations framework
HESAPC	Hospital Episode Statistics Admitted Patient Care
HFRS	Hospital Frailty Risk Score
HIV	Human Immunodeficiency Virus
HRA	Health Research Authority
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th revision
ICU	Intensive Care Unit
IL-6 RA	Interleukin-6 receptor antagonist
IQR	Interquartile range
ISARIC4C	International Severe Acute Respiratory Infection Consortium Coronavirus Clinical Characterisation Consortium
IV	Intravenous
JAKI	Janus kinase inhibitor
MEDLINE	Medical Literature Analysis and Retrieval System Online

metaTWAS	Transcriptome-wide association study and meta-analysis
MICE	Multiple Imputation by Chained Equations
NHS	National Health Service
NHSBSA	National Health Service Business Services Authority
NLR	Neutrophil:lymphocyte ratio
NPEx	National Pathology Exchange
NPV	Negative predictive value
NRS	National Records of Scotland
O-E	Observed minus Expected
ONS	Office for National Statistics
OPCS-4	Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4
PCR	Polymerase chain reaction
PE	Pulmonary embolism
PEDW	Patient Episode Database Wales
PHS	Public Health Scotland
PPV	Positive predictive value
RCD	Routinely collected healthcare data
RCT	Randomised controlled trial
REC	Research Ethics Committee
RECOVERY	Randomised Evaluation of COVID-19 Therapy
RNA-Seq	Ribonucleic acid Sequencing
RR	Risk or Rate Ratio
SAIL	Secure Anonymised Information Linkage Databank
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus-2
SGSS	Second Generation Surveillance System
SMR01	Scottish Morbidity Record 1
SNOMED	Systematized Nomenclature of Medicine
TRE	Trusted Research Environment
UK	United Kingdom
UKHSA	United Kingdom Health Security Agency
VTE	Venous thromboembolism
WHO	World Health Organization
WLGP	Welsh Longitudinal General Practice Dataset

Chapter 1

Introduction

1.1 Chapter Summary

This chapter introduces the research questions of interest for this thesis. First, it outlines the epidemiological and clinical background to Coronavirus disease 2019 (COVID-19). It then summarises knowledge gaps in the research area of treatment for hospitalised patients with COVID-19 and how this thesis aims to address these knowledge gaps.

1.2 Research Context

1.2.1 COVID-19

COVID-19, caused by the virus Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has led to a global pandemic resulting in more than 700 million cases and 7 million deaths[1].

Coronaviruses are a family of viruses that can cause acute respiratory illness in humans. SARS-CoV-2 is a novel coronavirus that emerged in China in late 2019. It potentially originated from a zoonotic source – where a virus that caused disease in animals mutated and began to cause illness in humans[2]. SARS-CoV-2 spreads from person-to-person through droplets and aerosols in the air containing the virus[3].

1.2.2 Epidemiology

The first cases of an outbreak of severe pneumonia of unknown cause were identified in Wuhan, China, in December 2019. The causative agent was subsequently found to be SARS-CoV-2[4]. By March 2020, the World Health Organization (WHO) formally declared COVID-19 a global pandemic, amidst rapidly escalating case numbers and deaths worldwide[5]. Global weekly deaths reached a peak of over 100,000 in January 2021[1].

In England, a national 'lockdown' was declared on 23 March 2020[6]. The United Kingdom (UK) experienced severe health consequences from the pandemic, particularly in the first two national 'waves': between March 2020 to June 2020 and November 2020 to February 2021, COVID-19 directly caused thousands of deaths per week (Figure 1-1). COVID-19 was the leading cause of death in England and Wales in both 2020 and 2021[7].

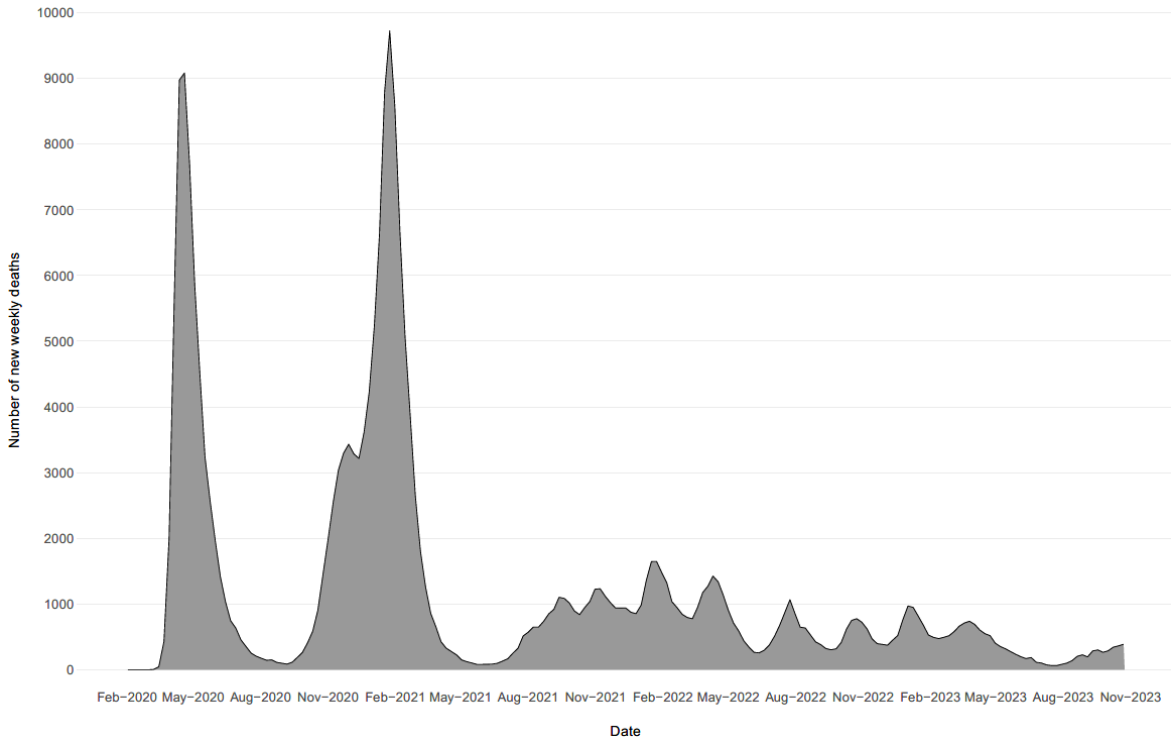


Figure 1-1: Weekly new COVID-19 deaths over time in the United Kingdom.
Produced from the publicly accessible 'Daily COVID-19 cases and deaths by date reported to WHO' dataset downloaded from the World Health Organization[8].

COVID-19 immunity, vaccination and treatment began to reduce mortality over the following 2 years. Large case outbreaks have still occurred, with major health and economic consequences, often coinciding with the emergence of new viral variants to which there were reduced levels of population immunity.

The WHO ended its declaration of COVID-19 as a global public health emergency in May 2023[9]. While the effects of the pandemic have clearly reduced, COVID-19 continues to cause several thousand deaths a week globally as of March 2024[1]. The pandemic has been estimated to have had a true excess mortality burden three times higher than official cause of death estimates, and to have resulted in an average loss of life expectancy of over a year[10,11].

1.2.3 Natural history

In many cases, SARS-CoV-2 infection results in asymptomatic or mild illness, with a median incubation period of 4 days from virus exposure[12,13]. In symptomatic individuals, key clinical features include cough, fever, shortness of breath, and an altered sense of smell or taste, although many clinical presentations are possible[14].

In patients progressing to severe COVID-19, worsening breathlessness with hypoxaemia develops from approximately 1 week after illness onset. Severe COVID-19 can lead to respiratory failure, multi-organ failure, and death[15,16]. Risk factors for severe disease include age, male sex, obesity and chronic medical conditions, such as diabetes mellitus[17,18]. Patients with severe illness have high levels of pro-inflammatory cytokines and blood inflammatory markers[19]. Genetic factors influencing host anti-viral and inflammatory response have been implicated in the development of critical illness[20].

After acute illness, some patients go on to develop persistent symptoms, such as fatigue, often termed ‘post-COVID syndrome’ or ‘long COVID’[21].

1.2.4 Pathophysiology

In initial infection, SARS-CoV-2 binds to target host cells through attachment to the angiotensin converting enzyme-2 receptor found on cells of the respiratory tract epithelium, and other organ systems[22]. In many patients, effects are limited to the upper respiratory tract. In severe disease, infection progressing to the lower respiratory tract appears to trigger an over-active host immune response in some patients. The immune response can cause damage to the alveolar epithelium and associated microvascular structures[23]. This can result in further inflammation, increased vascular permeability and disordered coagulation that can lead to lung injury and thrombosis, including widespread microthrombi[23,24]. The proliferation of inflammation can become uncontrolled and lead to severe immunopathology through these mechanisms.

1.2.5 Treatment

COVID-19 pharmacological therapies broadly target one of two main biological processes underlying the development of severe COVID-19:

i) Viral replication;

Treatment given in the early stages of illness can target viral replication to reduce the potential to develop severe disease in patients at high risk of admission to hospital. These therapies include nirmatrelvir with ritonavir, remdesivir and molnupiravir[25,26]. Neutralising monoclonal antibody therapy, such as casirivimab-imdevimab and sotrovimab, have previously been recommended to treat later stage severe COVID-19, but are not currently used due to the lack of susceptibility of current dominant viral variants to these treatments.

ii) Host immune response;

Other treatments given in patients hospitalised with COVID-19 aim to modulate dysregulated host immune response to reduce disease severity. Efforts to discover effective COVID-19 treatments for severe disease have been led by the University of Oxford's Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial and the WHO's Solidarity trial - large-scale, randomised, controlled, platform trials evaluating treatments in patients hospitalised with COVID-19[27,28]. Immunomodulatory treatments have proven crucial, with RECOVERY demonstrating a short-term mortality benefit from three immunomodulatory therapies:

- Dexamethasone, a corticosteroid[29];
- Tocilizumab, an interleukin-6 receptor antagonist (IL-6 RA)[30];
- Baricitinib, a Janus kinase inhibitor (JAKI)[31].

These treatments have become the recommended standard of care for hospitalised patients with severe COVID-19 worldwide[25,26]. Nevertheless, important questions and

knowledge gaps remain in the context of new widespread use of these treatments for COVID-19[32-36].

1.3 Knowledge Gaps

1.3.1 Long-term follow-up

Data confirming the long-term efficacy and safety of the immunomodulatory treatments in COVID-19 are limited. Of patients admitted with COVID-19 who survive to hospital discharge, 10% are readmitted and 7% die within 90 days[37]. Discharged patients have a five times higher risk of death compared with matched general population controls over 6 months follow-up[38]. In RECOVERY, 12% of participants in the dexamethasone comparison and 15% of participants in the tocilizumab comparison had neither been discharged from hospital nor died within 28 days of randomisation. Longer-term follow-up is important to ascertain whether the demonstrated short-term benefits of the immunomodulatory treatments are sustained over time and to ensure that no emergent hazard is found.

1.3.2 Potential treatment-related harms

Each of the COVID-19 immunomodulatory treatment classes have other established therapeutic indications and are associated with a known profile of potential harms. Corticosteroids are associated with infections, thromboembolism, gastrointestinal (GI) bleeding, dysglycaemia, psychiatric reactions and vertebral or long bone fractures[39-41], including with short-term use[42,43]. The RECOVERY trial has reported that participants randomised to higher dose corticosteroids (20mg/day of dexamethasone) compared with usual care that included standard dose corticosteroids (6mg/day of dexamethasone), had an increased risk of mortality in the subgroup of participants who were hypoxic but not receiving ventilatory support at randomisation[44]. Those who received higher dose corticosteroids had an excess of non-COVID pneumonia and hyperglycaemia. IL-6 RAs are associated with infections, GI perforation, liver injury and neutropenia with long-term use[45]. JAKIs are associated with diverticulitis and GI perforation, liver injury and venous

thromboembolism (VTE) with long-term use[46]. Relatively little is known about the effects of short-term IL-6 RA and JAKI use. The use of combination immunomodulatory therapies for COVID-19 in clinical practice is recommended, with clinical judgment to weigh-up the balance of anticipated benefits and risks for individual patients[26,47].

Secondary infection (other infection complicating COVID-19) is a common and serious complication. It develops in an estimated 24% of hospitalised patients with COVID-19, and is associated with higher mortality[48-51]. 5-10% of hospital readmissions after COVID-19 are estimated to be due to sepsis[52,53]. In a multicentre European intensive care unit (ICU) cohort study, secondary infection occurred 60% more frequently in patients with COVID-19 than influenza, and 70% more frequently than in ICU patients with no viral infection[54]. Invasive fungal infections may occur in up to 25% of ICU patients with COVID-19, with an estimated 60% mortality rate[55]. Observational studies have postulated an association between secondary infections and corticosteroid[49,56,57], IL-6 RA[49,58,59] and JAKI treatment[60] but residual confounding by indication is still likely, emphasising the need for randomised studies.

Patients hospitalised with COVID-19 are at high risk of many other plausible immunomodulatory treatment-related harms including VTE, delirium, liver injury and metabolic complications[61-65]. Hyperglycaemia has been associated with higher mortality, including in those without pre-existing diabetes[66]. COVID-19 appears to increase the risk of incident diabetes by approximately 20% compared to other upper respiratory tract infections, and approximately 40% compared to population matched controls[67,68].

1.3.3 Illness recovery

Treatment given during acute hospital admission could represent an opportunity to modify pervasive sequelae of COVID-19. 1.5 million people in the UK self-report long COVID symptoms that affect their ability to perform daily activities[69]. While persistent symptoms can affect all COVID-19 cases, illness severity is associated with poorer functional

capacity and health-related quality of life[70-73]. At 6 months after hospitalisation, 55% of patients did not feel 'fully recovered', 18% of participants had stopped working and quality of life had deteriorated compared to pre-admission[70,71]. 22% of patients had elevated blood inflammatory markers after 6 months - suggesting a potential role for immunomodulation[70].

1.3.4 Treatment effects of corticosteroids across the disease severity spectrum

COVID-19 treatment guidelines recommend against giving corticosteroids for patients not requiring oxygen[25,26], based on the mortality subgroup analysis by respiratory support at randomisation in RECOVERY[29]. This analysis demonstrated significant heterogeneity of dexamethasone treatment effect across categories of respiratory support and did not exclude the possibility of clinically important harm in those not receiving oxygen (Figure 1-2).

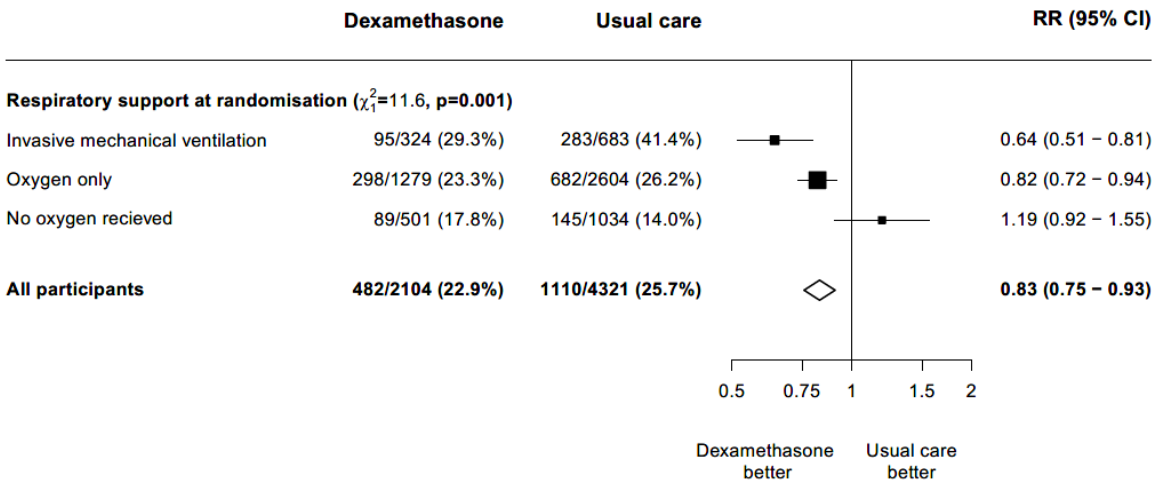


Figure 1-2: Effect of dexamethasone on 28-day mortality according to respiratory support at randomisation in the RECOVERY trial.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age group at randomisation.

In the secondary outcomes of invasive mechanical ventilation or death and discharge alive from hospital, the results of the respiratory support subgroup analysis showed similar evidence of heterogeneity.

There was still considerable short-term mortality in the RECOVERY dexamethasone 'no oxygen' subgroup (~15%), but the reasons for this are unclear. Analysis of cause-specific mortality could not delineate any differences between treatment groups, with 92% of all deaths in the study attributed to COVID-19. This raises uncertainty as to whether these patients died from progressive COVID-19, but corticosteroids were not beneficial when given at this stage of illness, or whether these patients could have died from other complications that were not captured as the underlying cause of death. The 'no oxygen' subgroup in RECOVERY were slightly older, had more co-morbidities, and had a shorter duration of illness at randomisation compared with participants in the 'oxygen only' and 'invasive ventilation' subgroup categories, however the mechanisms of interaction between corticosteroid treatment and disease severity remain unclear.

The 'oxygen' subgroup in the RECOVERY dexamethasone comparison was broad and potentially heterogeneous – patients could be receiving 1L/min of oxygen via nasal cannula in this group or be receiving high flow oxygen or non-invasive ventilation. Delineating this group could help improve understanding of when corticosteroid therapy becomes beneficial or harmful.

1.3.5 Treatment effects on biological measurements

Insights into the network of biological pathways through which the beneficial effects of immunomodulatory treatment are mediated are limited. Understanding this could inform future therapeutics research for COVID-19 and other viral pneumonias. Glucocorticoids regulate broad anti-inflammatory gene expression through genomic and non-genomic mechanisms[74]. Targeting treatment at more specific components of corticosteroid immunomodulation may enhance efficacy and reduce side effects[74,75].

Understanding, through high quality randomised evidence, the effect of immunomodulatory treatments on commonly-measured blood biomarkers, measures of oxygenation, or multiomics data, could help the design and interpretation of research

involving these treatments for acute severe respiratory infections. This data could also provide insights into the optimisation of COVID-19 immunomodulatory therapy for individual patients.

1.3.6 Bridging knowledge gaps with thesis

It is likely that clinicians will need to care for hospitalised patients with COVID-19 for the foreseeable future and immunomodulatory treatments will be part of clinical care. Given the absence of clinical equipoise, it is no longer ethical to pursue further randomised controlled trials (RCTs) among hospitalised patients comparing corticosteroids, IL-6 RAs or JAKIs with no immunomodulatory treatment for COVID-19. Maximising understanding of treatment effects from pre-existing, reliable data can optimise current and future treatment strategies.

This thesis aims to extend the randomised evaluations of the treatment effects of the RECOVERY COVID-19 immunomodulatory therapies to assess in-depth clinical and biological effects and address the identified knowledge gaps. The thesis extended analysis will minimise systematic and random error by leveraging RECOVERY's randomised design and large sample size[76,77]. The randomised comparisons of the RECOVERY immunomodulatory treatments will be linked with additional individual participant-level data from routinely collected healthcare data (RCD) sources and a large observational study in hospitalised patients with COVID-19 - the International Severe Acute Respiratory and emerging Infection Coronavirus Clinical Characterisation Consortium (ISARIC4C) (Figure 1-3). New analyses within the RECOVERY randomised comparisons will seek to address research questions relating to the identified knowledge gaps and the thesis aims.

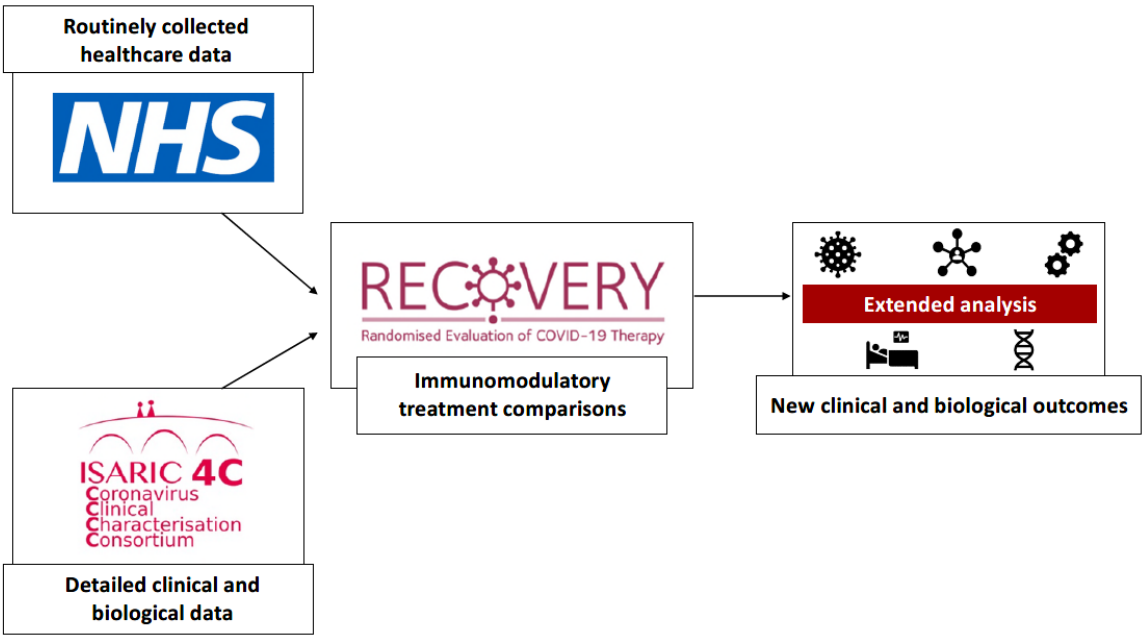


Figure 1-3: Overview of the concept of the thesis extended analysis.

1.4 Thesis Aims

This thesis aims to extend and explore the randomised evaluation of the effects of dexamethasone, tocilizumab and baricitinib for hospitalised patients with COVID-19 by:

i) Evaluating the quality and quantity of current evidence relating to the efficacy and safety of the immunomodulatory treatments for hospitalised patients with COVID-19 through a systematic review and meta-analysis.
ii) Evaluating the efficacy of the RECOVERY immunomodulatory treatments at long-term follow-up.
iii) Evaluating the safety of the RECOVERY immunomodulatory treatments at short-term and long-term follow-up.
iv) Evaluating the effects of the RECOVERY immunomodulatory treatments on illness recovery and long COVID.
v) Exploring the heterogeneity of dexamethasone treatment effect observed in the RECOVERY trial.
vi) Exploring the effects of the RECOVERY immunomodulatory treatments on biological measurements, such as commonly-measured blood biomarkers and gene expression data.

This knowledge would be anticipated to benefit patients and population health by:

- Allowing comprehensive assessment of the benefits and risks of immunomodulatory therapies in clinical practice, aiding decision-making for clinicians and patients;
- Understanding how the treatment effects of corticosteroids may differ across the disease severity spectrum of hospitalised patients with COVID-19, informing clinical use and future research;

- Informing future therapeutics research for COVID-19 and other viral pneumonias by reliably describing effects of the immunomodulatory treatments on biological measurements.

Aim i) is addressed in Chapter 2: Systematic Review and Meta-analysis. The methods employed for aims ii) to vi) are found in Chapter 3: Methods, with method development work relating to assessments derived from RCD covered in Chapter 4: Method Development. Results for aims ii) to iv) are presented in Chapter 5: Long-term Follow-up Analysis Results, and for aims v) and vi) in Chapter 6: Exploratory Analysis Results. All findings are then discussed in Chapter 7: Discussion, linking back to the thesis aims and highlighting the contribution of the research to the identified knowledge gaps, before summarising the key conclusions from the extended analysis.

Chapter 2

Systematic Review and Meta-analysis

2.1 Chapter Summary

This chapter presents a systematic review and meta-analysis of existing RCTs evaluating corticosteroids, IL-6 RAs or JAKIs, compared with usual care or placebo, for hospitalised patients with COVID-19. It addresses the first thesis aim: evaluating the quality and quantity of current evidence relating to the efficacy and safety of immunomodulatory treatments for COVID-19.

First, the chapter outlines the methods used in the systematic literature search, meta-analysis, and synthesis of findings. The RCTs located from the literature search are summarised and appraised for risk of bias. Meta-analysis results are then presented, including the key outcomes of mortality and secondary infection for each treatment class. Published results from RECOVERY are included but analyses within the proposed extended analysis are not included here. The overall findings are summarised and the implications for the work of this thesis are discussed.

2.2 Methods

2.2.1 Inclusion criteria

Studies were included in the systematic review if they met the following criteria:

- Study type: Randomised controlled trial.
- Population: Hospitalised patients with COVID-19.
- Interventions: Systemic corticosteroids or IL-6 RAs or JAKIs.
- Comparators: Usual care or placebo.
- Outcomes:

    i) Primary outcomes:

    For all interventions, at short-term (~28 days after randomisation) and long-term (~90 days after randomisation) follow-up:

        - All-cause mortality;
        - Secondary infection (not COVID-19).

    ii) Supplementary outcomes:

    For all interventions, at short-term (~28 days after randomisation) and long-term (~90 days after randomisation) follow-up:

        - Proportion of patients discharged alive from hospital;
        - Other potential immunomodulatory treatment-related harms (for example, GI complications);
        - Measures of illness recovery (for example, quality of life or functional status) or long COVID;
        - Biological measurements (for example, commonly-measured blood biomarkers, such as C-reactive protein (CRP)).

    For systemic corticosteroids only:

- Subgroup data for any of the above outcomes reported by level of respiratory support at randomisation.

As the COVID-19 pandemic has progressed, treatments comprising 'usual care' have evolved. In June 2020, after the results of the RECOVERY dexamethasone comparison, corticosteroids became standard of care for hospitalised patients with COVID-19 who required oxygen or ventilatory support[29,78]. RCTs performed after this time often include corticosteroids at the doses used in RECOVERY (dexamethasone 6mg once daily for up to 10 days – 'standard dose' corticosteroids) as part of usual care. Later, the other immunomodulatory treatments of tocilizumab and baricitinib also became components of 'usual care' but were less frequently included in RCT control groups. In this systematic review, the baseline co-administration of other immunomodulatory treatments within each trial is presented in the trial summary tables (Section 2.3.1).

RCTs comparing corticosteroids with no corticosteroids were evaluated separately to RCTs comparing higher dose corticosteroids (dexamethasone ≥12 mg daily or equivalent) with lower dose corticosteroids (dexamethasone 6-8 mg daily or equivalent) to facilitate comparisons of treatment effects and consider any evidence of a dose-response gradient in findings.

The follow-up time for long-term outcomes was originally specified as 6 months. However, it became clear that no meaningful evidence was available extending to this duration, hence a revised follow-up time of 90 days was instead used.

2.2.2 Search strategy

The Cochrane COVID-19 Study Register[79] and COVID-19 Open Living Evidence Synthesis[80] were searched from inception up to 31 March 2024, without language restrictions, for relevant studies using the following search terms and filters for randomised interventional studies:

i) corticosteroid* OR steroid* OR glucocorticoid* OR dexamethasone OR hydrocortisone OR methylprednisolone OR prednisolone OR betamethasone;

ii) IL-6 OR interleukin-6 OR IL-6 receptor OR interleukin-6 receptor OR tocilizumab OR sarilumab OR satralizumab OR siltuximab;

iii) JAK OR Janus kinase OR JAK inhibitor OR Janus kinase inhibitor OR baricitinib OR ruxolitinib OR tofacitinib OR abrocitinib OR delgocitinib OR fedratinib OR filgotinib OR oclacitinib OR peficitinib OR pacritinib OR deucravacitinib OR ritlecitinib.

Medical Literature Analysis and Retrieval System Online (MEDLINE) and Embase were searched from 1 September 2019 up to 31 March 2024, without language restrictions, using the search terms above, and the following search terms for COVID-19, with validated filters to select for RCTs[81]:

i) SARS-CoV-2 OR SARS-CoV2 OR SARSCoV2 OR COVID OR COVID-19 OR COVID19 OR 2019-nCoV OR Coronavirus OR Coronavirinae OR Coronavirus infections.

Titles and abstracts were screened against the inclusion criteria and potentially relevant studies extracted for full-text review. Reference lists were examined for further studies. The literature search was updated monthly between December 2021 and March 2023 to incorporate rapidly emerging new evidence. Subsequent search updates took place in September 2023 and April 2024.

The search strategy was developed with advice from an information specialist and a departmental research team experienced in carrying out systematic reviews. The strategy considered the challenges of searching for new relevant evidence in the context of the COVID-19 pandemic including a large burden of studies, rapidly changing evidence and the increased use of pre-print servers[82,83]. The utilised sources incorporate traditional

medical literature databases, pre-print servers and trial registry records, and appear comprehensive and rapidly updated[84].

2.2.3 Meta-analysis

Outcome data was extracted from available trial reports or the RECOVERY trial database. For each treatment comparison and outcome in the meta-analysis, the observed number of events for each randomised group was compared to the expected number if all patients were at equal risk, producing an observed minus expected (O-E) statistic and its variance. These are calculated from the standard formula for 2x2 contingency tables (except for mortality in RECOVERY, where they are estimated from the age- and baseline respiratory support-adjusted log rate ratios and their standard errors). The individual trial results were combined using the log of the event rate ratio - calculated as the inverse-variance weighted average S/V with variance 1/V (and 95% confidence interval (CI) S/V ± 1.96/√V), where S is the sum over all trials of the O-E statistic and V is the sum over all trials of its variance[85]. Formal statistical heterogeneity between individual trial results or subgroups was evaluated using the chi-squared test[86].

2.2.4 Certainty of evidence

The risk of bias for each trial and outcome was assessed using the Cochrane Risk of Bias 2 tool[87]. The certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework[88]. Using this framework, RCT evidence starts as high certainty and is downgraded according to evaluations of risk of bias, inconsistency, indirectness, imprecision, and publication bias. This results in a final grading of very low, low, moderate, or high, representing an assessment of the level of certainty that the true effect is similar to the estimated effect observed. Justifications for certainty of evidence grading are presented in Section 2.3.6.

2.3 Results

2.3.1 Overview of search results

A total of 77 COVID-19 immunomodulatory therapy RCTs meeting the inclusion criteria were found – 13 RCTs comparing corticosteroids with no corticosteroids, 31 IL-6 RA trials, 16 JAKi RCTs, and 17 trials comparing higher dose corticosteroids with lower dose corticosteroids (Figure 2-1).

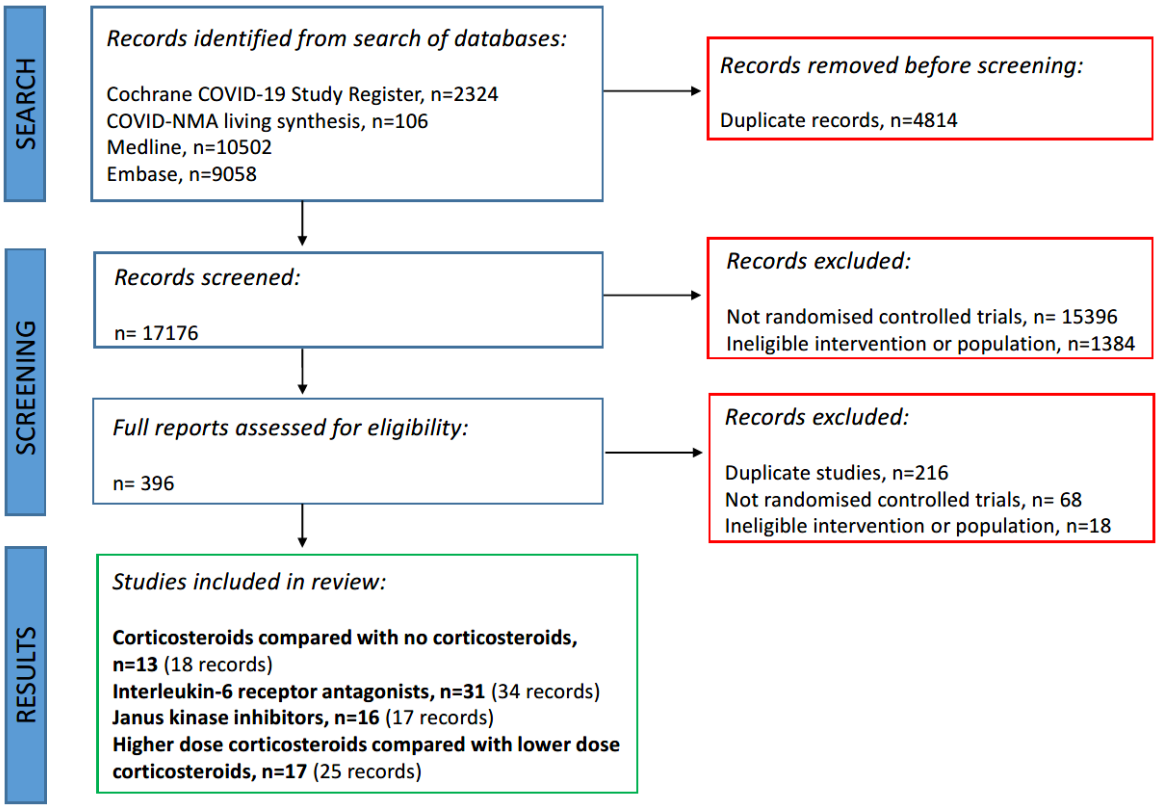


Figure 2-1: Flowchart of systematic literature search.

A summary of the RCTs included in each of the immunomodulatory treatment comparisons are presented in Table 2-1 to Table 2-4. The risk of bias assessment for each trial and outcome can be found in Supplementary Table 1 to Supplementary Table 4.

Table 2-1: Randomised controlled trials evaluating corticosteroids compared with no corticosteroids in hospitalised patients with COVID-19.

Trial Name	Trial Registry Record	Locations	Dates of recruitment	Population*	Treatment Groups	Number of patients randomised
RECOVERY[29]	NCT04381936	UK	March – June 2020	Mild – Critical	Dexamethasone Usual care	6425
Metcovid[89,90]	NCT04343729	Brazil	April – June 2020	Moderate - Critical	Methylprednisolone Placebo	416
REMAP-CAP[91,92]	NCT02735707	Europe, Oceania, North America	March – June 2020	Severe - Critical	Hydrocortisone Usual care	403
CoDex[93]	NCT04327401	Brazil	April – June 2020	Critical	Dexamethasone Usual care	299
CAPE COVID[94]	NCT02517489	France	March – June 2020	Severe - Critical	Hydrocortisone Placebo	149
Tang et al.[95]	NCT04273321	China	February – March 2020	Moderate - Severe	Methylprednisolone Usual care	86
CORTIVID[96]	NCT04438980	Spain	May 2020 – March 2021	Mild - Moderate	Methylprednisolone Placebo	72
Edalatifard et al.[97]	IRCT20200404046947N1	Iran	April – June 2020	Moderate - Severe	Methylprednisolone Usual care	68
Glucocovid[98]	EudraCT 2020-001934-37	Spain	April – July 2020	Moderate - Severe	Methylprednisolone Usual care	64
Jamaati et al.[99]	IRCT20151227025726N17	Iran	March 2020	Moderate - Severe	Dexamethasone Usual care	50
SMART[100]	NCT03852537	USA	March – November 2020	Mild - Critical	Methylprednisolone Usual care	44
COVID-STEROID[101,102]	NCT04348305	Denmark	April – June 2020	Severe - Critical	Hydrocortisone Placebo	30
Farahani et al.[103]	IRCT20200406046963N1	Iran	April – May 2020	Severe - Critical	Methylprednisolone Usual care	29
					Total	8135

**Population: Mild = hospitalised with no oxygen requirement, Moderate = hospitalised with oxygen requirement but no ventilatory support, Severe=hospitalised with non-invasive ventilation or high flow oxygen support, Critical = Hospitalised with invasive mechanical ventilation or extra corporeal membrane oxygenation.*

Table 2-2: Randomised controlled trials evaluating interleukin-6 receptor antagonists compared with usual care/placebo in hospitalised patients with COVID-19.

Trial Name	Trial Registry Record	Locations	Dates of recruitment	Population*	Treatment Groups	Number of patients randomised
RECOVERY[30]	NCT04381936	UK	April 2020 – January 2021	Moderate - Critical 82% baseline steroids	Tocilizumab Usual care	4116
Sivapalasingam et al. (Phase 3)[104]	NCT04315298	USA	March – July 2020	Moderate - Critical 34% baseline steroids	Sarilumab Usual care	1404
REMAP-CAP[92,105 92]	NCT02735707	Europe, Oceania, Saudi Arabia	April – November 2020	Severe - Critical >80% baseline steroids	Tocilizumab Sarilumab Usual care	826
REMDACTA[106]	NCT04409262	Brazil, Europe, USA	June 2020 – January 2021	Moderate - Critical 85% baseline steroids	Tocilizumab Placebo	649
Sivapalasingam et al. (Phase 2)[104]	NCT04315298	USA	March – July 2020	Moderate - Critical 16% baseline steroids	Sarilumab Usual care	457
CORIMUNO-TOCIDEX[107]	NCT04476979	France	July 2020 – May 2021	Moderate 100% baseline steroids	Tocilizumab + Dexamethasone Dexamethasone	453
COVACTA[108]	NCT04320615	Europe, North America	April – May 2020	Moderate - Critical 22% baseline steroids	Tocilizumab Placebo	452
Lescure et al.[109]	NCT04327388	South America, Canada, Europe, Asia	March – July 2020	Moderate - Critical 20% baseline steroids	Sarilumab Placebo	420
EMPACTA[110]	NCT04372186	North America, Africa, South America	May – August 2020	Moderate - Severe >80% baseline steroids	Tocilizumab Placebo	388
Rutgers et al.[111]	EudraCT2020-001375-32	Netherlands	April 2020 – January 2021	Moderate- Critical 88% baseline steroids	Tocilizumab Usual care	354
COV-AID[112]	NCT04330638	Belgium	April – December 2020	Moderate – Critical 62% baseline steroids	Tocilizumab Siltuximab Usual care	342
Stone et al.[113]	NCT04356937	USA	April – June 2020	Mild - Severe 0% baseline steroids	Tocilizumab Placebo	243
Sancho-Lopez et al.[114]	EudraCT 2020-002037-15	Spain	August 2020 – March 2021	Moderate 100% baseline steroids	Sarilumab Usual care	201
Malik et al.[115]	NCT04560205	Pakistan	May – October 2020	Moderate – Severe Baseline steroids unknown	Tocilizumab Placebo	190

Mastrorosa[116]	EudraCT 2020-001390-76	Italy	May 2020 – May 2021	Moderate – Severe 38% baseline steroids	Sarilumab Usual care	185
Soin et al.[117]	CTRI/2020/05/025369	India	May – August 2020	Moderate - Critical >90% baseline steroids	Tocilizumab Usual care	180
CORIMUNO-SARI-1[118]	NCT04324073	France	March – April 2020	Moderate 20% baseline steroids	Sarilumab Usual care	148
CORIMUNO-TOCI-1[119]	NCT04331808	France	March – April 2020	Moderate 47% baseline steroids	Tocilizumab Usual care	131
Veiga et al.[120]	NCT04403685	Brazil	May – July 2020	Moderate - Critical 70% baseline steroids	Tocilizumab Usual care	129
Salvarani et al.[121]	NCT04346355	Italy	March – June 2020	Moderate - Severe <5% baseline steroids	Tocilizumab Usual care	126
SARICOR[122]	NCT04357860	Spain	July 2020 – March 2021	Mild - Severe 90% baseline steroids	Sarilumab Usual care	118
Swadi et al.[123]	Not known	Iraq	June 2021 – February 2022	Severe - Critical High baseline steroids	Tocilizumab Usual care	100
Rabie et al.[124]	NCT0487185	Egypt	May 2020 – May 2022	Moderate – Critical Baseline steroids unknown	Tocilizumab Usual care	100
CORIMUNO-TOCI-2[125]	NCT04331808	France	March – April 2020	Severe - Critical <5% baseline steroids	Tocilizumab Usual care	97
CORIMUNO-SARI-2[125]	NCT04324073	France	March – April 2020	Severe- Critical <5% baseline steroids	Sarilumab Usual care	91
COVIDSTORM[126]	NCT04577534	Finland	August 2020 – June 2021	Moderate - Severe 94% baseline steroids	Tocilizumab Usual care	88
Wang et al.[127]	ChiCTR2000029765	China	February – March 2020	Mild - Severe 10% baseline steroids	Tocilizumab Usual care	65
Branch-Elliman et al.[128]	NCT04359901	USA	April 2020 – February 2021	Mild - Severe 86% baseline steroids	Sarilumab Usual care	50
IMMCoVA[129]	NCT04412291	Sweden	June 2020 – March 2021	Moderate - Severe 98% baseline steroids	Tocilizumab Usual care	49
Talaschian et al.[130]	IRCT20081027001411N4	Iran	July – October 2020	Moderate - Severe 33% baseline steroids	Tocilizumab Usual care	40
Garcia-Vicuna et al.[131]	NCT04357808	Spain	April – October 2020	Mild - Severe 83% baseline steroids	Sarilumab Usual care	30
					Total	12222
**Population: Mild = hospitalised with no oxygen requirement, Moderate = hospitalised with oxygen requirement but no ventilatory support, Severe=hospitalised with non-invasive ventilation or high flow oxygen support, Critical = Hospitalised with invasive mechanical ventilation or extra corporeal membrane oxygenation.*						

Table 2-3: Randomised controlled trials evaluating Janus kinase inhibitors compared with usual care/placebo for hospitalised patients with COVID-19.

Trial Name	Trial Registry Record	Locations	Dates of recruitment	Population*	Treatment Groups	Number of patients randomised
RECOVERY[31]	NCT04381936	UK	February – December 2021	Mild - Critical 95% baseline steroids 23% baseline IL-6 RAs	Baricitinib Usual care	8156
COV-BARRIER[132]	NCT04421027	North America, South America, Europe, Asia	June 2020 – January 2021	Mild – Severe 79% baseline steroids IL-6 RAs excluded	Baricitinib Placebo	1525
ACTT-2[133]	NCT04401579	North America, Asia, Europe	May – July 2020	Mild - Critical 0% baseline steroids IL-6 RAs excluded	Baricitinib Placebo	1033
RUXCOVID[134]	NCT04362137	North America, South America, Europe	May – October 2020	Mild – Severe 58% baseline steroids IL-6 RAs excluded	Ruxolitinib Placebo	432
Guimarães et al.[135]	NCT04469114	Brazil	September – December 2020	Mild – Severe 79% baseline steroids IL-6 RAs unknown	Tofacitinib Placebo	289
PANCOVID[136]	EudraCT2020-001156-18	Spain	October 2020 – September 2021	Mild – Severe 100% baseline steroids IL-6 RAs unknown	Baricitinib Usual care	287
Bari-SolidAct[137]	NCT04891133	Europe	June 2021 – March 2022	Severe – Critical 95% baseline steroids 29% baseline IL-6 RAs	Baricitinib Placebo	284
TACTIC-R[138]	NCT04390464	UK	May 2020 – May 2021	Mild – Critical 86% baseline steroids 6% baseline IL-6 RAs	Baricitinib Usual care	282
RUXCOVID-DEVENT[139]	NCT04377620	USA, Russia	May 2020 – February 2021	Critical Baseline steroids unknown IL-6 RAs unknown	Ruxolitinib Placebo	211
Cafardi et al.[140]	NCT04404361	USA	June 2020 – February 2021	Moderate – Severe 97% baseline steroids 2% baseline IL-6 RAs	Pacritinib Placebo	200
TOFACOV[141]	NCT04332042	Italy	September 2020 – December 2021	Mild – Moderate 94% baseline steroids IL-6 RAs unknown	Tofacitinib Usual care	116

COVINIB[142]	NCT04346147	Spain	September 2020 – June 2021	Mild – Moderate 1% baseline steroids IL-6 RAs excluded	Baricitinib Usual care	112
COV-BARRIER critically ill[143]	NCT04421027	North America, South America	December 2020 – April 2021	Critical 86% baseline steroids IL-6 RAs excluded	Baricitinib Placebo	101
Murugesan et al.[144]	Not known	India	October – December 2020	Mild – Moderate 100% baseline steroids IL-6 RAs unknown	Tofacitinib Usual care	100
Dastan et al.[145]	IRCT20151227025726N30	Iran	March – August 2022	Moderate – Severe 100% baseline steroids 100% baseline IL-6 RAs	Baricitinib + Tocilizumab Tocilizumab	68
Cao et al.[146]	Not known	China	February 2020	Moderate – Severe 71% baseline steroids IL-6 RAs unknown	Ruxolitinib Placebo	42
					Total	13238

**Population: Mild = hospitalised with no oxygen requirement, Moderate = hospitalised with oxygen requirement but no ventilatory support, Severe=hospitalised with non-invasive ventilation or high flow oxygen support, Critical = Hospitalised with invasive mechanical ventilation or extra corporeal membrane oxygenation. IL-6 RAs = Interleukin-6 receptor antagonists*

Table 2-4: Randomised controlled trials evaluating higher dose corticosteroids compared with lower dose corticosteroids in hospitalised patients with COVID-19.

Trial Name	Trial Registry Record	Locations	Dates of recruitment	Population*	Treatment Groups	Number of patients randomised
RECOVERY[44]	NCT04381936	UK, Asia, Africa	May 2021 – May 2022	Moderate 8% baseline IL-6 RAs <1% baseline JAKIs	Dexamethasone 20mg Dexamethasone 6mg	1272
COVID STEROID 2[147,148]	NCT04509973	Europe, India	August 2020 – May 2021	Severe- Critical 10% baseline IL-6 RAs 1.5% baseline JAKIs	Dexamethasone 12mg Dexamethasone 6mg	1000
MEDEAS[149]	NCT04636671	Italy	April 2021 – May 2022	Moderate – Severe Baseline IL-6 RAs not known Baseline JAKIs not known	Methylprednisolone 80mg Dexamethasone 6mg	677
COVIDICUS[150]	NCT04344730	France	April 2020 – January 2021	Moderate – Critical 1% baseline IL-6 RAs Baseline JAKIs not known	Dexamethasone 20mg Dexamethasone 6mg	546
Salvarani et al.[151]	NCT04673162	Italy	December 2020 – March 2021	Moderate – Severe 5% baseline IL-6 RAs 2% baseline JAKIs	Methylprednisolone 1g Dexamethasone 6mg	304
Taboada et al.[152]	NCT04726098	Spain	January – May 2021	Moderate 12% baseline IL-6 RAs Baseline JAKIs not known	Dexamethasone 20mg Dexamethasone 6mg	200
Toroghi et al.[153]	IRCT20100228003449N31	Iran	October 2020 – January 2021	Moderate-Severe Baseline IL-6 RAs not known Baseline JAKIs not known	Dexamethasone 16-24mg Dexamethasone 8mg	144
Dastenae et al.[154]	IRCT20210223050466N1	Iran	April – June 2021	Moderate – Critical Baseline IL-6 RAs not known Baseline JAKIs not known	Methylprednisolone 60mg Dexamethasone 8mg	143
ROIDS-Dose[155]	NCT04834375	USA	March – December 2021	Moderate – Critical 25% baseline IL-6 RAs Baseline JAKIs not known	Dexamethasone 2mg/kg Dexamethasone 6mg	142
Gautam et al.[156]	Not located	India	April – June 2021	Moderate – Severe Baseline IL-6 RAs not known Baseline JAKIs not known	Methylprednisolone 2mg/kg Dexamethasone 8mg	140
Corral-Gudino et al.[157]	NCT04780581	Spain	February – August 2021	Moderate Baseline IL-6 RAs not known Baseline JAKIs not known	Methylprednisolone 250mg Dexamethasone 6mg	128

Sadeghi et al.[158]	IRCT20190606043826N2	Iran	January 2020 – November 2021	Moderate – Severe Baseline IL-6 RAs not known Baseline JAKIs not known	Dexamethasone 24mg Dexamethasone 8mg	126
Wu et al.[159]	NCT04707534	USA	January – December 2021	Moderate – Critical Baseline IL-6 RAs not known Baseline JAKIs not known	Dexamethasone 20mg Dexamethasone 6mg	110
Maskin et al.[160]	NCT04395105	Argentina	June 2020 – March 2021	Critical Baseline IL-6 RAs not known Baseline JAKIs not known	Dexamethasone 16mg Dexamethasone 6mg	100
Ranjbar et al.[161]	IRCT20200204046369N1	Iran	August – November 2020	Moderate – Severe Baseline IL-6 RAs not known Baseline JAKIs not known	Methylprednisolone 2mg/kg Dexamethasone 6mg	93
Montalvan et al.[162]	Not located	Honduras	September – October 2020	Moderate – Severe Baseline IL-6 RAs not known Baseline JAKIs not known	Dexamethasone 24mg Dexamethasone 8mg	81
Soliman et al.[163]	NCT04909918	Egypt	May – December 2021	Severe – Critical 60% baseline IL-6 RAs Baseline JAKIs not known	Methylprednisolone 1mg/kg Dexamethasone 8mg	60
					Total	5266

**Population: Mild = hospitalised with no oxygen requirement, Moderate = hospitalised with oxygen requirement but no ventilatory support, Severe=hospitalised with non-invasive ventilation or high flow oxygen support, Critical = Hospitalised with invasive mechanical ventilation or extra corporeal membrane oxygenation.*
IL-6 RAs = Interleukin-6 receptor antagonists
JAKIs = Janus Kinase inhibitors

2.3.2 Corticosteroids compared with no corticosteroids

2.3.2.1 Mortality

Systemic corticosteroids were associated with an estimated 18% proportional reduction in 28-day all-cause mortality compared with no corticosteroids, in the meta-analysis across 12 eligible trials (Figure 2-2, High certainty of evidence).

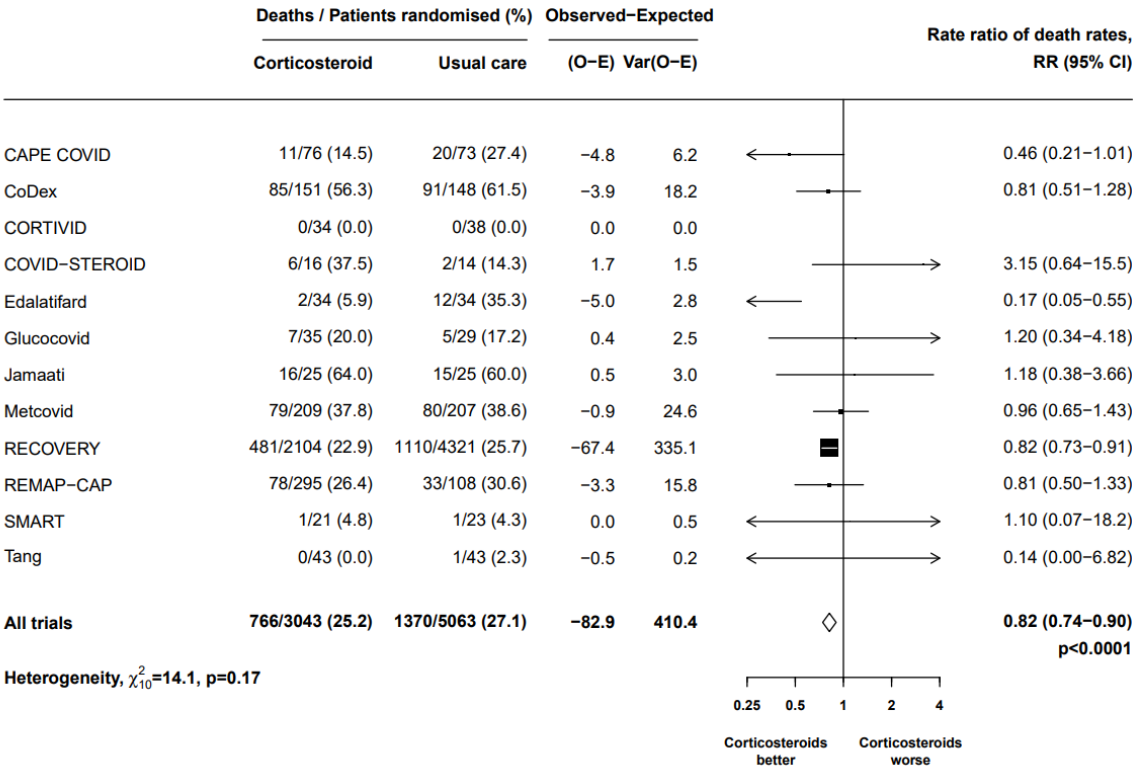


Figure 2-2: Meta-analysis of 28-day all-cause mortality in randomised controlled trials of systemic corticosteroids compared with no corticosteroids in hospitalised patients with COVID-19. This outcome has been assessed in the RECOVERY dexamethasone comparison.

Only four of these trials have assessed mortality beyond 28 days (Figure 2-3, Very low certainty of evidence).

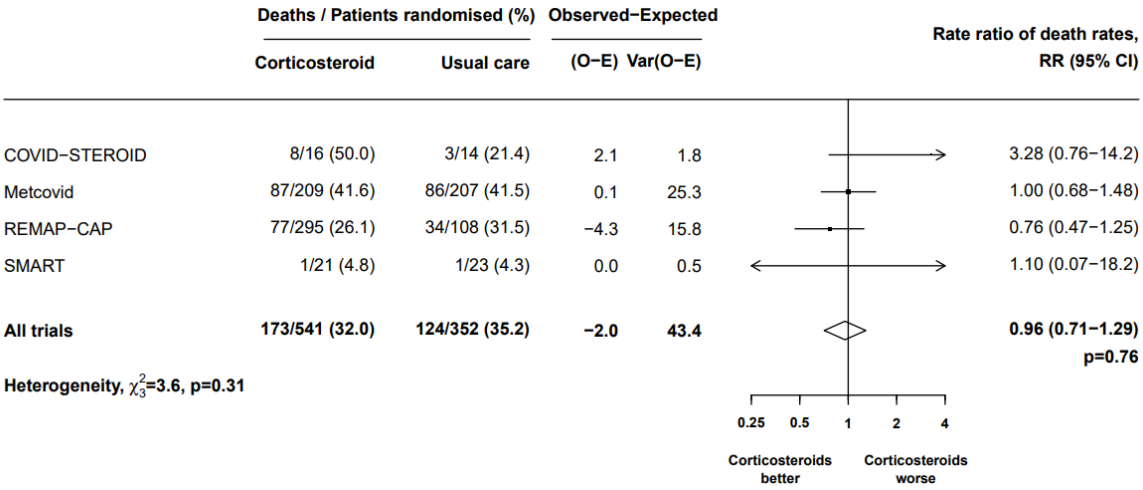


Figure 2-3: Meta-analysis of 90-day all-cause mortality in randomised controlled trials of systemic corticosteroids compared with no corticosteroids in hospitalised patients with COVID-19. This outcome has not been assessed in the RECOVERY dexamethasone comparison.

2.3.2.2 Secondary infections

Eight small RCTs - representing 15% of the total patients randomised across all trials in this treatment comparison - have reported data on secondary infections within 28 days (Figure 2-4, Very low certainty of evidence). No trials in this treatment comparison have assessed secondary infections at longer-term follow-up.

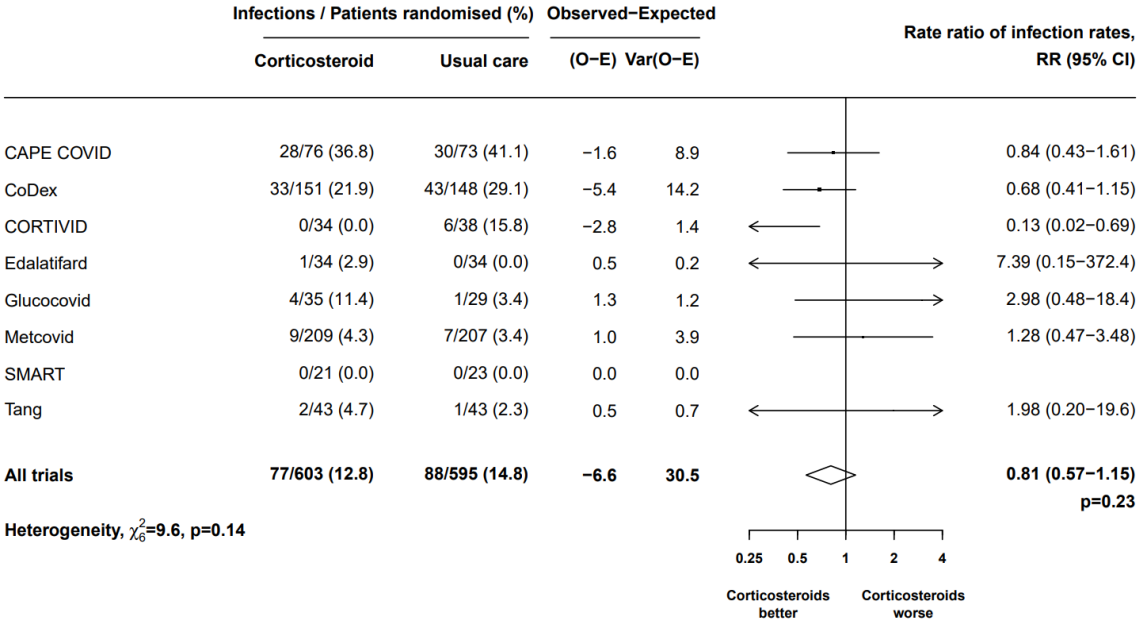


Figure 2-4: Meta-analysis of secondary infections within 28 days in randomised controlled trials of systemic corticosteroids compared with no corticosteroids in hospitalised patients with COVID-19. This outcome has not been assessed in the RECOVERY dexamethasone comparison.

2.3.2.3 Other potential treatment-related harms

Outcomes relating to hyperglycaemia were reported in six small RCTs. Results were consistent with an increased risk of hyperglycaemia with corticosteroid therapy, but the certainty of evidence was very low (as assessed with GRADE) and there was evidence of statistical heterogeneity between individual study results (Figure 2-5).

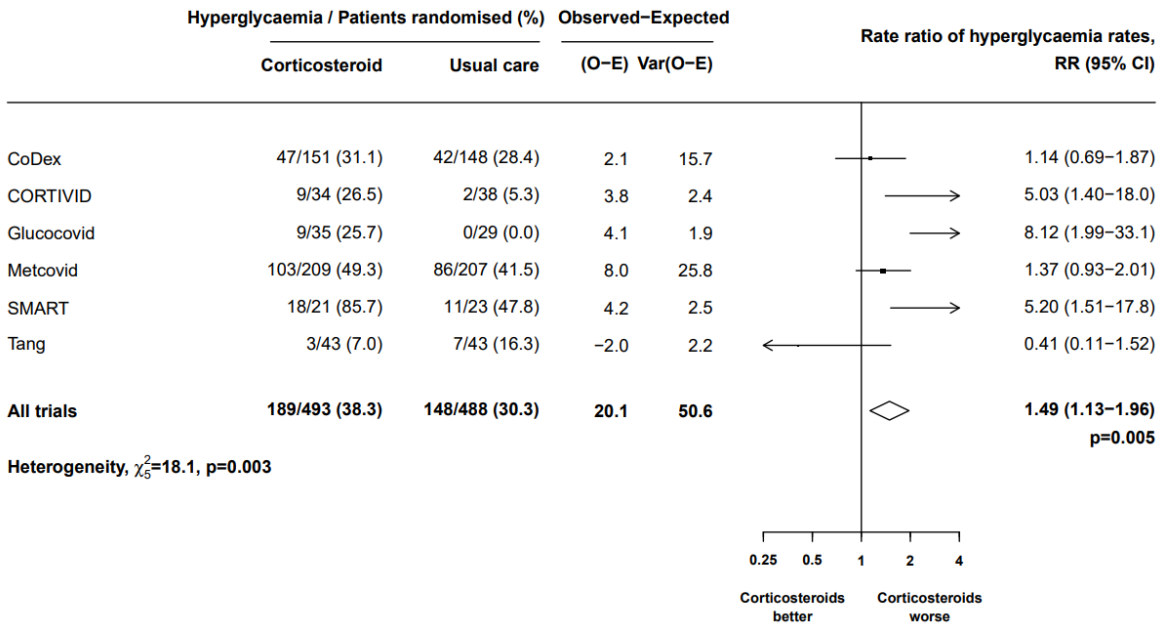


Figure 2-5: Meta-analysis of hyperglycaemia within 28 days in randomised controlled trials of systemic corticosteroids compared with no corticosteroids in hospitalised patients with COVID-19. This outcome has not been assessed in the RECOVERY dexamethasone comparison.

There was insufficient data for other supplementary outcomes of potential corticosteroid treatment-associated harms - GI complications (1 event across all RCTs), VTE (4 events), psychiatric complications (10 events), incident diabetes (0 events) and fractures (0 events).

Results for the supplementary outcome of discharge alive from hospital can be found in Supplementary Figure 1, and for the measures of illness recovery or long COVID, and biological measurements, see Appendix, Section A.1.1.

2.3.2.4 Respiratory support subgroups

Of the identified RCTs, only RECOVERY reported outcomes by baseline respiratory support subgroup, with evidence of significant heterogeneity of treatment effect for 28-day mortality. Participants at higher levels of respiratory support at randomisation appeared to experience a greater dexamethasone treatment benefit than those at lower levels of respiratory support at randomisation (see Section 1.3.4).

2.3.3 IL-6 RAs

2.3.3.1 Mortality

IL-6 RA treatment was associated with an overall estimated 12% proportional reduction in 28-day mortality compared with usual care or placebo, in the meta-analysis across 30 eligible RCTs assessing this outcome (Figure 2-6, High certainty of evidence). Evidence of efficacy was stronger in trials using tocilizumab as the IL-6 RA treatment compared with trials using other IL-6 RAs.

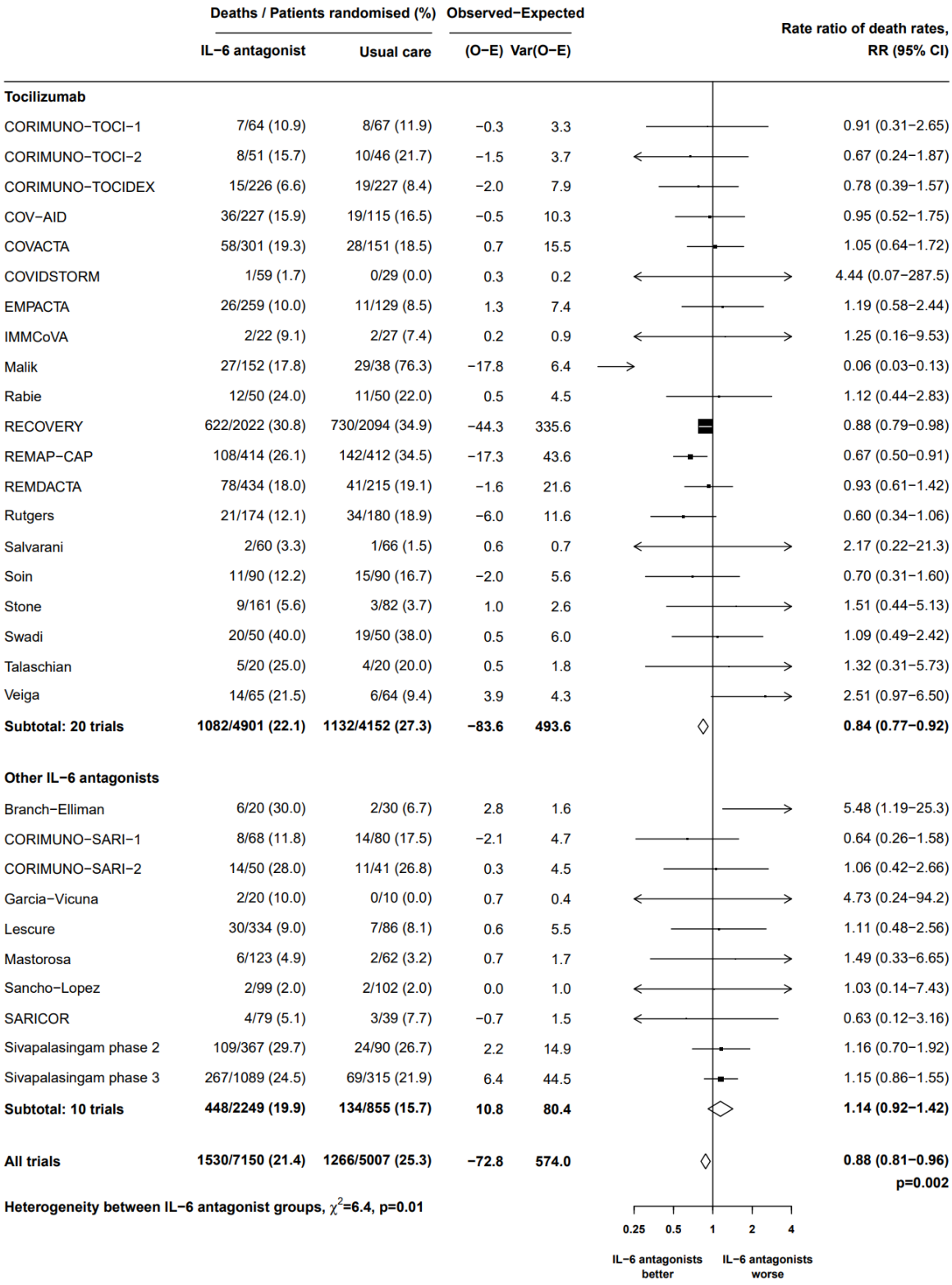


Figure 2-6: Meta-analysis of all-cause mortality within 28 days in randomised controlled trials of interleukin-6 receptor antagonists compared with usual care/placebo in hospitalised patients with COVID-19.
IL-6 antagonist groups are defined by the use of tocilizumab as the intervention or the use of other IL-6 receptor antagonists (sarilumab or siltuximab).
This outcome has been assessed in the RECOVERY tocilizumab comparison.

Longer-term mortality was assessed in twelve IL-6 RA RCTs. The overall effect size estimate was similar to that at 28 days, but CIs were slightly wider (Figure 2-7, Moderate certainty of evidence). The reported trials represented approximately one third of the total patients randomised across all trials in this treatment comparison.

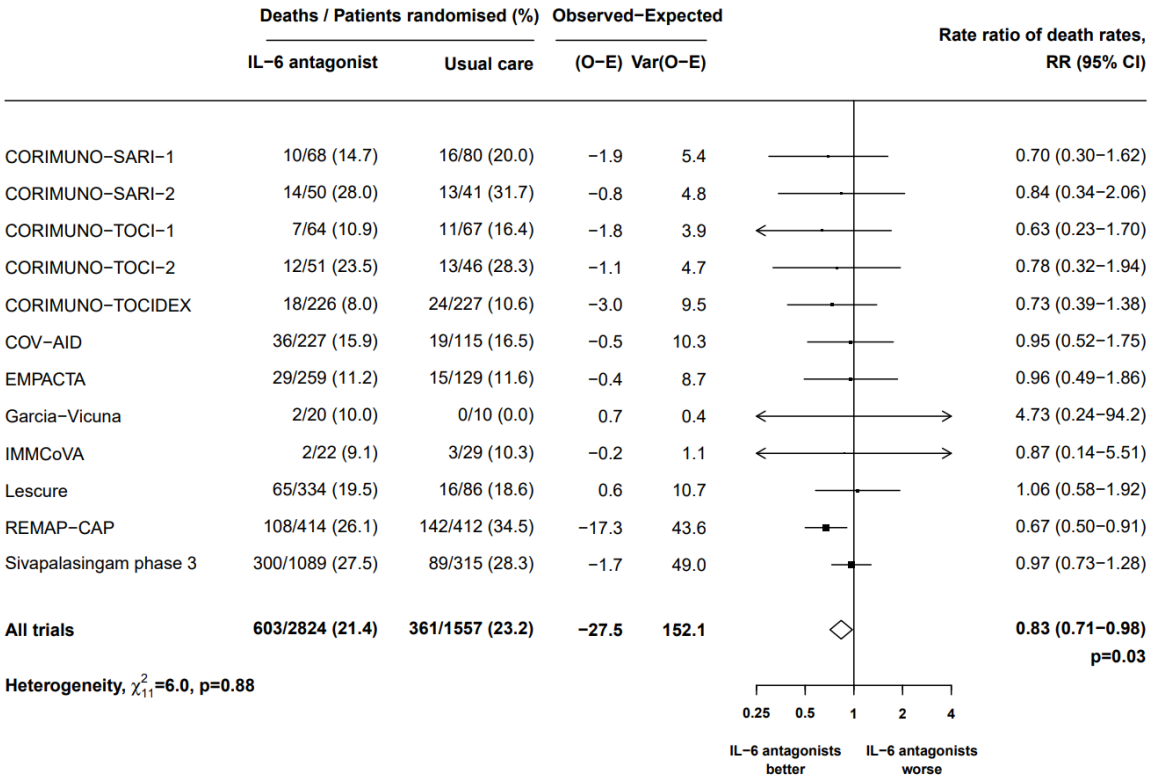


Figure 2-7: Meta-analysis of all-cause mortality within 90 days in randomised controlled trials of interleukin-6 receptor antagonists compared with usual care/placebo in hospitalised patients with COVID-19.
This outcome has not been assessed in the RECOVERY tocilizumab comparison.

2.3.3.2 Secondary infections

IL-6 RAs did not appear associated with an increased risk of secondary infection within 28 days (RR 0.85 [95% CI 0.72 – 1.00]) (Figure 2-8, Low certainty of evidence). Observed statistical heterogeneity between individual trials for the outcome of secondary infection did not appear to be explained by differences between trials assessing tocilizumab compared with other IL-6 RAs, disease severity, placebo-controlled compared with open-label trials, trials at lower risk of bias for this outcome compared with higher risk, or trials

with higher rates of baseline corticosteroid co-administration (>50%) compared with those with lower rates of corticosteroids co-administration (<50%) (Chi-squared test for heterogeneity for all between group differences, p>0.1).

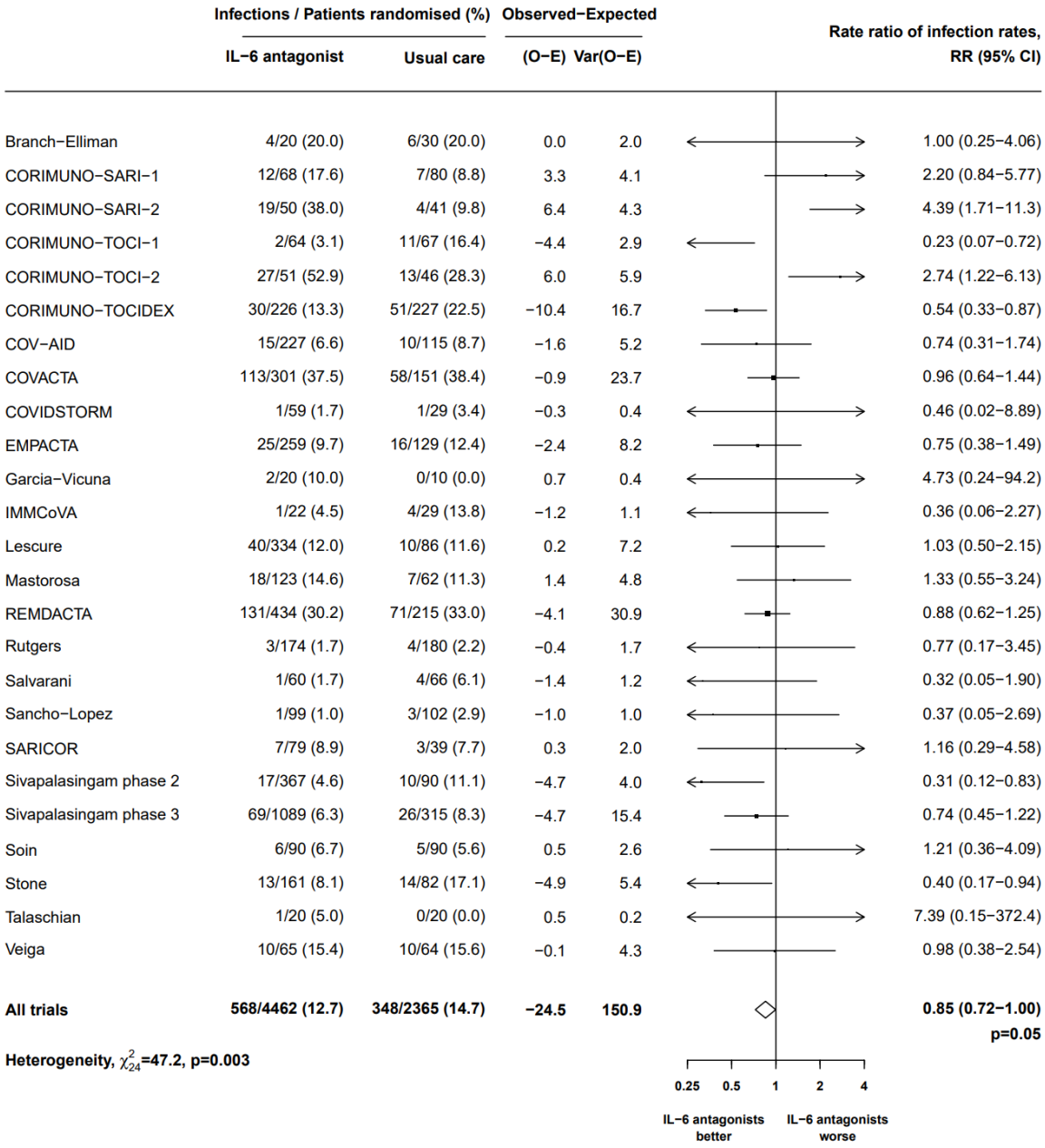


Figure 2-8: Meta-analysis of secondary infections within 28 days in randomised controlled trials of interleukin-6 receptor antagonists compared with usual care/placebo in hospitalised patients with COVID-19.
This outcome has not been assessed in the RECOVERY tocilizumab comparison.

Longer-term infection data was limited to four RCTs, three of which were assessed to be at high risk of bias for this outcome (Figure 2-9, Very low certainty of evidence).

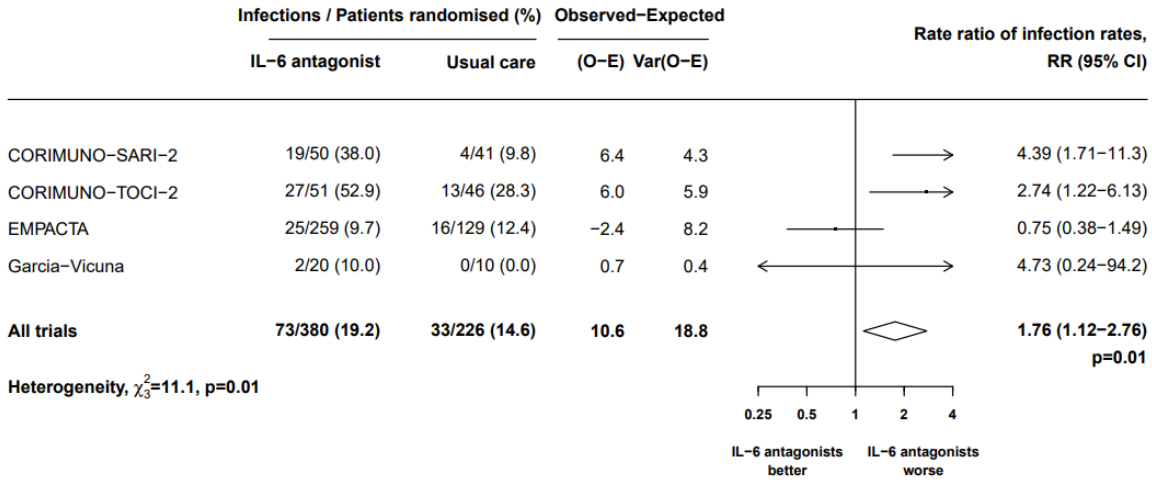


Figure 2-9: Meta-analysis of secondary infections within 90 days in randomised controlled trials of interleukin-6 receptor antagonists compared with usual care/placebo in hospitalised patients with COVID-19.
This outcome has not been assessed in the RECOVERY tocilizumab comparison.

2.3.3.3 Other potential treatment-related harms

IL-6 RAs appeared associated with a higher risk of abnormal liver function test results (RR 1.61 [95% CI 1.23 – 2.10], p=0.0005; Supplementary Figure 2; Low certainty of evidence) and a higher risk of neutropenia (RR 5.08 [95% CI 2.91 – 8.86], p <0.0001; Supplementary Figure 3; Low certainty of evidence).

There was insufficient data for other supplementary outcomes of potential IL-6 RA treatment-related harms - GI complications (13 event across all RCTs) and thrombocytopenia (8 events).

For results of the supplementary outcomes of discharge alive from hospital see Supplementary Figure 4 and Supplementary Figure 5, and for measures of illness recovery or long COVID, and biological measurements, see Appendix, Section A.1.2.

2.3.4 JAKIs

2.3.4.1 Mortality

JAKIs were associated with an overall estimated 21% proportional reduction in 28-day mortality, compared with usual care or placebo, in the meta-analysis of 16 eligible RCTs assessing this outcome (Figure 2-10, High certainty of evidence).

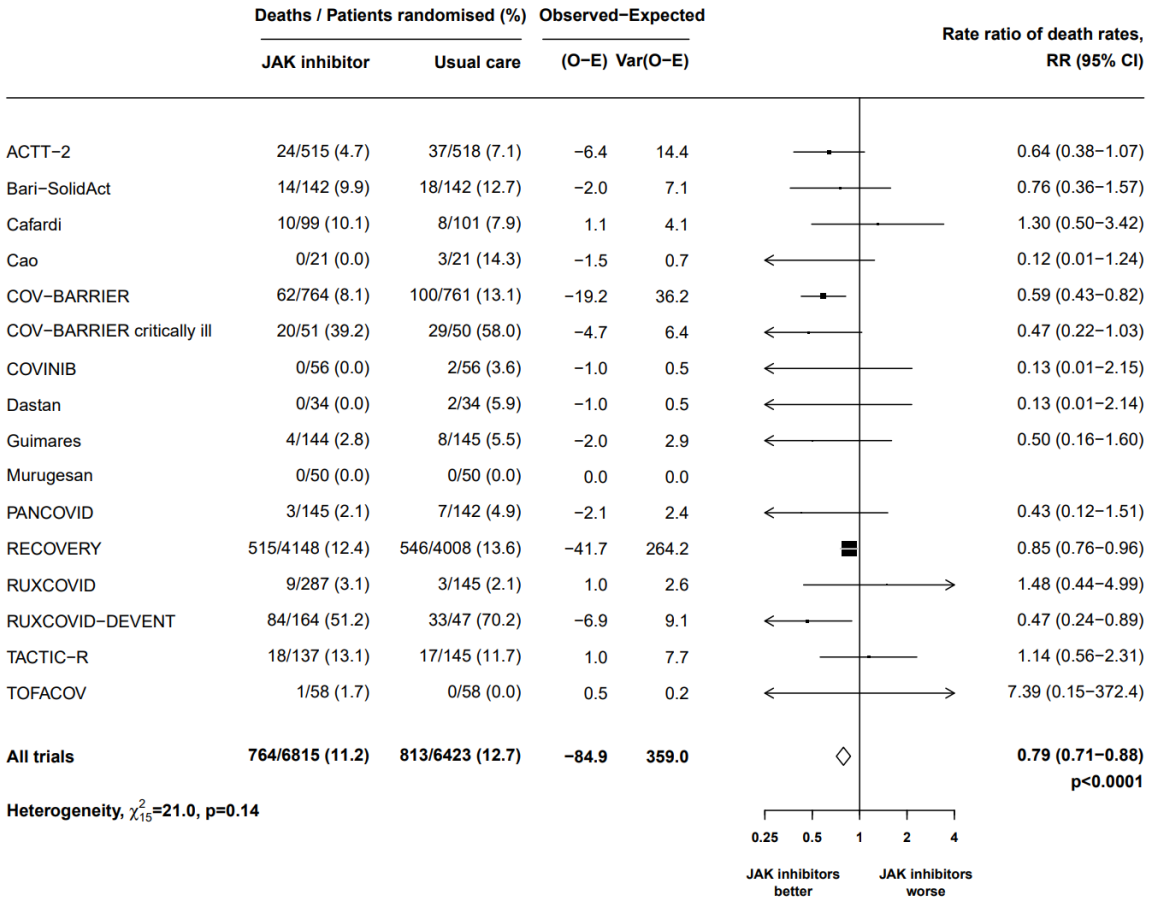


Figure 2-10: Meta-analysis of all-cause mortality within 28 days in randomised controlled trials of Janus kinase inhibitors compared with usual care/placebo in hospitalised patients with COVID-19. This outcome has been assessed in the RECOVERY baricitinib comparison.

Only four of these trials reported an outcome of longer-term mortality (Figure 2-11, Very low certainty of evidence).

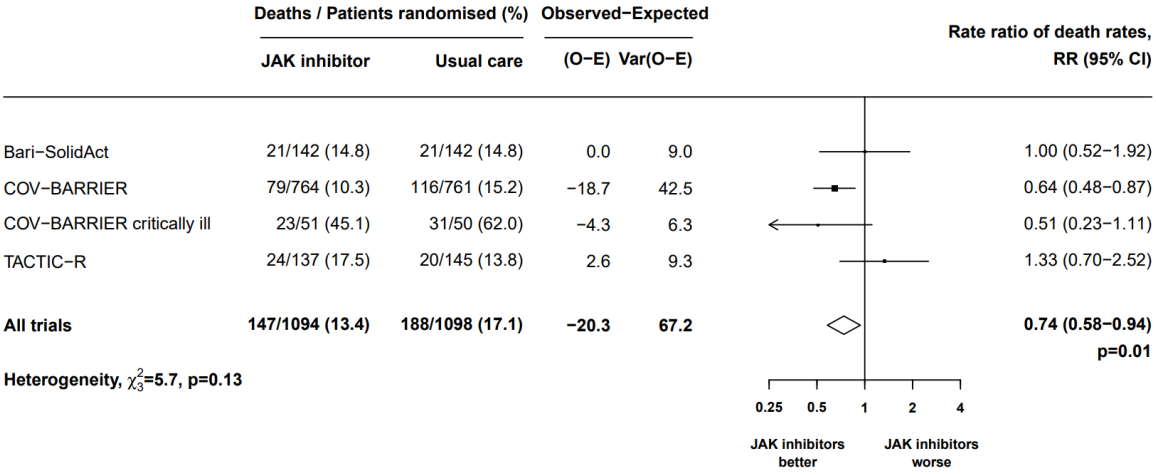


Figure 2-11: Meta-analysis of all-cause mortality within 90 days in randomised controlled trials of Janus kinase inhibitors compared with usual care/placebo, in hospitalised patients with COVID-19. This outcome has not been assessed in the RECOVERY baricitinib comparison.

2.3.4.2 Secondary infections

JAKIs appear unlikely to be associated with an increased risk of secondary infection within 28 days (RR 0.94 [95% CI 0.84 – 1.05]) (Figure 2-12, Moderate certainty of evidence).

A single small RCT reported infections at longer-term follow-up (Bari-SolidAct).

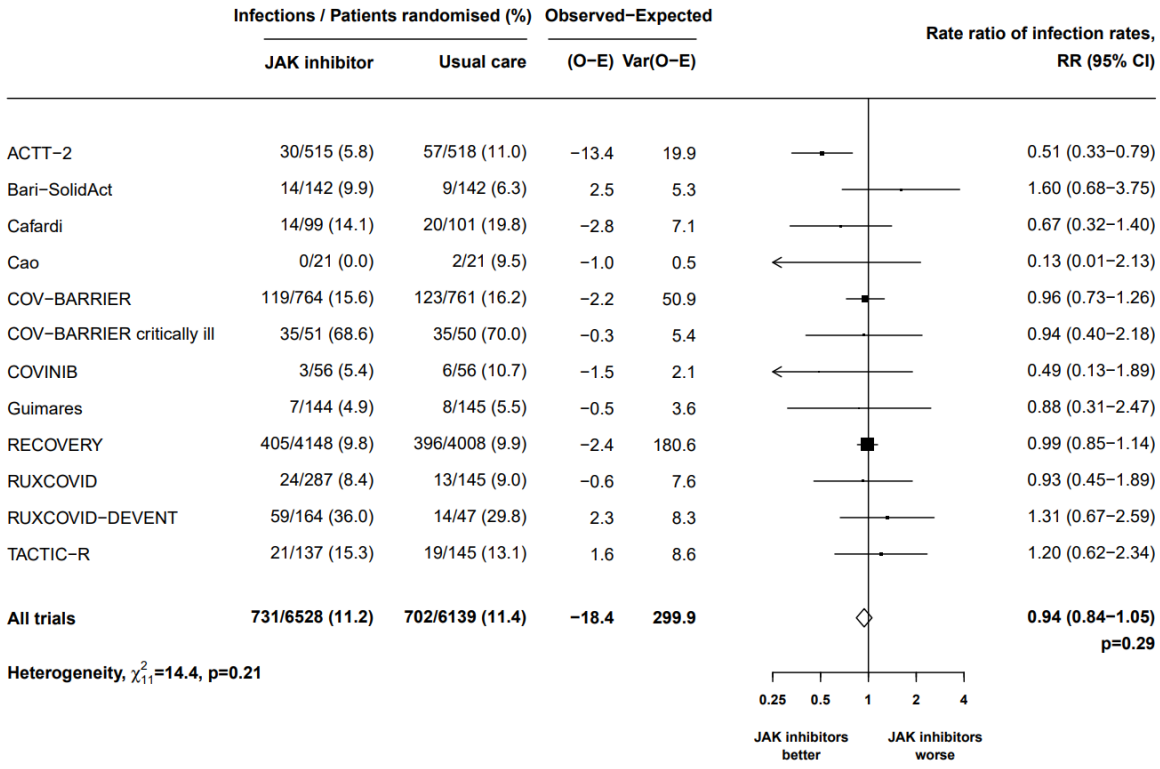


Figure 2-12: Meta-analysis of secondary infections within 28 days in randomised controlled trials of Janus kinase inhibitors compared with usual care/placebo, in hospitalised patients with COVID-19. This outcome has been assessed in the RECOVERY baricitinib comparison.

2.3.4.3 Other potential treatment-related harms

Eleven JAKI trials have reported VTE by treatment group with no clear evidence of an increased risk associated with JAKIs (RR 1.01 [95% CI 0.84 – 1.22], p=0.89; Supplementary Figure 6; Moderate certainty of evidence).

For results of other supplementary outcomes of potential JAKI treatment-related harms - GI complications and abnormal liver function, and the supplementary outcomes of discharge alive from hospital see Supplementary Figure 7 to Supplementary Figure 10, and for illness recovery or long COVID, and biological measurements, see Appendix, Section A.1.3.

2.3.5 Higher dose corticosteroids compared with lower dose corticosteroids

2.3.5.1 Mortality

The effect of higher dose corticosteroids on short-term mortality is presently unclear (Figure 2-13, Low certainty of evidence). There was significant statistical heterogeneity between results of trials in a high risk patient population (>80% of participants requiring high flow nasal oxygen, non-invasive or invasive ventilation at randomisation), trials in a low risk patient population (>80% of participants requiring only simple, or no, oxygen at randomisation) and trials in a mixed patient population.

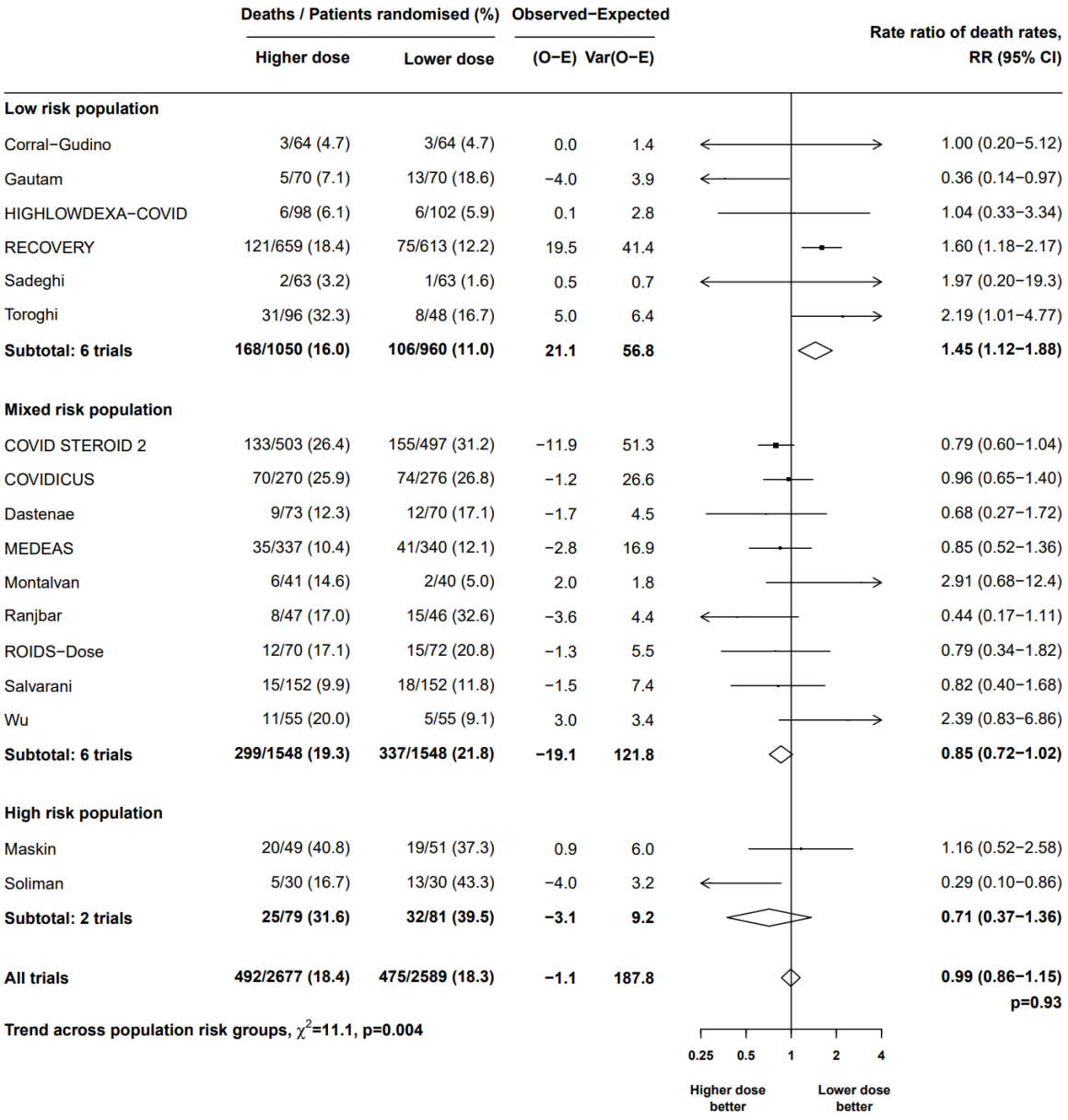


Figure 2-13: Meta-analysis of all-cause mortality within 28 days in groups defined by baseline disease severity in randomised controlled trials of higher dose corticosteroids compared with lower dose corticosteroids in hospitalised patients with COVID-19.
Population risk groups were defined by the proportion of participants in respiratory support categories. Low risk = >80% of participants requiring no or simple oxygen at baseline. High risk = >80% of participants requiring ventilatory support at baseline. Mixed = Not fulfilling criteria for low or high risk.
This outcome has been assessed in the completed subgroup of the RECOVERY higher dose dexamethasone comparison (participants who were hypoxic but did not require ventilatory support at randomisation).

Longer-term mortality has been assessed in seven higher dose corticosteroid trials, representing approximately half of the total number of patients randomised across all trials for this treatment comparison (Figure 2-14, Very low certainty of evidence).

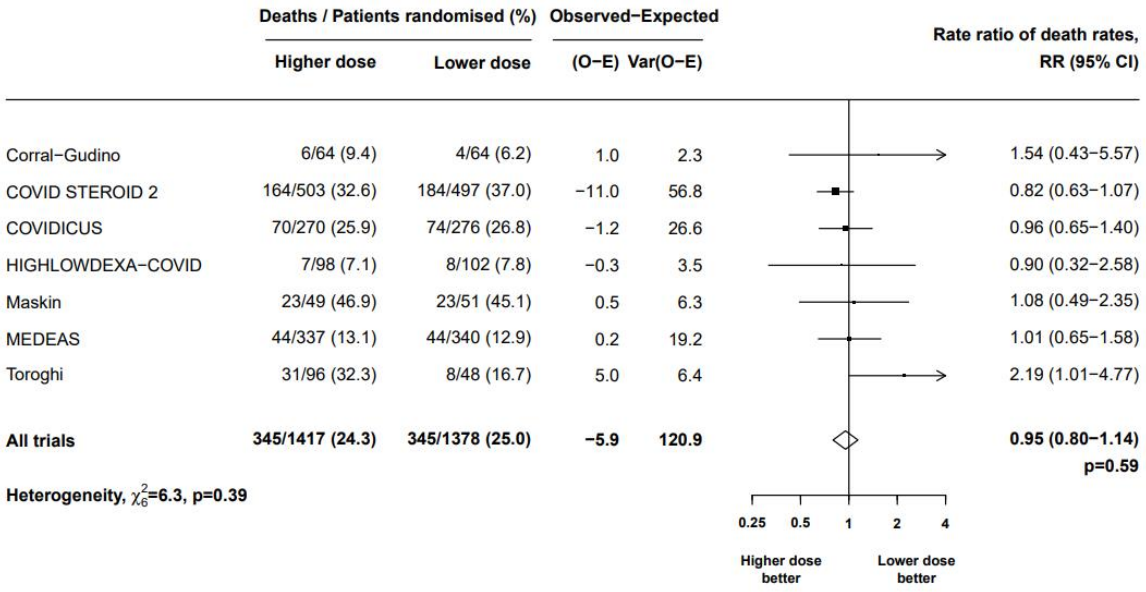


Figure 2-14: Meta-analysis of all-cause mortality within 90 days in randomised controlled trials of higher dose corticosteroids compared with lower dose corticosteroids in hospitalised patients with COVID-19.
This outcome has not been assessed in the completed subgroup of the RECOVERY higher dose dexamethasone comparison (participants who were hypoxic but did not require ventilatory support at randomisation).

2.3.5.2 Secondary infections

Eleven RCTs have reported secondary infections within 28 days (Figure 2-15, Low certainty of evidence). No identified trials reported secondary infections at longer-term follow-up.

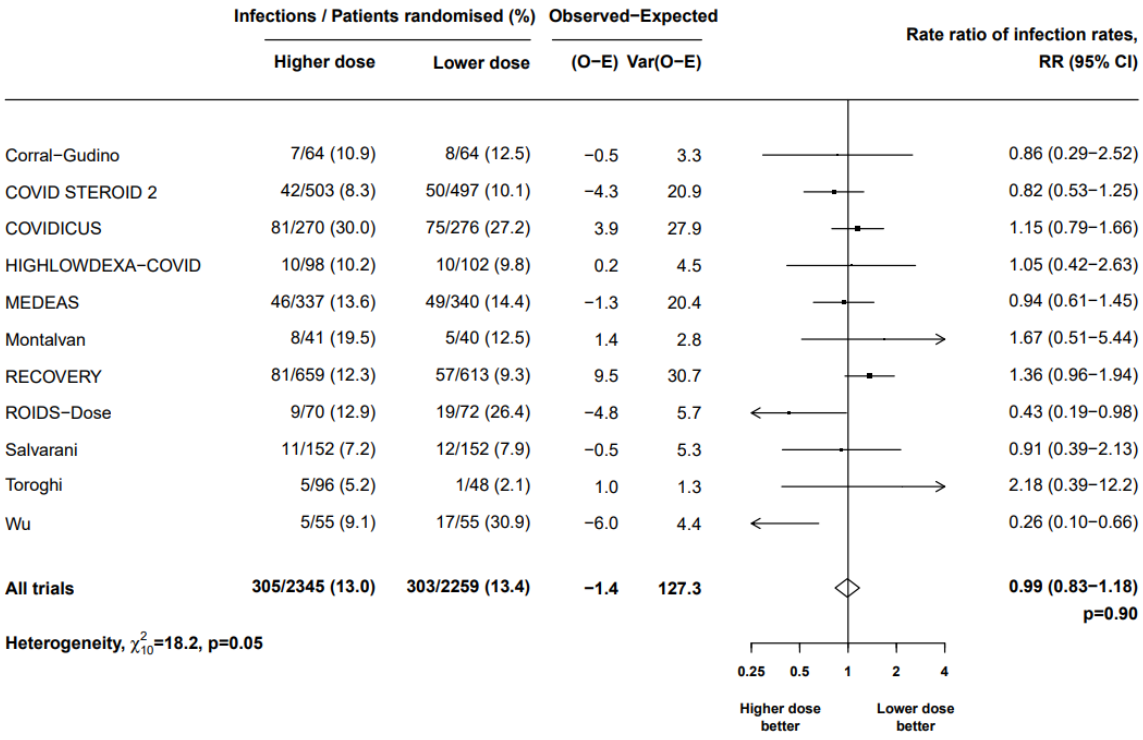


Figure 2-15: Meta-analysis of secondary infections within 28 days in randomised controlled trials of higher dose corticosteroids compared with lower dose corticosteroids in hospitalised patients with COVID-19.
This outcome has been assessed in the completed subgroup of the RECOVERY higher dose dexamethasone comparison (participants who were hypoxic but did not require ventilatory support at randomisation).

2.3.5.3 Other potential treatment-related harms

Hyperglycaemia-related outcomes were assessed in eleven higher dose corticosteroid RCTs with findings suggesting an increased risk of hyperglycaemia with higher dose corticosteroids (Figure 2-16, Moderate certainty of evidence). There was some evidence of a dose-response gradient in treatment effect with a higher risk of hyperglycaemia also observed in trials comparing corticosteroid treatment with no corticosteroids (Figure 2-5).

The main outlying trial (Gautam) in this analysis was assessed as at high risk of bias for this outcome (Supplementary Table 4).

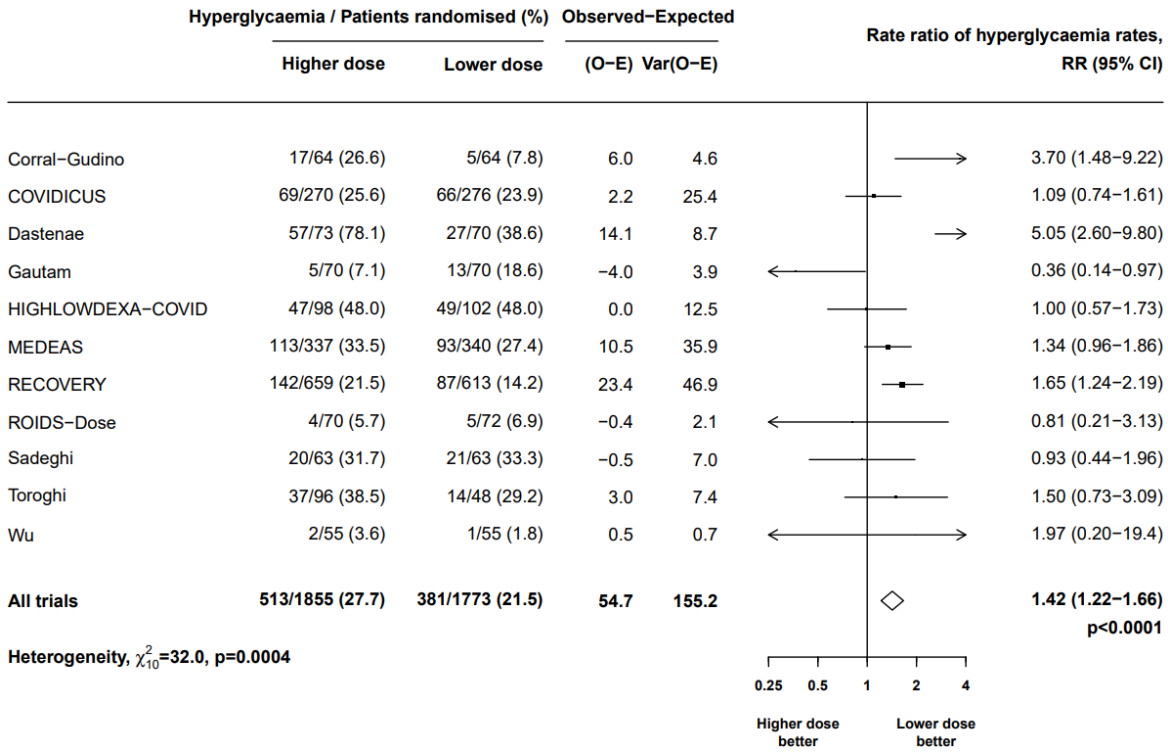


Figure 2-16: Meta-analysis of hyperglycaemia within 28 days in randomised controlled trials of higher dose corticosteroids compared with lower dose corticosteroids in hospitalised patients with COVID-19.
This outcome has been assessed in the completed subgroup of the RECOVERY higher dose dexamethasone comparison (participants who were hypoxic but did not require ventilatory support at randomisation).

For results of the other supplementary outcomes of potential corticosteroid treatment-related harms – VTE, GI complications and psychiatric complications, and for the supplementary outcome of discharge alive from hospital see Supplementary Figure 11 to Supplementary Figure 14. There was insufficient data for the assessment of incident diabetes or fractures. For the supplementary outcomes of measures of illness recovery or long COVID, and biological measurements, see Appendix, Section A.1.4.

2.3.6 Summary of findings

The summary of identified evidence across all assessments in each immunomodulatory treatment comparison is presented in Table 2-5.

Table 2-5: Summary of findings table for systematic review and meta-analysis of randomised controlled trials of corticosteroids, interleukin-6 receptor antagonists and Janus kinase inhibitors compared with usual care/placebo in hospitalised patients with COVID-19 .

Outcome	Pooled risk ratio [95% Confidence Interval]	Total number of events	Certainty of evidence (GRADE)*	Comments
Corticosteroids compared with no corticosteroids				
Mortality within 28 days	0.82 [0.74 – 0.90]	2136	High	
Mortality within 90 days	0.96 [0.71 – 1.29]	297	Very low	Certainty of evidence downgraded due to: Serious risk of bias for missing outcome data in largest contributing trial[90] Serious imprecision Potential for publication bias with only 4/13 identified trials contributing
Secondary infection within 28 days	0.81 [0.57 – 1.15]	165	Very low	Certainty of evidence downgraded due to: Serious risk of bias for concerns about the randomisation process[95,98], deviations from intended interventions[93], missing outcome data[89], outcome measurement bias[89] and selection of reported result[89,94,95] Indirectness with heterogeneous outcome definitions Imprecision Potential for publication bias with 8/13 identified trials contributing
Secondary infection within 90 days	-	0	-	Meta-analysis not performed due to insufficient data
Hyperglycaemia within 28 days	1.49 [1.13 – 1.96]	337	Very low	Certainty of evidence downgraded due to:

				Risk of bias for concerns about the randomisation process[95,98], deviations from intended interventions[93], missing outcome data[89] and selection of reported result[89,94,95] Indirectness with heterogeneous outcome definitions Unexplained inconsistency Potential for publication bias with 6/13 identified trials contributing
Discharge alive from hospital within 28 days	1.13 [1.06 – 1.20]	4175	Moderate	Certainty of evidence downgraded due to: Potential for publication bias with only 2/13 identified trials contributing
Discharge alive from hospital within 90 days	-	0	-	Meta-analysis not performed due to insufficient data.
Gastrointestinal complications	-	1	-	
Venous thromboembolism	-	4	-	
Psychiatric complications	-	10	-	
Incident diabetes	-	0	-	
Fractures	-	0	-	
Illness recovery	-	-	-	Meta-analysis not performed due to heterogeneous methods of outcome measurement and analysis. 1 of 3 trials assessing some form of illness recovery outcome reported a significant treatment benefit with corticosteroids – see Appendix, Section A.1.1.1 for details of results.
Biological measurements	-	-	-	Meta-analysis not performed due to heterogeneous methods of outcome measurement and analysis. 3 of 3 trials assessing a C-reactive protein measurement outcome reported significantly lower levels with corticosteroids – see Appendix, Section A.1.1.2 for details of results. 1 of 3 trials assessing a viral clearance outcome reported a significantly prolonged time to viral clearance with corticosteroids – see Appendix, Section A.1.1.2 for details of results.
Interleukin-6 receptor antagonists (IL-6 RAs)				
Mortality within 28 days	0.88 [0.81 – 0.96]	2796	High	

Mortality within 90 days	0.83 [0.71 – 0.98]	964	Moderate	Certainty of evidence downgraded due to: Potential for publication bias with 12/31 identified trials contributing
Secondary infection within 28 days	0.85 [0.72 – 1.00]	916	Low	Certainty of evidence downgraded due to: Risk of bias for measurement of outcome[106,108] and selection of reported result[104,106,108] Unexplained inconsistency in results
Secondary infection within 90 days	1.76 [1.12 – 2.76]	106	Very low	Certainty of evidence downgraded due to: Risk of bias for measurement of outcome and selection of reported result[110,125,131] Serious imprecision Unexplained inconsistency in results High risk of publication bias with 4/31 identified trials contributing
Abnormal liver function within 28 days	1.61 [1.23 – 2.10]	323	Low	Certainty of evidence downgraded due to: Risk of bias for measurement of outcome and selection of reported result[104,109,125] Indirectness with heterogeneous outcome definitions
Neutropenia within 28 days	5.08 [2.91 – 8.86]	58	Low	Certainty of evidence downgraded due to: Risk of bias for measurement of outcome and selection of reported result[113,118,119] Imprecision Potential for publication bias with 11/31 identified trials contributing Certainty of evidence upgraded due to: Large magnitude of treatment effect

Discharge alive from hospital within 28 days	1.17 [1.09 – 1.26]	5164	High	
Discharge alive from hospital within 90 days	1.18 [0.78 – 1.78]	416	Very low	Certainty of evidence downgraded due to: Serious imprecision High risk of publication bias with 3/31 identified trials contributing
Gastrointestinal complications	-	13	-	Meta-analysis not performed due to insufficient data.
Thrombocytopenia	-	8	-	
Illness recovery	-	-	-	Meta-analysis not performed due to insufficient data. 1 of 1 trials assessing some form of illness recovery outcome reported a significant treatment benefit with IL-6 RAs – see Appendix, Section A.1.2.1 for details of results.
Biological measurements	-	-	-	Meta-analysis not performed due to heterogeneous methods of outcome measurement and analysis. 8 of 12 trials assessing a C-reactive protein measurement outcome reported significantly lower levels with IL-6 RAs – see Appendix, Section A.1.2.2 for details of results.
Janus kinase inhibitors (JAKIs)				
Mortality within 28 days	0.79 [0.71 – 0.88]	1577	High	
Mortality within 90 days	0.74 [0.58 – 0.94]	335	Very low	Certainty of evidence downgraded due to: Serious imprecision Potential for publication bias with 4/16 identified trials contributing
Secondary infection within 28 days	0.94 [0.84 – 1.05]	1433	Moderate	Certainty of evidence downgraded due to: Risk of bias for measurement of outcome and selection of reported result[133,134,143]
Secondary infection within 90 days	-	23	-	Meta-analysis not performed due to insufficient data
Venous thromboembolism within 28 days	1.01 [0.84 – 1.22]	463	Moderate	Certainty of evidence downgraded due to: Indirectness with heterogeneous outcome definitions
Gastrointestinal complications within 28 days	1.37 [0.69 – 2.72]	35	Very low	Certainty of evidence downgraded due to:

				Serious imprecision Unexplained inconsistency in results Indirectness with heterogeneous outcome definitions Potential for publication bias with 3/16 identified trials contributing
Abnormal liver function within 28 days	0.90 [0.66 – 1.22]	201	Very low	Certainty of evidence downgraded due to: Risk of bias for measurement of outcome and selection of reported result[133,134,139] Indirectness with heterogeneous outcome definitions Imprecision Potential for publication bias with 9/16 identified trials contributing
Discharged alive from hospital within 28 days	1.14 [1.09 – 1.19]	9339	High	
Discharged alive from hospital within 90 days	1.14 [0.69 – 1.87]	493	Very low	Certainty of evidence downgraded due to: Serious imprecision Potential for publication bias with 2/16 identified trials contributing
Illness recovery	-	-	-	Meta-analysis not performed due to insufficient data 0 of 1 trials assessing some form of illness recovery outcome reported a significant treatment benefit with JAKIs – see Appendix, Section A.1.3.1 for details of results.
Biological measurements	-	-	-	Meta-analysis not performed due to heterogeneous methods of outcome measurement and analysis. 1 of 4 trials assessing a C-reactive protein measurement outcome reported significantly lower levels with JAKIs – see Appendix, Section A.1.3.2 for details of results.
Higher dose corticosteroids compared with lower dose corticosteroids				
Mortality within 28 days	0.99 [0.86 – 1.15]	967	Low	Certainty of evidence downgraded due to:

				Imprecision Unexplained inconsistency in results
Mortality within 90 days	0.95 [0.80 – 1.14]	690	Very low	Certainty of evidence downgraded due to: Imprecision Serious potential for publication bias with 7/17 identified trials contributing and not including the largest trial contributing to unexplained inconsistency in short-term mortality
Secondary infection within 28 days	0.99 [0.83 – 1.18]	608	Low	Certainty of evidence downgraded due to: Risk of bias for measurement of outcome and selection of reported result[149,159] Indirectness with heterogeneous outcome definitions
Secondary infection within 90 days	-	0	-	Meta-analysis not performed due to insufficient data
Hyperglycaemia within 28 days	1.42 [1.22 – 1.66]	894	Moderate	Certainty of evidence downgraded due to: Indirectness with heterogeneous outcome definitions Unexplained inconsistency in results Certainty of evidence upgraded due to some evidence of dose-response gradient in treatment effect
Gastrointestinal complications within 28 days	1.30 [0.69 – 2.45]	39	Very low	Certainty of evidence downgraded due to: Risk of bias for measurement of outcome and selection of reported result[150] Serious imprecision Potential for publication bias with 6/17 identified trials contributing
Venous thromboembolism within 28 days	0.77 [0.53 – 1.10]	121	Very low	Certainty of evidence downgraded due to: Risk of bias for measurement of outcome and selection of reported result[147,152]

				Indirectness with heterogeneous outcome definitions Serious imprecision
Psychiatric complications within 28 days	1.18 [0.79 – 1.77]	132	Very low	Certainty of evidence downgraded due to: Risk of bias for measurement of outcome and selection of reported result[149,160] Indirectness with heterogeneous outcome definitions Serious imprecision Potential for publication bias with 5/17 identified trials contributing
Discharge alive from hospital within 28 days	0.78 [0.65 – 0.94]	1782	Moderate	Certainty of evidence downgraded due to: Imprecision
Discharge alive from hospital within 90 days	-	115	-	Meta-analysis not performed due to insufficient data
Incident diabetes	-	0	-	
Fractures	-	0	-	
Illness recovery	-	-	-	Meta-analysis not performed due to insufficient data 0 of 1 trials assessing some form of illness recovery outcome reported a significant treatment benefit with higher dose corticosteroids – see Appendix, Section A.1.4.1 for details of results.
Biological measurements	-	-	-	Meta-analysis not performed due to heterogeneous methods of outcome measurements and analysis 2 of 4 trials assessing a C-reactive protein measurement outcome reported significantly lower levels with higher dose corticosteroids – see Appendix, Section A.1.4.2 for details of results
**See Section 2.2.4 for further information regarding the assessment of certainty of evidence.*				

2.4 Discussion

2.4.1 Mortality

There is high quality evidence supporting the short-term mortality benefit of corticosteroids, IL-6 RAs and JAKIs for hospitalised patients with COVID-19. However, across all treatments, longer-term mortality data is sparse. Assessment of longer-term mortality within RECOVERY would add substantially to the current evidence base, providing clinicians, patients and policymakers with clearer answers as to the durability of treatment benefit. For example, the addition of long-term follow-up in the RECOVERY dexamethasone comparison to the current evidence would more than treble the total number of deaths recorded in the meta-analysis.

2.4.2 Secondary infections

The certainty of evidence regarding secondary infections is limited by important risk of bias and inadequate statistical power. Most RCTs have relied on adverse event reporting systems, rather than systematic pre-specified data collection on all participants. Adverse event report data collection can lead to under-reporting of events and outcome ascertainment bias, particularly in open-label trials[164,165]. Longer-term data is limited but treatment-related infection risks may persist or develop after initial follow-up[42,62,166]. Evaluation of short-term secondary infection risk in trials that included patients with high rates of corticosteroid co-administration did not suggest any enhanced risk with IL-6 RAs or JAKIs used in addition to corticosteroids, but there is very little evidence regarding the use of corticosteroids, IL-6 RAs and JAKIs in combination. Amongst JAKI trials, all but one (ACTT-2) included a population with high rates of steroid co-administration, but only RECOVERY and Bari-SolidAct included a population with rates of baseline IL-6 RA co-administration of more than 20%.

Assessment of secondary infections within the RECOVERY dexamethasone and tocilizumab comparisons and longer-term follow-up in the baricitinib comparison would add considerably to the current evidence. A conservative estimate of a 5% incidence of secondary infections within 28 days in the RECOVERY dexamethasone comparison population would more than double the current event numbers reported for this outcome in the meta-analysis. This could provide important evidence to guide clinicians' mitigation of any infection risk when using these treatments for COVID-19, and to begin to understand the optimal approach to co-administration of immunomodulatory treatments. Use of both clinical and microbiological outcome definitions of secondary infections would aid the comprehensiveness of such an assessment, as most trials have used one or the other.

2.4.3 Other potential treatment-related harms

Evidence regarding other potential immunomodulatory treatment-related harms suggests that corticosteroids may increase the risk of hyperglycaemia and IL-6 RAs may increase the risk of abnormal liver function tests and neutropenia, with short-term use for hospitalised patients with COVID-19. However, the certainty of this evidence is still low – limited by important risk of bias relating to non-systematic outcome measurement, imprecision, and heterogeneous outcome definitions across different trials. The effect of these biochemical abnormalities on clinical complications is also uncertain - for example, it is unclear whether clinically significant liver injury or infections relating to neutropenia could be occurring with IL-6 RAs. Hyperglycaemia has been associated with increased in-hospital mortality in COVID-19 patients[66].

Other potential treatment-related harms appear severely under-reported, including VTE and delirium, which are estimated to occur in 5% and 25% of hospitalised patients with COVID-19 respectively[63,64,167]. Longer-term follow-up for additional potential treatment-related harms, such as incident diabetes or fractures with corticosteroids[42,43], have not

been reported in any trials to date. Given the widespread use of immunomodulatory therapies globally for COVID-19, understanding any moderately-sized risks of any of these potential complications is important. On a population level, results could inform healthcare planning, and on an individual level about the relevance of these risks for hospitalised patients with COVID-19, leading to suitable levels of monitoring and mitigation, if required. A systematic evaluation for potential treatment-related harms in RECOVERY would support this process by providing meaningful evidence at short-term and long-term follow-up.

2.4.4 Illness recovery

There is very little randomised evidence regarding the impact of immunomodulatory treatments on measures of illness recovery, such as functional status or quality of life, or long COVID. Understanding any impact of treatment given during the acute illness on these outcomes is important as this represents a potential opportunity to modify the clinical course of illness recovery, where long-term outcomes - that are meaningful to patients - can have a major impact on the individual and society[69-71].

2.4.5 Biological measurements

Understanding the impact of immunomodulatory treatments on biological measurements could improve the design and interpretation of future research relating to these treatments in COVID-19 and other acute respiratory infections. It may provide evidence regarding surrogate markers of efficacy relevant to future research and potentially flag markers associated with poor treatment response for further evaluation. The current evidence suggests corticosteroids and IL-6 RAs probably reduce CRP, higher levels of which have been associated with disease severity and mortality[168,169].

No existing randomised evidence of treatment effects at a genetic level was found. Multi-omics profiling could identify biological pathways that treatments are acting upon in COVID-19, for example through differential gene expression analysis in serial host

transcriptomic samples[170]. The immunomodulatory effects of corticosteroids are broad - regulating the expression of a range of anti-inflammatory genes, through both genomic and non-genomic mechanisms. Delineating these processes in COVID-19 could have implications for the evaluation of further therapeutics that target identified biological pathways in order to enhance efficacy and reduce side effects associated with the broad effect of corticosteroids[74,75]. Assessment of treatment effects on gene expression measurements could also provide preliminary evidence regarding the use of gene expression data as a surrogate efficacy marker in future randomised trials.

2.4.6 Corticosteroid effects across the disease severity spectrum

RECOVERY was the only RCT identified in the systematic review that compared corticosteroids with no corticosteroids by subgroups of disease severity, finding significant heterogeneity in treatment effect across respiratory support groups for the outcome of 28-day mortality. These results are discussed in Section 1.3.4.

The role of higher dose corticosteroids in the treatment of COVID-19 is currently unclear. Across all higher dose corticosteroid RCTs identified, there was a suggestion of similar heterogeneity according to level of respiratory support, but this was assessed at trial population, rather than individual participant, level.

In RECOVERY, higher dose corticosteroids increased mortality compared with lower dose corticosteroids, in those requiring simple, or no, oxygen[44]. Evaluation in patients requiring higher levels of respiratory support is ongoing. Analysing treatment effects in the completed higher dose corticosteroid subgroup in RECOVERY could support the understanding of the heterogeneity of treatment effect seen in the first RECOVERY dexamethasone comparison and inform future research regarding corticosteroid treatment in other acute severe respiratory infections. For example, in community-acquired pneumonia evidence regarding the efficacy of corticosteroids remains uncertain[171-173].

2.5 Conclusions

This systematic review and meta-analysis has evaluated the quantity and quality of existing randomised evidence relating to the efficacy and safety of immunomodulatory therapies for hospitalised patients with COVID-19. There are key areas in which the certainty of evidence is low, or data is insufficient. While there is high quality evidence regarding the effects of corticosteroids, IL-6 RAs and JAKIs on short-term mortality, evidence is lacking for assessments of longer-term efficacy, potential treatment-related harms, illness recovery and effects on biological measurements. The effect of corticosteroids across the disease severity spectrum, the role of higher dose corticosteroids, and the optimal co-administration strategy of immunomodulatory treatment in COVID-19 all remain poorly understood.

RECOVERY is the largest single RCT in each of the immunomodulatory treatment classes, representing around three quarters of the total patients randomised across all reported trials assessing corticosteroids compared with no corticosteroids, two thirds in those assessing JAKIs, one third in those assessing IL-6 RAs, and one quarter in those assessing higher dose corticosteroids compared with lower dose corticosteroids. The proposed extended analysis of the RECOVERY immunomodulatory treatments in line with the thesis aims (Section 1.4) should add substantially to the current evidence, by increasing the quantity of reliable data evaluating treatment effects and minimising random and systematic error through RECOVERY's randomised design.

Chapter 3

Methods

3.1 Chapter Summary

This chapter describes the research methods used in all aspects of the extended analysis.

First, the chapter outlines the overall study design and methodological approach. A description of the data sources and how they were used in the extended analysis is then given. Definitions and derivations of the final analysis assessments are listed, broken down by contributing data sources and analysis component. The statistical methods utilised for the analysis of these assessments are described. Finally, the ethical and information governance considerations and the processes involved in establishing the study data linkage are discussed.

The details of the method development undertaken to finalise the definitions of the extended analysis assessments derived from RCD are presented in a separate chapter – Chapter 4: Method Development.

3.2 Study Design and Population

Individual participant-level data was linked from three data sources: the RECOVERY trial; RCD (defined as healthcare-related data that was collected "without specific a priori research goals", such as medical administrative data and electronic health records[174]); and the ISARIC4C study. RCD was linked for 95.5% of all RECOVERY participants. ISARIC4C data was linked for 51.9% of all RECOVERY participants (rising to 75% of the RECOVERY dexamethasone comparison). The extended analysis used novel assessments derived from linking these data sources and performed analyses within the original RECOVERY randomised comparison populations for dexamethasone (standard dose and higher dose comparisons separately), tocilizumab, and baricitinib, all compared with usual care (Figure 3-1). The aim of this approach was to preserve the randomised controlled design of RECOVERY in order to minimise bias but enable evaluation of extended outcomes in line with the thesis aims (Section 1.4).

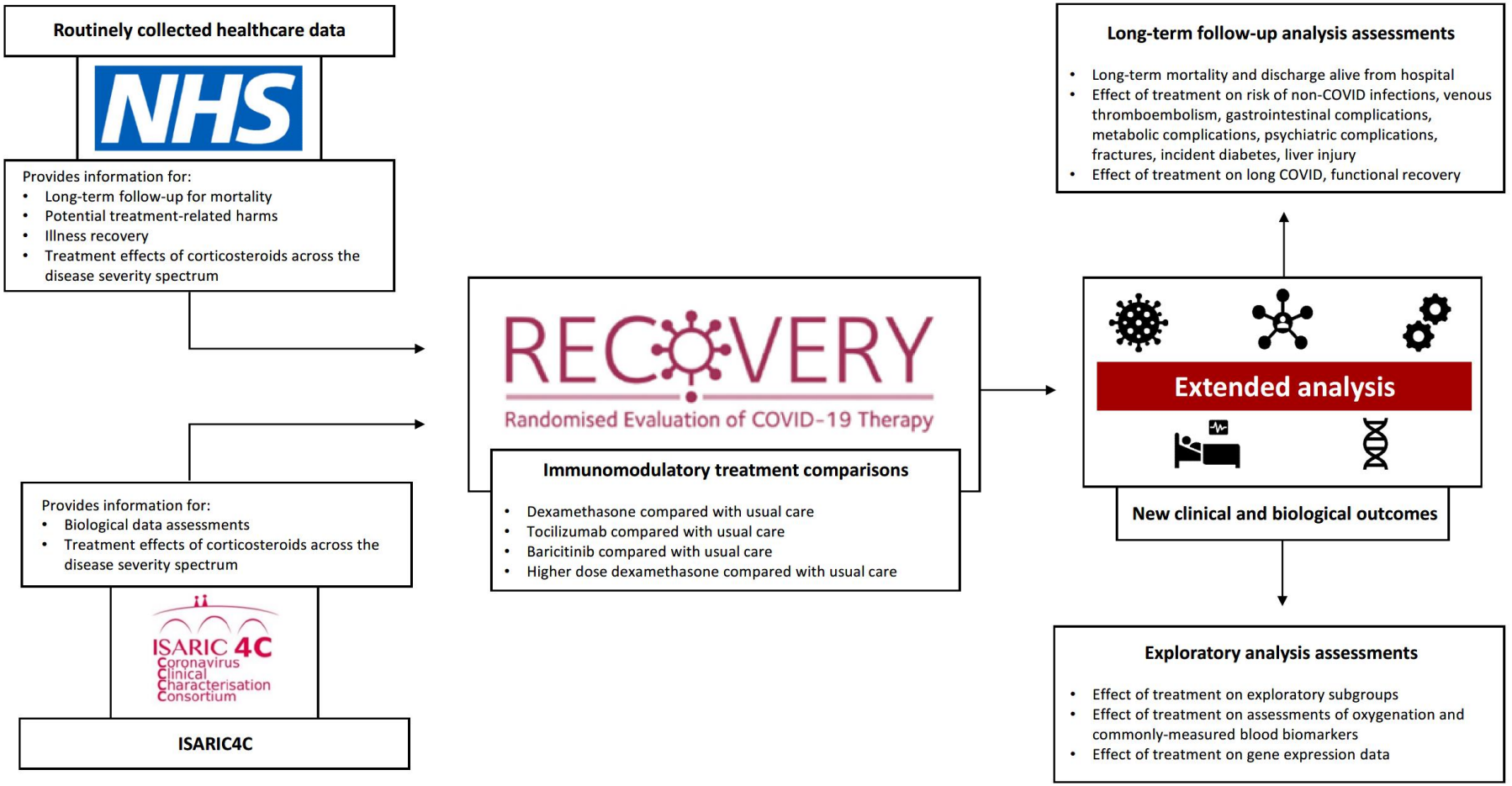


Figure 3-1: Overview of the extended analysis study design.

The extended analysis was broadly split into two components:

i) Long-term follow-up assessments:

These assessments were grouped together as largely clinical outcomes relating to long-term follow-up of the immunomodulatory treatment comparisons. This included the efficacy and safety outcomes of longer-term mortality, potential treatment-related harms, and effects on illness recovery. They were primarily derived from RCD and RECOVERY data sources, with some contribution from ISARIC4C data, where relevant. These assessments were pre-specified in a Data Analysis Plan (Appendix, Section B.1.1) and almost all were carried out in the full intention-to-treat population for each RECOVERY treatment comparison.

ii) Exploratory assessments:

These assessments included further exploratory subgroup analyses and analyses of biological measurements. These assessments were derived from integrated ISARIC4C, RCD and RECOVERY data sources. Many of the assessments in this component of the analysis were pre-specified in a Data Analysis Plan (Appendix, Section B.1.2) but further post-hoc exploratory assessments were carried out where initial analyses led to results meriting further exploration in line with the thesis aims. Many assessments in this component of the extended analysis were carried out in the 'RECOVERY-ISARIC population' for each treatment comparison - a subset of the full intention-to-treat population that included all RECOVERY participants who had linked data in ISARIC4C.

All data exploration, processing, and method development to produce the final analysis dataset was undertaken blinded to individual participant treatment allocation. The data analysis plans were written and agreed with the thesis supervisory team and RECOVERY and ISARIC4C Chief Investigators prior to unblinding to randomised treatment allocation.

3.3 Data Sources

The following data sources were used to produce the final extended analysis dataset:

i) RECOVERY case report form (CRF) data collection.

ii) RCD, including hospital admission, death, primary care and microbiology datasets.

iii) ISARIC4C CRF and biological sample study data collection.

They are summarised in Table 3-1 with further details provided below.

Table 3-1: Summary of the data sources used for the extended analysis.

Data Source	Data collection details	Components used for extended analysis
RECOVERY		
Randomisation case report form (CRF)[175]	Completed by local site staff at randomisation	Demographics e.g. age, sex Acute illness details e.g. respiratory support Co-morbidities Current COVID-19 treatment Randomised treatment allocation
Follow-up CRF[176]	Completed by local site staff at the earliest of discharge, death, or 28 days after randomisation	Vital status (died, discharged alive from hospital, still in hospital) Date of hospital discharge Safety outcomes where available: Thrombotic events, clinically significant bleeding, non-coronavirus infection, metabolic complications
International site 6-month follow-up CRF[177]	Completed by local site staff at 6 months after randomisation by telephone or in-person follow-up	Vital status Underlying cause of death Dates of any hospital readmission and discharge with associated diagnoses
Routinely collected data (RCD) – Hospital admission datasets		
Hospital Episode Statistics Admitted Patient Care[178] NHS Central Register Scottish Morbidity Record One[181] Patient Episode Data Wales[182]	Information on patient level NHS inpatient hospital care in England, Scotland, and Wales, collected from hospital providers for the primary purpose of healthcare service delivery planning	Dates of hospital admission and discharge Diagnoses recoded (ICD-10 codes[179]) Procedures performed (OPCS-4 codes[180])
RCD – Death datasets		
Office for National Statistics[183] National Records of Scotland[184]	Information on deaths registered in England, Scotland and Wales via death certificates	Date of death

		Underlying cause and diagnoses leading to death from death certificate (ICD-10 codes)
RCD – Primary care datasets		
General Practice Extraction Service Data for Pandemic Planning and Research[185,186]	Compiled by NHS Digital from English GP practices for COVID-19 healthcare planning	Primary care diagnoses, medication prescriptions, laboratory test results (SNOMED codes[187])
Welsh Longitudinal General Practice Dataset[188]	Information on general practice attendances, investigations, diagnoses and prescribed medication in Wales	Primary care diagnoses, medication prescriptions, laboratory test results (Read codes[189])
NHS Business Services Authority Medicines[190]	Records of medications dispensed in pharmacies in England and Wales	Medications dispensed (BNF codes[191])
RCD – Microbiology datasets		
Second Generation Surveillance System[192,193]	Positive results collected by UK Health Security Agency from diagnostic laboratories in England	Dates of sample collection Specimen type Organism identified
National Pathology Exchange COVID-19 Non-hospital testing[194]	Data relating to SARS-CoV-2 antigen and polymerase chain reaction testing conducted under pillar 2 of the government's testing programme (non-hospital testing)	Dates of sample collection SARS-CoV-2 test result
ISARIC4C		
In-hospital structured CRF[195]	Completed by local site staff at study enrolment and updated daily for up to 14 days and at hospital discharge	Daily physiological measurements Daily blood test results Microbiology testing results Functional status at hospital discharge
Biological samples[196]	Collected from consenting patients at recruitment, study day 3, study day 9, study day 14 and >28 days post-hospital discharge	Gene expression data

3.3.1 RECOVERY

3.3.1.1 Trial overview

RECOVERY is a randomised, controlled, open-label, platform trial that evaluated pharmacological treatments for hospitalised patients with COVID-19. Within the trial platform, participants could be randomised simultaneously to 1 or more active treatment comparisons. Available treatment comparisons were added or removed as knowledge evolved about COVID-19 therapy. For each comparison, eligible and consenting participants were randomly assigned to either the active treatment plus usual standard

care or usual standard care alone using online, simple randomisation with allocation concealment. The primary outcome for the trial was all-cause mortality within 28 days.

Since beginning enrolment in March 2020, over 48,000 participants have entered RECOVERY, across 173 UK hospital trust sites. Recruitment expanded internationally from February 2021, with 22 sites in Asia and Africa[27]. Fifteen COVID-19 treatment comparisons have produced results; amongst these were the immunomodulatory treatments of dexamethasone, tocilizumab and baricitinib – all of which were demonstrated to reduce short-term mortality[29-31], and are used to treat hospitalised patients with COVID-19 in current clinical practice[25,26]. Higher dose dexamethasone has completed evaluation in the subgroup of participants who were hypoxic but did not require respiratory support at randomisation, in whom it was found to increase short-term mortality[44]. The subgroup of participants in this treatment comparison who required ventilatory support at randomisation was stopped on 31 March 2024, with analysis ongoing. Other treatments that have completed evaluation are casirivimab-imdevimab, lopinavir-ritonavir, hydroxychloroquine, azithromycin, colchicine, convalescent plasma, aspirin, dimethyl fumarate, empagliflozin, molnupiravir and nirmatrelvir-ritonavir[197-206].

Dexamethasone, baricitinib and higher dose dexamethasone were all components of the main trial randomisation at different time points (Table 3-2). The tocilizumab comparison was available as a second randomisation for patients with progressive disease meeting inclusion criteria. This second randomisation could occur at the same time as, or up to 21 days after, they had been entered in the main randomisation. During the time of assessment of tocilizumab, the main randomisation could have included active treatments of dexamethasone, lopinavir-ritonavir, hydroxychloroquine, azithromycin, colchicine, convalescent plasma, casirivimab-imdevimab or aspirin[30].

Table 3-2: Details of the RECOVERY immunomodulatory treatment comparisons.

Immunomodulatory treatment	Dates of randomisation	Inclusion criteria	Exclusion criteria	Number of patients randomised	
				Treatment	Usual care
Dexamethasone 6mg once daily for 10 days or until hospital discharge, by mouth or intravenously	March – June 2020 Main randomisation	Clinically suspected or laboratory confirmed COVID-19 No medical history that might, in the opinion of the attending clinician, put patient at substantial risk if they were to participate in the trial	Known contra-indication to short-term corticosteroids	2104	4321
Tocilizumab 400-800mg (depending on weight), intravenously, with a second dose able to be given 12-24 hours later if the patient's condition had not improved	April 2020 – January 2021 Second randomisation	Within 21 days of main randomisation Clinical evidence of progressive COVID-19: oxygen saturations <92% on room air or receiving oxygen therapy or CRP ≥75 mg/L No medical history that might, in the opinion of the attending clinician, put patient at substantial risk if they were to participate in the trial	Known hypersensitivity to tocilizumab Evidence of active TB infection Clear evidence of active bacterial, fungal, viral or other infection besides COVID-19	2022	2094
Baricitinib 4mg once daily for 10 days or until hospital discharge, by mouth	February – December 2021 Main randomisation	Clinically suspected or laboratory confirmed COVID-19 No medical history that might, in the opinion of the attending clinician, put patient at substantial risk if they were to participate in the trial	Age <2 years Estimated glomerular filtration rate <15mL/min/1.73m^2 or on dialysis or haemofiltration Neutrophil count <0.5 x 10^9/L Evidence of active TB infection Pregnancy Breastfeeding	4148	4008

Higher dose dexamethasone 20mg once daily for 5 days followed by 10mg once daily for 5 days, or until hospital discharge, by mouth or intravenously	May 2021 – May 2022 (For participants with hypoxia but not requiring ventilatory support at randomisation) May 2021 – March 2024 (For participants requiring ventilatory support at randomisation) Main randomisation	Clinically suspected or laboratory confirmed SARS-CoV-2 infection associated disease No medical history that might, in the opinion of the attending clinician, put patient at substantial risk if they were to participate in the trial Clinical evidence of hypoxia (receiving oxygen or oxygen saturations <92% on room air)	Known contra-indication to short-term corticosteroids	659* 246†	613* 231†
**No ventilatory support subgroup* *†Ventilatory support subgroup*					

3.3.1.2 Case report form data

The RECOVERY randomisation CRF provided information on participants' baseline demographic characteristics; including age, sex, and ethnicity; co-morbidities; acute illness features, including duration of symptoms, duration of hospital stay, respiratory support status and COVID-19 treatments; and trial randomisation date and treatment allocation.

A participant's follow-up CRF was completed at the earliest of discharge from hospital, death, or 28 days after randomisation. It provided data on the participant's vital status – whether they had died, had been discharged alive from hospital, or were still in hospital - and a corresponding date. Safety outcome data was used from the follow-up CRF when available. No specific safety outcome data was available for participants in the dexamethasone and tocilizumab comparisons. The following safety outcomes were collected for participants in the baricitinib and higher dose dexamethasone comparisons:

i) Thrombotic events (pulmonary embolism; deep vein thrombosis; ischaemic stroke; myocardial infarction; systemic arterial embolism; other). Collected from 6 November 2020.

ii) Clinically significant bleeding (intra-cranial bleeding or bleeding that required intervention or a blood transfusion; site of bleeding). Collected from 6 November 2020.

iii) Non-coronavirus infection (site of infection; putative organism). Collected from 24 February 2021.

The following safety outcomes were collected for participants in the higher dose dexamethasone comparison:

iv) Metabolic complications (ketoacidosis; hyperglycaemic hyperosmolar state; other hyperglycaemia requiring new use of insulin; severe hypoglycaemia). Collected from 28 July 2021.

For participants recruited at international study sites (affecting some participants in the higher dose dexamethasone treatment comparison), an additional follow-up CRF was completed to document a participant's vital status at 28 days and a further follow-up form was completed by local study site staff at 6 months after randomisation. This was due to the absence of available RCD at international sites. The 6-month follow-up CRF collected data on: vital status, including cause of death; and details of any hospital readmissions, including dates of admission and discharge, and associated diagnoses.

3.3.2 RCD

3.3.2.1 Dataset collation and use

Extensive linked RCD sources have been collated by a RECOVERY trial data linkage team from data custodians such as NHS Digital, Public Health Scotland (PHS), Secure Anonymised Information Linkage (SAIL) and the UK Health Security Agency (UKHSA), as part of RECOVERY follow-up. The hospitalisation and death datasets have been used in the main RECOVERY trial analysis by contributing information on mortality, discharge alive from hospital, and use of ventilation within 28 days[177]. The remaining datasets had not previously been used in RECOVERY and were utilised for the first time for the thesis extended analysis. Apart from outcomes relating to mortality, discharge alive from hospital and hospital-recorded diagnoses, the thesis author independently derived all other assessments in the extended analysis, using variables within the RCD datasets. The process of the method development of assessments derived from RCD is presented in Chapter 4. The definitions and statistical methods for the outcomes of mortality, discharge alive from hospital and hospital-recorded diagnoses are adapted from the main trial Statistical Analysis Plan and Definitions and Derivations document[177,207]. The extension of follow-up for these outcomes beyond 28 days was novel for the extended analysis.

The most recent extract for each of the RCD datasets was used for the final analysis, as of October 2023.

3.3.2.2 Hospital admission datasets

i) *Hospital Episode Statistic Admitted Patient Care (HESAPC)*

HESAPC is a dataset containing individual patient-level information for all admissions at NHS hospitals in England[178]. Data is collected by NHS Digital from hospital providers, processed, validated, and cleaned, and used to create the HESAPC dataset which is released monthly and used for healthcare service delivery planning[208].

In the HESAPC dataset, each row corresponds to a continuous period of inpatient care under one consultant and clinical specialty – termed an 'episode'. A number of episodes can be grouped together to form 'spells' – continuous periods of inpatient care within the same hospital[209]. Each episode contains demographic data about the patient, the start and end dates of the episode, details of timing and locations of admission and discharge, the diagnoses recorded during the episode using International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) codes[179], and any procedures performed during the episode using Office of Population Censuses and Surveys Classification of Surgical Operation and Procedures, 4th revision (OPCS-4) codes[180] and associated procedure dates. Diagnostic codes are assigned a position from 1 up to a maximum of 20. Codes in position 1 represent the primary diagnosis associated with admission or extension of hospital stay, with the remainder representing other diagnoses associated with the episode[210].

Data was available for 5 years prior to enrolment in RECOVERY and for the duration of ongoing follow-up. For the extended analysis, pre-randomisation episodes were used in the derivation of additional baseline characteristics or incident disease outcomes and post-randomisation episodes were used in the derivation of additional outcomes, based on recorded ICD-10 and OPCS-4 diagnosis or procedure codes. Full definitions of these assessments are detailed in Section 3.4. The timing of each episode relative to an individual participant's randomisation date was defined according to the following rules:

- Pre-randomisation episodes: the episode end date was before the participant's date of randomisation.
- Post-randomisation episodes: the episode start date was after the participant's date of randomisation.
- Peri-randomisation episodes: the episode start date was on, or before, the participant's date of randomisation and the episode end date was on, or after, the participant's date of randomisation.

Peri-randomisation episode records were not used to determine assessments in the main analysis (although were investigated in sensitivity analyses). This is because it was not possible to tell from the record whether events within these episodes occurred before or after randomisation.

The start date of the episode containing the relevant ICD-10 diagnosis code or the OPCS-4 procedure date was used as the event date for all analyses. Repeat diagnosis codes with a start date occurring within less than or equal to 30 days, or occurring within the same hospital admission spell, were excluded from analyses, as these diagnoses were felt unlikely to represent a new incidence of illness.

ii) *Patient Episode Data Wales (PEDW)*

PEDW contains individual patient-level data relating to admissions to NHS hospitals in Wales[182]. The data fields used in the extended analysis were equivalent to those used in HESAPC. PEDW is structured by episodes of care in the same way as HESAPC.

iii) *NHS Central Register Scottish Morbidity Record One (SMR01)*

The SMR01 dataset collects patient-level data on acute inpatient and day case discharges from NHS hospitals in Scotland[181]. The data fields used in the extended analysis were equivalent to those used in HESAPC, although SMR01 is structured with each episode corresponding to a period of hospital care in one 'significant facility' – a type

of clinical facility such as a hospital ward or intensive care unit. The same approach and rules were used in assessment derivation and event timing as in HESAPC.

3.3.2.3 Death datasets

i) *Office for National Statistics (ONS) mortality data*

The ONS mortality data covers all deaths registered in England and Wales[183]. It contains information on date of death, underlying cause, and diagnoses leading to and contributing to death, using information recorded on the death certificate coded into ICD-10 diagnosis codes.

In the extended analysis, the dataset contributed information to the fact and date of death, and the occurrence of safety outcomes and diagnoses leading to death (part 1 of the death certificate) using ICD-10 codes.

ii) *National Records of Scotland (NRS) mortality data*

The NRS mortality data contains information relating to all deaths registered in Scotland, including causes of death from the death certificate coded into ICD-10 codes[184]. The data used in the extended analysis was the equivalent to those used from ONS mortality data.

3.3.2.4 Primary care datasets

i) *General Practice Extraction Service Data for Pandemic Planning and Research (GDPPR)*

GDPPR data was collected by NHS Digital from all GP practices in England for the purposes of COVID-19 healthcare planning and research[185]. The data includes patient demographics and medical information; including diagnoses, some laboratory results (e.g. routine blood tests), and some medication prescriptions, coded in Systematized Nomenclature of Medicine (SNOMED) concept IDs with corresponding dates. Each dataset row corresponds to a SNOMED-coded clinical entry.

The SNOMED concept IDs included in the dataset were determined by NHS Digital's release of clusters of codes that were deemed appropriate for pandemic planning and research[186]. This means that this dataset could be used for many, but not all, of the extended analysis assessments. For example, infection codes were limited to respiratory tract infections and no codes were available for diagnoses of VTE.

For the extended analysis, GDPPR record entries prior to an individual's randomisation date were used to identify additional baseline characteristics and records after an individual's randomisation date were used to identify outcomes. Corresponding diagnosis dates were used as event dates for all analyses. Repeat diagnostic codes occurring within 30 days of the previous diagnosis date were excluded as these diagnoses were felt unlikely to represent a new incidence of illness.

ii) Welsh Longitudinal General Practice Dataset (WLGP)

WLGP provided primary care data for participants in Wales[188]. The data fields used were equivalent to those used in GDPPR. WLGP uses Read version 2 codes, which were mapped to equivalent SNOMED concept IDs using mapping tools available from the NHS Digital Technology Reference Update Distribution website[211].

iii) *NHS Business Services Authority (NHSBSA) Medicines Dataset*

NHSBSA Medicines contains information on medicines dispensed in primary care in England and Wales, including British National Formulary (BNF) medicine codes and the month of prescription processing[190]. Prescriptions that were issued but not dispensed are not included in the dataset.

Date precision was limited to the month of prescription processing (rather than a specific date). The following rules were applied regarding identifying event timing relative to randomisation:

- Pre-randomisation prescriptions: the processing month was before the participant's month of randomisation.

Pre-randomisation records were used to determine conditions that existed prior to randomisation for baseline characteristics or incident disease outcomes.

- Post-randomisation prescriptions: the processing month was after the participant's month of randomisation.

Post-randomisation records were used to determine outcome events that occurred after randomisation. For 28-day follow-up, prescriptions were counted in the 1 month after the month of randomisation. For 6-month follow-up, prescriptions were counted in the 6 months after the month of randomisation. Equivalent time periods were used for other follow-up time points.

- Peri-randomisation prescriptions: the processing month was the same as the participant's month of randomisation.

Peri-randomisation records were not used to determine assessments in the main analysis (although were investigated in sensitivity analyses). It was not possible to tell from the record whether these prescriptions occurred before or after randomisation.

3.3.2.5 Microbiology datasets

i) *UK Health Security Agency (UKHSA) dataset*

The UKHSA (formerly Public Health England) dataset derives details of positive microbiology sample results from the Second Generation Surveillance System (SGSS). SGSS is an application that captures, stores and manages data on infectious diseases from diagnostic laboratories in England[192]. Reporting through SGSS is a voluntary surveillance programme, but highly encouraged. Quality assessment data comparing ascertainment of SGSS with mandatory surveillance for *Staphylococcus aureus, Escherichia coli, Klebsiella* species, and *Pseudomonas aeruginosa* bloodstream

infections, found that 94% of cases reported via the mandatory surveillance scheme were also reported through SGSS[193].

For the extended analysis, data on microbiological isolates from blood cultures and respiratory tract specimens were available, including the sample collection date, specimen type, and organism identified. This data was used to identify the occurrence of non-COVID infections, and the sample collection date was used as the event date for analyses.

ii) *National Pathology Exchange (NPEx) COVID-19 UK non-hospital testing results*

The NPEx dataset contains results of SARS-CoV-2 antigen and polymerase chain reaction (PCR) testing conducted under pillar 2 of the government's testing programme[194]. This incorporates testing done outside of hospital through drive-through test centres, mobile testing units, home testing and care home testing. An overall result is given as 'Positive', 'Negative' or 'Unknown' using SNOMED concept IDs.

For the extended analysis, the overall result was used to identify time to viral clearance with the sample collection date used as the event date for analyses.

3.3.3 ISARIC4C

3.3.3.1 Study overview

ISARIC4C is a large cohort study that has collected comprehensive clinical data on over 200,000 hospitalised patients with COVID-19 in the UK, with biological sample data in a subset[196].

ISARIC4C data collection is structured in several 'tiers', giving different breadths and depths of insight into the disease:

i) Tier 0 - Clinical data collection only.

Clinical data was collected via the CRF, but no biological samples were obtained for the study. This data was collected without participant consent under specific regulations for the purposes of COVID-19 research (Section 3.7.1).

ii) Tier 1 - Single biological sample.

Samples were collected on the day of recruitment, in addition to the clinical data above (see Section 3.3.3.4 for the list of samples collected). Participants gave consent for the sample collection and use for COVID-19 research purposes.

iii) Tier 2 - Serial biological sampling.

Samples were collected, with consent, on the day of recruitment, study days 3, 9, and 14 during hospital admission, and convalescence (>28 days after hospital discharge).

3.3.3.2 Data linkage and use

The data linkage with ISARIC4C was novel for this thesis and was established through an information governance project facilitated by the thesis author (Section 3.7.2).

3.3.3.3 In-hospital structured CRF

The in-hospital structured CRF included data collection on:

i) Demographics, including age and sex.
ii) Admission signs and symptoms.
iii) Physiological measurements recorded on admission and daily for up to 14 days – including level of ventilatory support, fraction of inspired oxygen (FiO_2), oxygen therapy type, and oxygen saturations.
iv) Blood test results recorded on admission and daily for up to 14 days – including full blood count, alanine aminotransferase (ALT), glucose, creatinine, and CRP.
v) Infectious disease pathogen testing – date, sample type, microbiological test result, including SARS-CoV-2 testing.
vi) Biological samples collected (for Tier 1 and Tier 2 participants).

For the extended analysis, this data was used to derive exploratory biological assessments and subgroup analyses. CRF dates were mapped relative to individual participant randomisation dates to determine pre-and post- randomisation clinical and biological data.

3.3.3.4 Biological sampling

Biological sampling occurred in the consenting subset of participants in Tier 1 and Tier 2 at one or more time points (Section 3.3.3.1). At each time point, the following sample set was collected:

i) Respiratory samples – nasal synthetic absorptive matrix strip, throat and nose swab in viral transport medium, endotracheal aspirate if intubated for pathogen studies;
ii) Urine for pathogen studies;
iii) Stool for pathogen studies;
iv) Oral fluid for evaluation of patient humoral immune response;
v) Blood :
    - Serum – for biomarkers, serology;
    - Ethylenediaminetetraacetic acid (EDTA) – for biomarkers, pathogen nucleic acid, host dexoxyribonucleic acid (DNA) for genomic studies, cellular immunology;
    - Sodium citrate – for coagulation function;
    - Ribonucleic acid (RNA) tube – for microarray/RNA sequencing pathogen and host transcriptome.

For the extended analysis, the transcriptomic data was used to derive gene expression assessments. Sample collection dates were mapped relative to individual participant randomisation dates to determine sampling that occurred pre-and post-randomisation.

3.4 Long-term Follow-up Analysis Assessments

The final pre-specified long-term follow-up analysis assessments are summarised in Table 3-3 and their full definitions given below. The final clinical codelists used for each assessment are available in Appendix, Section B.2. Additional exploratory analyses were carried out after unblinding and preliminary analysis results and are presented and interpreted as such. All outcomes were assessed at 28 days and 6 months after randomisation unless otherwise stated.

Table 3-3: Summary of final long-term follow-up assessments used in the thesis extended analysis.

Assessment type	Assessment name	Time points assessed	Data sources
Primary outcomes	All-cause mortality (time to event)[1]	6 months	RECOVERY Hospital admission datasets Death datasets
	Time to first occurrence of major non-COVID infection[2]	28 days 6 months	Hospital admission datasets Death datasets Microbiology datasets RECOVERY
Secondary outcomes	Discharge alive from hospital (time to event)[1]	6 months	RECOVERY Hospital admission datasets
	Any non-COVID infection[2]	28 days 6 months	Hospital admission datasets Death datasets Primary care datasets Microbiology datasets RECOVERY
	Time to first occurrence of microbiologically confirmed non-COVID infection[2]	28 days 6 months	Microbiology datasets RECOVERY
	Time to first occurrence of bloodstream infection[2]	28 days 6 months	Microbiology datasets RECOVERY
	Long COVID[2]	18 months	Primary care datasets
	Time to first occurrence of gastrointestinal complication (bleeding, ulceration or perforation)[2]	28 days 6 months	Hospital admission datasets Death datasets RECOVERY
	Venous thromboembolism[2]	28 days 6 months	Hospital admission datasets Death datasets RECOVERY
Tertiary outcomes	Bacterial infection[2]	28 days 6 months	Hospital admission datasets Death datasets Primary care datasets Microbiology datasets RECOVERY
	Fungal infection[2]	28 days 6 months	Hospital admission datasets Death datasets Primary care datasets Microbiology datasets RECOVERY

	Time to first occurrence of metabolic complication (hyperglycaemia, hypoglycaemia or diabetic ketoacidosis)[2]	28 days 6 months	Hospital admission datasets Death datasets Primary care datasets RECOVERY
	Incident diabetes[2]	12 months	Hospital admission datasets Death datasets Primary care datasets
	Time to first occurrence of long bone or vertebral fracture[2]	28 days 6 months	Hospital admission datasets Death datasets Primary care datasets
	Psychiatric complications[2]	28 days 6 months	Hospital admission datasets Death datasets Primary care datasets
	Time to first occurrence of clinically-defined liver injury[2]	28 days 6 months	Hospital admission datasets Death datasets Primary care datasets
	Preserved ability to self-care at hospital discharge[2]	Time of discharge	ISARIC4C
Exploratory analyses	Diagnoses leading to death	6 months	Death datasets
	Hospital-recorded diagnoses (categorisation of primary diagnosis recorded in hospital)[1]	6 months	Hospital admission datasets
	Time to first occurrence of hyperglycaemia[2]	28 days	ISARIC4C
	Time to first occurrence of neutropenia[2]	28 days	ISARIC4C
	Time to first occurrence of biochemically-defined liver injury[2]	28 days	ISARIC4C
	Time to first occurrence of acute kidney injury[2]	28 days	ISARIC4C RECOVERY
	Time to viral clearance[2]	28 days	Microbiology datasets ISARIC4C
Subgroup analyses	Of primary outcomes by subgroups at randomisation: Age Time since illness onset Respiratory support Hospital Frailty Risk Score[3] Non-COVID infection baseline risk group[2] Use of corticosteroids and/or tocilizumab	28 days 6 months	RECOVERY Hospital admission datasets Primary care datasets
Sensitivity analyses	Of primary and secondary outcomes by: Restricting to primary diagnostic position codes from hospital admission datasets Inclusion of peri-randomisation episode diagnoses from hospital admission datasets Exclusion of respiratory tract infection diagnoses (non-COVID infection outcomes only)	28 days 6 months	RECOVERY Hospital admission datasets Death datasets Primary care datasets Microbiology datasets

[1]Derived as part of the main RECOVERY trial follow-up, not by the thesis author
[2]Novel derivation as part of thesis work by the thesis author
[3]Derived by the thesis author using codelists from Gilbert et al. (see Section 3.4.5.2).

3.4.1 Primary Outcomes

3.4.1.1 All-cause mortality

Information on mortality came from the RECOVERY follow-up CRFs, hospital admission datasets and mortality datasets.

The primary source of data for fact and date of death was the ONS and NRS mortality data as these represent the official national death registries.

Time to all-cause mortality was assessed at 6 months after randomisation as the primary efficacy outcome. As a post-hoc exploratory analysis, mortality was also assessed at 2 year follow-up.

3.4.1.2 Time to first occurrence of major non-COVID infection

Non-COVID infection that was associated with inpatient hospital care or death.

This was defined as any of the following;

i) Non-COVID infection ICD-10 diagnosis code (Appendix Section B.2.1.1) in any diagnostic position in a post-randomisation episode of hospital care (from HESAPC, SMR01 or PEDW).
ii) Non-COVID infection ICD-10 code recorded in part 1 of death certificate (from ONS or NRS mortality datasets).
    - A small number of 'pneumonia' codes only counted towards the outcome if there was no co-existent SARS-CoV-2 ICD-10 code from the death certificate*.
iii) Clinically important microbiological culture result: a positive blood or respiratory tract specimen (from UKHSA dataset) from a microbiological sample collected

* *Causes of death listed as "SARS-CoV-2 Pneumonia" frequently resulted in recording of both an ICD-10 code for SARS-CoV-2 and a separate code for Pneumonia (see Appendix Section B.2.1.1).*

after randomisation, excluding common contaminants and commensals from the site of specimen collection (Supplementary Table 5).

iv) Non-COVID infection recorded on RECOVERY 28-day follow-up CRF (for participants in the baricitinib and higher dose dexamethasone comparisons).

v) Hospital admission with non-COVID infection recorded on RECOVERY international site 6-month follow-up CRF (for participants in the higher dose dexamethasone comparison).

This assessment was the primary safety outcome.

In the baricitinib and higher dose dexamethasone comparisons, this assessment was assessed as a categorical outcome, rather than a time to event outcome, as no precise dates were available from the RECOVERY 28-day follow-up CRF.

3.4.2 Secondary Outcomes

3.4.2.1 Time to discharge alive from hospital

Time to discharge alive from hospital was assessed at 6 months after randomisation and was defined as the number of days a participant remained in hospital for acute care after randomisation. Discharge excluded transfer to another acute hospital but included transfer to community hospital for rehabilitation or a hospice for end-of-life care.

Information on date of discharge came from the RECOVERY follow-up CRF and hospital admission datasets. A participant was considered to have transferred between hospitals (i.e. not discharged) if there was another admission to a hospital on that, or the next, day where either the method or source of the admission recorded indicated transfer from another hospital. The first date of discharge which did not fulfil these criteria for an inter-hospital transfer after first or second randomisation was used to determine time to discharge.

3.4.2.2 Occurrence of any non-COVID infection

Any non-COVID infection, regardless of care location or outcome.

This was defined as any component of the definition of 'Time to first occurrence of major non-COVID infection' above, or additionally, any of the following:

i) Non-COVID infection SNOMED concept ID (Appendix Section B.2.3.1) from GDPPR or WLGP with a diagnosis date after randomisation, together with a clinically relevant concomitant antimicrobial prescription (from NHSBSA medicines dataset).
    - Non-COVID infection SNOMED concept IDs available were limited to respiratory tract infection (see Section 3.3.2.4).
    - Clinically relevant concomitant antimicrobial prescriptions included those for penicillin, amoxicillin, broad-spectrum beta-lactam antibiotics e.g. co-amoxiclav, macrolides, tetracyclines, sulphonamides or respiratory fluoroquinolones, as these are potentially indicated for respiratory tract infections in UK clinical practice.
    - A concomitant antimicrobial prescription could occur in the month of diagnosis or 1 month later (due to the structure of prescription processing dates by month within the NHSBSA medicines dataset, see Section 3.3.2.4).
ii) Prescribed antimicrobial BNF code from NHSBSA medicines dataset (Appendix Section B.2.4.1) occurring after the month of randomisation.
    - Participants who had 5 or more prescriptions for the same antimicrobial in the month of randomisation and 6 subsequent months (total 7 months) were excluded as these were felt likely relate to long-term use of an antimicrobial e.g. for prophylaxis, rather than a new episode of infection.

3.4.2.3 Time to first occurrence of microbiologically confirmed non-COVID infection

A non-COVID infection diagnosed by microbiological testing e.g. bacterial culture.

This was defined as:

i) Clinically important microbiological result: a positive blood or respiratory tract specimen (from UKHSA dataset) from a microbiological sample collected after randomisation. A clinically important microbiological culture result was typically any positive result except those that would be commonly considered a contaminant or commensal from the anatomical site of specimen collection (Supplementary Table 5).
ii) Bloodstream infection recorded on RECOVERY follow-up CRFs (for participants in the baricitinib and higher dose dexamethasone comparisons).
iii) Hospital admission with bloodstream infection recorded on RECOVERY international site 6-month follow-up CRF (for participants in the higher dose dexamethasone comparison).

In the baricitinib and higher dose dexamethasone comparisons, this assessment was assessed as a categorical outcome, rather than a time to event outcome, as no precise dates were available from the RECOVERY 28-day follow-up CRF.

3.4.2.4 Time to first occurrence of bloodstream infection

This was defined as:

i) Clinically important blood culture result (from UKHSA dataset) from a blood culture sample collected after randomisation, excluding common contaminants and commensals from the site of specimen collection (Supplementary Table 5).
ii) Bloodstream infection recorded on RECOVERY follow-up CRFs (for participants in the baricitinib and higher dose dexamethasone comparisons).

iii) Hospital admission with bloodstream infection recorded on RECOVERY international site 6-month follow-up CRF (for participants in the higher dose dexamethasone comparison).

In the baricitinib and higher dose dexamethasone comparisons, this assessment was assessed as a categorical outcome, rather than a time to event outcome, as no precise dates were available from the RECOVERY 28-day follow-up CRF.

3.4.2.5 Time to first occurrence of long COVID

Defined as:

i) The occurrence of a post-randomisation long COVID SNOMED concept ID (Appendix Section B.2.3.2) (from GDPPR or WLGP dataset).

Long COVID SNOMED concept IDs were not released for use in the NHS until November 2020, and did not begin to be used widely in UK primary care clinical coding until early 2021[212].

This assessment was evaluated at 18 months after randomisation.

3.4.2.6 Time to first occurrence of GI complication

GI complications included GI haemorrhage, ulceration, or perforation.

Defined as any of the following:

i) GI complication ICD-10 diagnosis code (Appendix Section B.2.1.2) in any diagnostic position in a post-randomisation episode of hospital care (from HESAPC, PEDW or SMR01).
ii) GI complication ICD-10 code recorded in part 1 of death certificate (from ONS or NRS mortality dataset).
iii) GI complication OPCS-4 procedure code (Appendix Section B.2.2.1) (from HESAPC, PEDW or SMR01).

iv) GI bleeding recorded on RECOVERY follow-up CRFs (for participants in the baricitinib and higher dose dexamethasone comparisons).

v) Hospital admission with GI bleeding recorded on RECOVERY international site 6-month follow-up CRF (for participants in the higher dose dexamethasone comparison).

In the baricitinib and higher dose dexamethasone comparisons, this assessment was assessed as a categorical outcome, rather than a time to event outcome, as no precise dates were available from the RECOVERY 28-day follow-up CRF.

3.4.2.7 Time to first occurrence of VTE

VTE included pulmonary embolism (PE), deep vein thrombosis (DVT), and other anatomical sites of thrombosis in non-superficial venous structures e.g. cerebral venous thrombosis or renal vein thrombosis.

Defined as any of the following:

i) VTE ICD-10 code (Appendix Section B.2.1.3) in the first diagnostic position in a post-randomisation episode of hospital care (from HESAPC, PEDW or SMR01).

ii) VTE ICD-10 code in any diagnostic position in a post-randomisation episode of hospital care, together with any of:
    - A post-randomisation anticoagulation prescription (Appendix Section B.2.4.2) (from GDPPR, WLGP or BSA medicines dataset);
    - Death within 28 days of diagnosis.

iii) VTE ICD-10 code recorded in part 1 of death certificate (from ONS or NRS mortality data).

iv) VTE recorded on RECOVERY 28-day follow-up CRF (for participants in the baricitinib and higher dose dexamethasone comparisons).

v) Hospital admission with VTE recorded on RECOVERY international site 6-month follow-up CRF (for participants in the higher dose dexamethasone comparison).

In the baricitinib and higher dose dexamethasone comparisons, this assessment was assessed as a categorical outcome, rather than a time to event outcome, as no precise dates were available from the RECOVERY 28-day follow-up CRF.

3.4.3 Tertiary Outcomes

3.4.3.1 Occurrence of bacterial infection

A non-COVID infection that was recorded as being of bacterial aetiology (either clinical diagnosis or microbiological confirmation), regardless of care location or outcome.

This was defined as any of the following:

i) Explicit bacterial infection ICD-10 code (Appendix Section B.2.1.1) in any diagnostic position in a post-randomisation episode of hospital care (from HESAPC, PEDW or SMR01).
ii) Explicit bacterial infection ICD-10 code recorded in part 1 of death certificate (from ONS or NRS mortality data).
iii) Clinically important bacteriology result (from UKHSA dataset), excluding common contaminants and commensals from the site of specimen collection (Supplementary Table 5).
iv) Explicit bacterial infection SNOMED concept ID (Appendix Section B.2.3.1) from GDPPR or WLGP dataset.
v) Anti-bacterial BNF code (Appendix Section B.2.4.1) (from NHSBSA dataset).
vi) Bacterial infection recorded on RECOVERY 28-day follow-up CRF (for participants in the baricitinib and higher dose dexamethasone comparisons).
vii) Hospital admission with bacterial infection recorded on RECOVERY international site 6-month follow-up CRF (for participants in the higher dose dexamethasone comparison).

3.4.3.2 Occurrence of fungal infection

A non-COVID infection that was recorded as being of fungal aetiology (either clinical diagnosis or microbiological confirmation), regardless of care location or outcome.

This was defined as any of the following:

i) Explicit fungal infection ICD-10 code (Appendix Section B.2.1.1) in any diagnostic position in a post-randomisation episode of hospital care (from HESAPC, PEDW or SMR01).
ii) Explicit fungal infection ICD-10 code recorded in part 1 of death certificate (from ONS or NRS mortality data).
iii) Clinically important mycology result (from UKHSA dataset), excluding common contaminants and commensals from the site of specimen collection (Supplementary Table 5).
iv) Explicit fungal infection SNOMED concept ID (Appendix Section B.2.3.1) from GDPPR or WLGP dataset.
v) Anti-fungal BNF code (Appendix Section B.2.4.1) (from NHSBSA dataset).
vi) Fungal infection recorded on RECOVERY 28-day follow-up CRF (for participants in the baricitinib and higher dose dexamethasone comparisons).
vii) Hospital admission with fungal infection recorded on RECOVERY international site 6-month follow-up CRF (for participants in the higher dose dexamethasone comparison).

3.4.3.3 Time to first occurrence of metabolic complication

Metabolic complications included hyperglycaemia, hypoglycaemia, and diabetic ketoacidosis.

Defined as any of the following:

i) Metabolic complication ICD-10 code (Appendix Section B.2.1.4) in any diagnostic position in a post-randomisation episode of hospital care (from HESAPC, PEDW or SMR01).
ii) Metabolic complication ICD-10 code recorded in part 1 of death certificate (from ONS or NRS mortality data).
iii) Metabolic complication SNOMED concept ID (Appendix Section B.2.3.4) from GDPPR or WLGP dataset.
iv) Metabolic complication recorded on RECOVERY 28-day follow-up CRF (for participants in the higher dose dexamethasone comparison).

In the higher dose dexamethasone comparison, this assessment was assessed as a categorical outcome, rather than a time to event outcome, as no precise dates were available from the RECOVERY follow-up CRF.

3.4.3.4 Occurrence of incident diabetes

A new diagnosis of diabetes mellitus.

Participants with baseline (pre-existing) diabetes mellitus were excluded from the analysis of this outcome, defined as any of the following:

i) RECOVERY trial dataset baseline diabetes mellitus listed as 'Yes' (from randomisation CRF).
ii) Diabetes mellitus ICD-10 code (Appendix Section B.2.1.5) in any diagnostic position in any pre-randomisation episode of hospital care (from HESAPC, PEDW or SMR01).
iii) Diabetes mellitus SNOMED Concept ID (Appendix Section B.2.3.5) with a diagnosis date at any time prior to the date of randomisation (from GDPPR or WLGP dataset).
iv) HbA1c ≥48 mmol/mol with a date at any time prior to the date of randomisation (from GDPPR or WLGP dataset).

v) Blood glucose ≥11.1 mmol/L with a date at any time prior to the date of randomisation (from GDPPR or WLGP dataset).
vi) Prescription of insulin or anti-diabetic medication (excluding metformin and SGLT-2 inhibitors, which may have other indications for use outside of diabetes) (Appendix Section B.2.3.5; Section B.2.4.3) with a prescription date or processing month prior to the date or month of randomisation (from GDPPR or WLGP, or NHSBSA datasets respectively).

Incident diabetes mellitus was defined as any of the following:

i) Diabetes mellitus ICD-10 code in any diagnostic position in a post-randomisation episode of hospital care (from HESAPC, PEDW or SMR01).
ii) Diabetes mellitus ICD-10 code recorded in part 1 or part 2 of death certificate (from ONS or NRS mortality data).
iii) Diabetes mellitus diagnosis SNOMED Concept ID (from GDPPR or WLGP dataset).
iv) HbA1C ≥48 mmol/mol (from GDPPR or WLGP dataset).
v) Blood glucose ≥11.1mmol/L (from GDPPR or WLGP dataset).
vi) New prescription of insulin or anti-diabetic medication, excluding metformin and SGLT-2 inhibitors (from GDPPR, WLGP or NHSBSA datasets).

This assessment was evaluated at 12 months after randomisation to allow time for a diagnosis of diabetes to be made and relevant codes to be entered in the datasets.

3.4.3.5 Time to first occurrence of long bone or vertebral fracture

Long bone or vertebral fracture included fracture of any part of the spine, humerus, radius, ulna, pelvis, femur, tibia, or fibula.

Defined as any of the following:

i) Long bone or vertebral fracture ICD-10 code (Appendix Section B.2.1.6) in any diagnostic position in a post-randomisation episode of hospital care (from HESAPC, PEDW or SMR01).
ii) Long bone or vertebral fracture ICD-10 code recorded in part 1 of death certificate (from ONS or NRS mortality data).
iii) Long bone or vertebral fracture OPCS-4 procedure code (Appendix Section B.2.2.2) (from HESAPC, PEDW or SMR01).
    - For non-specific fracture OPCS-4 procedure codes, an anatomical location OPCS-4 procedure code was sought from the same episode of care that confirmed whether the fracture was of a long bone or vertebra.
iv) Long bone or vertebral fracture SNOMED concept ID (Appendix Section B.2.3.6) in primary care record (from GDPPR or WLGP dataset).

3.4.3.6 Occurrence of psychiatric complication

Psychiatric complications included acute confusional state, psychotic episode, manic episode, or new prescription of anti-psychotic medication.

Defined as any of the following:

i) Psychiatric complication ICD-10 code (Appendix Section B.2.1.7) in any diagnostic position in a post-randomisation episode of hospital care (from HESAPC, PEDW or SMR01).
ii) Psychiatric complication ICD-10 code recorded in part 1 of death certificate (from ONS or NRS mortality data).
iii) Psychiatric complication SNOMED concept ID (Appendix Section B.2.3.7) in primary care record (from GDPPR or WLGP dataset).
iv) New prescription of anti-psychotic medication (Appendix Section B.2.3.7; Section B.2.4.4) in participants who had no previous record of anti-psychotic medication in the 6 months prior to randomisation (from GDPPR, WLGP or NHSBSA datasets).

3.4.3.7 Time to first occurrence of clinically-defined liver injury

Clinically-defined liver injury included acute liver failure, acute hepatitis, or aminotransferase result ≥5x upper limit of normal[213].

Defined as any of the following:

i) Liver injury ICD-10 code (Appendix Section B.2.1.8) in any diagnostic position in a post-randomisation episode of hospital care (from HESAPC, PEDW or SMR01).
ii) Liver injury ICD-10 code recorded in part 1 of death certificate (from ONS or NRS mortality data).
iii) Aminotransferase result ≥5x upper limit of normal (Appendix Section B.2.3.8) (from GDPPR or WLGP dataset).

3.4.3.8 Preserved ability to self-care at hospital discharge

Defined as the response to the question 'Ability to self-care at discharge versus before illness' on the ISARIC4C CRF.

The responses were split into a binary variable where:

- Responses 'Same as before illness' or 'Better' were classified as "Same or better" and counted as the outcome being present.
- Response 'Worse' was classified as "Worse" and counted as the outcome being absent.

This outcome was assessed in the subset of participants in the RECOVERY-ISARIC population for each comparison who had data for this assessment.

3.4.4 Exploratory analyses

3.4.4.1 Diagnoses leading to death

Diagnoses recorded in any aspect of part 1 of a participant's death certificate, who died within 6 months of randomisation, were extracted from ONS and NRS mortality data in the form of ICD-10 codes. A death certificate consists of two parts - with part 1 outlining the

sequence leading to death and the underlying cause[214]. The sequence leading to death includes all conditions recorded in any line of part 1. The underlying cause of death is represented by the lowest completed line of part 1 of the death certificate. Part 2 represents conditions that contributed but were not part of the direct sequence leading to death.

For the extended analysis, all ICD-10 codes listed in part 1 of the death certificate (i.e. all diagnoses included in the sequence leading to death) were included and tabulated by the categories defined in the main trial for analysis of cause-specific mortality (Table 3-4). The analysis of cause-specific mortality in the main trial used only the underlying cause of death within 28 days.

Table 3-4: Categories of diagnoses leading to death and hospital-recorded diagnoses.

Category	Sub-category	Additional sub-category*
COVID-19		
Other infection	Skin soft tissue	Bacterial/Fungal/Viral/TB/Other/Unspecified
	Abdominal	Bacterial/Fungal/Viral/TB/Other/Unspecified
	Respiratory	Bacterial/Fungal/Viral/TB/Other/Unspecified
	Bone and joint	Bacterial/Fungal/Viral/TB/Other/Unspecified
	Urinary	Bacterial/Fungal/Viral/TB/Other/Unspecified
	Bloodstream	Bacterial/Fungal/Viral/TB/Other/Unspecified
	Other	Bacterial/Fungal/Viral/TB/Other/Unspecified
	Unspecified	Bacterial/Fungal/Viral/TB/Other/Unspecified
Cardiovascular	Cardiac	MI/other CHD/Heart failure/other cardiac
	Stroke	Haemorrhagic/ischaemic/unknown
	Other vascular	Arterial thrombo-embolism/venous thromboembolism/other vascular
Other	Cancer	
	Diabetes	
	Extra-cranial bleed or perforation	GI/other
	Liver	
	Renal	
	Respiratory (not infection)	
	Other medical cause	
External		
Unknown		
**Further division of 'Sub-category' column*		

3.4.4.2 Hospital-recorded diagnoses

Diagnoses recorded as the primary reason for a period of in-hospital care within 6 months of randomisation were extracted from HESAPC, SMR01 and PEDW. ICD-10 codes were

restricted to the first diagnostic position and codes in other positions were not considered. ICD-10 codes within the same block (e.g. I25.1 and I25.2) were considered to relate to the same hospital-recorded diagnosis. For each hospital spell the first ICD-10 code recorded within the relevant block was extracted along with a start and end date. The start date was defined as the start of the first episode in which an ICD-10 code in the relevant block was recorded within that spell. The end date was defined as the end of the episode in which an ICD-10 code in the relevant block was recorded within that spell. The start date for each diagnosis extracted from the hospital admission dataset was used for time-to-event analyses.

Diagnoses for which the first record in that spell was in an episode which started after randomisation were considered to be post-randomisation and were used for the analyses.

Diagnoses were tabulated by the categories defined in the main trial for analysis of cause-specific mortality (Table 3-4). Additional subcategories were considered with any categories containing a small number of events (e.g. fewer than 10) combined with other relevant categories.

3.4.4.3 Time to first occurrence of neutropenia

Neutropenia was defined as an absolute neutrophil count of <1.8 $x10^9$/L (the diagnostic threshold recommended in adult patients[215]). Full blood count results, including the absolute neutrophil count, were recorded up to once daily from ISARIC4C enrolment for 14 days, or until hospital discharge, or death, on the ISARIC4C CRF. The recorded values were cleaned and converted to the same units (cell count $x10^9$/L). Negative neutrophil values were removed and neutrophil count values >200 $x10^9$/L were assigned a maximum value of 200 $x10^9$/L.

This assessment was evaluated at 28 days after randomisation in the RECOVERY-ISARIC population.

3.4.4.4 Time to first occurrence of hyperglycaemia

Hyperglycaemia was defined as a recorded value of glucose of ≥11.1 mmol/L (the diagnostic threshold recommended for consideration of diabetes[216]). Glucose was recorded up to once daily from ISARIC4C enrolment for 14 days, or until hospital discharge, or death, on the ISARIC4C CRF. The recorded values were cleaned and converted to the same units (mmol/L). Negative glucose values were removed and glucose values >50 mmol/L were assigned a maximum value of 50 mmol/L.

This assessment was evaluated at 28 days after randomisation in the RECOVERY-ISARIC population.

3.4.4.5 Time to first occurrence of biochemically-defined liver injury

Biochemically-defined liver injury was defined as an ALT value ≥225 IU/L (approximately 5 times the upper limit of normal range). ALT was recorded up to once daily from ISARIC4C enrolment for 14 days, or until hospital discharge, or death, on the ISARIC4C CRF. The recorded values were cleaned and converted to the same units (IU/L). Negative ALT values were removed and ALT values >5000 IU/L were assigned a maximum value of 5000 IU/L.

This assessment was evaluated at 28 days after randomisation in the RECOVERY-ISARIC population.

3.4.4.6 Time to first occurrence of acute kidney injury (AKI)

AKI was defined as a ≥1.5 fold increase in serum creatinine from baseline (the diagnostic threshold used to define AKI[217]). Baseline creatinine was defined as the closest creatinine measurement available before randomisation. Creatinine was recorded up to once daily from ISARIC4C enrolment for 14 days, or until hospital discharge, or death, on the ISARIC4C CRF, and on the RECOVERY randomisation CRF for some participants. The recorded values were cleaned and converted to the same units (µmol/L). Negative

creatinine values were removed and creatinine values >1000 µmol/L were assigned a maximum value of 1000 µmol/L.

This assessment was evaluated at 28 days after randomisation in the RECOVERY-ISARIC population.

3.4.4.7 Time to viral clearance

Viral clearance was defined as a SARS-CoV-2 test of any type that was recorded as negative (from the ISARIC4C CRF or NPEx dataset).

This assessment was evaluated at 28 days after randomisation and was restricted to participants who had a repeat SARS-CoV-2 test within 28 days of randomisation in the RECOVERY-ISARIC population.

3.4.5 Additional baseline characteristics

Additional baseline characteristics for the extended analysis were derived from RCD sources.

3.4.5.1 Immunosuppression

The presence or absence of baseline immunosuppression was obtained from the hospital admission or primary care datasets according to a defined list of ICD-10, OPCS-4, SNOMED or BNF codes. The categories and codes selected were based on immunosuppression categories from the Chief Medical Officer for England for patients identified as being at very high risk of hospitalisation for COVID-19[218], and the Green Book criteria for immunosuppression due to disease or treatment[219].

Participants were coded as having immunosuppression at baseline if they had any of the following:

i) Cancer undergoing active chemotherapy: Cancer diagnosis ICD-10 code (Appendix Section B.2.1.9) in any diagnostic position in the 5 years prior to randomisation AND chemotherapy ICD-10 (Appendix Section B.2.1.9) or OPCS-4

code (Appendix Section B.2.2.3) in any diagnostic position in the 6 months prior to randomisation (from HESAPC, PEDW or SMR01).

ii) Haematological malignancy or bone marrow transplant: Haematological malignancy or transplant ICD-10 code (Appendix Section B.2.1.9) in any diagnostic position or OPCS-4 code (Appendix Section B.2.2.3) in the 2 years prior to randomisation (from HESAPC, PEDW or SMR01).

iii) Solid organ transplant: solid organ transplant ICD-10 (Appendix Section B.2.1.9) or OPCS-4 code (Appendix Section B.2.2.3) in any diagnostic position in the 5 years prior to randomisation (from HESAPC, PEDW or SMR01).

iv) Hyposplenism: hyposplenism ICD-10 (Appendix Section B.2.1.9) or splenectomy OPCS-4 code (Appendix Section B.2.2.3) in any diagnostic position in the 5 years prior to randomisation (from HESAPC, PEDW or SMR01).

v) Other immunosuppression: other long-term immunosuppression ICD-10 code (Appendix Section B.2.1.9) in any diagnostic position in the 5 years prior to randomisation or other short-term immunosuppression ICD-10 code (Appendix Section B.2.1.9) in any diagnostic position or OPCS-4 code (Appendix Section B.2.2.3) in the 6 months prior to randomisation (from HESAPC, PEDW or SMR01).

vi) Permanent immunosuppression SNOMED code (Appendix Section B.2.3.9) in the 2 years prior to randomisation (from GDPPR or WLGP).

vii) Temporary immunosuppression SNOMED code (Appendix Section B.2.3.9) in the 6 months prior to randomisation (from GDPPR or WLGP).

viii) Immunosuppressive drug SNOMED (Appendix Section B.2.3.9) or BNF code (Appendix Section B.2.4.5) in the 6 months prior to randomisation (from GDPPR, WLGP or NHSBSA Medicines).

If a participant had no immunosuppression code in any of the hospital admission or primary care datasets but did have a record at any time point in any of these datasets,

they were classified as not having immunosuppression. If a participant did not have a record at any time point in a hospital admission or primary care dataset they were classified as immunosuppression status 'Unknown'.

3.4.5.2 Hospital Frailty Risk Score (HFRS)

The presence and quantification of frailty was derived from a published risk score - the HFRS, which was developed and validated in over 1 million patients using HES records[220]. The score uses a list of 109 weighted ICD-10 codes (Appendix Section B.2.1.10) that were found to be most strongly associated with frailty and then validated as associated with worse clinical outcomes in terms of mortality, prolonged hospitalisation, and readmission.

The score for each participant in the 2 years prior to randomisation from HESAPC, PEDW or SMR01 ICD-10 codes was summed to give a total score which was then divided into ordinal categories; Low risk (score <5), Intermediate risk (5-15) and High risk (>15). This categorical division and look-back time period was used in the original HFRS development and validation study[220].

If a participant had no HFRS codes but did have a record at any time point in a hospital admission dataset they were classified as having a score of 0. If a participant did not have a record at any time point in a hospital admission dataset, they were classified as HFRS 'Unknown'.

3.4.5.3 Severe mental illness

The presence or absence of baseline severe mental illness (bipolar affective disorder, psychosis, schizophrenia, schizoaffective disorder, or severe depression) was obtained from hospital admission, or primary care datasets, according to a defined list of ICD-10 codes (Appendix Section B.2.1.11) and SNOMED concept IDs (Appendix Section B.2.3.10). The codes selected were based on the codelist published for the NHS COVID-

19 Population Risk Assessment Tool[221] which used methodology from the QCOVID risk prediction algorithm[222].

Participants were defined as having severe mental illness at baseline if they had an ICD-10 severe mental illness code (from HESAPC, PEDW or SMR01) in any diagnostic position, or a SNOMED severe mental illness concept ID (from GDPPR or WLGP) in the 5 years prior to randomisation.

If a participant had no severe mental illness code in either codelist but did have a record at any time point in the hospital admission, GDPPR or WLGP datasets, they were classified as not having severe mental illness. If a participant did not have a record at any time point in these datasets, they were classified as severe mental illness status 'Unknown'.

3.4.6 Subgroup analyses

Pre-specified subgroup analyses were conducted for the following outcomes at 28 days and 6 months after randomisation:

i) All-cause mortality;

ii) Time to first occurrence of major non-COVID infection.

The following subgroups were examined based on information at randomisation:

i) Age (<70; 70-79; ≥80 years);

ii) Time since illness onset (≤7 days; >7 days);

iii) Requirement for respiratory support at baseline (None; Oxygen only; Non-invasive ventilation; Invasive mechanical ventilation);

iv) Predicted non-COVID infection Risk Group: three risk groups with approximately equal number of non-COVID infections based on factors recorded at randomisation (see Section 3.6.7.3);

v) HFRS (Low risk; Intermediate risk; High risk): a RCD-derived assessment of frailty based on recorded ICD-10 codes prior to randomisation (see Section 3.4.5.2)

vi) Use of corticosteroids (for the tocilizumab comparison) and/or tocilizumab (for the baricitinib and higher dose dexamethasone comparisons);

Baseline characteristics for the trial cohort were obtained from the randomisation CRF or derived from RCD (Section 3.4.5).

Further post-hoc exploratory analyses were examined in the following subgroups:

i) Immunosuppression at baseline (Yes; No): derived from RCD sources (see Section 3.4.5.1);

ii) Non-COVID infection (Yes; No) at baseline: according to the presence or absence of evidence of major non-COVID infection in the 7 days prior to randomisation, derived from the major non-COVID infection outcome (see Section 3.4.1.2);

iii) Diabetes mellitus (Yes; No): according to the presence or absence of evidence of diabetes mellitus at baseline derived for the incident diabetes outcome (see Section 3.4.3.4). This subgroup analysis was examined in the dexamethasone and higher dose dexamethasone comparisons only.

3.4.7 Sensitivity analyses

The following planned sensitivity analyses were carried out for the primary and secondary outcomes:

3.4.7.1 Restricting to first diagnostic position events

For the primary and secondary outcomes, by restricting the diagnostic code position that the outcome was derived from within the hospital admission datasets to the first diagnostic position only (see Section 3.3.2.2).

3.4.7.2 Inclusion of peri-randomisation episode events

For the primary and secondary outcomes, by including events that occurred within the hospital admission episode that the patient was randomised within (i.e. peri-randomisation episode events, see Section 3.3.2.2).

3.4.7.3 Removal of respiratory tract infection events

For the primary and secondary infection outcomes, by excluding respiratory tract infection events. Planned on the basis that clinically diagnosed respiratory tract infections and healthcare record coding entries may be indistinguishable from deterioration of underlying COVID-19 disease.

3.5 Exploratory Analysis Assessments

3.5.1 Outcome selection and classification

Physiological measurements, commonly-measured blood biomarkers and gene expression data assessments (collectively termed 'biological assessments') were pre-specified for evaluation based on clinical discussion, the systematic review and meta-analysis, and data availability. The analysis of candidate assessments needed to have potential for clinical or research utility, or to improve knowledge of the underlying biological mechanisms of treatment effect.

Within the evaluation of the biological assessments, the assessments of ordinal scale score and CRP were pre-specified as being of greatest interest to the clinical trajectory of acute COVID-19 disease and are presented and interpreted as such, although all assessments in this section of the analysis are exploratory. Further post-hoc exploratory analyses were performed, based on the preliminary results from the pre-specified long-term follow-up and exploratory analysis assessments.

3.5.2 Physiological measurements

3.5.2.1 Daily rate of change in ordinal scale score

Defined as the subject-specific slope between baseline and study day 7 (where study day 1 is the date of randomisation) using all available measurements of ordinal scale score for that participant.

An 8-point ordinal scale was derived according to a participant's oxygenation requirement and vital status on each relevant study day, using data from the ISARIC4C CRF and RECOVERY (Table 3-5).

Table 3-5: Definition of the ordinal scale score used in the extended analysis.

Ordinal Scale Score	Description
1	Discharged alive from hospital
2	In hospital, no supplemental oxygen
3	Low oxygen requirement: FiO_2 > 0.21 & ≤ 0.32
4	Moderate oxygen requirement: FiO_2 > 0.32 & < 0.50
5	High oxygen requirement: FiO_2 ≥ 0.50
6	On non-invasive ventilation or high flow nasal oxygen
7	On invasive mechanical ventilation
8	Death
FiO_2= Fraction of inspired oxygen.	

The daily ordinal scale score was derived according to the following variables and data sources:

i) RECOVERY:

- All-cause mortality outcome and study day of death.
- Discharged alive from hospital outcome and study day of discharge.
- Respiratory support status at randomisation.

ii) ISARIC4C CRF daily assessment form – recorded up to once daily from ISARIC4C enrolment for 14 days, or until hospital discharge or death:

- Use of invasive ventilation or extra corporal membrane oxygenation.
- Use of non-invasive ventilation.
- Use of high flow nasal oxygen.
- Use of oxygen therapy.
- FiO_2 value.
- Percentage of inspired oxygen (converted to FiO_2 by dividing by 100).
- L/min of inspired oxygen (converted to FiO_2 using the following ISARIC4C study data processing conversion of L/min ~ FiO_2: 0 ~ 0.21; ≤ 2 ~ 0.24; ≤ 3 ~ 0.28; ≤ 4 ~ 0.32; ≤ 5 ~ 0.36; ≤ 6 ~ 0.40; ≤ 10 ~ 0.50; ≤ 15 ~ 0.70).

The baseline ordinal scale score measurement was defined as the ordinal scale score on the day of randomisation or the closest measurement within 5 days prior to randomisation.

The ordinal scale score was treated as a continuous variable in the daily rate of change analysis. This assessment was evaluated in the RECOVERY-ISARIC population.

3.5.2.2 Ordinal scale score at study day 5

Defined using the same categories as above, according to the following prioritisation:

i) Any ordinal scale score value on study day 5;
ii) Any ordinal scale score value on study day 4 or study day 6;
iii) An ordinal scale score of 1 (discharged alive from hospital) or 8 (death) on study day 3, study day 2 or study day 1.

The ordinal scale score was treated as an ordinal variable in the day 5 follow-up analysis. This evaluation was restricted to participants with an ordinal scale score at study day 5 in the RECOVERY-ISARIC population.

3.5.3 Commonly-measured blood biomarkers

Commonly-measured blood biomarker measurements were recorded up to once daily from ISARIC4C enrolment for 14 days, or until hospital discharge or death, on the ISARIC4C CRF.

The assessments were evaluated in the RECOVERY-ISARIC population of each treatment comparison.

3.5.3.1 Daily rate of change in CRP

Defined as the subject-specific slope between baseline and study day 7 using all available measurements of CRP for that participant.

Recorded values were cleaned and converted to the same units (mg/L). Negative CRP values were removed and CRP values >500mg/L were assigned a maximum value of 500mg/L.

The baseline CRP measurement was defined as the CRP on the day of randomisation or the closest measurement within 5 days prior to randomisation and could be derived from the RECOVERY randomisation CRF or the ISARIC4C CRF.

3.5.3.2 Daily rate of change in neutrophil:lymphocyte ratio (NLR)

Defined as the subject-specific slope between baseline and study day 7 using all available measurements of NLR for that participant. NLR was calculated as neutrophil count/lymphocyte count.

Recorded values were cleaned and converted to the same units (cells $x10^9$/L). Negative neutrophil or lymphocyte values were removed and neutrophil or lymphocyte count values >200 $x10^9$/L were assigned a maximum value of 200 $x10^9$/L.

The baseline NLR measurement was defined as the NLR on the day of randomisation or the closest measurement within 5 days prior to randomisation from the ISARIC4C CRF.

3.5.3.3 Daily rate of change in creatinine

Defined as the subject-specific slope between baseline and study day 7 using all available measurements of creatinine for that participant.

Recorded values were cleaned and converted to the same units (µmol/L).

The baseline creatinine measurement was defined as the creatinine measurement on the day of randomisation or the closest measurement within 5 days prior to randomisation and could be derived from the RECOVERY randomisation CRF or the ISARIC4C CRF.

3.5.3.4 Daily rate of change in glucose

Defined as the subject-specific slope between baseline and study day 7 using all available measurements of glucose for that participant.

Recorded values were cleaned and converted to the same units (mmol/L).

The baseline glucose measurement was defined as the glucose measurement on the day of randomisation or the closest measurement within 5 days prior to randomisation from the ISARIC4C CRF.

3.5.3.5 Daily rate of change in ALT

Defined as the subject-specific slope between baseline and study day 7 using all available measurements of ALT for that participant.

Recorded values were cleaned and converted to the same units (IU/L).

The baseline ALT measurement was defined as the ALT measurement on the day of randomisation or the closest measurement within 5 days prior to randomisation from the ISARIC4C CRF.

3.5.4 Gene expression data

3.5.4.1 Differential gene expression

RNA Sequencing (RNA-Seq) data from peripheral blood was available for Tier 1 and Tier 2 ISARIC4C participants and was recorded at ISARIC4C study day enrolment and 3, 9 or 14 days later.

Log-fold changes in gene expression were compared between randomised groups at day 3 after randomisation using differential expression analysis[223]. This assessment was restricted to participants who had gene expression data available at day 3 after randomisation in the RECOVERY-ISARIC dexamethasone comparison population. There was insufficient gene expression data to analyse other treatment comparisons.

3.5.4.2 Enrichment analysis

To aid the interpretation of the differential gene expression results the representation of differentially expressed genes were considered in different gene sets:

i) Unselected whole genome biological processes using a publicly-available database – the Gene Ontology database[224,225].

ii) Selected gene sets of interest: identified a priori from external research studies and gene lists were extracted from published reports (Appendix Section B.3):

- Genes that were differentially expressed between short-term oral prednisolone and placebo in a randomised trial[226];
- Genes that were putatively causally associated with the development of severe COVID-19 from Mendelian Randomisation studies[20,227,228];
- Genes that were putatively causally associated with the development of severe COVID-19 from transcriptome-wide association studies with meta-analysis (metaTWAS)[228];
- Genes that were differentially expressed by COVID-19 severity in observational studies[229,230].

The gene sets that were putatively causally associated with the development of severe COVID-19 were assessed as primary outcomes in this analysis in order to evaluate the hypothesis that a small, randomised trial using gene expression data at short-term follow-up could be used to infer evidence of efficacy of treatment based on reversal of putatively causal gene expression changes. The gene sets associated with COVID-19 severity from the observational studies were analysed as supplementary outcomes (as a causal association could not be inferred). The gene set from the prednisolone randomised trial was analysed as a positive control gene set, expected to demonstrate evidence of an effect of dexamethasone treatment.

3.5.5 Subgroup analyses

3.5.5.1 ISARIC4C inclusion

An assessment of the RECOVERY-ISARIC4C population representativeness in each treatment comparison was performed by analysing the outcome of 28-day mortality according to subgroups defined by inclusion or not in ISARIC4C. This approach aimed to

assess for any evidence of a difference in the RECOVERY-ISARIC population compared with the whole treatment comparison for the main RECOVERY primary outcome.

3.5.5.2 Extended baseline respiratory support

An additional pre-specified exploratory subgroup analysis was carried out for the outcome of all-cause mortality within 28 days in the dexamethasone comparison, using an extended categorisation of respiratory support at baseline from ISARIC4C: (None; Low or moderate oxygen (FiO_2 >0.21 & <0.50); High oxygen (FiO_2 ≥0.5); Non-invasive ventilation or high-flow nasal oxygen; invasive mechanical ventilation). The baseline categories of extended baseline respiratory support were derived in the same way as the equivalent baseline ordinal scale score values (see Section 3.5.2.1).

3.5.5.3 Physiological measurements and commonly-measured blood biomarkers

For the outcomes of daily rate of change in ordinal scale score and daily rate of change in CRP from baseline to study day 7, subgroups were examined based on the requirement for respiratory support at baseline (None; Oxygen only; Non-invasive ventilation; Invasive mechanical ventilation (including ECMO).

Further subgroups were examined in outcomes of interest based on the preliminary results of the long-term follow-up and exploratory analysis.

3.5.6 Sensitivity analyses

The following sensitivity analyses were carried out for the assessments of daily rate of change in ordinal scale score, CRP, NLR, creatinine, glucose and ALT:

3.5.6.1 Varying follow-up time

The follow-up time for which the subject-specific daily rate of change slope was calculated was changed to between baseline and study day 14, and between baseline and study day 28. The main analysis used the follow-up time between baseline and study day 7.

3.5.6.2 Varying analysis method

The analysis method for these outcomes was changed to using complete case analysis. The main analysis used multiple imputation methods (see Section 3.6.10).

3.6 Statistical Methods

3.6.1 Baseline comparability of randomised groups

For all analyses, the intention-to-treat population (all participants randomised, irrespective of treatment received) was used wherever possible. For assessments that were derived from ISARIC4C data, all RECOVERY participants who had linked data in ISARIC4C in that treatment comparison were included (the 'RECOVERY-ISARIC population'). For some assessments for which data was only available for a subset of the RECOVERY-ISARIC population, all participants for whom data was available were included and are presented and interpreted considering the impacts of these analysis population subsets.

The following baseline characteristics were described separately for patients randomised to each treatment comparison within the relevant analysis population:

i) Age;

ii) Sex;

iii) Time since COVID-19 symptoms onset;

iv) Time since hospitalisation;

v) Current respiratory support;

vi) Comorbidities (diabetes, heart disease, chronic lung disease, tuberculosis, HIV, severe liver disease, severe kidney impairment, immunosuppression, severe mental illness);

vii) HFRS (Section 3.4.5.2);

viii) Use of systemic corticosteroid (including those allocated to corticosteroid);

ix) Use of other relevant treatments (e.g. IL-6 RA).

For continuous variables, the mean (standard deviation) is presented unless the variable had a skewed distribution, in which case the median (interquartile range [IQR]) was used. For all categorical variables, the number and percentage of participants in the category are presented.

In the dexamethasone and baricitinib comparison populations, there was a known small age imbalance between the treatment groups, occurring by chance during simple randomisation. Participants allocated dexamethasone were a mean of 1.1 years older than participants allocated usual care[29], and participants allocated baricitinib were a mean of 0.8 years older than participants allocated usual care[31]. Age and respiratory support at randomisation were the strongest determinants of clinical outcome risk. Therefore, analysis methods adjusting for age and respiratory support group at randomisation were planned for all treatment comparisons.

In sub-population analyses, if there were any important imbalances between the randomised groups in key baseline subgroups, analyses were adjusted for the relevant baseline characteristic(s) in addition to age and respiratory support status and this is clearly stated in the results.

3.6.2 Analysis of time to event outcomes

For all treatment comparisons, time-to-event analyses were conducted using a Cox regression model adjusted for:

i) Baseline age in three categories (<70 years, 70 to 79 years and ≥80 years).

ii) Baseline respiratory support status in four categories when available (None; Oxygen only; Non-invasive ventilation; Invasive mechanical ventilation):

- For the dexamethasone comparison, data regarding non-invasive ventilation is not available, so the 'Oxygen only' and 'Non-invasive ventilation' categories were combined to give a single 'Oxygen, non-invasive ventilation unknown' category.
- For the tocilizumab comparison, only 9 participants did not require oxygen or ventilation, so the 'None' and 'Oxygen only' groups were combined to give a single 'No ventilator support' category.

The Cox regression model estimates adjusted hazard ratios, with 95% CIs and p-values (based on the Wald chi-square statistic[231]) reported. The proportional hazards assumption was checked by examining plots of the scaled Schoenfeld residuals against time and testing the Schoenfeld residuals for independence with time.

3.6.2.1 Censoring rules

The day of randomisation was defined as study day 1. Unless otherwise stated, participants were censored at the earliest of death, withdrawal of consent, exit from the NHS date (if available) or on study day 28 (for 28-day analyses), study day 184 (for 6-month analyses), or equivalent for longer-term follow-up.

For the outcome of all-cause mortality at 6 months, participants were censored at the earliest of withdrawal of consent, or study day 184. For the outcome of time to discharge alive from hospital at 6 months, participants were censored at the earliest of withdrawal of consent, or study day 184. Patients who died in hospital were censored after 6 months after randomisation in order to achieve an unbiased estimate of the recovery rate[232].

3.6.2.2 Competing risks

Many of the planned assessments required consideration of the impact of competing risks. For example, if a participant died this precluded them from developing a different outcome of interest, such as a treatment-related harm. There was a known differential risk of short-term mortality in active treatment groups of the immunomodulatory treatment comparisons. The primary analysis approach selected was to use a cause-specific hazard estimate from Cox Regression with censoring at time of death. This approach was in line with the thesis aims and well-suited to addressing aetiological research questions relating to treatment effects in RCTs (for example, “Does immunomodulatory treatment cause an increased risk of non-COVID infections?”), providing the cause-specific hazard for the competing risk (death) was also reported[233]. Alternative approaches, such as the cumulative incidence function, were considered for this study but as the

immunomodulatory treatments were known to alter the risk of short-term mortality, the cumulative incidence function may result in a biased estimate of the aetiological effect of treatment on other outcomes[234]. For categorical outcomes, the potential impact of competing risks was considered in the interpretation of results.

3.6.3 Analysis of categorical outcomes

For all treatment comparisons, age- and respiratory support-adjusted log-binomial regression models were constructed for the estimation of adjusted risk ratios, with 95% CIs and p-values reported.

3.6.4 Analysis of continuous outcomes

The mean daily rate of change (slope) was compared between randomised groups from randomisation to study day 7 using a linear regression model, where the subject-specific slope value is the outcome variable, adjusted for age group and respiratory support at randomisation. Subject-specific slope values were computed as the gradient of a linear regression model of all available participant measurements between study day 1 and study day 7, adjusted for baseline value, when available, for that assessment.

This approach allowed for 'informative censoring' in the daily rate of change analyses, based on the direction and magnitude of the subject-specific slope prior to an informative mechanism of subsequent missing data, such as death or hospital discharge, in contrast to alternative approaches, such as mixed models with repeat measures which do not allow for informative censoring[235,236].

3.6.5 Analysis of ordinal outcomes

For all treatment comparisons, age- and respiratory support-adjusted ordinal logistic regression models were constructed to assess the common odds ratio of better outcome for each pairwise comparison with the usual care group with 95% CIs and p-values reported [237].

3.6.6 Analysis of gene expression data

3.6.6.1 Differential expression analysis

Differential expression analysis was performed using the R package 'DESeq2'[238,239]. Raw RNA-Seq count data was first normalised for library size and composition. Log-fold changes in the normalised count data between randomised groups was assessed using a negative binomial model for each gene, adjusted for age group, sex and respiratory support group at randomisation. P-values were adjusted for multiple testing using the Bonferroni method[240].

3.6.6.2 Enrichment analysis

For the Gene Ontology pathway enrichment analysis, a list of differentially expressed genes between randomised groups was identified by selecting a cut-off of $\log_2$ fold change >1 or <-1, and adjusted p-value <0.05 from the differential expression analysis. This list of differentially expressed genes was compared with the background list of all genes included in the differential expression analysis to assess for over-representation of pathways defined by the Biological Processes in the Gene Ontology database using the R package 'topGO'[241]. Over-representation of pathways was assessed using the Fisher exact test comparing the differentially expressed genes with the non-differentially expressed genes in the background whole gene list[242]. P-values were adjusted for multiple testing using the Benjamini-Hochberg correction[243].

For the selected gene set enrichment analysis, a list of ranked genes using all genes from the differential expression analysis was used. The ranking was determined by ordering by the product of the fold change and $-\log_{10}$(p-value) for each gene. For each selected gene set, the distribution of genes in the ranked list was evaluated using the Kolmogorov-Smirnov test[244]. P-values were adjusted for multiple testing using the Benjamini-Hochberg correction[243].

3.6.7 Subgroup analyses

3.6.7.1 Tests for heterogeneity or trend

Tests for heterogeneity or trend of the proportional effect observed in specific subgroups were conducted to assess whether there was any good evidence that the effect in particular subgroups differed materially from the overall effect seen in all patients combined. In interpretation, allowance was given for multiple comparisons, whether the analysis was pre-specified or exploratory, and for other differences between the subgroups. For all treatment comparisons, tests for heterogeneity or linear trend (for 3 or more ordered groups) were performed through the inclusion of an interaction term between the treatment assignment and the subgroup of interest in the relevant regression model.

3.6.7.2 Assessment of correlated subgroups with standardisation

Further exploratory analyses of subgroups of interest were carried out by considering interactions with other key subgroups and standardisation techniques to attempt to mitigate for the potential for confounding in the evaluation of two correlated baseline subgroups[245]. Cox regression models were constructed including interaction terms between the treatment assignment and each of the key subgroups of interest. Treatment effect estimates within one subgroup of interest were then standardised to the overall distribution of the other factor of interest, such that the distribution of the second factor was the same in each of the subgroups of the first factor[246].

3.6.7.3 Baseline predicted non-COVID infection risk

Baseline-predicted risk of non-COVID infection was estimated using data from all RECOVERY participants and constructing a multivariable logistic regression model with major non-COVID infection at 6 months as the outcome variable, and including 13 pre-specified baseline characteristics as covariates (age, sex, duration since symptom onset, duration of hospital stay, respiratory support requirement, diabetes, heart disease, severe

liver disease, severe kidney disease, lung disease, immunosuppression, severe mental illness, HFRS group). The regression model additionally adjusted for treatment allocation (with usual care designated the reference category), and for all possible two-way interactions between the above baseline characteristics and treatment allocation. These additional terms were ignored when calculating baseline-predicted risk, however, to ensure that the estimates corresponded to risk if assigned usual care. Patients were then subdivided into three approximately equally-sized groups (Low/Medium/High) on the basis of their predicted risk.

3.6.8 Minimum detectable effect size

The immunomodulatory treatment comparisons have completed recruitment and therefore sample size was fixed. The extended analysis focused on minimum detectable effect size for each outcome (calculated from blinded data with knowledge of outcome sample sizes) and its clinical interpretation (Table 3-6).

Table 3-6: Minimum detectable effect sizes for planned study outcomes across all treatment comparisons, based on blinded data.

Outcome	Treatment Comparison	Number of events	Minimum detectable effect size (Risk increase with treatment)*		Minimum detectable effect size (Risk decrease with treatment)*	
			80% power at 2P <0.05	90% power at 2P <0.05	80% power at 2P <0.05	90% power at 2P <0.05
Time to first occurrence of major non-COVID infection at 28 days	Dexamethasone	788	HR 1.21	HR 1.25	HR 0.83	HR 0.80
	Tocilizumab	581	HR 1.23	HR 1.27	HR 0.81	HR 0.79
Major non-COVID infection at 28 days	Baricitinib	1,294	RR 1.16	RR 1.18	RR 0.87	RR 0.85
	Higher dose dexamethasone	199	RR 1.40	RR 1.46	RR 0.71	RR 0.68
Time to first occurrence of major non-COVID infection at 6 months	Dexamethasone	1,331	HR 1.16	HR 1.19	HR 0.86	HR 0.84
	Tocilizumab	794	HR 1.20	HR 1.23	HR 0.83	HR 0.81
Major non-COVID infection at 6 months	Baricitinib	1,637	RR 1.14	RR 1.16	RR 0.88	RR 0.86
	Higher dose dexamethasone	259	RR 1.35	RR 1.40	RR 0.74	RR 0.71
Any non-COVID infection at 28 days	Dexamethasone	1,186	RR 1.17	RR 1.20	RR 0.85	RR 0.83
	Tocilizumab	766	RR 1.20	RR 1.23	RR 0.83	RR 0.81
	Baricitinib	1,738	RR 1.13	RR 1.16	RR 0.88	RR 0.87
	Higher dose dexamethasone	247	RR 1.36	RR 1.41	RR 0.74	RR 0.71
Any non-COVID infection at 6 months	Dexamethasone	2,152	RR 1.13	RR 1.15	RR 0.89	RR 0.87
	Tocilizumab	1,218	RR 1.16	RR 1.19	RR 0.86	RR 0.84
	Baricitinib	2,725	RR 1.11	RR 1.12	RR 0.90	RR 0.89
	Higher dose dexamethasone	341	RR 1.30	RR 1.35	RR 0.77	RR 0.74
Time to first occurrence of microbiologically-confirmed non-COVID infection at 28 days	Dexamethasone	285	HR 1.35	HR 1.41	HR 0.74	HR 0.71
	Tocilizumab	263	HR 1.35	HR 1.40	HR 0.74	HR 0.71
Microbiologically-confirmed non-COVID infection at 28 days	Baricitinib	376	RR 1.29	RR 1.34	RR 0.78	RR 0.75
	Higher dose dexamethasone	18	RR 2.41	RR 2.63	RR 0.42	RR 0.38
Time to first occurrence of microbiologically-confirmed non-COVID infection at 6 months	Dexamethasone	388	HR 1.30	HR 1.35	HR 0.77	HR 0.74
	Tocilizumab	315	HR 1.32	HR 1.37	HR 0.76	HR 0.73
Microbiologically-confirmed non-COVID infection at 6 months	Baricitinib	444	RR 1.27	RR 1.31	RR 0.79	RR 0.76
	Higher dose dexamethasone	25	RR 2.17	RR 2.36	RR 0.46	RR 0.42
Time to first occurrence of bloodstream infection at 28 days	Dexamethasone	181	HR 1.44	HR 1.51	HR 0.69	HR 0.66
	Tocilizumab	167	HR 1.44	HR 1.50	HR 0.70	HR 0.66
Bloodstream infection at 28 days	Baricitinib	238	RR 1.36	RR 1.42	RR 0.73	RR 0.70
	Higher dose dexamethasone	13	RR 2.71	RR 2.98	RR 0.37	RR 0.34
	Dexamethasone	250	HR 1.38	HR 1.44	HR 0.73	HR 0.70

Time to first occurrence of bloodstream infection at 6 months	Tocilizumab	208	HR 1.39	HR 1.45	HR 0.72	HR 0.69
Bloodstream infection at 6 months	Baricitinib	278	RR 1.34	RR 1.39	RR 0.75	RR 0.72
	Higher dose dexamethasone	17	RR 2.45	RR 2.68	RR 0.41	RR 0.37
Time to long COVID at 18 months	Dexamethasone	184	HR 1.44	HR 1.51	HR 0.69	HR 0.66
	Tocilizumab	311	HR 1.32	HR 1.37	HR 0.76	HR 0.73
	Baricitinib	698	HR 1.21	HR 1.25	HR 0.82	HR 0.80
	Higher dose dexamethasone	17	HR 2.45	HR 2.68	HR 0.41	HR 0.37
Time to first occurrence of gastrointestinal (GI) complication at 28 days	Dexamethasone	44	HR 1.92	HR 2.06	HR 0.52	HR 0.49
	Tocilizumab	39	HR 1.92	HR 2.07	HR 0.52	HR 0.48
GI complications at 28 days	Baricitinib	70	RR 1.68	RR 1.79	RR 0.60	RR 0.56
	Higher dose dexamethasone	9	RR 3.17	RR 3.52	RR 0.32	RR 0.28
Time to first occurrence of GI complication at 6 months	Dexamethasone	115	HR 1.56	HR 1.65	HR 0.64	HR 0.61
	Tocilizumab	56	HR 1.76	HR 1.88	HR 0.57	HR 0.53
GI complications at 6 months	Baricitinib	111	RR 1.54	RR 1.62	RR 0.65	RR 0.62
	Higher dose dexamethasone	15	RR 2.56	RR 2.81	RR 0.39	RR 0.36
Time to first occurrence of venous thromboembolism (VTE) at 28 days	Dexamethasone	124	HR 1.54	HR 1.62	HR 0.65	HR 0.62
	Tocilizumab	150	HR 1.46	HR 1.53	HR 0.68	HR 0.65
VTE at 28 days	Baricitinib	447	RR 1.27	RR 1.31	RR 0.79	RR 0.76
	Higher dose dexamethasone	31	RR 2.04	RR 2.21	RR 0.49	RR 0.45
Time to first occurrence of VTE at 6 months	Dexamethasone	191	HR 1.43	HR 1.50	HR 0.70	HR 0.67
	Tocilizumab	202	HR 1.40	HR 1.46	HR 0.72	HR 0.69
VTE at 6 months	Baricitinib	513	RR 1.25	RR 1.29	RR 0.80	RR 0.78
	Higher dose dexamethasone	37	RR 1.95	RR 2.10	RR 0.51	RR 0.48
Bacterial infection at 28 days	Dexamethasone	834	RR 1.21	RR 1.24	RR 0.83	RR 0.81
	Tocilizumab	573	RR 1.23	RR 1.27	RR 0.81	RR 0.79
	Baricitinib	936	RR 1.18	RR 1.21	RR 0.85	RR 0.82
	Higher dose dexamethasone	176	RR 1.42	RR 1.49	RR 0.70	RR 0.67
Bacterial infection at 6 months	Dexamethasone	1,723	RR 1.14	RR 1.17	RR 0.87	RR 0.86
	Tocilizumab	984	RR 1.18	RR 1.21	RR 0.85	RR 0.83
	Baricitinib	1,923	RR 1.13	RR 1.15	RR 0.89	RR 0.87
	Higher dose dexamethasone	266	RR 1.34	RR 1.40	RR 0.74	RR 0.71
Fungal infection at 28 days	Dexamethasone	132	RR 1.52	RR 1.60	RR 0.66	RR 0.62
	Tocilizumab	86	RR 1.61	RR 1.71	RR 0.62	RR 0.59
	Baricitinib	208	RR 1.39	RR 1.45	RR 0.72	RR 0.69
	Higher dose dexamethasone	20	RR 2.33	RR 2.53	RR 0.43	RR 0.39
Fungal infection at 6 months	Dexamethasone	225	RR 1.40	RR 1.46	RR 0.72	RR 0.68
	Tocilizumab	131	RR 1.49	RR 1.57	RR 0.67	RR 0.64
	Baricitinib	275	RR 1.34	RR 1.39	RR 0.75	RR 0.72
	Higher dose dexamethasone	34	RR 1.99	RR 2.15	RR 0.50	RR 0.47

Incident diabetes at 12 months	Dexamethasone	41	RR 1.95	RR 2.10	RR 0.51	RR 0.48
	Tocilizumab	44	RR 1.86	RR 2.00	RR 0.54	RR 0.50
	Baricitinib	97	RR 1.57	RR 1.67	RR 0.63	RR 0.60
	Higher dose dexamethasone	3	RR 17.26	RR 19.23	RR 0.06	RR 0.05
Time to first occurrence of metabolic complication at 28 days	Dexamethasone	41	HR 1.95	HR 2.10	HR 0.51	HR 0.48
	Tocilizumab	53	HR 1.78	HR 1.91	HR 0.56	HR 0.52
	Baricitinib	109	HR 1.54	HR 1.63	HR 0.65	HR 0.61
Metabolic complications at 28 days	Higher dose dexamethasone	238	RR 1.36	RR 1.42	RR 0.73	RR 0.70
Time to first occurrence of metabolic complication at 6 months	Dexamethasone	103	HR 1.59	HR 1.68	HR 0.63	HR 0.59
	Tocilizumab	89	HR 1.60	HR 1.70	HR 0.62	HR 0.59
	Baricitinib	196	HR 1.40	HR 1.47	HR 0.71	HR 0.68
Metabolic complications at 6 months	Higher dose dexamethasone	246	RR 1.36	RR 1.42	RR 0.74	RR 0.71
Time to first occurrence of long bone or vertebral fracture at 28 days	Dexamethasone	26	HR 2.22	HR 2.41	HR 0.45	HR 0.42
	Tocilizumab	5	HR 4.72	HR 5.31	HR 0.21	HR 0.19
	Baricitinib	12	HR 2.79	HR 3.08	HR 0.36	HR 0.32
	Higher dose dexamethasone	3	RR 17.26	RR 19.23	RR 0.06	RR 0.05
Time to first occurrence of long bone or vertebral fracture at 6 months	Dexamethasone	82	HR 1.66	HR 1.77	HR 0.60	HR 0.57
	Tocilizumab	15	HR 2.56	HR 2.81	HR 0.39	HR 0.36
	Baricitinib	45	HR 1.85	HR 1.99	HR 0.54	HR 0.50
	Higher dose dexamethasone	7	RR 3.64	RR 4.06	RR 0.27	RR 0.25
Psychiatric complications at 28 days	Dexamethasone	159	RR 1.47	RR 1.55	RR 0.68	RR 0.65
	Tocilizumab	85	RR 1.61	RR 1.71	RR 0.62	RR 0.58
	Baricitinib	101	RR 1.56	RR 1.65	RR 0.64	RR 0.61
	Higher dose dexamethasone	6	RR 4.04	RR 4.52	RR 0.25	RR 0.22
Psychiatric complications at 6 months	Dexamethasone	298	RR 1.35	RR 1.40	RR 0.74	RR 0.71
	Tocilizumab	132	RR 1.49	RR 1.57	RR 0.67	RR 0.64
	Baricitinib	181	RR 1.42	RR 1.48	RR 0.70	RR 0.67
	Higher dose dexamethasone	25	RR 2.17	RR 2.36	RR 0.46	RR 0.42
Time to first occurrence of clinically-defined liver injury at 28 days	Dexamethasone	52	HR 1.84	HR 1.97	HR 0.54	HR 0.51
	Tocilizumab	57	HR 1.76	HR 1.87	HR 0.57	HR 0.53
	Baricitinib	136	HR 1.48	HR 1.56	HR 0.67	HR 0.64
	Higher dose dexamethasone	10	HR 3.02	HR 3.34	HR 0.33	HR 0.30
Time to first occurrence of clinically-defined liver injury at 6 months	Dexamethasone	84	HR 1.66	HR 1.76	HR 0.60	HR 0.57
	Tocilizumab	74	HR 1.66	HR 1.76	HR 0.60	HR 0.57
	Baricitinib	174	HR 1.43	HR 1.49	HR 0.70	HR 0.67
	Higher dose dexamethasone	15	HR 2.56	HR 2.81	HR 0.39	HR 0.36
**HR = Hazard Ratio, RR = Risk Ratio*						

3.6.9 Multiplicity of comparisons

No formal adjustment was made for the multiplicity of testing in analyses (except for the analysis of gene expression data). However, due allowance for multiple testing was made in the interpretation of the results: taking into account the nature of events (including timing, duration and severity), the comparison in question (i.e. interpreted in the light of observed effects on relevant other comparisons), and by requiring more extreme p-values to infer evidence of effect in such analyses.

3.6.10 Missing data

As outcomes were derived from RCD, the completeness of outcome ascertainment cannot be definitive. For the purposes of analyses, the absence of a relevant RCD-defined event was regarded as the outcome having not occurred for that participant. The data completeness of the RCD datasets – defined as a participant represented in any RCD dataset at any time - was presented as counts and percentages of all participants in the treatment comparison.

For subgroup analyses, if a large proportion of data was missing for a variable, a separate unknown category was reported for the subgroup. If a small proportion of data was missing, it did not contribute to the subgroup analysis but did to the overall result.

For participants within ISARIC4C for whom there were ≤1 measurement of the physiological or commonly-measured blood biomarkers within the specified time period, a subject-specific slope could not be calculated. Multiple imputation using chained equations (MICE) was used to impute a subject-specific slope[247]. The imputation was performed separately for each treatment arm in each comparison. The number of imputations used was ≥to the % of incomplete cases in the data, with a minimum of 10. Results across imputations were combined using the methods of Rubin[248].

The imputation model included the following variables that were identified as informing missingness in the rate of change variables or that there was strong clinical suspicion that they would be an important predictor of baseline or follow-up measurements of the parameters:

i) Baseline measurement of the relevant assessment parameter;
ii) Age;
iii) Baseline respiratory support group;
iv) Sex;
v) Ethnicity;
vi) Diabetes mellitus;
vii) Heart disease;
viii) Liver disease;
ix) Kidney disease;
x) Chronic lung disease;
xi) Severe mental illness
xii) Immunosuppression;
xiii) HFRS group;
xiv) Time to discharge alive from hospital group (an auxiliary variable in the following categories: discharged alive study day 1 to study day 4; discharged alive study day 5 to study day 7; discharged alive study day 8 to study day 14; discharged alive study day 15 to study day 28; not discharged alive by study day 28).

3.6.11 Software

All data cleaning, derivation, and statistical analyses were performed using R version 4.2, except the assessment of correlated subgroups using standardisation which were performed using SAS version 9.4[249].

3.7 Ethics and Information Governance

3.7.1 Ethics

The extended analysis was approved by the RECOVERY Trial Steering Committee as a sub-study of RECOVERY (Research Ethics Committee (REC) Reference 20/EE/0101). Separate formal ethical approval was not required as it did not extend beyond the scope of approval or require any new data collection beyond that which was already being captured for RECOVERY. This was confirmed through the completion of Health Research Authority Decision tools (Appendix Section B.4.1). All RECOVERY participants have given informed consent, including for access to personal medical information located in local or national health and research organisations for up to 10 years. They are free to withdraw consent from the trial at any point.

ISARIC4C (REC Reference 13/SC/0149) clinical data is collected without formal consent - this was approved for the specific purpose of COVID-19 research under a Control of Patient Information notice from March 2020 to July 2022 and then under Section 251 Regulation 5 of the NHS Act 2006 with support from the Confidentiality Advisory Group (Reference: 21/CAG/0125). Participants providing biological samples gave informed consent, including for data sharing with other approved COVID-19 research projects.

3.7.2 Data Linkage

ISARIC4C data linkage with RECOVERY was novel for this thesis. An analysis dataset, consisting of variables derived from RECOVERY and RCD, was transferred to a dedicated project space within a Trusted Research Environment (TRE) hosted by Public Health Scotland (PHS) - the Scottish National Safe Haven - and linked with all ISARIC4C data available for RECOVERY participants. This process consisted of both information governance procedures and the data transfer, and took place over the course of 20 months, between September 2021 and April 2023, led by the thesis author (Figure 3-2).

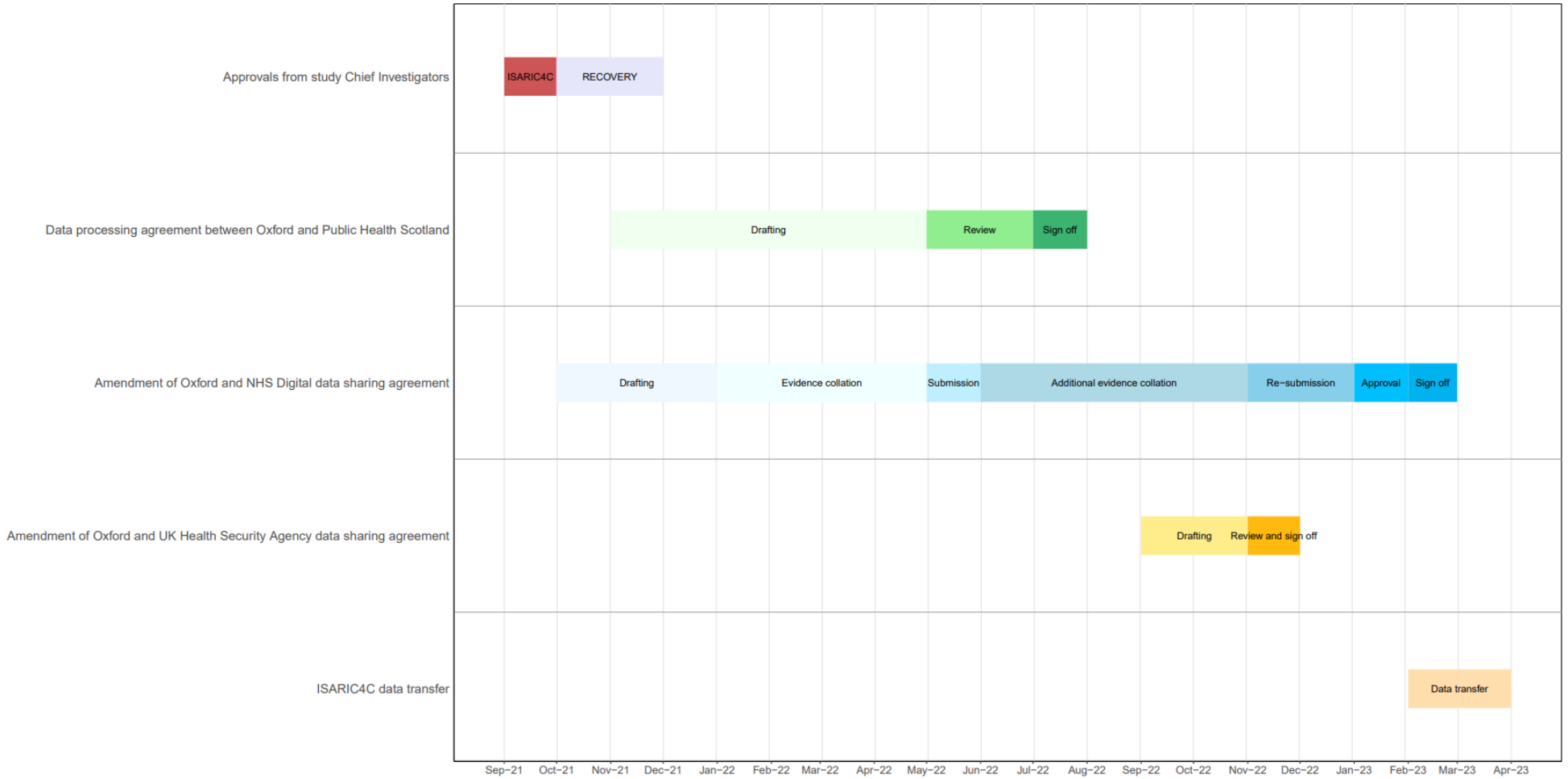


Figure 3-2: Timeline of the data linkage process for the extended analysis.

3.7.2.1 Information governance approvals

Obtaining information governance approvals for the data linkage consisted of the following main processes:

i) Approvals from study Chief Investigators:
   - September 2021: Approval agreed from ISARIC4C Lead Investigator. Data transfer plan agreed with requirement to transfer RECOVERY trial data and extended analysis variables derived from RCD datasets to PHS for linkage with ISARIC4C data.
   - October 2021 – December 2021: Extended analysis submitted as formal RECOVERY sub-study proposal. Discussed and approved at RECOVERY Trial Steering Committee meeting.

ii) Completion of data processing agreement between the University of Oxford and PHS:
   - November 2021 – May 2022: Drafting of data processing agreement from University Research Contracts team.
   - May 2022 – July 2022: Review of draft agreements and resolution of points of discussion between Oxford Research Contracts team and PHS legal team.
   - July 2022: Signing of agreement.

iii) Amendment of University of Oxford and NHS Digital data sharing agreement:
   - October 2021 – January 2022: Drafting of amendment text.
   - January 2022 – May 2022: Gathering of evidence required to support NHS Digital amendment submission and completion of process of a previously submitted RECOVERY amendment (to allow the subsequent new amendment to be submitted).
   - May 2022: Initial submission of amendment to NHS Digital.

- June 2022 – November 2022: Collation of additional evidence and requirements to support NHS Digital approval of amendment; completion of University of Oxford-PHS data processing agreement and assurance of proof of standards of information security from PHS regarding data processing. Information security assurance was provided through the completion of a Data Security and Protection Toolkit assessment and a PHS System Level Security Policy approved by NHS Digital.
- November 2022 –December 2022: Re-submission of amendment to NHS Digital and processing of application.
- January 2023: Review of amendment and recommendation for approval with further minor changes from NHS Digital Independent Group Advising on the Release of Data.
- January 2023 - February 2023: Completion of required minor changes and responses and signing of agreement (Reference DARS-NIC-365354-R3M0Q-v10.2).

iv) Amendment of University of Oxford and UKHSA data sharing agreement:

- September 2022: Request from UKHSA to amend data sharing agreement in the context of variables derived from UKHSA datasets being transferred to PHS.
- September 2022 – November 2022: Drafting and signing of amendment completed.

v) Completion of additional information governance documentation:

- Informing all other RCD data custodians of the additional data processing and confirming no changes to other data sharing agreements were required.
- RECOVERY Data Protection Impact Assessment updated with information about the extended analysis and signed off by university department lead.

- RECOVERY Data Privacy Notice updated with information about the extended analysis and published on study website.
- Inclusion of information about the extended analysis in the RECOVERY participant newsletter, sent in January 2024.

3.7.2.2 Data transfer

The data transfer between the University of Oxford and PHS took place between February 2023 and April 2023. The data flow is summarised in Figure 3-3. Identifiable information (NHS/CHI number and date of birth) for each adult RECOVERY participant was provided to PHS's electronic Data Research and Innovation Service (eDRIS) for the purposes of data linkage. The data was transferred securely using a Secure File Transfer client. Data linkage was performed by the eDRIS team using probabilistic matching of the patient identifiers (NHS/CHI number and date of birth). A bridging file was then returned to Oxford flagging RECOVERY participant study numbers in all treatment comparisons with a good ISARIC4C match (n=25,061).

The extended analysis dataset constructed in Oxford - consisting of all variables for the extended analysis derived from RECOVERY and RCD data - was filtered to include only those participants with a matching record in ISARIC4C, with the process checked by a second researcher. The filtered analysis dataset was then transferred securely using the same Secure File Transfer client to eDRIS. The eDRIS team placed the filtered extended analysis dataset and corresponding ISARIC4C data, linked by RECOVERY study number, into the TRE workspace. The workspace was accessible only to named researchers approved by the RECOVERY team, and eDRIS system administrators.

Analyses involving ISARIC4C data were performed within the TRE, which was remotely accessed via a secure Virtual Private Network with a 2-factor authentication process from a University of Oxford desktop computer. Obtaining ISARIC4C biological sample data required remote access to an additional high processing power computing environment

that stored the biological sample data – the Edinburgh Parallel Computing Centre Flexible Compute Space. The biological sample data was processed and filtered in this environment using the list of linked ISARIC4C study ID numbers for RECOVERY participants and the processed data was then transferred back to the TRE for analysis. Outputs from analyses were released from the TRE by authorised personnel after performing Statistical Disclosure Control checks.

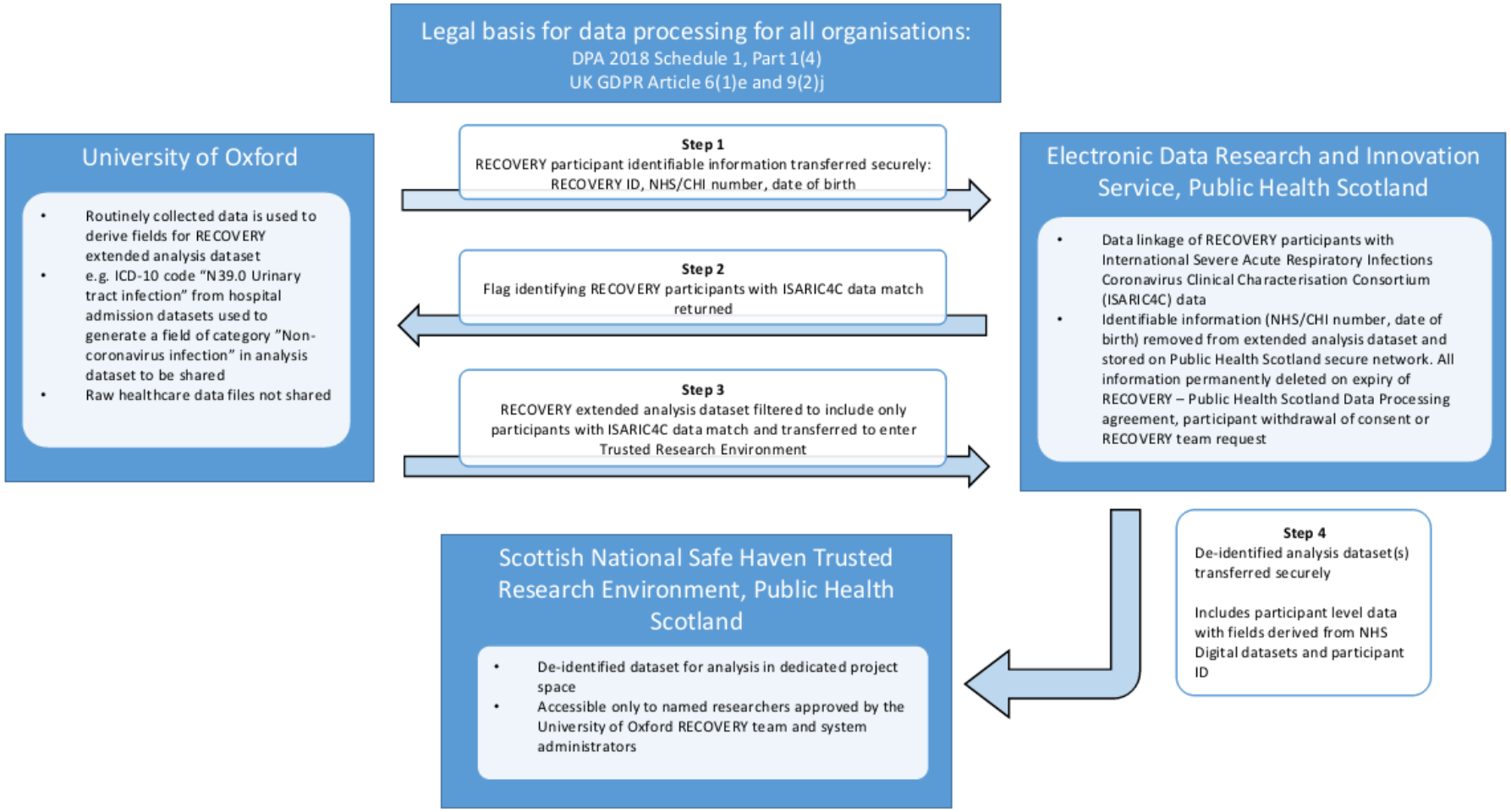


Figure 3-3: Data flow diagram for RECOVERY-ISARIC4C data linkage between the University of Oxford and Public Health Scotland.

Chapter 4

Method Development

4.1 Chapter Summary

This chapter details the development and validation of the final long-term follow-up analysis assessments derived from RCD.

An overview of the method development process is shown in Figure 4-1. The chapter begins with a systematic literature review and synthesis of evidence relating to the capture of relevant clinical conditions from diagnosis codes in RCD sources. The methodological steps of the definition development process are then described, including the development of clinical condition codelists and the validation and testing of the assessment definitions. The results of these are presented and discussed and the evidence used to finalise the derivation parameters used in the final analysis assessment definitions.

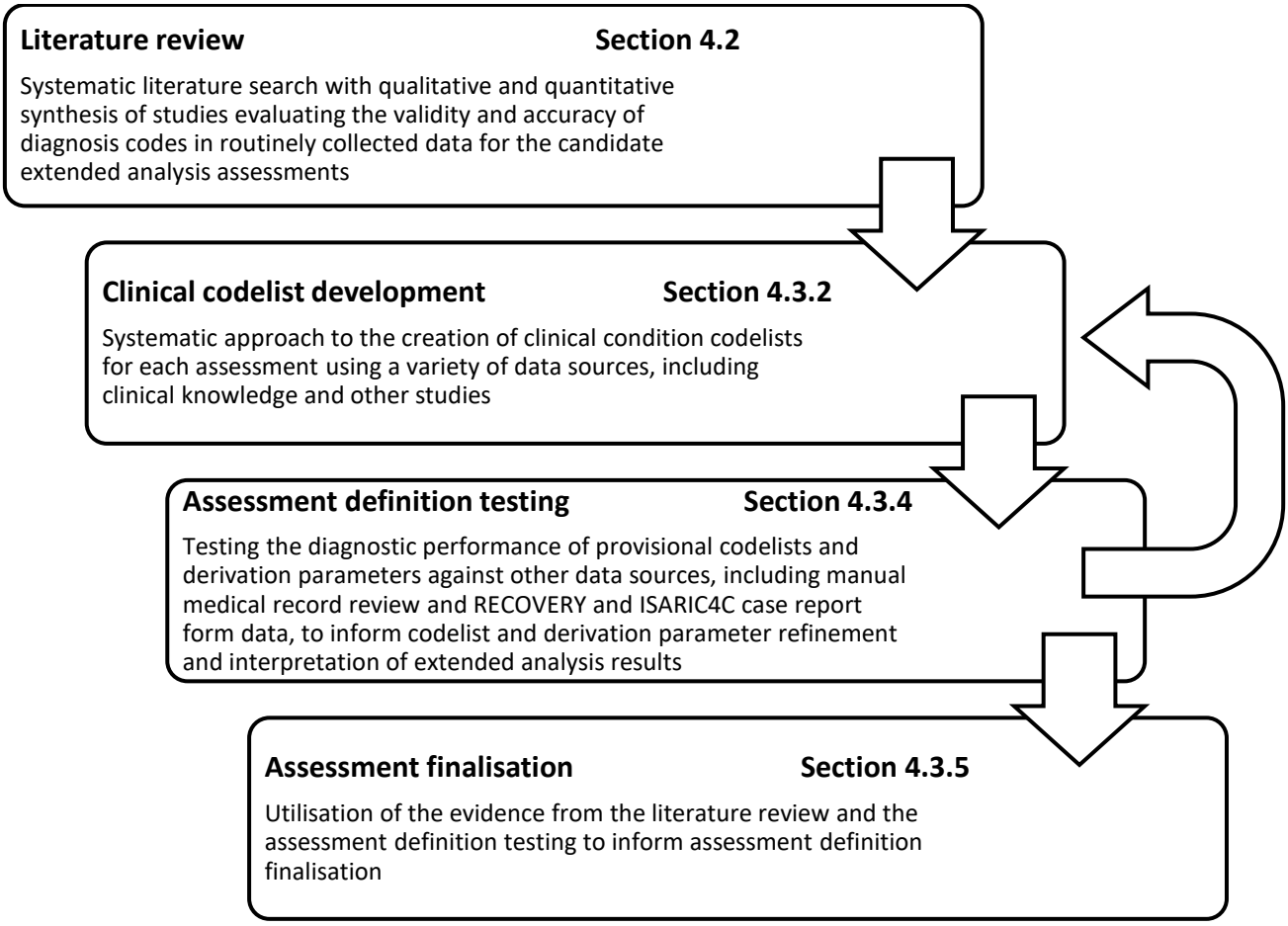


Figure 4-1: Overview of the method development process.
Section refers to relevant thesis chapter section.

4.2 Literature Review

4.2.1 Aims

The method development literature review aimed to systematically identify and synthesise existing evidence relating to the validity and diagnostic accuracy of deriving events of interest for the extended analysis from RCD sources.

4.2.2 Methods

4.2.2.1 Inclusion criteria

Studies were included if they met the following criteria:

i) Population: Adults (medical inpatients or community-based).

This population aimed to represent the target extended analysis study population of hospitalised patients with COVID-19 during their acute admission and long-term follow-up. All studies took place prior to the COVID-19 pandemic. Studies in post-operative surgical inpatients were excluded, as these populations have been specifically targeted for diagnosis coding improvement for surgical safety and quality monitoring[250,251].

ii) Index test for the target condition: The presence or absence of a target clinical condition derived from RCD sources using diagnosis codes.

Diagnosis codes needed to be from coding systems that will be used in the RCD datasets in the extended analysis - ICD or SNOMED. Studies using other coding systems were excluded.

iii) Reference standard for the target condition: Manual medical record review or prospective clinical/research data collection for the presence or absence of the target clinical condition.

Studies using automated electronic algorithms to define the reference standard were excluded.

iv) Target conditions: Clinical conditions that comprised candidate long-term follow-up analysis assessments for the extended analysis.

These included: non-COVID infections, VTE, GI complications (bleeding, perforation, or ulceration), metabolic complications (hyperglycaemia, diabetic ketoacidosis, or hypoglycaemia), incident diabetes mellitus, long COVID, long bone or vertebral fractures, psychiatric complications (delirium, mania, or psychosis), and liver injury. Studies evaluating specific hospital-acquired infections, such as *Clostridium difficile* infection or central line-associated bloodstream infections, were excluded.

v) Study type: Full text case validation or diagnostic accuracy study.

Two forms of study design were considered:

- Studies that only included reference standard case ascertainment in a population defined by their index test classification – referred to as 'case validation' studies.
- Studies that included a population where both the reference standard and index test case ascertainment were systematically applied to all participants - referred to as 'diagnostic accuracy' studies.

These study types are presented separately as the diagnostic performance parameters that can be measured without major bias from each study design differ (see Section 4.2.2.4).

4.2.2.2 Search strategy

MEDLINE and Embase electronic databases were systematically searched using synonyms for RCD, validity, or diagnostic accuracy, and each target condition in turn. Full search strategies can be found in the Appendix Section C.1. Titles and abstracts were screened against inclusion criteria and relevant studies extracted for full-text review.

Reference lists were examined for further studies. No language or date restrictions were used.

4.2.2.3 Data extraction

Data was extracted manually for the following parameters for each study, either directly from the study report or through standard algebraic derivations from other reported parameters[252]:

i) True positives: the number with the target condition (according to the reference standard) who are correctly found to have the target condition using the index test.
ii) True negatives: the number without the target condition (according to the reference standard) who are correctly found not to have the target condition using the index test.
iii) False positives: the number without the target condition (according to the reference standard) who are incorrectly found to have the target condition using the index test.
iv) False negatives: the number with the target condition (according to the reference standard) who are incorrectly found not to have the target condition using the index test.

4.2.2.4 Statistical methods

Results were separated by the case validation and diagnostic accuracy study designs and the diagnostic performance measures that could be reported from each study design were presented[253]. In case validation studies, where participants are selected based on their index test status, the index test positivity prevalence is altered within the studied population leading to biased estimates of sensitivity and specificity.

For case validation studies, the following measures were reported, with 95% CIs[254]:

i) Positive predictive value (PPV) ($\frac{True\ Positives}{True\ Positives + False\ Positives}$)

The median and IQR of the individual study PPV results from all case validation studies for each target condition were reported as a summary measure.

For diagnostic accuracy studies, the following measures were reported, with 95% CIs:

i) Sensitivity $\left(\frac{True\ Positives}{True\ Positives + False\ Negatives}\right)$

ii) Specificity $\left(\frac{True\ Negatives}{True\ Negatives + False\ Positives}\right)$

The pooled sensitivity and pooled specificity from all available diagnostic accuracy studies for each target condition were calculated using the bivariate approach[255], to produce a summary measure.

4.2.3 Results

4.2.3.1 Overview

The final literature search was carried out on 16 January 2023. A total of 117 relevant studies were found, with the largest number relating to diabetes, infections and VTE, and the fewest relating to long COVID, psychiatric complications and liver injury (Figure 4-2).

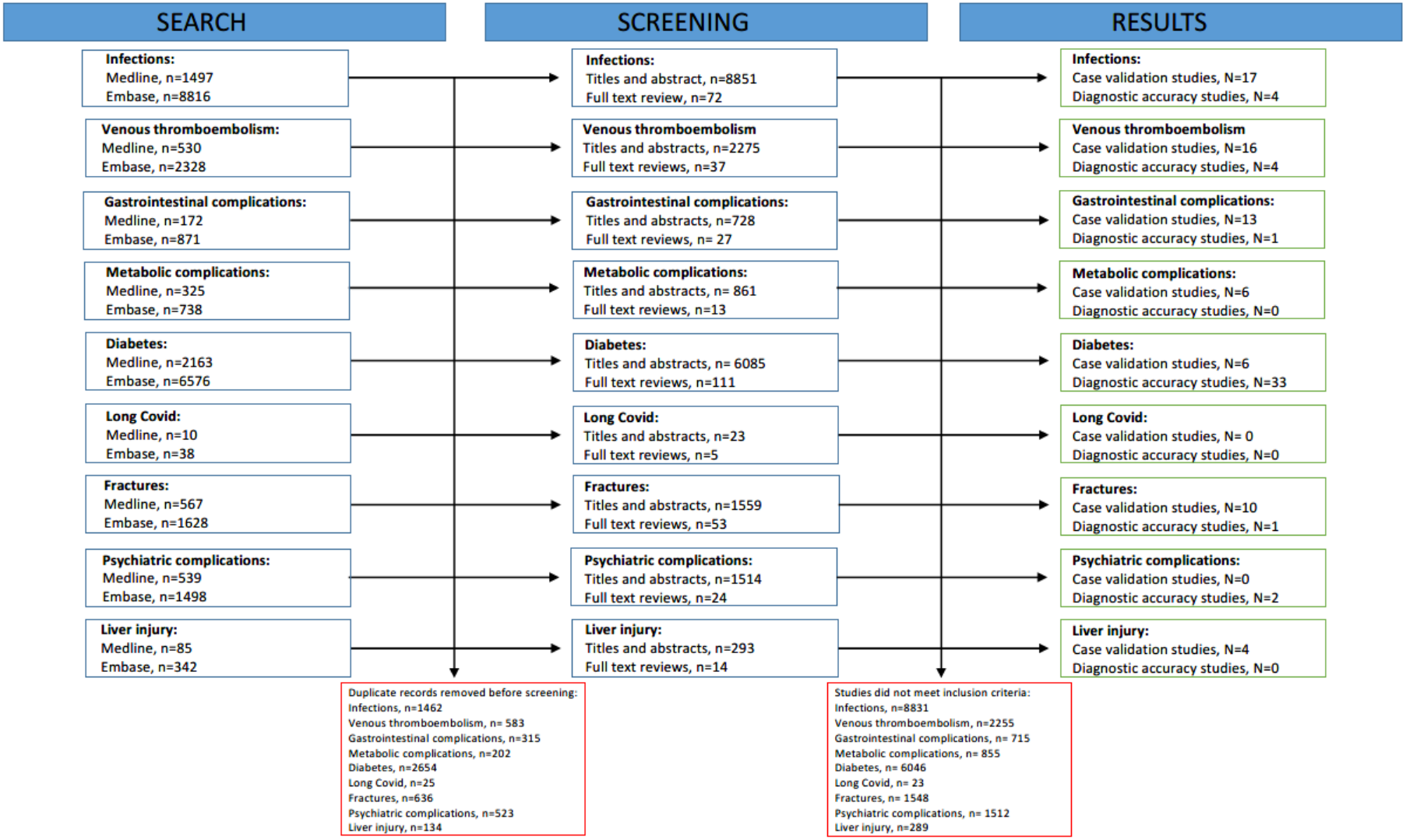


Figure 4-2: Flow diagram of method development systematic literature search.

4.2.3.2 Infections

Across 17 case validation studies of RCD-derived infection events there was a median PPV of 0.84 (IQR 0.72 – 0.90) (Table 4-1, Table 4-9). Results from four diagnostic accuracy studies were found to have a pooled sensitivity of 0.47 [95% CI 0.13 – 0.84] and a pooled specificity of 0.968 [95% CI 0.833 – 0.995] (Table 4-2, Table 4-9).

Table 4-1: Summary of case validation studies evaluating routinely collected data-derived infection events.

Study	Coding System	Population	Target Condition	Diagnostic Position	Total number of index cases	Reference standard	Positive Predictive Value (95% CI)
Curtis (2007)[256]	ICD-9	Inpatients with rheumatoid arthritis in USA	Bacterial infection	All	187	Adjudication of abstracted case notes by 2 independent clinical reviewers based on clinical judgement, with discrepancies resolved by 3rd study reviewer	0.84 (0.79 - 0.89)
Drahos (2013)[257]	ICD-9	Inpatients in USA	Pneumonia	Not stated	175	Adjudication of abstracted case notes by study clinical reviewers based on predetermined case definition	0.87 (0.82 - 0.92)
Grijalva (2008)[258]	ICD-9	Inpatients with rheumatoid arthritis in USA	Pneumonia	All Primary only	161 108	Adjudication of abstracted case notes by 2 study clinical reviewers based on clinical judgement, with discrepancies resolved by 3rd study reviewer	0.83 (0.77 - 0.89) 0.95 (0.89 - 0.98)
Holland-Bill (2014)[259]	ICD-10	Inpatients with cancer in Denmark	Any infection	Primary only	266	Medical chart review by study physician based on clinical judgement	0.97 (0.96 - 0.99)
Ingeman (2010)[260]	ICD-10	Inpatients with stroke in Denmark	Pneumonia and urinary tract infection	All	53	Medical chart review by study reviewer based on predetermined case definition	0.79 (0.68 - 0.90)
Jackson (2003)[261]	ICD-9	Inpatients age ≥ 65 in USA	Pneumonia	Not stated	2,455	Medical chart review based on clinical judgement	0.65 (0.63 - 0.67)
Kern (2015)[262]	ICD-9	Inpatients with chronic obstructive pulmonary disease in USA	Pneumonia	Not stated	388	Medical chart review by independent clinical reviewers based on clinical judgement	0.80 (0.76 - 0.84)
Levine (2013)[263]	ICD-9	Community-based patients in USA	Skin and soft tissue infections	Not stated	455	Medical chart review by 2 study reviewers based on pre-determined case definition, with discrepancies resolved by 3rd study reviewer	0.88 (0.86 - 0.91)
Marrie (1987)[264]	ICD-9	Inpatients in Canada	Pneumonia	Not stated	127	Prospective enrolment in pneumonia study based on physician diagnosis and radiology	0.57 (0.49 - 0.66)

Patkar (2009)[265]	ICD-9	Inpatients with rheumatoid arthritis in USA	Bacterial infection	All	162	Medical chart review by 2 study clinical reviewers based on clinical judgement with discrepancies resolved by 2 further study clinical reviewers	0.82 (0.76 - 0.88)
Sahli (2016)[266]	ICD-10	Inpatients in France	Any infection	All Primary only	200 100	Medical chart review by 2 study clinical reviewers based on clinical judgement with discrepancies resolved by 3rd study reviewer	0.83 (0.78 - 0.88) 0.97 (0.91 - 0.99)
Schneeweiss (2007)[267]	ICD-9	Inpatients in USA	Any infection	Primary only	158	Medical chart abstraction by study clinical reviewer blinded to predetermined case definition	0.89 (0.84 - 0.94)
Skull (2008)[268]	ICD-10	Inpatients age ≥65 in Australia	Pneumonia	All	2,318	Medical chart review based on clinical judgement	0.96 (0.95 - 0.97)
Smith (2021)[269]	ICD-9 and ICD-10	Community-based patients with multiple sclerosis in USA	Pneumonia and urinary tract infection	All	49	Medical chart review based on predetermined case definition	0.32 (0.19 - 0.45)
Weise (2018)[270]	ICD-9	Inpatients age ≥50 in USA	Any infection	Primary only	716	Adjudication of abstracted case notes by study reviewers based on predetermined case definitions	0.90 (0.88 - 0.92)
Whittle (1997)[271]	ICD-9	Inpatients in USA	Pneumonia	All	144	Medical chart review by 2 clinical reviewers based on predetermined case definitions with discrepancies resolved by 3 further study clinical reviewers	0.88 (0.83 - 0.93)
Yu (2011)[272]	ICD-9	Inpatients in USA	Pneumonia	All Primary only	3,991 1,808	Medical chart review by 2 reviewers based on clinical judgement	0.62 (0.61 - 0.64) 0.89 (0.88 - 0.91)

Table 4-2: Summary of diagnostic accuracy studies evaluating routinely collected data-derived infection events.

Study	Coding system	Population	Target condition	Diagnostic positions	Number of participants	Reference standard	Blinding to index result	Sensitivity (95% CI)	Specificity (95% CI)
Gedeborg (2007)[273]	ICD-9 and ICD-10	Intensive care patients in Sweden	Pneumonia	All Primary only	7,615* 7,615†	Independent intensive care unit database prospectively collected by clinicians	Yes	0.50 (0.46 - 0.55) 0.35 (0.30 - 0.41)	0.958 (0.954 - 0.963) 0.985 (0.982 - 0.988)
Glenn (2021)[274]	ICD-10	Inpatients with chronic kidney disease in USA	Any infection	Not stated	1,044‡	Research study data collection on hospital admissions and diagnoses	Yes	0.71 (0.65 - 0.76)	0.950 (0.935 - 0.965)
Henriksen (2014)[275]	ICD-10	Emergency department patients in Denmark	Any infection	Not stated	5,977§	Prospective medical chart review by study clinical reviewer based on clinical judgement	Yes	0.80 (0.78 - 0.81)	0.839 (0.826 - 0.851)
Ingeman (2010)[260]	ICD-10	Inpatients with stroke in Denmark	Pneumonia and urinary tract infection	All	564**	Medical chart review by study reviewer based on predetermined case definition	No	0.07 (0.03 - 0.10)	0.992 (0.983 - 1.000)

* *Index test positive, n=505. Reference standard positive, n=406.*
† *Index test positive, n=218. Reference standard positive, n=314.*
‡ *Index test positive, n=200. Reference standard positive, n=227.*
§ *Index test positive, n=2,560. Reference standard positive, n=2,511.*
** *Index test positive, n=13. Reference standard positive, n=201.*

All located studies used the ICD coding system, most commonly ICD version 9 (14/21 studies) and took place in North America, Europe, or Australia. The majority evaluated patients in hospital (19/21), with the target condition spread across common infection types, most frequently pneumonia (12/21), or any relevant infection (8/21).

Three individual case validation studies directly compared restricting codes to the primary diagnostic position with all diagnostic positions. Using only the primary diagnostic position increased relative PPV by between 15% and 44%, but reduced the absolute number of cases identified by approximately one third. In a single diagnostic accuracy study evaluating the effect of diagnostic position, restricting diagnoses to the primary position reduced sensitivity from 0.50 to 0.35 and increased specificity from 0.958 to 0.985. Across all studies evaluating primary diagnostic position infection diagnosis codes the reported PPV was between 0.88 and 0.97.

One study found the PPV of pneumonia diagnoses from hospital inpatients (0.88) to be higher than in the community (0.73)[262].The lowest reported PPV for infections (0.32) was in a study in community-based patients. Incorporating the use of other data sources, such as antimicrobial prescriptions and microbiological culture results, increased PPV in the studies where this was evaluated[257,269].

4.2.3.3 VTE

Across 16 case validation studies of RCD-derived VTE events there was a median PPV of 0.78 (IQR 0.64 – 0.84) (Table 4-3, Table 4-9). Results from four diagnostic accuracy studies were found to have a pooled sensitivity of 0.70 [95% CI 0.31 – 0.92] and a pooled specificity of 0.996 [95% CI 0.959 – 1.000] (Table 4-4, Table 4-9).

Table 4-3: Summary of case validation studies evaluating routinely collected data-derived venous thromboembolism events.

Study	Coding system	Population	Target condition	Diagnostic positions	Total number of index cases	Reference standard	Positive Predictive Value (95% CI)
Al Ani (2015)[276]	ICD-10	Emergency department patients in Canada	Venous thromboembolism	Not stated	100	Medical chart review by 2 reviewers based on predetermined definition, with discrepancies resolved by 3rd reviewer	0.49 (0.39 - 0.59)
Ammann (2018)[277]	ICD-9	Inpatients receiving intravenous immunoglobulin in USA	Venous thromboembolism	All Primary only	62 30	Adjudication of abstracted case notes by study clinical reviewer based on predetermined definition	0.61 (0.49 - 0.72) 0.90 (0.74 - 0.97)
Arnason (2006)[278]	ICD-9	Inpatients in Canada	Venous thromboembolism	Not stated	86	Medical chart review by independent reviewer based on predetermined definition	0.73 (0.64 - 0.83)
Burles (2017)[279]	ICD-10	Emergency department patients in Canada	Pulmonary embolism	All	1,453	Medical chart review by 2 reviewers based on clinical judgement, with discrepancies resolved by 3rd clinical reviewer	0.82 (0.80 - 0.84)
Drljevic (2014)[280]	ICD-10	Inpatients and outpatients with prostate cancer in Denmark	Venous thromboembolism	All	115	Medical chart review by clinical reviewer based on clinical judgement	0.85 (0.78 - 0.91)
Fang (2017)[281]	ICD-9	Inpatients in USA	Venous thromboembolism	All	2,890	Medical chart review by clinical reviewer based on predetermined definition	0.65 (0.63 - 0.66)
Gerstman (1990)[282]	ICD-9	Female inpatients age 15-44 in USA	Venous thromboembolism	Not stated	132	Medical chart review by 2 clinical reviewers based on predetermined definition, with discrepancies resolved by 3rd reviewer	0.43 (0.34 - 0.51)
Ingeman (2010)[260]	ICD-10	Inpatients with stroke in Denmark	Venous thromboembolism	All	19	Medical chart review by study reviewer based on predetermined case definition	0.83 (0.67 - 0.98)
Molander (2022)[283]	ICD-10	Inpatients with rheumatoid arthritis in Sweden	Venous thromboembolism	All	269	Medical chart review by study clinical reviewer based on predetermined case definition	0.87 (0.83 - 0.91)

Ohman (2018)[284]	ICD-8, ICD-9 and ICD-10	Inpatients in Sweden	Venous thromboembolism	All	2,450	Medical chart review by 3 clinical reviewers based on predetermined case definition, with discrepancies resolved by consensus	0.72 (0.70 - 0.74)
Prat (2018)[285]	ICD-10	Inpatients in France	Venous thromboembolism	Primary only	200	Medical chart review by 2 study clinical reviewers based on predetermined case definition, with discrepancies resolved by consensus	0.96 (0.93 - 0.99)
Sanfilippo (2015)[286]	ICD-9	Inpatients and outpatients with Non-Hodgkins lymphoma in USA	Venous thromboembolism	All	150	Medical chart review by 2 study clinical reviewers based on predetermined case definition	0.71 (0.64 - 0.79)
Scarvelis (2010)[287]	ICD-9	Inpatients in Canada	Pulmonary embolism	All	612	Medical chart review by 2 reviewers based on predetermined case definition, with discrepancies resolved by a 3rd reviewer	0.81 (0.78 - 0.84)
Severinsen (2010)[288]	ICD-8 and ICD-10	Inpatients and outpatients in Denmark	Venous thromboembolism	All Primary only	1,100 687	Medical chart review by study clinical reviewer based on predetermined case definition	0.58 (0.56 - 0.61) 0.77 (0.74 - 0.80)
Sundboll (2016)[289]	ICD-10	Inpatients and outpatients in Denmark	Venous thromboembolism	All	200	Medical chart review by study clinical reviewer based on clinical judgement	0.96 (0.93 - 0.99)
White (2010)[290]	ICD-9	Inpatients in USA	Venous thromboembolism	All Primary only	3,456 1,096	Medical chart review by 2 clinical reviewers based on predetermined case definition	0.82 (0.80 - 0.83) 0.95 (0.94 - 0.96)

Table 4-4: Summary of diagnostic accuracy studies evaluating routinely collected data-derived venous thromboembolism events.

Study	Coding system	Population	Target condition	Diagnostic positions	Number of participants	Reference standard	Blinding to index result	Sensitivity (95% CI)	Specificity (95% CI)
Birman-Deych (2005)[291]	ICD-9	Inpatients with atrial fibrillation in USA	Deep vein thrombosis	All	23,657*	Medical chart review by independent reviewer based on predetermined case definition	Yes	0.60 (0.55 - 0.66)	0.997 (0.996 - 0.997)
Heckbert (2004)[292]	ICD-9	Female inpatients and outpatients in USA	Pulmonary embolism	All	6,834†	Independent adjudicated clinical trial data collection as safety endpoint	Yes	0.80 (0.70 - 0.90)	0.999 (0.998 - 0.999)
Ingeman (2010)[260]	ICD-10	Inpatients with stroke in Denmark	Pulmonary embolism	All	564‡	Medical chart review by study reviewer based on predetermined case definition	No	0.00 (0.00 - 0.37)	0.997 (0.992 - 1.000)
Johnson (2021)[293]	ICD-10	Inpatients with signs/ symptoms of pulmonary embolism in USA	Pulmonary embolism	All	970§	Medical chart review by 2 study clinical reviewers based on predetermined case definition, with discrepancies resolved by a 3rd study clinical reviewer	Uncertain	0.92 (0.87 - 0.96)	0.908 (0.889 - 0.928)

* *Index test positive, n=279. Reference standard positive, n=332.*
† *Index test positive, n=58. Reference standard positive, n=61.*
‡ *Index test positive, n=0. Reference standard positive, n=8.*
§ *Index test positive, n=193. Reference standard positive, n=126.*

All located VTE studies took place in North America and Europe and used the ICD coding system.

Three case validation studies made direct comparisons between restricting to codes in the primary diagnostic position and all diagnostic positions. This increased relative PPV by between 16% and 48%, but reduced the absolute number of reference standard cases identified by between 24% and 63%. The highest reported PPV for VTE events (0.97) was in a study restricting events to the primary diagnostic position. Two studies found PPV was higher in diagnostic codes for hospitalised patients compared with those in the community[281,289]. Incorporating the use of other data sources, such as anticoagulant prescriptions and radiological investigations, increased PPV where this approach was utilised[281-283,286]. When both anticoagulant prescriptions and imaging procedure codes were evaluated, the addition of the imaging procedure code did not improve performance further compared with anticoagulant prescriptions alone[286]. There was consensus in the reviewed literature that the PPV of PE diagnostic codes was higher than that of DVT diagnostic codes, when directly comparing codes within the same study population[276,281,284,288].

4.2.3.4 GI complications

Across 13 case validation studies of RCD-derived GI complication events there was a median PPV of 0.72 (IQR 0.48 – 0.86) (Table 4-5, Table 4-9). Only a single diagnostic accuracy study was identified (Table 4-6).

.

Table 4-5: Summary of case validation studies evaluating routinely collected data-derived gastrointestinal complication events.

Study	Coding system	Population	Target condition	Diagnostic positions	Total number of index cases	Reference standard	Positive Predictive Value (95% CI)
Al Ani (2015)[276]	ICD-10	Emergency department patients in Canada	Gastrointestinal bleeding	Not stated	100	Medical chart review by 2 reviewers based on predetermined definition, with discrepancies resolved by 3rd reviewer	0.81 (0.73 - 0.88)
Arnason (2006)[278]	ICD-9	Inpatients in Canada	Gastrointestinal bleeding	Not stated	158	Medical chart review by independent reviewer based on predetermined definition	0.89 (0.84 - 0.94)
Abraham (2006)[294]	ICD-9	Inpatients and outpatients receiving non-steroidal anti-inflammatory drugs in USA	Gastrointestinal complications	All	606	Medical chart review by 2 study reviewers based on predetermined definition, with discrepancies resolved by a 3rd study clinical reviewer	0.27 (0.23 - 0.30)
Andrade (2002)[295]	ICD-9	Inpatients in USA	Gastrointestinal bleeding	All Primary only	884 347	Adjudication by 2 study reviewers of abstracted case notes based on predetermined definition, with discrepancies resolved by a 3rd study clinical reviewer	0.24 (0.21 - 0.26) 0.46 (0.40 - 0.51)
Cattaruzzi (1999)[296]	ICD-9	Inpatients in Italy	Gastrointestinal bleeding	Primary only	660	Medical chart review based on predetermined definition	0.68 (0.64 - 0.71)
Curtis (2011)[297]	ICD-9	Inpatients with rheumatoid arthritis in USA	Gastrointestinal perforation	All	92	Adjudication by 2 study clinical reviewers of abstracted case notes based on predetermined definition, with discrepancies resolved by consensus	0.92 (0.86 - 0.97)
Orso (2020)[298]	ICD-9	Inpatients in Italy	Gastrointestinal complications	Primary only	445	Medical chart review by clinical reviewer based on predetermined definition	0.87 (0.84 - 0.90)
Pisa (2013)[299]	ICD-9	Inpatients receiving non-steroidal anti-inflammatory drugs in Italy	Gastrointestinal complications	All	2,024	Adjudication by 3 study clinical reviewers of abstracted case notes based on predetermined definition, with discrepancies resolved by consensus	0.47 (0.45 - 0.49)
Raiford (1995)[300]	ICD-9	Inpatients in Canada	Gastrointestinal complications	Primary only	1,762	Adjudication by study reviewer of abstracted case notes based on predetermined definition	0.88 (0.86 - 0.89)

Shehab (2019)[301]	ICD-10	Inpatients receiving anticoagulants in USA	Gastrointestinal bleeding	All Primary only	252 191	Medical record review by study clinical reviewer based on predetermined definition	0.75 (0.70 - 0.80) 0.85 (0.79 - 0.89)
Tanigawa (2019)[302]	ICD-10	Inpatients in Japan	Gastrointestinal perforation	All Primary only	100 35	Medical record review by 2 clinical reviewers based on predetermined definition, with discrepancies resolved by 3rd clinical reviewer	0.47 (0.38 - 0.57) 0.66 (0.49 - 0.79)
Valkhoff (2014)[303]	ICD-9 and ICD-10	Inpatients and outpatients in Italy and Denmark	Gastrointestinal bleeding	Not stated	543	Adjudication by clinical reviewer of abstracted case notes based on predetermined definition	0.76 (0.72 - 0.79)
Wahl (2010)[304]	ICD-9	Inpatients receiving non-steroidal anti-inflammatory drugs in USA	Gastrointestinal complications	Not stated	193	Adjudication by 2 independent clinical reviewers based on clinical judgement, with discrepancies resolved by blinded 3rd clinical reviewer	0.56 (0.49 - 0.63)

Table 4-6: Summary of diagnostic accuracy study evaluating routinely collected data-derived gastrointestinal complication events.

Study	Coding system	Population	Target condition	Diagnostic positions	Number of participants	Reference standard	Blinding to index result	Sensitivity (95% CI)	Specificity (95% CI)
Joos (2019)[305]	ICD-10	Inpatients receiving anticoagulants in USA	Gastrointestinal bleeding	All	487*	Medical record review by 2 independent reviewers based on predetermined definition, with discrepancies resolved by 3rd independent reviewer	Yes	0.89 (0.77 - 1.00)	0.957 (0.939 - 0.976)

* *Index test positive, n=40. Reference standard positive, n=23*.

All studies found used the ICD coding systems, most commonly ICD-9 (10/14 studies), and all but one took place in North America or Europe.

Three case validation studies compared primary diagnostic position events with all positions, and reported between 13% and 92% higher PPVs, but identified between 15% and 51% fewer reference standard cases. A single study found that incorporating procedure code data into the identification algorithm increased PPV[294].

4.2.3.5 Diabetes mellitus

Across six case validation studies evaluating RCD-derived diagnosis of diabetes mellitus there was a median PPV of 0.93 (IQR 0.87 – 0.98) (Table 4-7, Table 4-9) and results from 33 diagnostic accuracy studies were found to have a pooled sensitivity of 0.87 [95% CI 0.84 – 0.90] and a pooled specificity of 0.979 [95% CI 0.968 – 0.986] (Table 4-8, Table 4-9).

Table 4-7: Summary of case validation studies evaluating routinely collected data-derived diagnoses of diabetes mellitus.

Study	Coding system	Population	Target condition	Diagnostic positions	Total number of index cases	Reference standard	Positive Predictive Value (95% CI)
Crane (2006)[306]	ICD-9	Outpatients with HIV in USA	Diabetes mellitus	Not stated	98	Medical record review	0.54 (0.44 - 0.64)
Gini (2016)[307]	ICD-9	Outpatients in Italy	Diabetes mellitus	Not stated	300	Medical record review by independent clinical reviewer based on clinical judgement	0.99 (0.98 - 1.00)
Juurlink (2006)[308]	ICD-9	Inpatients in Canada	Diabetes mellitus	All	1,647	Medical record review	0.91 (0.90 - 0.93)
Solberg (2006)[309]	ICD-9	Inpatients and outpatients in USA	Diabetes mellitus	Not stated	20	Medical record review by study clinical reviewer based on clinical judgement	0.92 (0.81 - 1.00)
Thygesen (2011)[310]	ICD-10	Inpatients in Denmark	Diabetes mellitus	Not stated	50	Medical record review by study clinical reviewer based on clinical judgement	0.93 (0.86 - 1.00)
Zgibor (2007)[311]	ICD-9	Outpatients with endocrine disorders in USA	Diabetes mellitus	Not stated	643	Medical record review by reviewer based on pre-determined definition	0.95 (0.93 - 0.96)

Table 4-8: Summary of diagnostic accuracy studies evaluating routinely collected data-derived diagnoses of diabetes mellitus.

Study	Coding system	Population	Target condition	Diagnostic positions	Number of participants	Reference standard	Blinding to index result	Sensitivity (95% CI)	Specificity (95% CI)
Ahmad (2017)[312]	ICD-9	Inpatients and outpatients age 45-84 in USA	Diabetes mellitus	Not stated	630*	Independent research study data collection based on predetermined case definition	Yes	0.76 (0.68 - 0.85)	0.952 (0.935 - 0.970)
Birman-Deych (2005)[291]	ICD-9	Inpatients with atrial fibrillation in USA	Diabetes mellitus	All	23,657†	Medical chart review by independent reviewer based on predetermined case definition	Yes	0.75 (0.74 - 0.76)	0.994 (0.993 - 0.995)
Borzecki (2004)[313]	ICD-9	Inpatients and outpatients with hypertension in USA	Diabetes mellitus	All	1,176‡	Medical record review based on predetermined case definition	Unclear	0.96 (0.95 - 0.98)	0.963 (0.950 - 0.976)
Chen (2010)[314]	ICD-9 and ICD-10	Outpatients age ≥35 in Canada	Diabetes mellitus	All	3,362§	Medical chart review by reviewer based on pre-determined case definition	Unclear	0.86 (0.82 - 0.90)	0.970 (0.964 - 0.976)
Fleming (2011)[315]	ICD-9	Inpatients and outpatients with breast or prostate cancer in USA	Diabetes mellitus	Not stated	4,300**	Medical chart review by reviewer based on pre-determined case definition	Unclear	0.80 (0.77 - 0.83)	0.935 (0.926 - 0.943)

* *Index test positive, n=93. Reference standard positive, n=89.*
† *Index test positive, n=4,987. Reference standard positive, n=6,519.*
‡ *Index test positive, n=382. Reference standard positive, n=365.*
§ *Index test positive, n=326. Reference standard positive, n=273.*
** *Index test positive, n=859. Reference standard positive, n=789.*

Fuentes (2019)[316]	ICD-10	Inpatients and outpatients age 18-69 in France	Diabetes mellitus	All	45,739*	Independent research study data collection based on predetermined case definition	Yes	0.94 (0.92 - 0.95)	0.999 (0.999 - 1.000)
Hara (2018)[317]	ICD-10	Inpatients and outpatients in Japan	Diabetes mellitus	Not stated	52,014†	Independent government screening data collection based on predetermined case definition	Yes	0.91 (0.91 - 0.92)	0.925 (0.923 - 0.927)
Harris (2010)[318]	ICD-9	Outpatients in Canada	Diabetes mellitus	Not stated	19,443‡	Medical record review by study reviewer based on predetermined case definition	Unclear	0.75 (0.73 - 0.77)	0.982 (0.980 - 0.984)
Humphries (2000)[319]	ICD-9	Inpatients undergoing percutaneous coronary intervention in Canada	Diabetes mellitus	Not stated	817§	Medical record review by study non-clinical reviewer based on predetermined case definition	Unclear	0.78 (0.71 - 0.85)	0.985 (0.976 - 0.994)
Hux (2002)[320]	ICD-9	Outpatients in Canada	Diabetes mellitus	All	3,317**	Medical record review based on predetermined case definition	Unclear	0.88 (0.85 - 0.91)	0.923 (0.914 - 0.933)
Jollis (1993)[321]	ICD-9	Inpatients undergoing coronary angiogram in USA	Diabetes mellitus	All	12,818††	Independent clinical database propsectively collected by clinicians	Yes	0.83 (0.81 - 0.84)	0.975 (0.972 - 0.978)

* *Index test positive, n=1,116. Reference standard positive, n=1,157.*
† *Index test positive, n=7,523. Reference standard positive, n=4,318.*
‡ *Index test positive, n=1,935. Reference standard positive, n=2,180.*
§ *Index test positive, n=120. Reference standard positive, n=142.*
** *Index test positive, n=576. Reference standard positive, n=399.*
†† *Index test positive, n=2,323. Reference standard positive, n=2,488.*

Kadhim-Saleh (2013)[322]	ICD-9	Older age outpatients in Canada	Diabetes mellitus	Not stated	313*	Medical record review based on predetermined case definition	Yes	0.97 (0.92 - 1.00)	0.981 (0.965 - 0.998)
Kashner (1998)[323]	ICD-9	Inpatients in USA	Diabetes mellitus	All	414†	Medical record review	Yes	0.91 (0.84 - 0.99)	0.954 (0.932 - 0.975)
Lee (2005)[324]	ICD-9	Inpatients and outpatients with heart failure in Canada	Diabetes mellitus	All	1,592‡	Medical record review by clinical reviewer based on predetermined case definition	Unclear	0.81 (0.78 - 0.84)	0.982 (0.974 - 0.990)
Lipscombe (2018)[325]	ICD-9 and ICD-10	Inpatients and outpatients in Canada	Diabetes mellitus	All	152,177§	Independent research study data collection based on predetermined case definition	Yes	0.94 (0.94 - 0.94)	0.917 (0.915 - 0.918)
Luthi (2007)[326]	ICD-10	Inpatients in Switzerland	Diabetes mellitus	All	890**	Medical record review by clinical reviewer based on predetermined case definition	Yes	0.69 (0.58 - 0.81)	0.950 (0.935 - 0.965)
Marrie (2012)[327]	ICD-9 and ICD-10	Inpatients and outpatients with multiple sclerosis in Canada	Diabetes mellitus	All	430††	Medical record review by 1 reviewer	Yes	0.78 (0.62 - 0.95)	0.935 (0.911 - 0.959)
McGinnis (2020)[328]	ICD-10	Inpatients and outpatients with high HIV	Diabetes mellitus	Not stated	1,753‡‡	Adjudication of abstraced medical records by 2 clinical	Unclear	0.84 (0.81 - 0.87)	0.933 (0.918 - 0.947)

* *Index test positive, n=56. Reference standard positive, n=53.*
† *Index test positive, n=65. Reference standard positive, n=53.*
‡ *Index test positive, n=444. Reference standard positive, n=526.*
§ *Index test positive, n=26,884. Reference standard positive, n=16,581.*
** *Index test positive, n=83. Reference standard positive, n=61.*
†† *Index test positive, n=41. Reference standard positive, n=19.*
‡‡ *Index test positive, n=536. Reference standard positive, n=543.*

		prevalence in USA				reviewers based on predetermined case definition, with discrepancies resolved by 3rd clinical reviewer			
Morris (1997)[329]	ICD-9	Inpatients and outpatients in Scotland	Diabetes mellitus	All	35,144*	Adjudication of abstracted medical records based on predetermined case definition	Uncertain	0.95 (0.94 - 0.97)	0.999 (0.999 - 0.999)
Nedkoff (2013)[330]	ICD-9 and ICD-10	Inpatients with coronary heart disease in Australia	Diabetes mellitus	All	3,943†	Medical record review by 1 non-clinical reviewer based on predetermined case definition	Unclear	0.90 (0.89 - 0.92)	0.967 (0.960 - 0.974)
Nimmo (2021)[331]	ICD-10	Inpatients with end stage kidney disease in UK	Diabetes mellitus	All	5,461‡	Independent research study data collection based on predetermined case definition	Yes	0.98 (0.97 - 0.98)	0.960 (0.954 - 0.967)
Peng (2017)[332]	ICD-10	Inpatients in Canada	Diabetes mellitus	All	4,007§	Medical chart review by clinical reviewer based on predetermined case definition	Unclear	0.84 (0.81 - 0.87)	0.954 (0.947 - 0.961)
Powell (2001)[333]	ICD-9	Inpatients with heart disease in Australia	Diabetes mellitus	All	1,765**	Medical chart review by study clinical reviewer based on predetermined case definition	Yes	0.88 (0.85 - 0.92)	0.995 (0.991 - 0.998)

* *Index test positive, n=641. Reference standard positive, n=636.*
† *Index test positive, n=1,146. Reference standard positive, n=1,169.*
‡ *Index test positive, n=1,616. Reference standard positive, n=1,496.*
§ *Index test positive, n=585. Reference standard positive, n=505.*
** *Index test positive, n=294. Reference standard positive, n=325.*

Preen (2004)[334]	ICD-9	Inpatients in Australia	Diabetes mellitus	Not stated	2,037*	Medical record review by 2 clinical reviewers based on clinical judgement	Yes	0.86 (0.80 - 0.92)	0.998 (0.997 - 1.000)
Quan (2002)[335]	ICD-9	Inpatients in Canada	Diabetes mellitus	All	1,200†	Medical record review by clinical reviewer based on predetermined case definition	Yes	0.81 (0.73 - 0.88)	0.967 (0.957 - 0.978)
Quan (2008)[336]	ICD-10	Inpatients in Canada	Diabetes mellitus	All	4,008‡	Medical chart review by clinical reviewer based on predetermined case definition	Unclear	0.76 (0.72 - 0.80)	0.986 (0.982 - 0.990)
Tu (2011)[337]	ICD-9	Outpatients in Canada	Diabetes mellitus	All	969§	Medical chart review based on predetermined case definition	Unclear	0.84 (0.76 - 0.92)	0.987 (0.979 - 0.994)
Van Doorn (2001)[338]	ICD-9	Inpatients age ≥70 in USA	Diabetes mellitus	Not stated	524**	Medical chart review by cliniacl reviewer based on predetermined case definition	Unclear	0.66 (0.57 - 0.75)	0.970 (0.953 - 0.986)
Weintraub (1999)[339]	ICD-9	Inpatients undergoing coronary angiogram in USA	Diabetes mellitus	All	11,833††	Independent clinical database propsectively collected based on predetermined case definition	Yes	0.87 (0.86 - 0.88)	0.990 (0.988 - 0.992)

* *Index test positive, n=109. Reference standard positive, n=124.*
† *Index test positive, n=119. Reference standard positive, n=104.*
‡ *Index test positive, n=409. Reference standard positive, n=477.*
§ *Index test positive, n=76. Reference standard positive, n=77.*
** *Index test positive, n=78. Reference standard positive, n=101.*
†† *Index test positive, n=2,356. Reference standard positive, n=2,603.*

Wilchesky (2004)[340]	ICD-9	Outpatients in Canada	Diabetes mellitus	Not stated	14,980*	Medical chart review based on predetermined case definition	Unclear	0.64 (0.63 - 0.66)	0.968 (0.965 - 0.971)
Williamson (2014)[341]	ICD-9	Older age outpatients in Canada	Diabetes mellitus	Not stated	1,920†	Medical chart review based on predetermined case definition	Yes	0.95 (0.93 - 0.97)	0.970 (0.962 - 0.978)
Wilson (2001)[342]	ICD-9	Inpatients in USA	Diabetes mellitus	Not stated	465‡	Medical record review by clinical reviewer based on predetermined case definition	Yes	0.89 (0.82 - 0.97)	0.988 (0.977 - 0.999)
Youngson (2016)[343]	ICD-9 and ICD-10	Inpatients with ST-elevation myocardial infarction in Canada	Diabetes mellitus	All	3,072§	Independent research study data collection based on predetermined case definition	Yes	0.94 (0.92 - 0.96)	0.944 (0.935 - 0.953)

* *Index test positive, n=2,162. Reference standard positive, n=2,752.*
† *Index test positive, n=355. Reference standard positive, n=323.*
‡ *Index test positive, n=59. Reference standard positive, n=61.*
§ *Index test positive, n=688. Reference standard positive, n=584.*

Sensitivity of derivation algorithms from diagnostic codes were increased by incorporating other data sources to detect diagnosis of diabetes mellitus, including laboratory records of glucose and HbA1c[306,337] and diabetes-specific medications[306,329,337]. Primary care databases were vital in identifying diabetes cases and appeared more reliable than using secondary care databases alone[334]. Some studies suggest a criteria of using more than 1 diagnosis code in a primary care dataset should be used to enhance PPV[309,313].

The findings of the studies relating to metabolic complications, long bone or vertebral fracture, psychiatric complications, and acute liver injury are presented in Supplementary Table 6 to Supplementary Table 10. There were no relevant studies relating to the diagnostic performance of codes relating to long COVID.

4.2.3.6 Summary of validity and diagnostic accuracy results

The summary measures of diagnostic performance from the case validation and diagnostic accuracy studies for each target condition are presented in Table 4-9.

Table 4-9: Summary measures of validity and diagnostic accuracy results from the systematic literature review of studies relating to thesis extended analysis outcomes.

Assessment	Median Positive Predictive Value (Interquartile range)	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)
Infections	0.84 (0.72 - 0.90)	0.47 (0.13 - 0.84)	0.968 (0.833 - 0.995)
Venous thromboembolism	0.78 (0.64 - 0.84)	0.70 (0.31 - 0.92)	0.996 (0.959 - 1.000)
Gastrointestinal complications	0.72 (0.48 - 0.86)	-	-
Diabetes mellitus	0.93 (0.87 - 0.98)	0.87 (0.84 - 0.90)	0.979 (0.968 - 0.986)
Metabolic complications	0.66 (0.56 - 0.76)	-	-
Long bone or vertebral fractures	0.85 (0.72 - 0.95)	-	-
Psychiatric complications	-	0.11 (0.01 - 0.70)	0.996 (0.987 - 0.999)
Acute liver injury	0.54 (0.40 - 0.69)	-	-
Long COVID	-	-	-

4.2.4 Discussion

4.2.4.1 Key methodological considerations

In the case validation and diagnostic accuracy studies identified in this literature review, RCD diagnosis codes broadly had high specificity, moderate-to-high PPV, and low sensitivity compared with manual medical record review. Diagnostic codes may have missed large numbers of true reference standard events, but false positives were reasonably uncommon. This suggests the absence of a diagnostic code was not well-suited to excluding that the diagnosis occurred, but when a diagnostic code was present within RCD, it was often a true event. This pattern of misclassification bias would typically result in a biased absolute risk estimate (due to systematically lower event numbers), but a low risk of bias for measures of relative risk (providing the mechanism of misclassification was independent of randomised treatment allocation) – the primary requirement for a randomised trial[256,273,344].

The performance of RCD diagnosis codes for assessing individual patient-level clinical events was variable - impacted by specific disease and data source factors[345]. The sensitivity, specificity, and PPV of RCD-derived events could be altered by modifying diagnosis codes or data source parameters in the derivation algorithm. Modifications that increased sensitivity usually came at the expense of specificity and PPV, and modifications that increased specificity and PPV usually came at the expense of sensitivity. For example, clinical condition codelists could be made more sensitive or specific by using a comprehensive or restrictive set of codes[256,265,345].

4.2.4.2 Validity and accuracy of diagnostic codes for extended analysis assessments

There was considerable variability in results between studies and target conditions. A first group of key planned extended analysis outcomes relating to potential immunomodulatory treatment-related harms, including non-COVID infections, VTE, and GI complications,

should have high specificity and acceptable PPV based on available existing evidence. The events are common enough that evaluation in the extended analysis should have meaningful accuracy and precision. PE diagnosis codes had better diagnostic performance than DVT codes. PEs are likely to represent the majority of VTE events in the extended analysis - available RECOVERY CRF data (outside of the dexamethasone and tocilizumab comparisons) suggests PEs were more common - with an estimated incidence of 4% for PE and 0.4% for DVT within 28 days of randomisation. Some of the GI complication studies identified reported lower PPVs but these had strict reference standard criteria. For example, they required GI bleeding to be confirmed by an endoscopic or surgical procedure in order to be classified as a confirmed case[294,295,299]. An additional GI complication diagnostic accuracy study, evaluating UK routine data ICD-10 diagnostic codes against adjudicated follow-up in a large randomised trial, was identified after the completion of the method development literature search[346]. This study reported a sensitivity of 0.55 [95% CI 0.49 – 0.61] and a specificity of 0.994 [95% CI 0.992 – 0.995] for routine data-derived GI bleeding events - which compares favourably to other target conditions.

A second group of planned extended analysis outcomes had important evidence gaps, or lower PPV or specificity reported – namely metabolic complications, liver injury, psychiatric complications and long COVID. Assessments of these conditions may have less accuracy when used in the extended analysis and will need to be interpreted accordingly. For metabolic complications, there were no studies directly evaluating hyperglycaemia diagnosis codes which would be anticipated to be the most common metabolic complication event in this study. Liver injury events had the lowest median PPV of all evaluated assessments, but this was based on a small number of studies and affected by strict outcome definitions which may have led to an under-estimate of the true PPV. These studies often required evidence of coagulopathy to qualify as reference

standard liver injury events. Both hyperglycaemia and liver injury events can also be evaluated from ISARIC4C CRF data to provide an alternative assessment using recorded blood test results, in addition to the RCD diagnosis code-derived assessment. For psychiatric complications, only studies evaluating delirium diagnosis codes were found. Delirium would be anticipated to be the most common extended analysis psychiatric complication event but the poor sensitivity suggests event numbers for this assessment could be too low to evaluate with meaningful precision. No studies of long COVID codes were identified, likely due to the recent development of the COVID-19 pandemic and the absence of a definitive diagnostic definition. Walker et al. performed a comprehensive review of long COVID clinical coding in UK primary care records across a cohort of 58 million patients[212]. Long COVID diagnostic codes were not issued for use until November 2020 and were not widely adopted in primary care coding until February 2021. This suggests that follow-up times may need to extend to well within this period to capture long COVID diagnoses and that diagnoses made before this time could be missed. The rate of coding found in primary care compared to population estimates of prevalence suggests that clinical coding vastly underestimates the self-reported high prevalence of long COVID symptoms in the UK population[69].

A third group of planned extended analysis outcome events - incident diabetes mellitus and long bone or vertebral fractures - appear to have good PPV, specificity and sensitivity. These assessments should be accurate, but their post-randomisation incidence may be too low to evaluate with meaningful precision. The best quality of evidence of diagnostic performance was found in studies evaluating RCD-derived diagnoses of diabetes mellitus.

4.2.4.3 Data source factors

Modification of data source factors represented a trade-off between sensitivity and specificity, and therefore between minimising bias in measures of relative risk compared with sufficient statistical power to allow meaningful precision in conclusions.

The literature review study results showed an overall pattern of primary position diagnosis codes displaying higher specificity and PPV compared to codes from all positions, findings which are supported in a previous systematic review of RCD-derived infection events[345]. The magnitude of this difference was inexact, but estimated PPV appeared roughly one third higher when restricting to primary diagnostic position only. However, restricting to primary diagnostic position also substantially reduces the number of detected events, missing roughly one half to two thirds of previously correctly identified reference standard events. This trade-off will be central to the decision on final definitions for the extended analysis assessments derived from RCD.

The use of multiple complementary data sources could be a useful tool to enhance sensitivity or specificity. Microbiology data could augment infection event data collection[347], medication prescription data appeared useful in VTE, diabetes, and psychiatric complications ascertainment[281,348,349], procedure data improved diagnostic performance in fracture event derivation[350], and laboratory data was useful for liver injury and diabetes[351,352]. These additional data sources, beyond clinical diagnostic codes, should aim to be included wherever feasible, with the breadth of collated RCD sources available in the extended analysis providing the potential to utilise this opportunity.

The care setting seemed to impact diagnostic performance in line with expected clinical presentation. For example, hospitalisation datasets appeared to have higher PPV for diagnosis code-derived events of acute medical conditions such as infections, VTE or GI complications[262,289,303]. Whereas for diabetes mellitus, a chronic health condition, primary care datasets had better sensitivity and specificity than secondary care datasets[353].

Factoring this into the inclusion of, and emphasis on, primary and secondary care datasets for the definitions of planned assessments should be considered.

4.2.4.4 Application of findings to RCD-derived assessments in randomised comparisons

None of the identified studies from the literature search used RCT data. Analyses using RCD for RCT follow-up have key differences compared with observational studies. The treatment allocation has been determined by randomisation, thereby eliminating confounding, particularly indication bias, which is highly relevant in COVID-19 treatment studies. High specificity but low sensitivity event derivation (like that observed in the studies identified in this literature review) applied to the RCT setting can minimise bias in the estimate of relative risk[354]. Low specificity events would result in extra false positive events being distributed between randomised treatment groups by chance. This could bias a treatment effect estimate towards the null, although, in large randomised trials the relative treatment effect estimate is robust even with substantial numbers of simulated extra false positive events[355]. Perfect specificity events would result in an unbiased estimate of the treatment effect. However, adequate sensitivity is required to detect a sufficient number of events to estimate the treatment effect with clinically meaningful precision. While RCD data quality remains important, if misclassification bias is not differential between randomised treatment groups this becomes less concerning than in non-randomised studies and should not affect conclusions[354,356]. The conclusions of RCTs are resistant to small imperfections in data, providing the misclassification remains non-differential and sample size is large.

RCD is collected by personnel who are independent of the trial and so bias between treatment groups related to outcome ascertainment should be less important. The importance of blinding (RECOVERY is an open-label trial) may also reduce because of this independence. However, RCD diagnoses are often coded directly from the medical notes of clinicians (who may be aware of the open-label trial treatment assignment) and

therefore it is possible some diagnoses recorded may still be indirectly influenced by knowledge of treatment assignment.

Event timing relative to randomisation is imperative in RCT follow-up to determine which events happened before and after randomisation. Within the hospitalisation datasets used in the extended analysis, episode structures are used which often span multiple days. When randomisation occurs within one of these episodes it is unclear as to whether events happened before or after randomisation. In the main HESAPC dataset, RECOVERY participants had a median peri-randomisation episode duration of 4 days. The effect of this RCT-specific consideration on diagnostic performance will be evaluated in the definition development testing (Section 4.3.3).

In the broader literature, direct comparisons of results of RCD follow-up with trial follow-up have found similar treatment effect estimates and precision, though most are limited to cardiovascular disease and cancer[357-362]. Interestingly, this was despite individual participant level event discrepancies as high as 40%, supporting the robustness of randomised analysis when discrepancies are not biased by treatment allocation. Indirect comparisons between RCD and traditional trial follow-up results for the same research question, but from different studies, have found mixed results. A systematic review comparing treatment effects in trials using exclusively RCD compared with those using traditional trial data found agreement on direction of treatment effect in the majority of cases, but in 63% of these the quantification of treatment effect was less favourable in the trials using RCD compared with traditional data[363]. The meta-analysis suggested a significant relative treatment effect estimate reduction of 20% with trials using RCD across all analysed trials without significant heterogeneity. The findings are caveated by potential differences in the populations between trials when using indirect comparisons. Furthermore, many of the clinical questions addressed looked at behavioural or preventative interventions and so the outcomes measured may be less reliably coded in

RCD than the planned assessment of clinical events in the extended analysis. When mortality outcomes alone were assessed (and as such were presumably less prone to misclassification bias) this treatment effect difference was less but remained approximately 10%. Conversely, another systematic review and meta-analysis assessed outcome in RCD-based registry trials compared to traditional RCTs and found no systematic difference between effect estimates between the two trial types[359]. The included studies were dominated by cardiovascular disease and cancer trials and these target condition differences may explain the differing conclusions.

4.2.4.5 Limitations of studies

Much of the available existing evidence came from case validation studies rather than full diagnostic accuracy studies. Within these case validation studies, there is inherent verification bias as only index test positive cases are having the reference standard assessment performed. Reference standard assessors are rarely blinded to the fact that all cases are index test positive and hence can be more likely to find confirmatory evidence in the medical record of the clinical event that they are looking for. This bias can be reduced by clear, predetermined case definitions, and multiple assessors, but this was not carried out in all studies. Across the infection, VTE and GI complications case validation studies, less than half of identified studies stated that validation was performed by multiple assessors using a predetermined definition.

Sensitivity and specificity measures are commonly reported from case validation studies but may be substantially biased in the direction of higher results. The effects of this major bias were aimed to be mitigated by reporting limited performance measures separately by study type[253]. However, this resulted in small numbers of studies contributing to pooled measures of sensitivity and specificity with corresponding imprecise estimates of diagnostic performance, particularly for sensitivity.

Within the full diagnostic accuracy studies meeting inclusion criteria, 40% reported uncertain or absent blinding of the reference standard assessors to the index test result. This leads to a risk of observer bias which can pre-dispose to over-estimation of reported measures of sensitivity and specificity.

Large numbers of the included studies used ICD-9 diagnostic codes rather than ICD-10. ICD-10 will be used in the extended analysis which could result in a change in performance. Where individual studies directly contrasted their results using ICD-10 compared to ICD-9 diagnostic codes, there were differences in performance, but the direction of changes in parameters differed according to assessment subtype. This suggested the effects of this change would be event-specific, with no clear overall pattern of effect of the change in ICD version[273,303]. There was not sufficient data to evaluate differences further. No identified studies used SNOMED codes; SNOMED is utilised in the primary care datasets available for the extended analysis and the likely performance of planned assessments that derive events using these codes is less certain.

Very few of the studies identified evaluated UK RCD sources, instead dominated by the USA, Canada, and Denmark (71% of all included studies). Diagnostic performance is likely to be influenced by individual methods of data collection and coding within each dataset. For example, many US studies use insurance claims databases as well as medical administrative datasets. The difference in dataset collection purpose may affect the type of diagnoses coded and their accuracy. In well-established Danish hospitalisation RCD, diagnoses are directly assigned by attending physicians rather than by clinical coding professionals from medical record review[259], which may improve their diagnostic performance. The consistency and accuracy of clinical coding is also likely to differ between settings, for example an Australian study included clinical coders receiving a very high level of training and audit, which may not be available in other settings[268]. The generalisability of the systematic review findings to data sources using ICD-10 codes in

the UK for this study is uncertain and emphasises the need for study-specific validation when possible.

4.2.5 Conclusions

Data quality and misclassification bias are a concern in RCD. Current evidence suggests most ICD diagnosis code-derived events from RCD are highly specific but poorly sensitive, resulting in preserved relative risk estimates – the primary aim of a randomised trial, but potentially biased absolute risk estimates. In the context of using RCD-derived events for outcome ascertainment in the extended analysis, the misclassification bias is likely to be non-differential across randomised treatment groups, resulting in a reduction in the precision of treatment effect estimates but preserving an unbiased point estimate.

Evidence suggests the utility of RCD for assessing individual patient-level diagnoses varies according to the specific disease, coding system and data source. Derivation parameters can be altered to modify diagnostic performance, including the diagnosis codes included in clinical codelists and diagnostic positions used. The use of multiple complementary data sources can enhance sensitivity or specificity. Knowledge of individual assessment differences should be factored into final assessment definitions and the interpretation of the results they produce.

The optimal approach to constructing definitions and derivations of assessments from RCD is study-specific and will differ depending on the data sources, assessments planned, study design and aims of the research. The final assessment definitions used in the thesis extended analysis will be based on the study aims and should be informed by corresponding study-specific validation results where possible. This is assessed further in the following Section 4.3.

4.3 Definition Development Process

4.3.1 Introduction

For each extended analysis assessment, a final definition was developed by systematically creating a clinical codelist and testing the provisional assessment against linked RECOVERY, ISARIC4C, or other available RCD data. This process evaluated the assessment validity, optimised data source parameters, and informed the final assessment selection and outcome hierarchy. Key considerations in the process were to balance specificity – to optimise assessment accuracy – and sensitivity – to optimise assessment precision; to consider the evidence from the method development literature review; and to maintain a degree of consistency in definitions across assessments. All method development testing was carried out blinded to RECOVERY randomised treatment allocation, unless explicitly stated.

The extended analysis assessments were chosen by integrating the thesis aims, the identified knowledge gaps from the Introduction and Systematic Review chapters, data availability within the RCD sources, findings from the method development literature review, and discussion with experts in clinical trials and infectious diseases.

4.3.2 Clinical codelist development

Once the candidate list of assessments to be investigated had been established, a set of clinical codelists for capturing the occurrence of these assessments from RCD was developed. The codelists were constructed in a series of steps, according to identified best practice research methods[364]:

i) Creation of a clear provisional definition for each assessment.

The scope of each outcome and baseline characteristic was decided and defined clearly. For example, GI complications was defined as any diagnosis of GI tract bleeding, ulceration, or perforation.

ii) Identification of data sources and associated coding systems.

The potential application of each RCD dataset and associated coding system was considered for each assessment. For example, GI complication events could arise from ICD-10 diagnosis codes in hospitalisation or mortality datasets, or OPCS-4 procedures codes from hospitalisation datasets. SNOMED clinical terms and BNF code medication prescriptions from primary care datasets were not included for GI complications because of an absence of appropriate code clusters from the GDPPR dataset and no suitably specific medication prescription identified from the medication dispensing dataset.

iii) Compilation of a comprehensive longlist of potentially relevant codes.

The longlist sought to include all possible codes for an assessment, maximising the sensitivity of the codelist using a combination of approaches:

- Review of relevant, pre-existing clinical codelists available from publications identified during the method development literature review;
- Search of any potentially relevant publically-available clinical codelist repositories from academic or healthcare institutions: University of Oxford[365], University of Manchester[366], London School of Hygiene and Tropical Medicine[367] and NHS Digital 'cluster refsets' for GDPPR data[368];
- Review of pre-existing internally developed codelists utilised at the Oxford Population Health department (for example, the RECOVERY trial 'Cause of Death' ICD-10 code classification);
- Manual review of complete ICD-10, OPCS-4, and BNF coding system lists categorising potentially relevant codes for any assessment. Manual review

of the full SNOMED clinical terms list was not feasible as there are >300,000 clinical terms;

- Search of each coding system list using a pre-determined set of search terms relating to each assessment;
- A specific separate classification was used for capturing microbiologically-diagnosed non-COVID infections. A list of all organisms identified from the UKHSA secondary infection dataset was extracted. These were coded by the thesis author (a microbiology clinician) into probable categories of 'clinically relevant' or 'not clinically relevant' isolates, based on clinical knowledge of the organism and specimen type, with the aim of excluding common contaminants or commensals from the anatomical site of specimen collection.

iv) Manual review of longlist to exclude inappropriate codes.

Review of the longlist for each assessment to consider the appropriateness of each individual code, discarding obvious errors or codes that were likely to be poorly specific.

v) Testing with other data sources and refinement.

The clinical codelist then underwent further minor revision during the assessment definition testing phase. Codes that had clearly been missed or were very poorly specific in testing were re-reviewed and added or removed, as appropriate.

vi) Independent review of codelist by second clinician, with any disagreements resolved by discussion to reach consensus.

A second clinician reviewed the provisional codelists, directly comparing them to the stated assessment definition. Any uncertainties were discussed, and a consensus reached for code inclusion within the assessment clinical codelist. Once this step was complete, the clinical codelists for each assessment were finalised.

4.3.3 Assessment definition testing methods

4.3.3.1 Assessment definitions

For the each of the assessments tested, the provisional assessment codelist created for step v) above was used for early testing within the RCD and then the finalised assessment codelist (Appendix Section B.2) was used for diagnostic accuracy compared with RECOVERY and ISARIC4C.

4.3.3.2 Manual dataset review

An RCD record review of a random sample of up to 50 RECOVERY participants (in any treatment comparison) with each outcome or baseline characteristic present at any time, based on the provisional assessment codelist, was performed. The purpose of this review was to ascertain if the provisional definitions had reasonable face validity based on clinical judgement and no quantitative data collection was performed.

For the HESAPC dataset, this was done using a university department software programme ('Heliograph') that allows clinicians to manually review a participant's full HESAPC record split by spells and by episodes, allowing an easy overview of a patient's hospital admission and associated diagnostic codes. A similar process was performed in other datasets by filtering manually by participant ID and reviewing records via the RStudio data viewer window.

4.3.3.3 Case validation compared with manual medical record review

For a single RECOVERY study site, a manual electronic medical record review was performed for all participants who were defined as having an RCD-derived outcome present, according to the provisional assessment codelist, at any time within the HESAPC record. This aimed to function as a further validity assessment of RCD-derived outcome events – providing a quantitative estimate of PPV to compare between thesis assessments and the wider literature identified.

A pre-determined case definition for each assessment was recorded and then the medical record was reviewed between the start and end date of the episode from which the event was derived to evaluate for the presence (true positive) or absence (false positive) of that outcome in the medical record, according to the pre-determined case definition. The PPV, with 95% CIs, for each assessment was calculated and reasons for false positives were recorded. All medical record reviews were performed by the thesis author, with knowledge of the RCD-derived outcome categorisation.

4.3.3.4 Evaluation of medication use by RCD-derived outcome status

A further RCD data source, not used for any extended analysis assessment derivation, was obtained from NHS Digital as part of RECOVERY trial follow-up - the Electronic Prescribing and Medications Administration (EPMA) secondary care medicines dataset. EPMA includes records of prescribed and administered medications from a subset (~15%) of English hospitals[369]. EPMA was utilised to compare rates of relevant medication use between participants with an RCD-derived outcome present and absent in any diagnostic position within the first 28 days after randomisation. The purpose of this testing was to provide an alternative assessment of validity of relevant outcomes, based on the objective presence or absence of medication administration.

A definition of relevant medication use was determined prior to testing for each relevant outcome, based on clinical judgement, and a codelist including these medications was constructed:

i) For infection diagnoses, systemic (intravenous (IV) or oral) anti-bacterials or anti-fungals.
ii) For GI bleeding diagnoses, IV proton pump inhibitors at a dose greater than or equal to the licensed dose for GI bleeding.
iii) For VTE diagnoses, subcutaneous, IV or oral anticoagulants at a dose greater than or equal to the licensed dose for treatment of VTE.

iv) For metabolic complications, subcutaneous or IV short-acting insulin, or oral glucose, or IV glucose at a concentration ≥10%.

v) For psychiatric complications, IV, oral or intramuscular haloperidol.

The prevalence of specified medication use was presented for participants with the outcome present (according to RCD-derived assessment definitions) and with the outcome absent. Medication use prevalence was calculated as follows:

i) For those with the outcome present,

$$\frac{\text{Number of participants who had a record of the medication being administered within the same hospital episode as the outcome event or within 3 days of the event date if not derived from hospital admission datasets}}{\text{Total number of participants who had a record of any medication being administered within the same hospital episode as the outcome event or within 3 days of the event date if not derived from the hospital admission datasets}}$$

ii) For those with the outcome absent,

$$\frac{\text{Number of participants who had a record of the medication being administered within 3 days of the median outcome event study day across all RECOVERY participants}}{\text{Total number of participants who had a record of any medication being administered within 3 days of the median outcome event study day across all RECOVERY participants}}$$

4.3.3.5 Validation of HFRS

The HFRS (derived from hospital admission RCD datasets) (Section 3.4.5.2) was evaluated against frailty assessments groups derived independently from the primary care RCD datasets.

Primary care frailty assessment groups were determined by available frailty SNOMED concept IDs within the 5 years prior to randomisation, comprising of either; an electronic Frailty Index (eFI) score – a validated score identifying participants living with frailty from primary care health records[370-372]; a Clinical Frailty Scale (CFS) score[373]; or a recorded global clinical judgement of frailty.

i) Fit: eFI score 0 to 0.12, or CFS 1 to 3 (‘Very fit’, ‘Well’, or ‘Managing well’).

ii) Mild: eFI score >0.12 to 0.24, or CFS 4 to 5 ('Vulnerable' or 'Mildly frail'), or 'Mild frailty' global clinical judgement recorded.

iii) Moderate: eFI score >0.24 to 0.36, or CFS 6 ('Moderately frail'), or 'Moderate frailty' global clinical judgement recorded.

iv) Severe: eFI score >0.36, or CFS 7 to 9 ('Severely frail', 'Very severely frail', 'Terminally ill'), or 'Severe frailty' global clinical judgement recorded.

Where a participant had multiple primary care frailty assessments recorded the closest record to randomisation was used.

The correlation between the primary care frailty assessment group and the HFRS group was assessed using Spearman's rank correlation coefficient[374].

The distribution of CFS score according to HFRS group was evaluated using the Kruskall-Wallis test[375].

4.3.3.6 Diagnostic accuracy compared with a reference standard of RECOVERY CRF data

The diagnostic accuracy of the extended analysis finalised codelists (representing the index test) using differing data source parameters was evaluated against a reference standard of RECOVERY trial data collection from the randomisation and follow-up CRFs. This was possible because later in RECOVERY, data was collected on these outcomes but not for the earlier treatment comparisons, such as the dexamethasone and tocilizumab comparisons (see Section 3.3.1.2). The purpose of the analysis was to offer further validation of assessments and provide quantitative estimates of diagnostic performance that could be used to compare between assessment definitions, inform data source parameter choices, and can be used in the interpretation of the final extended analysis results.

The following RCD-derived assessments were evaluated:

i) Outcomes:

- Major non-COVID infection during the index hospital admission, assessed against a reference standard of non-coronavirus infection reported on the RECOVERY follow-up CRF.
- Bloodstream infection during the index hospital admission, assessed against a reference standard of bloodstream infection (a subset of non-coronavirus infection) reported on the RECOVERY follow-up CRF.
- VTE during the index hospital admission, assessed against a reference standard of VTE (a subset of thrombosis) reported on the RECOVERY follow-up CRF.
- GI bleeding (a subset of GI complications) during the index hospital admission, assessed against a reference standard of GI bleeding (a subset of clinically significant bleeding) reported on the RECOVERY follow-up CRF.
- Metabolic complications during the index hospital admission, assessed against a reference standard of metabolic complications reported on the RECOVERY follow-up CRF.

ii) Baseline characteristics:

- Immunosuppression, assessed against a reference standard of severe immunocompromise reported on the RECOVERY randomisation CRF;
- Diabetes mellitus (excluding CRF-derived diagnoses), assessed against a reference standard of diabetes mellitus reported on the RECOVERY randomisation CRF.

iii) Changes in the following data source derivation parameters were considered for the above outcomes:

- Timing of events: Including 'peri-randomisation' episode events was compared with including only post-randomisation episodes of care (see Section 3.3.2.2).
- Diagnostic positions: Including events from the primary diagnostic position only was compared with including events from all diagnostic positions (see Section 3.3.2.2). For major non-COVID infection, the PPV of including events from different ranges of diagnostic position were assessed to ascertain any differences.

iv) Effect of additional data sources:

- For the outcome of major non-COVID infection, the diagnostic performance of a definition including events derived from hospitalisation and death datasets was compared against a definition including hospitalisation, death, and microbiology datasets.
- For the outcome of VTE, the diagnostic performance of a definition including events derived from hospitalisation and death datasets was compared against a definition including hospitalisation, death, and confirmatory anticoagulation prescriptions from the primary care datasets.

The following parameters were reported for each diagnostic accuracy evaluation, with 95% CIs[254]:

i) Observed agreement

$$\left(\frac{True\ Positives + True\ Negatives}{True\ Positives + True\ Negatives + False\ Positives + False\ Negatives}\right);$$

ii) Sensitivity $\left(\frac{True\ Positives}{True\ Positives + False\ Negatives}\right)$;

iii) Specificity $\left(\frac{True\ Negatives}{True\ Negatives + False\ Positives}\right)$;

iv) PPV $\left(\frac{True\ Positives}{True\ Positives + False\ Positives}\right)$;

v) Negative predictive value (NPV) ($\frac{True\ Negatives}{True\ Negatives + False\ Negatives}$);

vi) Kappa (κ) agreement statistic – a measure of inter-rater agreement for classification of an item into two mutually exclusive categories[376].

4.3.3.7 Diagnostic accuracy compared with a reference standard of ISARIC4C CRF data

The diagnostic performance of the relevant finalised extended analysis assessment codelist (representing the index test) was assessed against a reference standard of ISARIC4C CRF data reporting infections (subsets pneumonia, bacteraemia), VTE, GI bleeding, liver dysfunction, hyperglycaemia and hypoglycaemia, and immunocompromise.

The methods for assessing diagnostic performance and reported parameters were the same as for those used with the reference standard of the RECOVERY CRF data. The purpose of this analysis was to use the ISARIC4C CRF data to represent an alternative 'gold-standard' given uncertainty as to the true, most accurate, reference standard. This reduced reliance on diagnostic accuracy data interpretation from a single evaluation.

The ISARIC4C CRF data represented the occurrence of the event during the index hospitalisation (as the timing of the event could not be determined from the ISARIC4C CRF), rather than being restricted to post-randomisation (as in RECOVERY), resulting in a greater number of reference standard events that occurred pre-randomisation. This will result in a higher number of index test false negatives, and therefore a lower measure of sensitivity, NPV and agreement compared with the RECOVERY CRF data comparison. This prevents interpretation of absolute values of these parameters but patterns relating to altering data source parameters would be preserved, hence all parameters are still presented. Specificity and PPV estimates should be broadly comparable to the RECOVERY CRF data comparison.

4.3.3.8 Randomised comparisons using RECOVERY trial compared with RCD follow-up.

A final testing validation step was undertaken after finalising the assessment definitions and unblinding to randomised treatment allocation.

The presence of the RECOVERY non-coronavirus infection and thrombosis safety outcomes on the CRF for participants in the baricitinib comparison allowed for a direct comparison of the performance of the RCD follow-up outcomes of major non-COVID infection and VTE (excluding CRF diagnoses), with the trial follow-up in a randomised comparison. For these outcomes, comparisons of event numbers and treatment effect rate ratio estimates, with 95% CIs, were presented for outcomes derived from RCD and trial data collection follow-up methods. The heterogeneity between the two follow-up methods was assessed using the chi-squared test. The purpose of this analysis was to assess the validity of RCD-derived outcomes for drawing conclusions about treatment effects within a RECOVERY randomised comparison – the definitive goal of the extended analysis.

4.3.4 Assessment definition testing results

4.3.4.1 Case validation compared with manual medical record review

The PPV of RCD-derived outcomes compared with the reference standard of manual medical record review ranged from 0.80 [95% CI 0.61 – 0.91] for GI complications to 1.00 [95% CI 0.89 – 1.00] for bloodstream infection (Table 4-10).

Table 4-10: Summary of results of case validation of thesis routinely collected data-derived outcome events compared with a reference standard of manual medical record review.

Outcome	Total number of index cases	Index cases confirmed by review	Positive Predictive Value (95% CI)
Major non-COVID infection	93	85	0.91 (0.84 - 0.96)
Bloodstream infection	31	31	1.00 (0.89 - 1.00)
Venous thromboembolism	60	58	0.97 (0.89 - 0.99)
Gastrointestinal complication	25	20	0.80 (0.61 - 0.91)
Metabolic complication	38	34	0.89 (0.76 - 0.96)
Long bone or vertebral fracture	19	16	0.84 (0.62 - 0.94)
Psychiatric complication	45	43	0.96 (0.85 - 0.99)

Clinically-defined liver injury	38	32	0.84 (0.70 - 0.93)

The most frequent reasons for false positives were either a chronic co-morbidity coded as a current diagnosis or an absence of any supportive evidence of the diagnosis in the medical record. For example, coded occurrences of a past medical history of recurrent urinary tract infections, PE, peptic ulcer disease, or hip fracture were all observed.

4.3.4.2 Medication use by RCD-derived outcome status

Medication administration prevalence was higher in participants with the outcome present across all assessments (Table 4-11), ranging from 1.5 times higher for GI complications to 6.3 times higher for metabolic complications. For all outcomes evaluated, except GI complications, medication administration prevalence was at least twice as common in those with the outcome present compared with those with the outcome absent.

Table 4-11: Prevalence of medication administration in the secondary care prescribing routinely collected dataset split by participants with the outcome of interest present or absent.

Outcome	Medications assessed	Medication administration prevalence in those with outcome present	Medication administration prevalence in those with outcome absent
Major non-COVID infection	Any oral or intravenous anti-bacterial or anti-fungal	562/696 (81%)	214/616 (35%)
Bloodstream infection	Any oral or intravenous anti-bacterial or anti-fungal	69/73 (95%)	239/695 (34%)
Venous thromboembolism	Oral, intravenous or subcutaneous anticoagulant at a dose greater than or equal to that licensed for treatment of venous thromboembolism	85/109 (78%)	342/1172 (29%)
Gastrointestinal complication	Oral or intravenous proton pump inhibitor at a dose greater than or equal to that licensed for treatment of peptic ulceration	24/50 (48%)	123/378 (33%)
Metabolic complication	Oral glucose or intravenous glucose at a concentration greater than or equal to 10% or subcutaneous or intravenous rapid-acting insulin	33/86 (38%)	39/641 (6%)
Psychiatric complication	Oral, intravenous or intramuscular haloperidol	7/100 (7%)	13/566 (2%)

4.3.4.3 Validity of HFRS

In the assessment of the validity of the HFRS, there was strong evidence that primary care frailty assessment groups were correlated with HFRS groups (Spearman's rank correlation rho = 0.35, p<0.0001) (Figure 4-3).

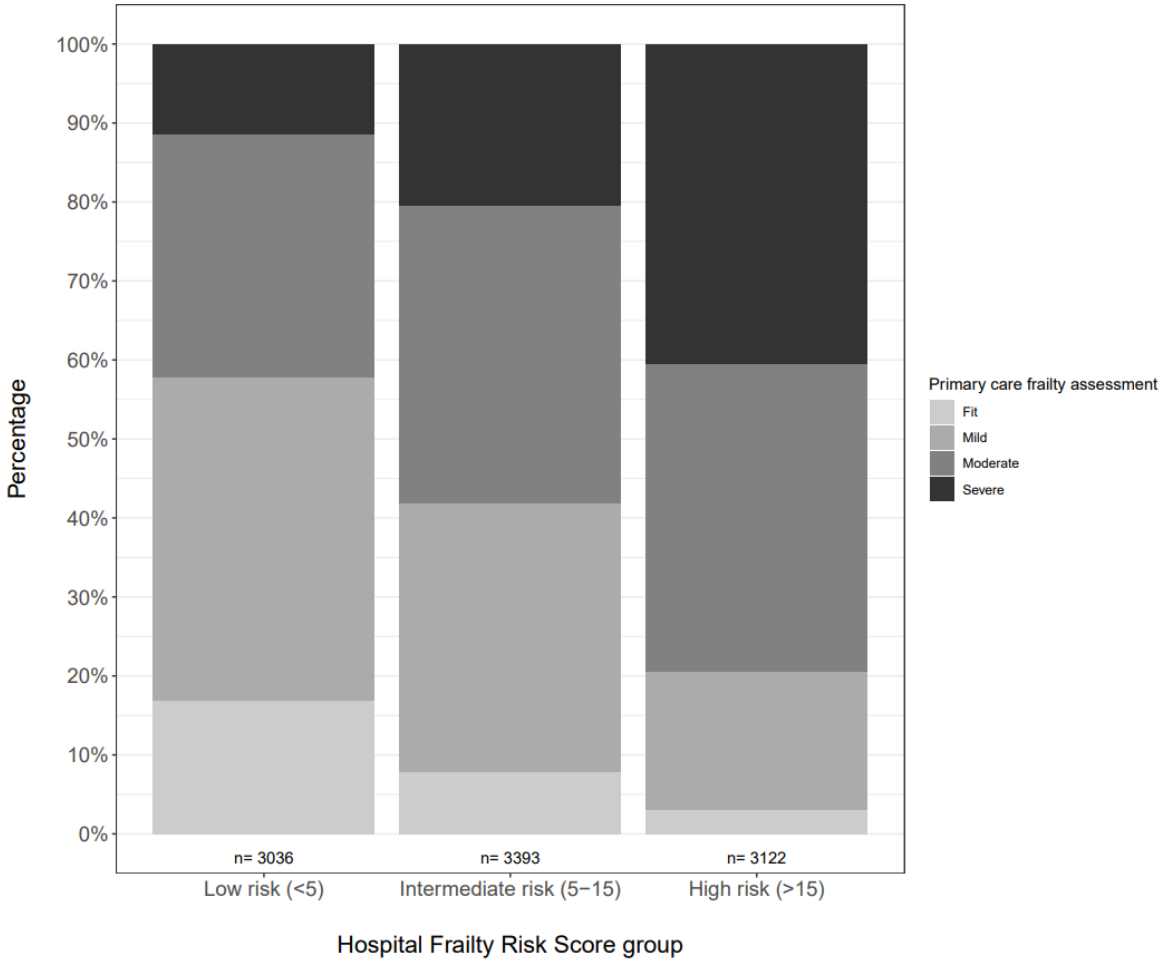


Figure 4-3: Distribution of primary care frailty assessment categories across Hospital Frailty Risk Score groups.

Where the CFS score was measured, it was significantly higher in participants in higher HFRS groups (H statistic = 295.9, p<0.0001), with a median CFS score of 3 ('Managing well') in the low HFRS group, 4 ('Vulnerable) in the intermediate HFRS group, and 6 ('Moderately Frail') in the high HFRS group (Figure 4-4).

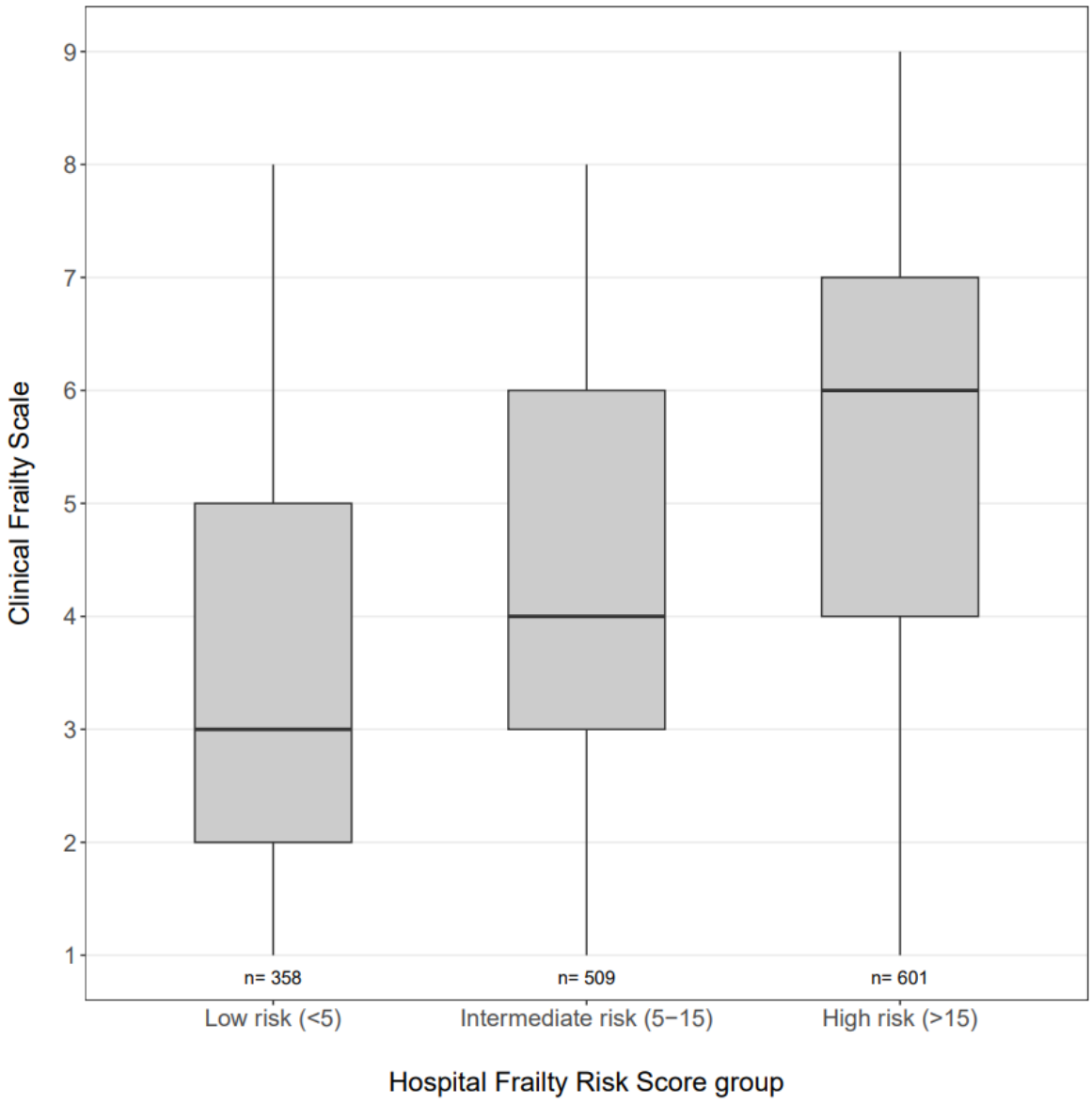


Figure 4-4: Distribution of Clinical Frailty Scale scores by Hospital Frailty Risk Score group.

4.3.4.4 Diagnostic accuracy compared with RECOVERY CRF data

Across the tested assessment definitions, observed agreement was >0.85 except for major non-COVID infection including peri-randomisation episode events (0.762) (Table 4-12). As other outcome events were rare, varying the definition parameters otherwise had minimal effect on observed agreement.

Table 4-12: Diagnostic performance of different assessment definitions compared with a reference standard of the RECOVERY case report form data.

Assessment	Timing and diagnostic positions of events included	Participants, n (%)				Observed agreement (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)	Kappa (95% CI)
		Present in both data sources[a]	Present in CRF data only[b]	Present in routine data only[c]	Present in neither data source[d]						
Major non-COVID infection	Post-randomisation All positions	142 (3.7)	260 (6.7)	151 (3.9)	3307 (85.7)	0.894 (0.883 - 0.903)	0.35 (0.31 - 0.40)	0.956 (0.949 - 0.963)	0.48 (0.43 - 0.54)	0.927 (0.918 - 0.935)	0.35 (0.30 - 0.40)
	Peri- and post-randomisation All positions	291 (7.5)	111 (2.9)	807 (20.9)	2651 (68.7)	0.762 (0.748 - 0.775)	0.72 (0.68 - 0.77)	0.767 (0.752 - 0.780)	0.27 (0.24 - 0.29)	0.960 (0.952 - 0.967)	0.28 (0.25 - 0.31)
	Post-randomisation Primary position only	84 (2.2)	318 (8.2)	75 (1.9)	3383 (87.6)	0.898 (0.888 - 0.907)	0.21 (0.17 - 0.25)	0.978 (0.973 - 0.983)	0.53 (0.45 - 0.60)	0.914 (0.905 - 0.923)	0.26 (0.21 - 0.31)
Major non-COVID infection (no microbiology data)	Post-randomisation All positions	97 (2.5)	305 (7.9)	111 (2.9)	3347 (86.7)	0.892 (0.882 - 0.902)	0.24 (0.20 - 0.29)	0.968 (0.961 - 0.973)	0.47 (0.40 - 0.53)	0.916 (0.907 - 0.925)	0.27 (0.22 - 0.32)
Bloodstream infection	Post-randomisation All positions	22 (0.5)	37 (0.9)	50 (1.2)	3891 (97.3)	0.978 (0.973 - 0.982)	0.37 (0.26 - 0.50)	0.987 (0.983 - 0.990)	0.31 (0.21 - 0.42)	0.991 (0.987 - 0.993)	0.32 (0.22 - 0.43)
Venous thromboembolism	Post-randomisation All positions	259 (0.8)	1165 (3.6)	241 (0.7)	31030 (94.9)	0.957 (0.955 - 0.959)	0.18 (0.16 - 0.20)	0.992 (0.991 - 0.993)	0.52 (0.47 - 0.56)	0.964 (0.962 - 0.966)	0.25 (0.23 - 0.28)
	Peri- and post-randomisation All positions	882 (2.7)	542 (1.7)	998 (3.1)	30273 (92.6)	0.953 (0.951 - 0.955)	0.62 (0.59 - 0.64)	0.968 (0.966 - 0.970)	0.47 (0.45 - 0.49)	0.982 (0.981 - 0.984)	0.51 (0.49 - 0.53)
	Post-randomisation Primary position only	71 (0.2)	1353 (4.1)	62 (0.2)	31209 (95.5)	0.957 (0.954 - 0.959)	0.05 (0.04 - 0.06)	0.998 (0.997 - 0.998)	0.53 (0.45 - 0.62)	0.958 (0.956 - 0.961)	0.08 (0.07 - 0.10)
Venous thromboembolism (no medication codes)	Post-randomisation All positions	290 (0.9)	1134 (3.5)	294 (0.9)	30977 (94.7)	0.956 (0.954 - 0.958)	0.20 (0.18 - 0.23)	0.991 (0.989 - 0.992)	0.50 (0.46 - 0.54)	0.965 (0.963 - 0.967)	0.27 (0.24 - 0.30)
Gastrointestinal complications	Post-randomisation All positions	58 (0.2)	181 (0.5)	94 (0.3)	32803 (99)	0.992 (0.991 - 0.993)	0.24 (0.19 - 0.30)	0.997 (0.997 - 0.998)	0.38 (0.31 - 0.46)	0.995 (0.994 - 0.995)	0.29 (0.23 - 0.35)
	Peri- and post-randomisation All positions	138 (0.4)	101 (0.3)	488 (1.5)	32409 (97.8)	0.982 (0.981 - 0.984)	0.58 (0.51 - 0.64)	0.985 (0.984 - 0.986)	0.22 (0.19 - 0.25)	0.997 (0.996 - 0.997)	0.31 (0.27 - 0.35)

	Post-randomisation Primary position only	22 (0.1)	217 (0.7)	12 (<0.1)	32885 (99.2)	0.993 (0.992 - 0.994)	0.09 (0.06 - 0.14)	1.000 (0.999 - 1.000)	0.65 (0.48 - 0.79)	0.993 (0.993 - 0.994)	0.16 (0.10 - 0.22)
Metabolic complications	Post-randomisation All positions	14 (0.5)	222 (8.6)	16 (0.6)	2329 (90.2)	0.908 (0.896 - 0.918)	0.06 (0.04 - 0.10)	0.993 (0.989 - 0.996)	0.47 (0.30 - 0.64)	0.913 (0.901 - 0.923)	0.09 (0.04 - 0.13)
	Peri- and post-randomisation All positions	57 (2.2)	179 (6.9)	70 (2.7)	2275 (88.1)	0.904 (0.892 - 0.914)	0.24 (0.19 - 0.30)	0.970 (0.962 - 0.976)	0.45 (0.37 - 0.54)	0.927 (0.916 - 0.937)	0.27 (0.20 - 0.33)
	Post-randomisation Primary position only	2 (0.1)	234 (9.1)	2 (0.1)	2343 (90.8)	0.909 (0.897 - 0.919)	0.01 (0.00 - 0.03)	0.999 (0.997 - 1.000)	0.50 (0.15 - 0.85)	0.909 (0.897 - 0.920)	0.01 (-0.01- 0.03)
Baseline immunosuppression	Pre-randomisation All positions	285 (17.2)	90 (5.4)	147 (8.9)	1134 (68.5)	0.857 (0.839 - 0.873)	0.76 (0.71 - 0.80)	0.885 (0.867 - 0.902)	0.66 (0.61 - 0.70)	0.926 (0.910 - 0.940)	0.61 (0.57 - 0.66)
Baseline diabetes	Pre-randomisation All positions	11274 (23.5)	1060 (2.2)	4051 (8.4)	31675 (65.9)	0.894 (0.891 - 0.896)	0.91 (0.91 - 0.92)	0.887 (0.883 - 0.890)	0.74 (0.73 - 0.74)	0.968 (0.966 - 0.969)	0.74 (0.74 - 0.75)

[a] *Index test positive, reference standard positive (True Positive)*
[b] *Index test negative, reference standard positive (False Negative)*
[c] *Index test positive, reference standard negative (False Positive)*
[d] *Index test negative, reference standard negative (True Negative)*

Sensitivity spanned a wide range (0.01 – 0.91), but was typically low to moderate when peri-randomisation and pre-randomisation events were not considered. Across all assessments, sensitivity was substantially increased by including peri-randomisation events and substantially reduced by restricting to primary diagnostic position events.

Specificity was >0.95 in the evaluated outcome assessments, except for major non-COVID infection including peri-randomisation episode events (0.767). Specificity was increased by restricting to primary diagnostic position events and reduced by including peri-randomisation events.

PPV ranged from 0.22 – 0.65 in the outcome definitions and was increased by restricting to primary diagnostic position events and reduced by including peri-randomisation events.

The kappa statistic varied substantially according to definition parameters and was particularly influenced by changes in sensitivity, generally increasing with higher sensitivity definitions.

Excluding the microbiology data from the major non-COVID infection definition resulted in lower sensitivity and PPV, and a small increase in specificity. Excluding confirmatory anticoagulation prescription data had a modest overall impact on diagnostic performance but sensitivity was slightly higher, and PPV and specificity were slightly lower.

For the evaluated baseline characteristics derived from RCD, all measures of diagnostic performance were reasonably high, whilst preserving the pattern of higher specificity than sensitivity and higher NPV than PPV. Kappa statistics suggested ‘substantial’ agreement for baseline immunosuppression (0.61) and baseline diabetes (0.74).

In the assessment of PPV by differing ranges of diagnostic position for the outcome of major non-COVID infection, there was no evidence of a change in PPV as the number of diagnostic positions included increased (Figure 4-5). Event numbers were small in the higher diagnostic positions.

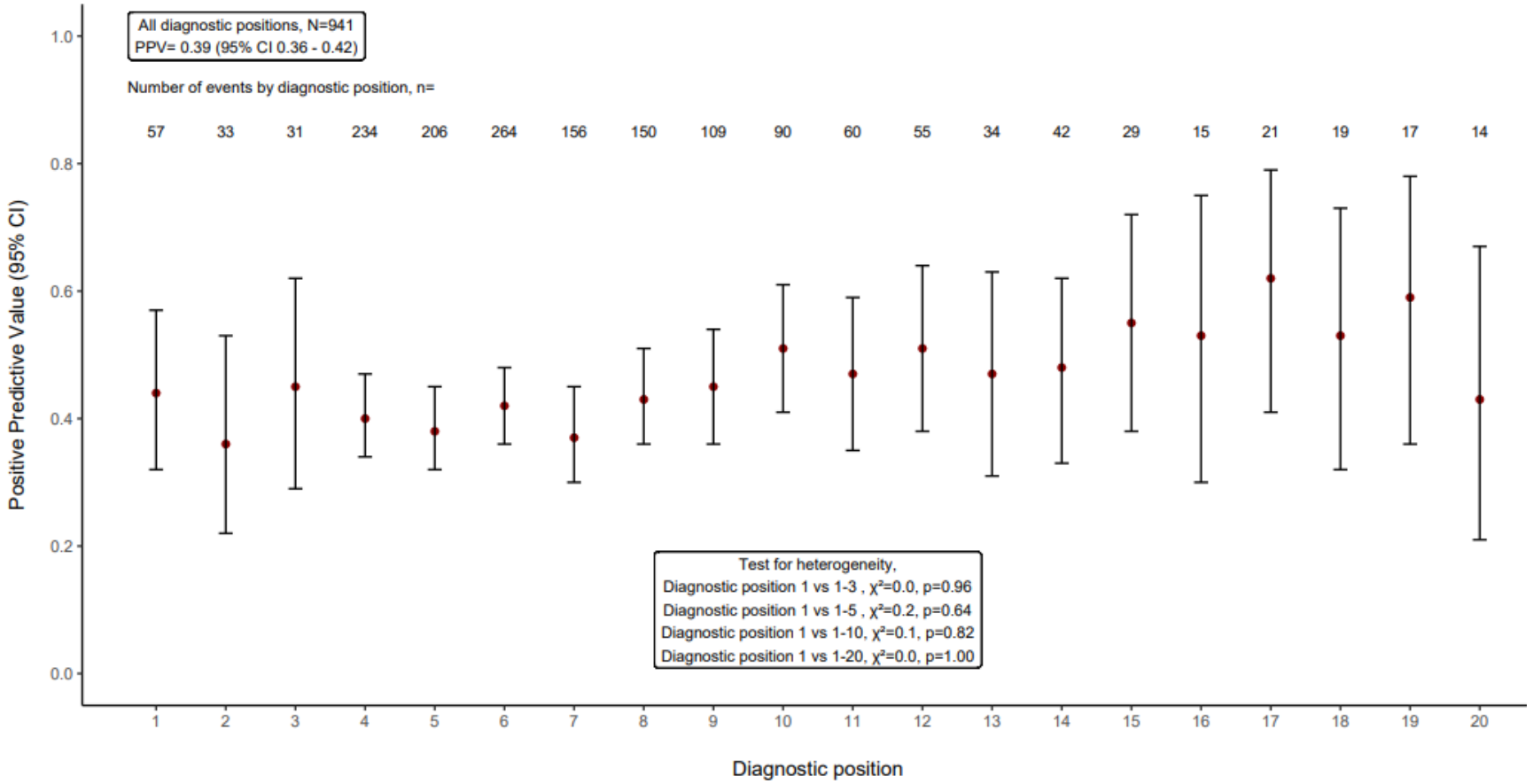


Figure 4-5: Positive predictive value of routinely collected data-derived major non-COVID infection events by diagnostic position, compared to a reference standard of RECOVERY case report form data.

4.3.4.5 Diagnostic accuracy compared with ISARIC4C CRF data

Using the reference standard of ISARIC4C CRF data, observed agreement, sensitivity, NPV and kappa statistics were all lower, as anticipated by the inclusion of many more events that will have happened before randomisation in the reference standard ISARIC4C CRF data (Table 4-13).

Table 4-13: Diagnostic performance of different assessment definitions compared with a reference standard of the ISARIC4C case report form data.

Assessment	Timing of events included	Diagnostic positions included	Number of index test positives	Observed agreement (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)	Kappa (95% CI)
Major non-COVID infection*	Post-randomisation	All	1533	0.791 (0.786 - 0.797)	0.16 (0.15 - 0.17)	0.949 (0.946 - 0.952)	0.44 (0.41 - 0.46)	0.819 (0.813 - 0.824)	0.14 (0.13 - 0.16)
	Peri- and post-randomisation	All	6877	0.672 (0.666 - 0.679)	0.49 (0.48 - 0.51)	0.717 (0.711 - 0.724)	0.30 (0.29 - 0.31)	0.850 (0.844 - 0.855)	0.17 (0.16 - 0.18)
	Post-randomisation	Primary only	1125	0.797 (0.792 - 0.803)	0.13 (0.12 - 0.14)	0.965 (0.962 - 0.968)	0.47 (0.44 - 0.50)	0.815 (0.810 - 0.821)	0.12 (0.11 - 0.14)
Major non-COVID infection, without microbiology data*	Post-randomisation	All	891	0.793 (0.787 - 0.798)	0.09 (0.08 - 0.10)	0.969 (0.967 - 0.972)	0.41 (0.38 - 0.45)	0.810 (0.804 - 0.815)	0.08 (0.07 - 0.09)
Bloodstream infection†	Post-randomisation	N/A	540	0.949 (0.946 - 0.952)	0.22 (0.19 - 0.25)	0.983 (0.981 - 0.985)	0.38 (0.34 - 0.42)	0.964 (0.962 - 0.967)	0.25 (0.22 - 0.28)
Venous thromboembolism‡	Post-randomisation	All	236	0.941 (0.937 - 0.945)	0.17 (0.15 - 0.20)	0.991 (0.989 - 0.992)	0.55 (0.49 - 0.61)	0.949 (0.945 - 0.953)	0.24 (0.21 - 0.28)
	Peri- and post-randomisation	All	827	0.945 (0.940 - 0.948)	0.60 (0.56 - 0.63)	0.967 (0.963 - 0.970)	0.54 (0.51 - 0.57)	0.974 (0.971 - 0.977)	0.54 (0.51 - 0.57)
	Post-randomisation	Primary only	61	0.941 (0.936 - 0.945)	0.05 (0.04 - 0.07)	0.998 (0.997 - 0.999)	0.66 (0.53 - 0.76)	0.942 (0.938 - 0.946)	0.09 (0.06 - 0.12)
Gastrointestinal complications§	Post-randomisation	All	107	0.988 (0.986 - 0.989)	0.16 (0.12 - 0.21)	0.997 (0.996 - 0.997)	0.34 (0.25 - 0.43)	0.991 (0.990 - 0.992)	0.21 (0.15 - 0.27)
	Peri- and post-randomisation	All	459	0.979 (0.977 - 0.981)	0.54 (0.47 - 0.60)	0.984 (0.982 - 0.985)	0.27 (0.23 - 0.31)	0.995 (0.994 - 0.996)	0.35 (0.30 - 0.39)
	Post-randomisation	Primary only	24	0.989 (0.988 - 0.991)	0.05 (0.03 - 0.09)	0.999 (0.999 - 1.000)	0.50 (0.31 - 0.69)	0.990 (0.988 - 0.991)	0.09 (0.04 - 0.14)
Liver injury**	Post-randomisation	All	257	0.908 (0.904 - 0.911)	0.05 (0.04 - 0.06)	0.991 (0.990 - 0.992)	0.35 (0.29 - 0.41)	0.915 (0.911 - 0.918)	0.06 (0.05 - 0.08)

* *Reference standard positive, n=4,236. Total participants, N=21,203.*
† *Reference standard positive, n=931. Total participants, N=20,908.*
‡ *Reference standard positive, n=745. Total participants, N=12,261.*
§ *Reference standard positive, n=226. Total participants, N=20,999.*
** *Reference standard positive, n=1,854. Total participants, N=20,919.*

Metabolic complications††	Post-randomisation	All	218	0.850 (0.846 - 0.855)	0.04 (0.03 - 0.05)	0.995 (0.994 - 0.996)	0.57 (0.50 - 0.63)	0.853 (0.849 - 0.858)	0.06 (0.04 - 0.07)
Baseline immunosuppression ‡‡	Pre-randomisation	All	1235	0.939 (0.936 - 0.943)	0.61 (0.58 - 0.64)	0.964 (0.961 - 0.967)	0.55 (0.53 - 0.58)	0.971 (0.968 - 0.973)	0.55 (0.52 - 0.57)

†† Reference standard positive, n=3,147. Total participants, N=20.849.
‡‡ Reference standard positive, n=1,125. Total participants, N=16,341.

Specificity was >0.94 in all the evaluated assessments, except major non-COVID infection including peri-randomisation episode events (0.717).

PPV ranged from 0.27 (GI complications including peri-randomisation episode events) to 0.66 (VTE restricted to primary diagnostic position events).

Like the patterns observed with the RECOVERY CRF reference standard, sensitivity generally increased when peri-randomisation diagnoses were included, and generally decreased when restricting to the primary diagnostic position. Specificity and PPV were reduced when peri-randomisation diagnoses were included and increased when restricting to the primary diagnostic position only.

When microbiology data was not included, sensitivity of the major non-COVID infection outcome was reduced by approximately 40%, though specificity was slightly increased (0.949 to 0.969).

4.3.4.6 Randomised comparisons for RCD-derived outcomes

In the baricitinib randomised comparison, the treatment effect estimate and 95% CI for the outcome of major non-COVID infection within 28 days was very similar when using routine data follow-up compared with trial follow-up in terms of both point estimate and precision (Figure 4-6). Approximately 40% of RCD non-COVID infection events were confirmed in the trial follow-up data collection, with an overall event discrepancy rate between the two sources of 12.8% [95% CI 12.1 – 13.6%].

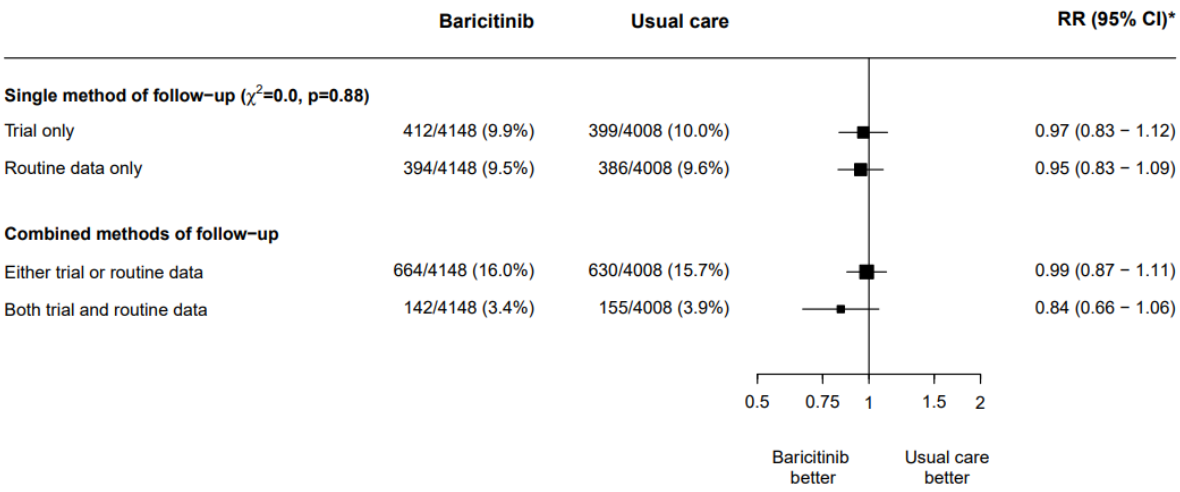


Figure 4-6: Major non-COVID infection at 28 days in the RECOVERY baricitinib comparison by method of follow-up data collection.
**RR (95% CI) = Rate or risk ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.*

Amongst the RCD datasets used, the largest proportion of major non-COVID infection events came from the hospital admission datasets (Figure 4-7). Approximately 40% of hospital admission dataset events were confirmed in a second data source (including the CRF data). The microbiology datasets provided around half the number of events as the hospital admission datasets, with two thirds of microbiology dataset events confirmed in a second data source. The death datasets provided around a tenth of the hospital admission dataset event numbers, with around 60% of death dataset events confirmed in a second data source.

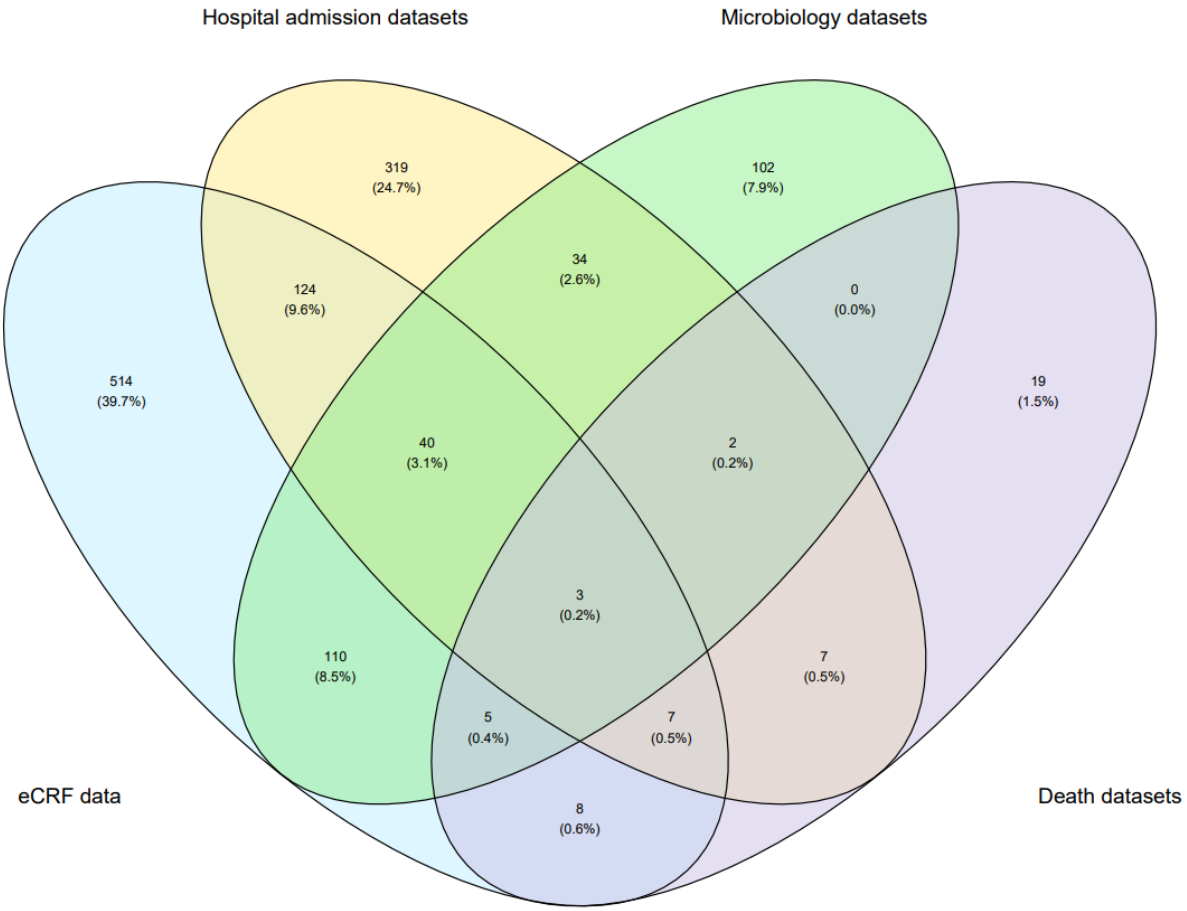


Figure 4-7: Venn diagram of data sources of major non-COVID infection events within 28 days in the RECOVERY baricitinib comparison.

For the outcome of VTE, the RCD treatment effect estimate appeared slightly lower, and was more imprecise, but there was not statistically significant heterogeneity between the follow-up results (Figure 4-8). Approximately one third of RCD VTE events were confirmed in the trial follow-up data collection, with an overall event discrepancy rate between the two sources of 4.8% [95% CI 4.4 – 5.3%].

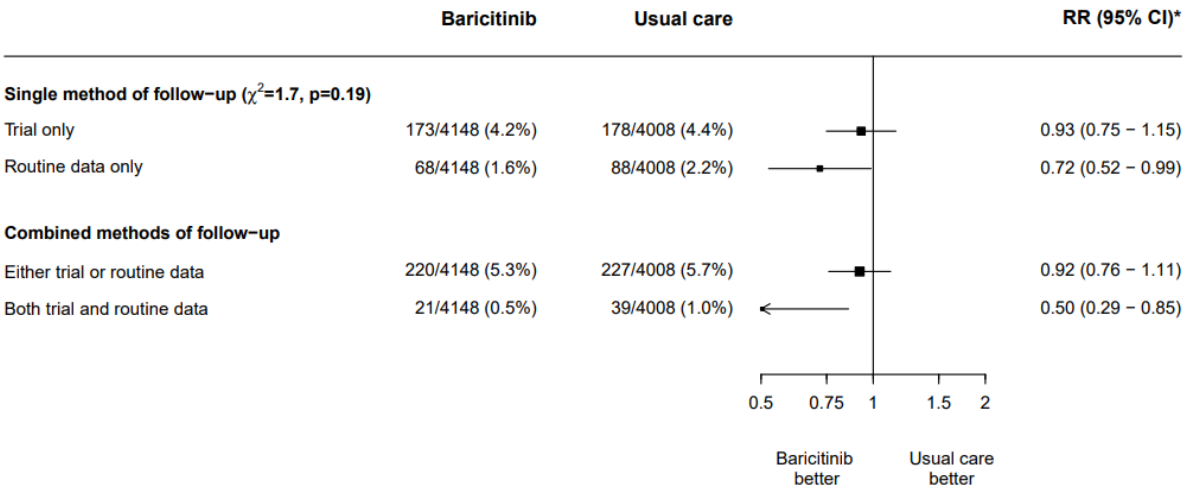


Figure 4-8: Venous thromboembolism at 28 days in the RECOVERY baricitinib comparison by method of follow-up data collection.
**RR (95% CI) = Rate or risk ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.*

4.3.5 Discussion

4.3.5.1 Summary of results

The face validity of outcome events identified by the assessment definitions was good. In the case validation analysis results, 80-100% of RCD-derived events were confirmed by manual medical record review. The results generally compared favourably with the wider case validation studies identified in the literature review (Table 4-9). The extended analysis outcome definition PPV estimates were above the literature review PPV upper quartile results for the outcomes of major non-COVID infection, VTE, metabolic complications and acute liver injury; between the median and upper quartile for GI complications, and between the lower quartile and median for long bone or vertebral fractures. The case validation analysis had small numbers and was assessed at only a single centre, so the precision of the results was low and the generalisability across all hospitals uncertain. Where false positives occurred, the most identifiable reason was for past medical history to be coded as a current diagnosis. Relevant acute medication use in

those with an outcome event present was higher than those without an outcome event. HFRS correlated well with independent primary care assessments of frailty.

Diagnostic accuracy results compared with the reference standard of RECOVERY or ISARIC4C CRF data, demonstrated that the RCD-derived event definitions had high specificity but low sensitivity, a pattern consistent with the wider literature. Specificity could meaningfully be increased by restricting to primary diagnostic position events, but at the expense of sensitivity and the precision of results through a reduction in event numbers. Sensitivity could meaningfully be increased by including peri-randomisation hospitalisation episode diagnoses, but at the expense of specificity. Kappa statistics suggested fair agreement (0.21 – 0.40) with CRF data for most outcomes[377]. The kappa statistic results were heavily influenced by the sensitivity of event derivation, particularly for rare outcomes. The dependence of the kappa statistic on event prevalence has been criticised in previous studies, where findings of high observed agreement and low kappa values are commonly seen when events have a low prevalence, as found here[378,379]. An alternative prevalence- and bias-adjusted kappa statistic[380] would have given results ranging from 0.79 to 0.98 for all outcomes (when assessed using parameters of all diagnostic positions in post-randomisation episodes), but the interpretation of this statistic is less well-established[378].

When applied to the randomised comparison setting of the baricitinib treatment comparison in RECOVERY, the RCD follow-up for major non-COVID infection was closely aligned with the trial follow-up results, both in terms of treatment effect estimates and precision. This occurred despite individual participant level outcome discrepancies in approximately 13% of cases. This robustness of overall findings in randomised comparisons using RCD-derived outcomes has been reported in other studies, even with a 40% discrepancy rate between follow-up sources at the individual participant level[357-359]. The overall conclusion of a likely absence of treatment-related risk of VTE did not differ.

The direction of the difference in estimates was reassuring, as the concern was an increased risk of VTE with baricitinib treatment. The event numbers for this outcome were smaller in the RCD follow-up, meaning the potential effect of random error was higher.

4.3.5.2 Parameter selection

The key parameters that can be modified to alter diagnostic performance of the outcomes in the hospitalisation datasets (the largest contributor to event numbers) were the diagnostic positions used and the inclusion or exclusion of events occurring within the peri-randomisation episode. There was a sensitivity-specificity trade-off between deriving outcomes that have a low likelihood of being false positives and maintaining sufficient event numbers to produce results of a meaningful level of precision. In general, decisions that promote high specificity and PPV of final assessment definitions are favoured for the extended analysis in order to minimise bias in relative risk estimates in the randomised comparisons[344] (Section 4.2.4.4).

i) Diagnostic position

Specificity and PPV could be increased by restricting to the primary diagnostic position, however about 40% of reference standard non-COVID infection events were lost, half of VTE events, two-thirds of GI complication events, and 90% of metabolic complication events. There was no evidence of a reduction in PPV for major non-COVID infection events by including higher diagnostic positions, suggesting choosing a cut-off at an alternative diagnostic position level would be arbitrary. The testing data was limited to evaluating the diagnostic performance of index hospitalisation events within 28 days of randomisation as this was the period for which the CRF data, acting as a reference standard, was available for. In RECOVERY, most outcome events do occur early following randomisation during acute illness, however, the index hospitalisation was different compared with later follow-up time periods. Earlier diagnostic positions were often taken up by COVID diagnostic codes. In the RECOVERY HESAPC dataset, 46% of

all index hospitalisation episodes contained the ICD-10 codes U07.1 (COVID-19, Virus identified), B97.2 (Coronavirus, as the cause of diseases, classified to other chapters) and J12.8 (Other viral pneumonia) in the first 3 diagnostic positions, as recommended in clinical coding guidelines[381]. This means that unless including codes beyond the first 3 diagnostic positions, many index hospitalisation events could not be detected.

ii) Peri-randomisation episode events

Sensitivity can be notably increased by including peri-randomisation episode events, but at the expense of increasing false positives. 57% of all CRF-recorded GI bleeding events, 62% of VTE events, and 72% of non-COVID infection events could be detected by including the peri-randomisation episode in the derivation – increasing true positive event numbers by 2-4 times compared with using post-randomisation episodes only. However, in all cases the number of new false positive events identified was greater than the number of new true positive events, resulting in an overall reduction in PPV and specificity when peri-randomisation events were included.

This very large sensitivity variation linked to peri-randomisation episodes is quite unique to the current study context. RECOVERY is a randomised trial in acutely ill patients with high rates of complications early in their hospital admission, occurring around the time of randomisation. In the whole RECOVERY population, participants were randomised a median of 2 days (IQR 1–3 days) and a mean of 3.4 days since hospitalisation. This affects the way outcomes can be derived from RCD. In many trials, outcome events would be expected to occur months or even years after randomisation and rarely would it be expected that such a high proportion of events would occur during the hospital episode in which randomisation occurred. It is also possible that events that are occurring very close to randomisation are less biologically plausible to be related to the study treatment, however, no known post-randomisation events should be systematically excluded from an analysis as this would introduce bias due to missing outcome data.

iii) Use of additional data sources

The inclusion of microbiology data in the major non-COVID infection definition increased sensitivity by about one third, decreased specificity, and slightly increased PPV. Derived events appeared of reasonably equal validity from each data source. The inclusion of confirmatory anticoagulant medication codes in the VTE definition slightly reduced sensitivity, and slightly increased specificity and PPV. The method development literature review identified that the use of additional data sources enhanced the performance of RCD event derivation. While the effects observed in testing were modest, including the additional data sources improved PPV slightly and were supported by the wider existing evidence.

iv) Conclusions

It was concluded that the main analysis outcome definitions should include all diagnostic positions, post-randomisation events only, and include use of available additional data sources. These definitions maintain a balance between avoiding false positive events and providing sufficient precision to be able to produce clinically meaningful results for most outcomes.

Sensitivity analyses would be performed for primary and secondary outcomes by restricting to the primary diagnostic position (enhanced specificity) and, separately, including peri-randomisation episode events (enhanced sensitivity). It would be anticipated that the primary diagnostic position treatment effect analysis point estimates would be the closest to the true effect but with wider CIs compared to the main analysis, providing an important check of the robustness of the main analysis interpretation. The peri-randomisation episode events sensitivity analysis may bias the treatment effect point estimate towards the null, so if an observed important treatment effect persisted in this analysis it would increase confidence in the certainty of the finding.

4.3.5.3 Limitations of method development testing

i) Outcomes with less evaluation

For the outcomes of long COVID, incident diabetes, long bone or vertebral fractures, psychiatric complications, and liver injury, minimal testing has been able to be performed to assess validity, mostly due to the absence of a suitable reference standard to compare against. Fractures, psychiatric complications, and liver injury events maintained high PPV in the case validation analysis but only a limited number of events were assessed at a single study site.

Long COVID and incident diabetes are likely to be detected at longer-term follow-up in primary care. The good diagnostic performance of the baseline diabetes derivation suggests that incident diabetes should be able to be identified in the same way with good reliability. The use of RCD to derive diabetes diagnoses is backed up by strong evidence in the wider literature review where RCD-derived diabetes diagnoses had an estimated sensitivity of 0.87, specificity of 0.979, and PPV of 0.93. A follow-up time of 12 months was chosen for the diabetes outcome to allow sufficient time for the diagnosis to be made but maintain some plausibility that it could be related to immunomodulatory treatment. Long COVID diagnostic codes have been newly created since the COVID-19 pandemic. They were introduced for use in NHS primary care in November 2020 and were not in widespread use until February 2021[212]. This is up to 11 months after participants were recruited into the RECOVERY dexamethasone comparison so the follow-up period for this outcome was specified to be 18 months to have an opportunity to capture diagnoses in this population. The recently issued ICD-10 Long COVID code (U09.9) is not used in the hospitalisation datasets, and so is unable to be used in the long COVID outcome definition.

ii) Defining a reference standard

The reference standard of CRF data was not necessarily a true 'gold-standard'. For example, the objective nature of a recorded positive blood culture result in a microbiology dataset has a high likelihood of being a true positive case. However, two-thirds of index hospitalisation positive blood cultures recorded in the UKHSA dataset (after removal of expected contaminants) were not recorded as a bloodstream infection on the CRF. The occurrence of some outcome events has a higher degree of subjectivity. For example, the diagnosis of non-COVID infection may not always be objective and two different clinicians may come to a different conclusion and diagnosis from the same patient and situation. Mitigation of the impact of this uncertain reference standard is attempted by testing against both ISARIC4C and RECOVERY CRF data and cross-validation with manual medical record review and medication administration records, as well as integrating findings from the literature review, to provide a more complete picture. Decisions on final definitions used results across all testing and evidence, rather than relying on a single reference source and set of results. Reassuringly, the specificity and PPV estimate for both the RECOVERY and ISARIC4C CRF data comparison were broadly similar across all tested outcomes. There were higher event numbers for the assessments of infection, VTE, GI complications, metabolic complications, and baseline immunosuppression using the ISARIC4C reference standard, resulting in more precise estimates.

The RECOVERY and ISARIC4C CRF data was restricted to the initial study recruitment hospital admission and so testing relating to later follow-up periods is limited. This thesis aims to evaluate outcomes to 6-month follow-up and beyond, so decisions taken relating to testing performance are skewed towards earlier follow-up. However, this remains the time when the majority of outcome events occurred, even in the 6-month analyses, so is an essential time period to optimise assessment performance.

iii) Methodological limitations

The case validation testing was performed by a single assessor (the thesis author) who was aware that the cases represented index test positives. This could introduce verification bias due to motivation to find supportive evidence from the medical record. This was attempted to be reduced by specifying a definition for each outcome in advance. The case validation only took place at a single study site for feasibility reasons. This limits confidence in generalisability to all hospitals as there may be variation in clinical coding performance.

4.3.5.4 Finalising assessment definitions and outcome hierarchy

The final definitions of long-term follow-up analysis assessments derived from RCD used in the thesis were decided on using the results of the method development literature review, definition development process, and testing. The pre-specified definition for each assessment (given in full in Section 3.4) was finalised prior to unblinding to treatment allocation and performing the extended analysis.

Primary, secondary, and tertiary outcomes were categorised based on a combination of clinical rationale of importance, blinded event numbers, quality of existing external evidence relating to using RCD diagnostic codes for deriving events of that type, and performance in the assessment definition testing. Major non-COVID infection (using hospitalisation, death, and microbiology datasets) was selected as a primary safety outcome due to its importance across all immunomodulatory treatments, the frequency of occurrence of this complication, and relatively strong performance across the method development testing results and wider evidence search. Sub-categorisations of non-COVID infection were specified to provide a comprehensive overall evaluation of treatment effects on infections. This included using all available datasets, including primary care datasets; restricting to microbiologically-confirmed infections; evaluating bloodstream infections (as a highly specific assessment of a serious infection) and bacterial and fungal infections as separate outcomes. The results across all these

outcomes in combination will need to be synthesised in the overall interpretation of treatment effect on infections. A further sensitivity analysis, excluding respiratory tract infections, was pre-specified based on the clinical hypothesis that progression of severe COVID-19 may be difficult to distinguish from incident non-COVID respiratory tract infection. VTE, GI complications, and long COVID were selected as secondary outcomes due to importance clinically and to the thesis aims. There was reasonable internal and external evidence to support the performance of VTE and GI complication diagnostic codes, and any treatment effect detected on the presence of long COVID would be clinically important, despite the absent method development validation. Metabolic complications, incident diabetes, long bone or vertebral fracture, psychiatric complications, and liver injury were selected as tertiary outcomes as blinded event numbers were small, the prior anticipated possibility of treatment-related risk was restricted to a single immunomodulatory treatment, or external and internal testing for the performance of RCD diagnostic codes was of limited quality.

4.3.6 Conclusions

The definition development process provided a systematic approach for finalising definitions for each of the assessments derived from RCD used in the extended analysis and ensured methodological consistency. The literature review and method development testing results demonstrated that RCD-derived clinical events are generally of high specificity and low-to-moderate sensitivity, and should provide reasonably unbiased estimates of relative risk in randomised comparisons.

Finalised main analysis definitions use all diagnostic positions and post-randomisation episode events to provide a balance between high specificity and adequate sensitivity. This approach is backed up by sensitivity analyses that meaningfully alter specificity and sensitivity to test the robustness of results. The validation undertaken increases confidence in the overall extended analysis findings, and individual assessment results

can be interpreted in accordance with the external literature and study-specific testing performed.

Chapter 5

Long-term Follow-up Analysis Results

5.1 Chapter Summary

This is the first of two chapters detailing the results of the extended analysis. This chapter presents the long-term follow-up assessment results; which includes a randomised evaluation of the effects of the RECOVERY immunomodulatory therapies on efficacy, including long-term mortality; safety, including non-COVID infection; and illness recovery and long COVID. These results correspond to the second, third, and fourth aims of the thesis (Section 1.4).

The chapter begins with an overview of the data completeness of the linked data from RCD sources, ISARIC4C and RECOVERY. It then presents the long-term follow-up assessment results for each of the RECOVERY COVID-19 immunomodulatory treatments in turn – dexamethasone, tocilizumab, baricitinib, and the completed subgroup of higher dose dexamethasone.

5.2 Data Completeness

An overview of the participants included in the thesis extended analysis is presented in Figure 5-1.

RCD was available for 6299/6425 (98.0%) of participants in the RECOVERY dexamethasone comparison. Of those with no RCD, 74/126 were recruited in Northern Ireland where such data is not available at a national level. ISARIC4C data was linked for 4797/6425 (75%) of participants in the RECOVERY dexamethasone comparison – this is described hereafter as the 'RECOVERY-ISARIC dexamethasone comparison population'.

In the RECOVERY tocilizumab comparison, RCD was available for 4075/4116 (99.0%) of participants. ISARIC4C data was linked for 2341/4116 (57%) – the 'RECOVERY-ISARIC tocilizumab comparison population'.

In the RECOVERY baricitinib comparison, RCD was available for 7833/8156 (96.0%) of participants. Of those with no linked RCD, 210/323 were recruited in Northern Ireland. ISARIC4C data was linked for 3602/8156 (44%) of the baricitinib comparison – the 'RECOVERY-ISARIC baricitinib comparison population'.

In the completed subgroup of the RECOVERY higher dose dexamethasone comparison (those with hypoxia but not requiring ventilatory support), RCD was available for 505/1272 (39.7%) of participants. Of those with no RCD, 760/767 were recruited in Africa or Asia where such data is not available. 121/1272 (9.5%) of participants in the completed subgroup of the RECOVERY higher dose dexamethasone comparison had linked ISARIC4C data – no analyses were performed in this population.

An evaluation of the representativeness of the RECOVERY-ISARIC populations relative to the whole RECOVERY comparison populations is presented in Chapter 6 (Section 6.2).

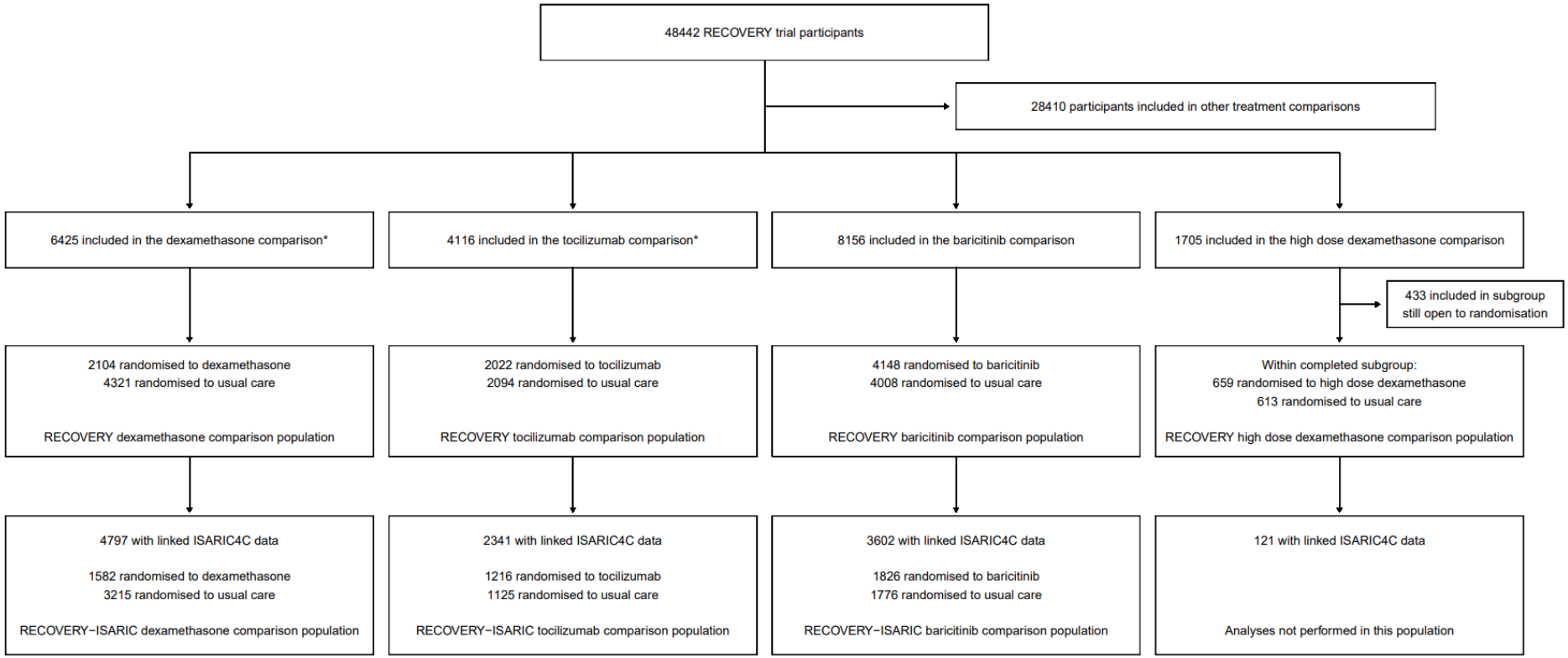


Figure 5-1: Flow diagram of RECOVERY participants in the thesis extended analysis by immunomodulatory treatment comparison.

5.3 Dexamethasone Randomised Comparisons

5.3.1 Baseline characteristics

In the RECOVERY dexamethasone comparison population, participants randomised to dexamethasone were a mean of 1.1 years older than those randomised to usual care (66.9 vs 65.8 years) (Table 5-1). Baseline characteristics derived from linked RCD data, including HFRS, immunosuppression, and Charlson Co-morbidity Index score, were well-matched between treatment groups.

Table 5-1: Baseline characteristics according to randomised treatment allocation for participants in the RECOVERY dexamethasone comparison.

	Dexamethasone (N=2104)	Usual Care (N=4321)
Demographics		
Age[1]	66.9 (15.4)	65.8 (15.8)
Age Group		
Age <70	1,141 (54%)	2,505 (58%)
Age >=70 <80	469 (22%)	860 (20%)
Age >=80	494 (23%)	956 (22%)
Sex		
Female	765 (36%)	1,571 (36%)
Male	1,339 (64%)	2,750 (64%)
Acute illness features		
Time since symptom onset		
Time of onset <=7 days	916 (44%)	1,801 (42%)
Time of onset >7 days	1,184 (56%)	2,507 (58%)
Days since admission to hospital[2]	2 (1, 5)	2 (1, 4)
Respiratory support		
No oxygen or ventilation	501 (24%)	1,034 (24%)
Oxygen or non-invasive ventilation	1,279 (61%)	2,604 (60%)
Mechanical ventilation or ECMO	324 (15%)	683 (16%)
Baseline non-COVID infection	631 (30%)	1,267 (29%)
Baseline co-morbidities		
Diabetes	521 (25%)	1,025 (24%)
Heart disease	586 (28%)	1,171 (27%)
Chronic lung disease	415 (20%)	931 (22%)
Tuberculosis	6 (0.3%)	19 (0.5%)
HIV	12 (0.6%)	20 (0.5%)
Severe liver disease	37 (1.8%)	82 (1.9%)
Severe kidney impairment	166 (7.9%)	358 (8.3%)
Severe mental illness	346/2,062 (17%)	731/4,225 (17%)
Immunosuppression	136/2,062 (6.6%)	299/4,231 (7.1%)
Charlson score[2]	4 (2, 6)	4 (2, 6)
Hospital Frailty Risk Score group		
Low risk (<5)[3]	922 (45%)	1,934 (46%)
Intermediate risk (5-15)[3]	679 (33%)	1,346 (32%)
High risk (>15)[3]	451 (22%)	928 (22%)
Unknown	52 (2.5%)	113 (2.6%)
Other treatments		

Tocilizumab	49 (2.3%)	139 (3.2%)
[1]*Mean (Standard Deviation)* [2]*Median (Lower quartile, Upper quartile)* [3]*n (%) excludes 'Unknown'*		

5.3.2 Long-term mortality

Allocation to dexamethasone was associated with a significant improvement in the primary efficacy outcome of all-cause mortality at 6 months, compared with usual care: 596/2104 (28%) of participants in the dexamethasone group and 1297/4321 (30%) of participants in the usual care group died within 6 months of randomisation (RR 0.87 [95% CI 0.79–0.96], p=0.004) (Figure 5-2, Table 5-2).

Table 5-2: Effect of allocation to dexamethasone on primary long-term follow-up outcomes.

	Dexamethasone (n=2104)	**Usual Care (n=4321)**	**Rate or Risk Ratio (95% CI)**	**p-value**
Primary outcomes				
Mortality within 6 months	596 (28%)	1,297 (30%)	0.87 (0.79 - 0.96)	0.004
Major non-COVID infection within 28 days	276 (13%)	512 (12%)	1.06 (0.92 - 1.23)	0.44
Major non-COVID infection within 6 months	473 (22%)	858 (20%)	1.08 (0.97 - 1.21)	0.18

An exploratory analysis of all-cause mortality at 2-year follow-up showed a preserved significant reduction in mortality with dexamethasone treatment (RR 0.86 [95% CI 0.79 – 0.94], p=0.0008) (Figure 5-3, Figure 5-4). A further 717 participants in the dexamethasone comparison died between 28-day and 2-year follow-up time points - an increase in event numbers of 45% compared to the initial follow-up at 28 days.

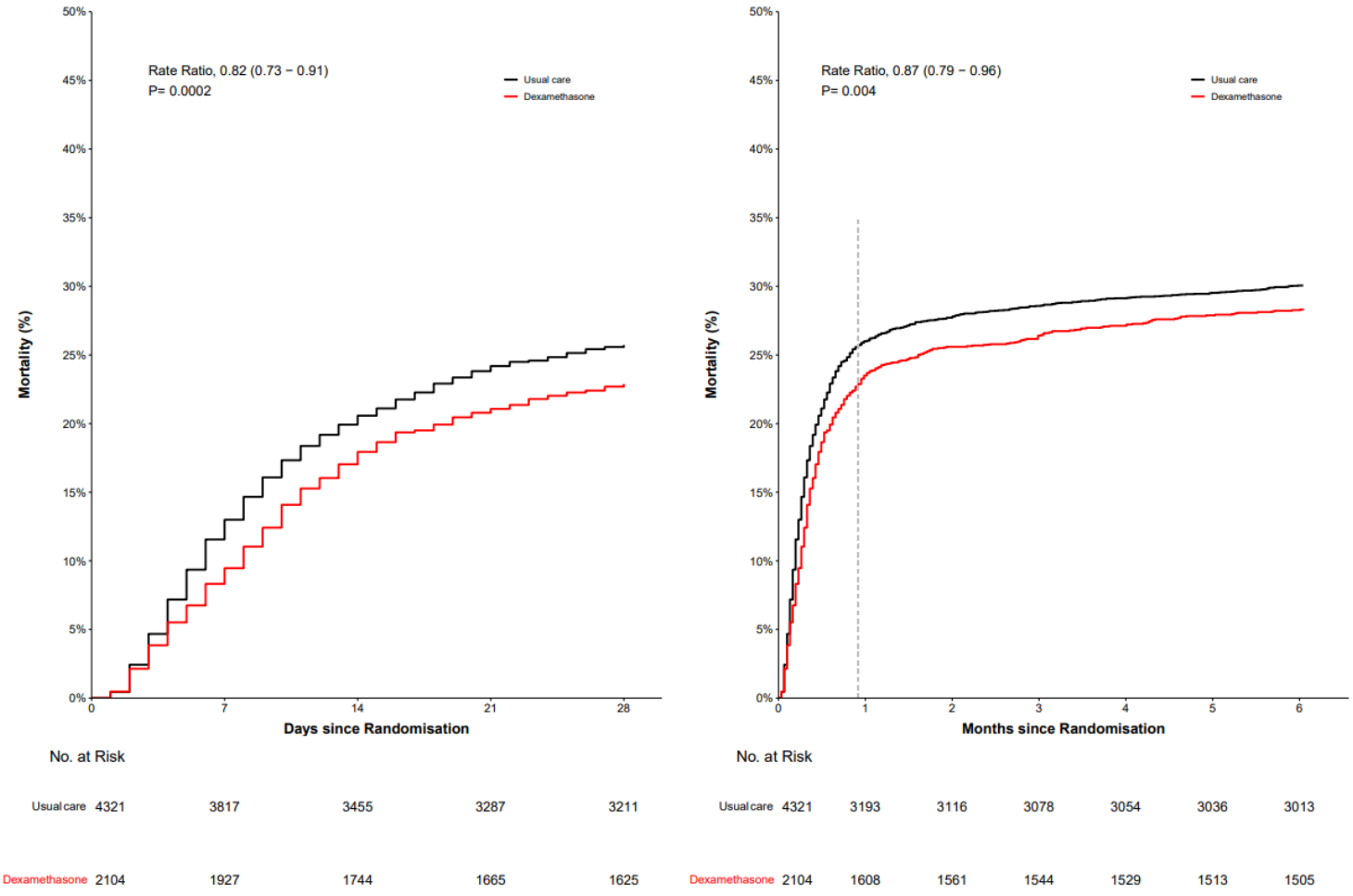


Figure 5-2: Effect of allocation to dexamethasone on all-cause mortality in the RECOVERY dexamethasone comparison.
Left panel: 28-day mortality. Right panel: 6-month mortality.
The Kaplan-Meier curves have not been adjusted for age and respiratory support group. The rate ratios have been adjusted for age and respiratory support group at randomisation.

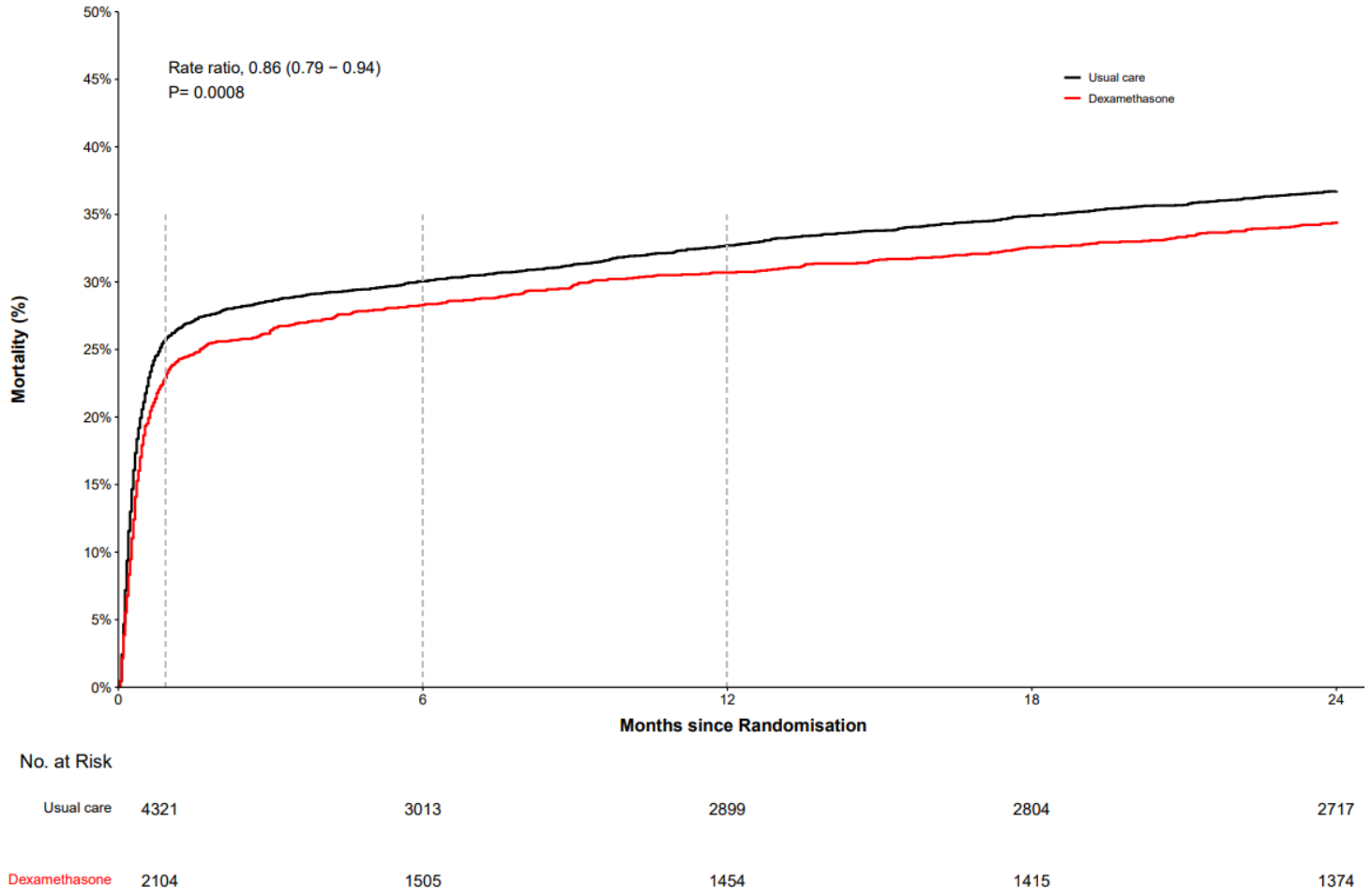


Figure 5-3: Effect of allocation to dexamethasone on 2-year mortality in the RECOVERY dexamethasone comparison.
The Kaplan-Meier curves have not been adjusted for age and respiratory support group. The rate ratios have been adjusted for age and respiratory support group at randomisation.

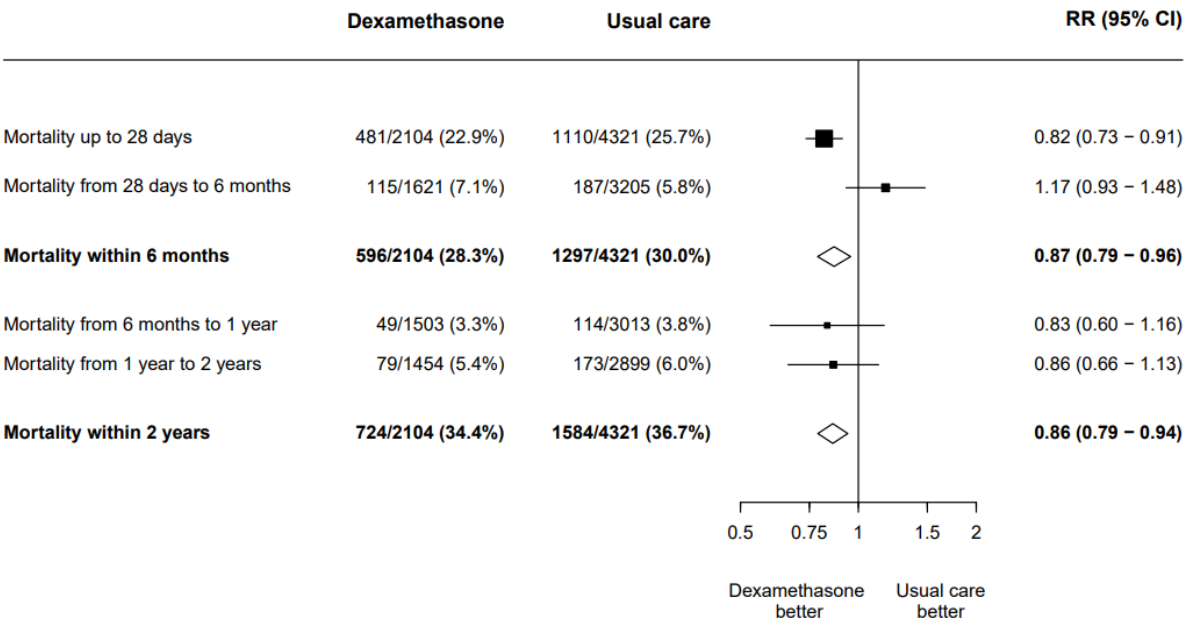


Figure 5-4: All-cause mortality in all participants in the RECOVERY dexamethasone comparison, stratified by follow-up time period.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group and randomisation.

Exploratory analyses of diagnoses leading to death at 6 month follow-up demonstrated a significant dexamethasone treatment benefit on mortality related to COVID-19 but no clear efficacy or harm for other causes (Supplementary Table 11).

5.3.3 Non-COVID infection

There was no statistically significant difference between treatment groups in the primary safety outcome of major non-COVID infection (Figure 5-5, Table 5-2). At 28 days, 276 (13%) of participants allocated dexamethasone and 512 (12%) allocated usual care experienced the outcome (RR 1.06 [95% CI 0.92–1.23], p=0.44). At 6 months, this was 473 (22%) in the dexamethasone group and 858 (20%) in the usual care group (RR 1.08 [95% CI 0.97–1.21], p=0.18). The treatment effect estimate was similar comparing between randomisation and 28 days, and 28 days to 6 months (Figure 5-6).

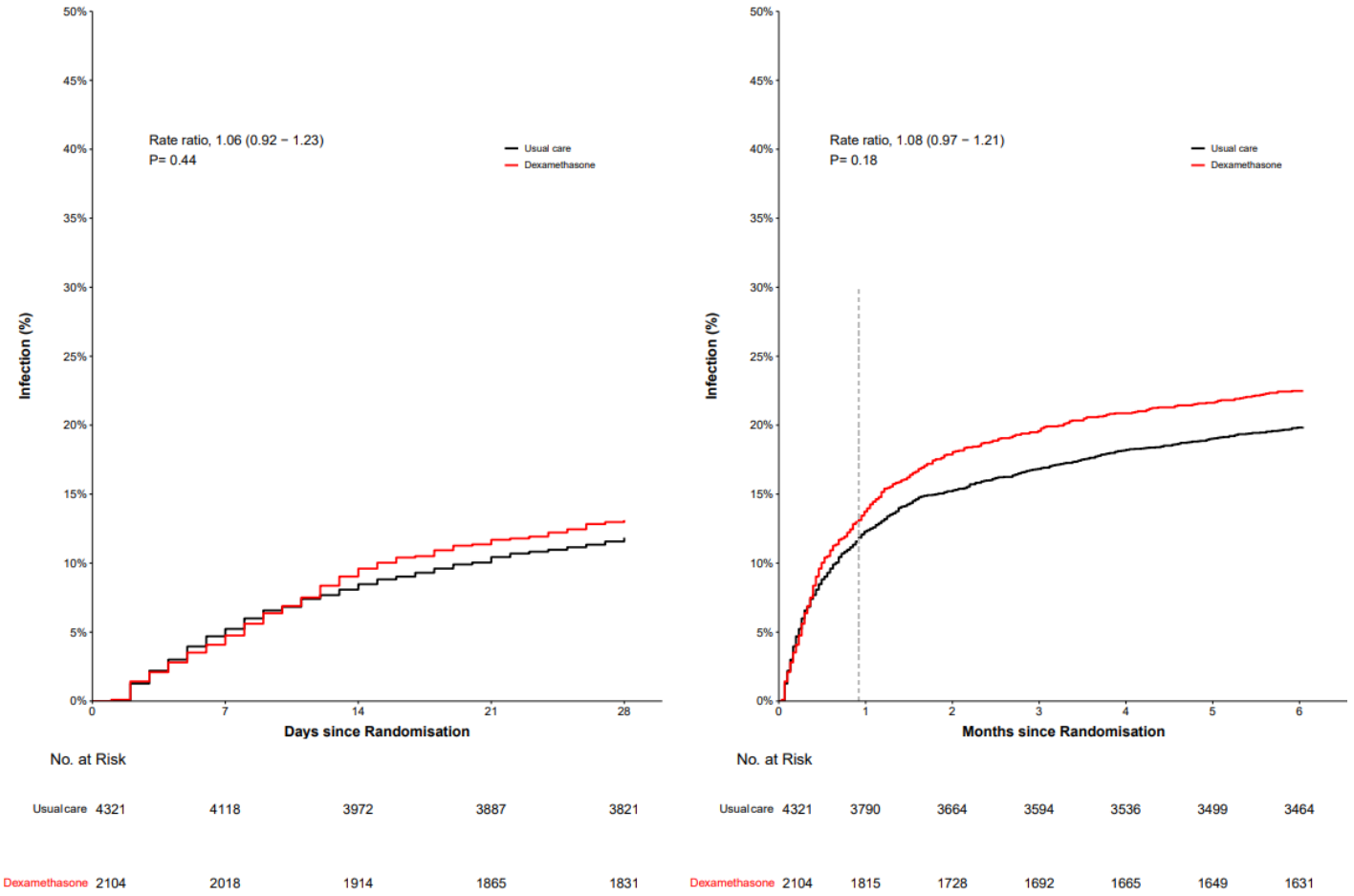


Figure 5-5: Effect of allocation to dexamethasone on major non-COVID infection in the RECOVERY dexamethasone comparison.
Left panel: Major non-COVID infection within 28 days. Right panel: Major non-COVID infection within 6 months.
The Kaplan-Meier curves have not been adjusted for age and respiratory support group. The rate ratios have been adjusted for age and respiratory support group at randomisation.

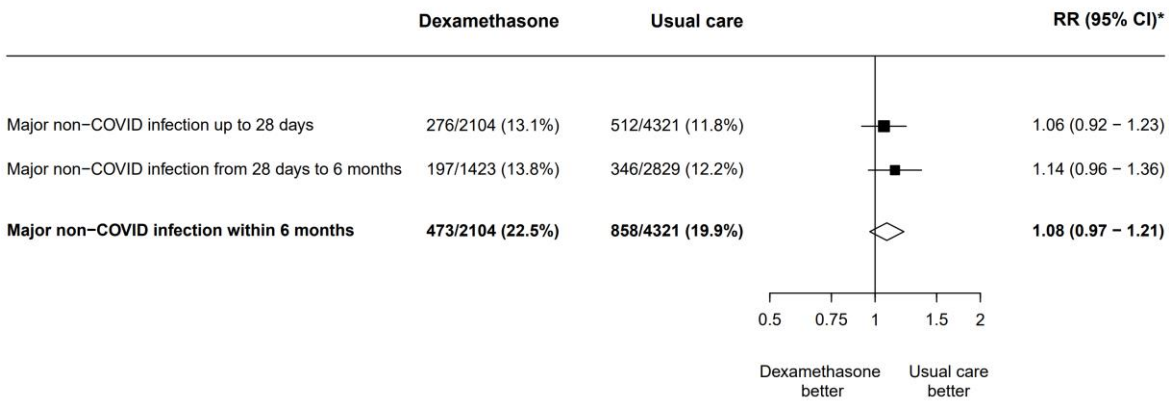


Figure 5-6: Major non-COVID infection in the RECOVERY dexamethasone comparison stratified by follow-up time period.
**RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.*

Within the major non-COVID infection events, the most commonly identified organism type was bacterial, making up just over half of identified events, followed by fungal (approximately 15%), with one third of events not associated with a specific organism type (Table 5-3). The most common anatomical site was the lower respiratory tract (around half of identified events), followed by urinary tract and bloodstream infections. Half of the total events identified occurred within the first 3 weeks after randomisation. At 28-day follow-up, 80% of events had occurred during the index hospitalisation (the hospital admission within which the participant was randomised), falling to just over half of identified events at 6 month follow-up. Events were most commonly identified from the hospital admission datasets, with around one third of events in the microbiology datasets and approximately one tenth of events in the death datasets.

Table 5-3: Major non-COVID infection event details by randomised treatment allocation in the RECOVERY dexamethasone comparison.

	Major non-COVID infection within 28 days		Major non-COVID infection within 6 months	
	Dexamethasone (n=2104)*	**Usual Care (n=4321)***	**Dexamethasone (n=2104)***	**Usual Care (n=4321)***
Organism				
Bacterial	158 (7.5)	310 (7.2)	279 (13)	504 (12)
Fungal	47 (2.2)	72 (1.7)	67 (3.2)	117 (2.7)
Viral (not SARS-CoV-2)	6 (0.3)	13 (0.3)	20 (1.0)	31 (0.7)
Tuberculosis	0 (0)	0 (0)	2 (<0.1)	2 (<0.1)
Other organism	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Unspecified organism	86 (4.1)	151 (3.5)	153 (7.3)	281 (6.5)
Anatomical site				
Pneumonia/Lower respiratory tract	143 (6.8)	272 (6.3)	249 (12)	481 (11)
Bloodstream	72 (3.4)	109 (2.5)	99 (4.7)	151 (3.5)
Urinary tract	39 (1.9)	57 (1.3)	116 (5.5)	178 (4.1)
Intra-abdominal	9 (0.4)	24 (0.6)	38 (1.8)	76 (1.8)
Skin and soft tissue	10 (0.5)	30 (0.7)	43 (2.0)	89 (2.1)
Bone and joint	5 (0.2)	3 (<0.1)	9 (0.4)	13 (0.3)
Upper respiratory tract	4 (0.2)	4 (<0.1)	5 (0.2)	6 (0.1)
Other anatomical site	29 (1.4)	52 (1.2)	52 (2.5)	102 (2.4)
Unspecified anatomical site	25 (1.2)	54 (1.2)	33 (1.6)	61 (1.4)
Event timing				
Median event study day (IQR)	10 (5, 15)	8 (4, 16)	19 (9, 50)	20 (7, 52)
Occurred during index hospitalisation	215 (10)	429 (9.9)	252 (12)	493 (11)
Data source				
Hospital admission datasets	181 (8.6)	325 (7.5)	372 (18)	658 (15)
Microbiology dataset	96 (4.6)	189 (4.4)	135 (6.4)	253 (5.9)
Death datasets	33 (1.6)	50 (1.2)	61 (2.9)	91 (2.1)
Total				
Major non-COVID infection	276 (13)	512 (12)	473 (22)	858 (20)

**n (%)*
IQR = Interquartile range

Bloodstream infections (BSIs) may have been more frequent in the dexamethasone group (Table 5-4). Within 28 days, 72/2104 (3.4%) of participants allocated dexamethasone were diagnosed with a BSI, compared with 109/4321 (2.5%) in the usual care group (RR 1.33 [95% CI 0.99–1.79], p=0.06). Within 6 months, this was 99 (4.7%) allocated dexamethasone and 151 (3.5%) allocated usual care (RR 1.29 [95% CI 1.00–1.67], p=0.05). Amongst identified BSIs, approximately 90% were bacterial and 10% were fungal (Supplementary Table 12). 60% of the bacterial BSIs identified were caused by Gram negative bacteria, most commonly *Escherichia coli*, *Klebsiella* species and *Pseudomonas aeruginosa*; and 40% were caused by Gram positive bacteria, most commonly *Enterococcus* species and *Staphylococcus aureus*. At 6-month follow-up, around three quarters of identified BSIs had occurred during the index hospitalisation (Supplementary Table 16).

Table 5-4: Effect of allocation to dexamethasone on secondary and tertiary infection outcomes.

	Dexamethasone (n=2104)	Usual Care (n=4321)	Rate or Risk Ratio (95% CI)	p-value
Secondary outcomes				
Any non-COVID infection within 28 days	402 (19%)	784 (18%)	1.05 (0.95 - 1.17)	0.34
Any non-COVID infection within 6 months	732 (35%)	1,420 (33%)	1.05 (0.98 - 1.13)	0.16
Microbiologically confirmed non-COVID infection within 28 days	96 (4.6%)	189 (4.4%)	1.00 (0.78 - 1.28)	>0.99
Microbiologically confirmed non-COVID infection within 6 months	135 (6.4%)	253 (5.9%)	1.03 (0.84 - 1.28)	0.75
Bloodstream infection within 28 days	72 (3.4%)	109 (2.5%)	1.33 (0.99 - 1.79)	0.06
Bloodstream infection within 6 months	99 (4.7%)	151 (3.5%)	1.29 (1.00 - 1.67)	0.05
Tertiary outcomes				
Bacterial infection within 28 days	277 (13%)	557 (13%)	1.03 (0.90 - 1.17)	0.68
Bacterial infection within 6 months	581 (28%)	1,142 (26%)	1.04 (0.96 - 1.13)	0.35
Fungal infection within 28 days	50 (2.4%)	82 (1.9%)	1.27 (0.89 - 1.78)	0.18
Fungal infection within 6 months	78 (3.7%)	147 (3.4%)	1.10 (0.83 - 1.43)	0.50

No significant differences were observed in other secondary and tertiary non-COVID infection outcomes (Table 5-4).

Sensitivity analyses of the major non-COVID infection primary outcome and non-COVID infection secondary outcome resulted in similar findings to the main analysis (Supplementary Table 13).

Tabulations of all infection outcomes by event type, timing and data sources are presented in Supplementary Table 14 to Supplementary Table 18.

5.3.4 Other clinical benefits

The proportion of participants discharged alive from hospital within 6 months was significantly higher in the dexamethasone group compared with the usual care group (77% vs 74%, RR 1.11 [95% CI 1.04–1.18], p <0.001), with a treatment effect estimate similar to that observed at 28 days (Figure 5-7, Table 5-5).

There was no significant difference observed between treatment groups in the occurrence of long COVID or the ability to self-care at hospital discharge (Table 5-5).

Table 5-5: Effect of allocation to dexamethasone on other clinical benefits.

	Dexamethasone (n=2104)	**Usual Care (n=4321)**	**Rate or Risk Ratio (95% CI)**	**p-value**
Secondary outcomes				
Discharged alive from hospital within 6 months	1,610 (77%)	3,189 (74%)	1.11 (1.04 - 1.18)	<0.001
Long COVID within 18 months	64 (3.0%)	120 (2.8%)	1.05 (0.78 - 1.42)	0.75
Tertiary outcomes				
Preserved ability to self-care at hospital discharge[1]	709/902 (79%)	1,427/1,773 (80%)	0.91 (0.74 - 1.12)	0.36
[1]Assessed in participants in the RECOVERY-ISARIC dexamethasone comparison population who were discharged alive from hospital and had an assessment recorded.				

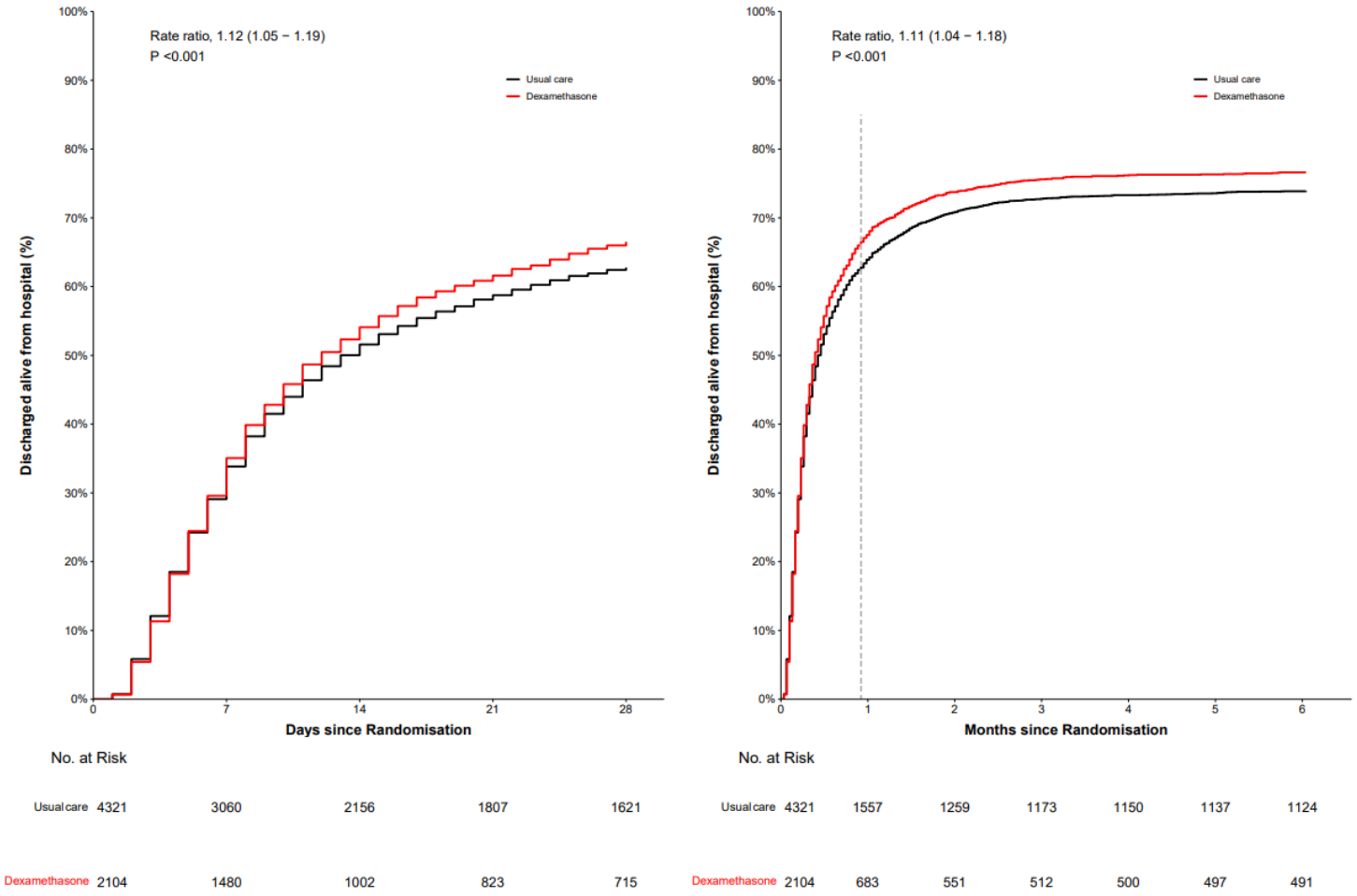


Figure 5-7: Effect of allocation to dexamethasone on discharge alive from hospital in the RECOVERY dexamethasone comparison.
Left panel: Discharged alive within 28 days. Right panel: Discharged alive within 6 months.
The Kaplan-Meier curves have not been adjusted for age and respiratory support group. The rate ratios have been adjusted for age and respiratory support group at randomisation.

5.3.5 Other potential treatment-related harms

Metabolic complications may have been more frequent in the dexamethasone treatment group (Table 5-6). Most metabolic complication events were of documented hyperglycaemia or hypoglycaemia (60%), with ketoacidosis making up 12% of identified metabolic complication events at 6-month follow-up (Supplementary Table 19). Three quarters of metabolic complication events at 28-day follow-up occurred in participants with some evidence of pre-existing diabetes mellitus. In the RECOVERY-ISARIC dexamethasone comparison population, participants in the dexamethasone group had a higher rate of hyperglycaemia compared with those in the usual care group (RR 1.72 [95% CI 1.38 – 2.16], p<0.001) (Table 5-6). Two thirds of the hyperglycaemia events occurred in participants with evidence of pre-existing diabetes. There was no evidence of heterogeneity in the outcome of hyperglycaemia within 28 days according to baseline diabetes status in the RECOVERY-ISARIC dexamethasone comparison population (diabetes present, RR 1.50 [95% CI 1.14 – 1.96], diabetes absent, RR 2.01 [95% CI 1.36 – 2.97], χ^2=1.5, p=0.23). Participants in the dexamethasone group may have had a lower rate of biochemically-defined AKI, compared with the usual care group (RR 0.73 [95% CI 0.56 – 0.95], p=0.02) (Table 5-6).

Table 5-6: Effect of allocation to dexamethasone on other potential treatment-related harms.

	Dexamethasone (n=2104)	Usual Care (n=4321)	Rate or Risk Ratio (95% CI)	p-value
Secondary outcomes				
Gastrointestinal complication within 28 days	19 (0.9%)	25 (0.6%)	1.48 (0.81 - 2.69)	0.20
Gastrointestinal complication within 6 months	44 (2.1%)	71 (1.6%)	1.21 (0.83 - 1.77)	0.31
Venous thromboembolism within 28 days	48 (2.3%)	76 (1.8%)	1.27 (0.89 - 1.83)	0.19
Venous thromboembolism within 6 months	72 (3.4%)	119 (2.8%)	1.20 (0.90 - 1.61)	0.21
Tertiary outcomes				
Metabolic complication within 28 days	20 (1.0%)	21 (0.5%)	1.86 (1.01 - 3.44)	0.05
Metabolic complication within 6 months	43 (2.0%)	60 (1.4%)	1.41 (0.96 - 2.09)	0.08

Incident diabetes within 12 months[1]	15/1,376 (1.1%)	26/2,920 (0.9%)	1.24 (0.65 - 2.31)	0.50
Fracture within 28 days	10 (0.5%)	16 (0.4%)	1.16 (0.53 - 2.55)	0.72
Fracture within 6 months	33 (1.6%)	49 (1.1%)	1.28 (0.82 - 1.99)	0.28
Psychiatric complication within 28 days	57 (2.7%)	102 (2.4%)	1.11 (0.80 - 1.52)	0.51
Psychiatric complication within 6 months	100 (4.8%)	198 (4.6%)	1.00 (0.79 - 1.26)	1.00
Clinically-defined liver injury within 28 days	16 (0.8%)	36 (0.8%)	0.91 (0.50 - 1.64)	0.75
Clinically-defined liver injury within 6 months	23 (1.1%)	61 (1.4%)	0.75 (0.47 - 1.22)	0.25
Exploratory outcomes				
Hyperglycaemia within 28 days[2]	141/1,581 (8.9%)	170/3,215 (5.3%)	1.72 (1.38 - 2.16)	<0.001
Acute kidney injury within 28 days[2,3]	75/1,581 (4.7%)	203/3,215 (6.3%)	0.73 (0.56 - 0.95)	0.02
Neutropenia within 28 days[2]	23/1,581 (1.5%)	80/3,215 (2.5%)	0.58 (0.37 - 0.93)	0.02
Biochemically-defined liver injury within 28 days[2]	38/1,581 (2.4%)	71/3,215 (2.2%)	1.08 (0.73 - 1.60)	0.70
Viral clearance within 28 days[4]	106/242 (44%)	253/501 (50%)	0.80 (0.64 - 1.00)	0.05

[1]Assessed in participants with no evidence of diabetes mellitus at baseline.
[2]Assessed in participants in the RECOVERY-ISARIC dexamethasone comparison population.
[3]Acute kidney injury was defined as a ≥1.5x increase in serum creatinine from baseline.
[4]Assessed in participants in the RECOVERY-ISARIC dexamethasone comparison population who had a repeat SARS-CoV-2 test recorded within 28 days.

No significant differences were observed in other secondary and tertiary outcomes; including GI complications, VTE, long bone or vertebral fractures, and psychiatric complications (Table 5-6). Tabulations of all outcomes by event type, timing and data sources are presented in Supplementary Table 19 to Supplementary Table 26.

Sensitivity analyses of secondary outcomes were similar for GI complications. For VTE using first diagnostic position events only, the point estimate for the treatment effect was higher than the results for the main analysis but event numbers were small (1.8% for dexamethasone vs 1.0% for usual care within 6 months, RR 1.67 [95% CI 1.08 – 2.59], p=0.02) (Supplementary Table 27).

Amongst remaining exploratory outcomes, there may have been a lower rate of neutropenia and there may also have been a lower rate of viral clearance in the dexamethasone group (Table 5-6). Survivor bias is a concern in the viral clearance analysis.

The exploratory analysis of primary hospital-recorded diagnoses demonstrated no definitive differences between treatment groups (Supplementary Table 28).

5.3.6 Subgroup analyses

Pre-defined subgroup analyses of mortality at 6 months demonstrated significant heterogeneity in treatment effect according to respiratory support group at randomisation, HFRS, time since COVID-19 symptom onset and baseline non-COVID infection (Figure 5-8). This was consistent with the findings of the dexamethasone 28-day follow-up (Supplementary Figure 15). The greatest mortality benefit of dexamethasone treatment was seen in participants on higher levels of respiratory support at randomisation and those with a low frailty risk score. A longer duration of symptoms (more likely in those receiving higher levels of respiratory support) and an absence of concurrent non-COVID infection at randomisation may also have been associated with a greater dexamethasone treatment benefit. The possibility of harm remained in participants not on oxygen at randomisation and with a high frailty risk score.

Subgroup analyses of major non-COVID infection at 28 days and 6 months, suggested possible heterogeneity according to age group (with higher age groups possibly having a greater treatment-related risk) but in the context of an overall null result for this outcome (Figure 5-9, Figure 5-10).

Findings from these pre-specified subgroup analyses are explored further in Chapter 6 (Section 6.3).

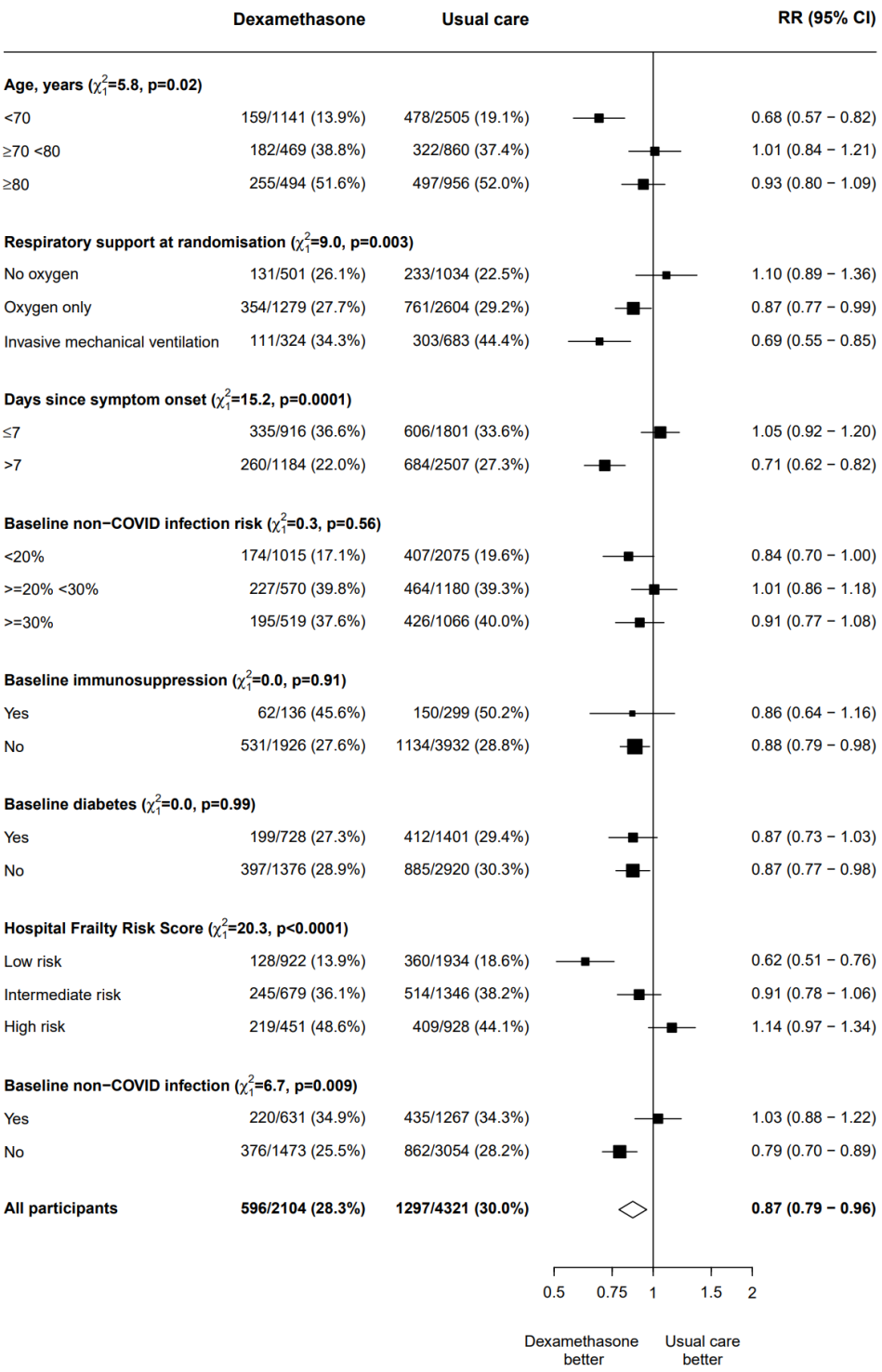


Figure 5-8: Subgroup analysis of effect of allocation to dexamethasone on all-cause mortality within 6 months.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.

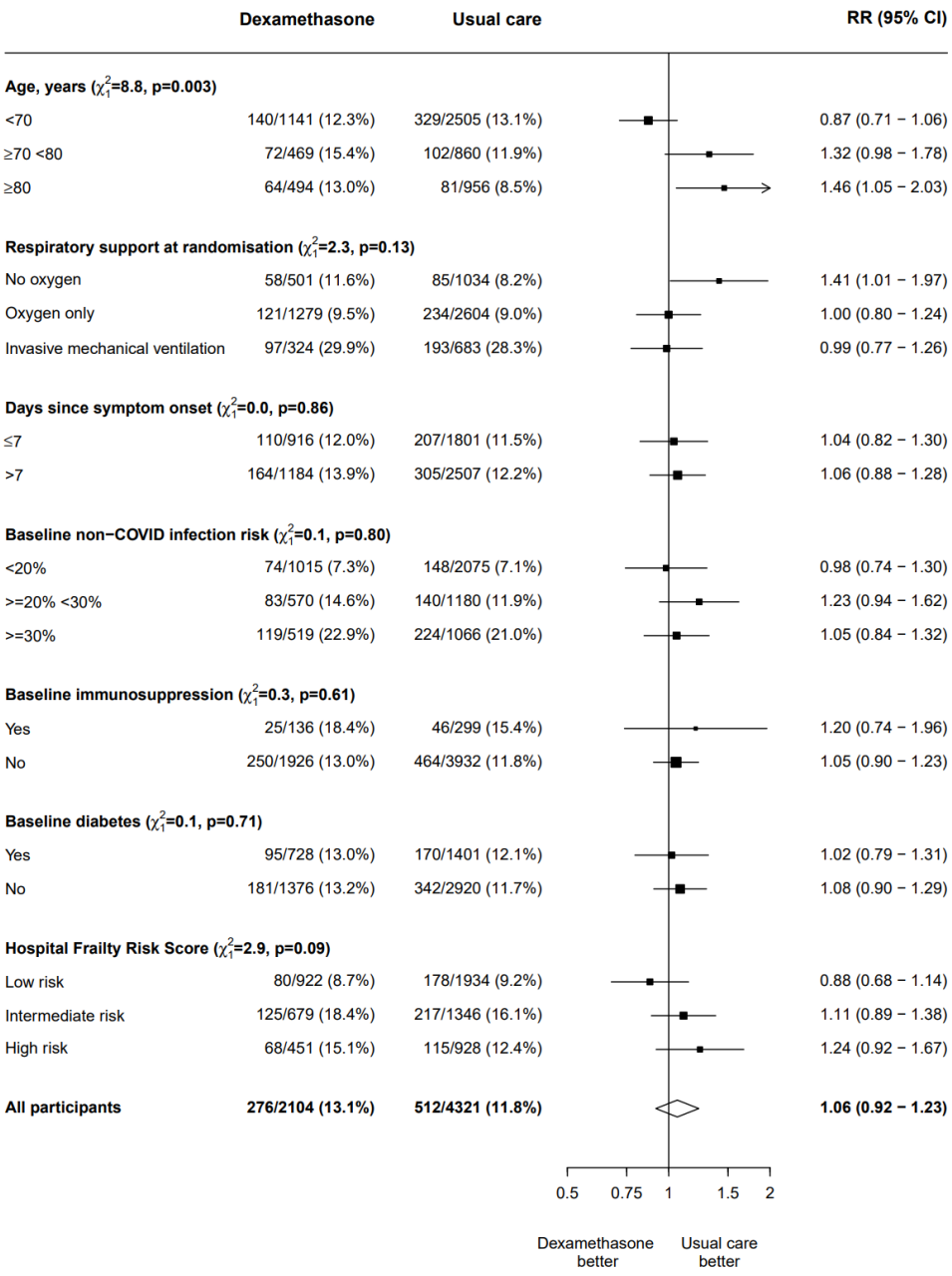


Figure 5-9: Subgroup analysis of effect of allocation to dexamethasone on major non-COVID infection within 28 days.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.

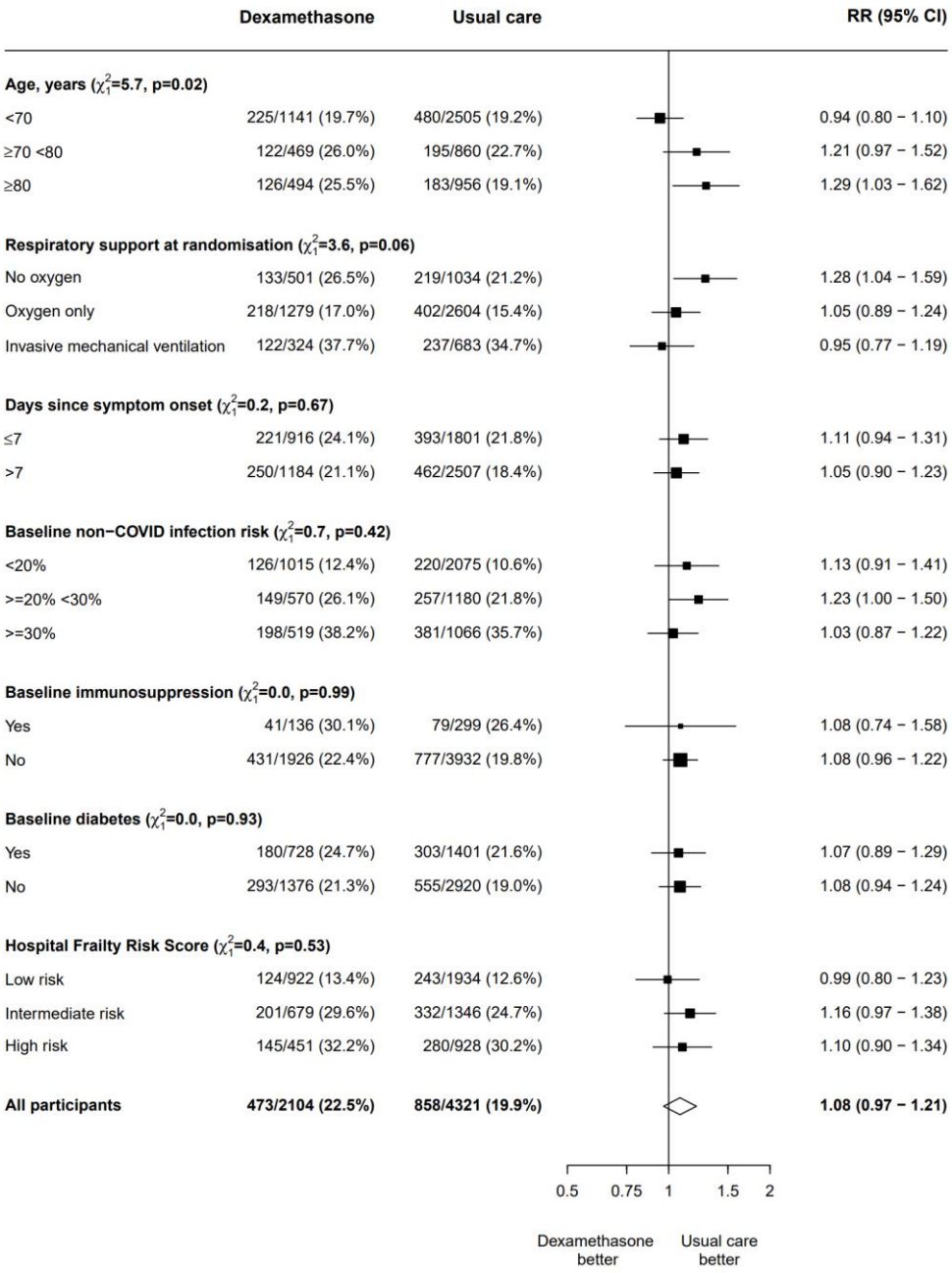


Figure 5-10: Subgroup analysis of effect of allocation to dexamethasone on major non-COVID infection within 6 months.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.

5.4 Tocilizumab Randomised Comparisons

5.4.1 Baseline characteristics

Randomised groups were well-matched in the RECOVERY tocilizumab treatment comparison, including newly derived baseline characteristics (Table 5-7).

Table 5-7: Baseline characteristics according to randomised treatment allocation for participants in the RECOVERY tocilizumab comparison.

	Tocilizumab (N=2022)	Usual Care (N=2094)
Demographics		
Age[1]	63.3 (13.7)	63.9 (13.6)
Age Group		
Age <70	1,332 (66%)	1,354 (65%)
Age >=70 <80	477 (24%)	481 (23%)
Age >=80	213 (11%)	259 (12%)
Sex		
Female	685 (34%)	656 (31%)
Male	1,337 (66%)	1,438 (69%)
Acute illness features		
Time since symptom onset		
Time of onset <=7 days	830 (41%)	827 (40%)
Time of onset >7 days	1,192 (59%)	1,266 (60%)
Days since admission to hospital[2]	1 (1, 2)	1 (1, 2)
Respiratory support		
No ventilator support	935 (46%)	933 (45%)
Non-invasive ventilation	819 (41%)	867 (41%)
Mechanical ventilation or ECMO	268 (13%)	294 (14%)
Baseline non-COVID infection	479 (24%)	487 (23%)
Laboratory measurements		
C-reactive protein, mg/L[2]	143 (107, 203)	144 (106, 205)
Creatinine, µmol/L[2]	77 (62, 98)	77 (62, 100)
Baseline co-morbidities		
Diabetes	569 (28%)	600 (29%)
Heart disease	435 (22%)	497 (24%)
Chronic lung disease	473 (23%)	484 (23%)
Tuberculosis	3 (0.2%)	5 (0.2%)
HIV	7 (0.4%)	8 (0.4%)
Severe liver disease	14 (0.7%)	10 (0.5%)
Severe kidney impairment	118 (5.9%)	99 (4.8%)
Severe mental illness	290/1,997 (15%)	316/2,066 (15%)
Immunosuppression	133/1,997 (6.7%)	124/2,067 (6.0%)
Charlson score[2]	3 (2, 5)	3 (2, 5)
Hospital Frailty Risk Score group		
Low risk (<5)[3]	1,218 (61%)	1,239 (60%)
Intermediate risk (5-15)[3]	581 (29%)	619 (30%)
High risk (>15)[3]	194 (9.7%)	200 (9.7%)
Unknown	29 (1.4%)	36 (1.7%)
Other treatments		
Corticosteroids	1,664 (82%)	1,721 (82%)

[1]Mean (Standard Deviation)
[2]Median (Lower quartile, Upper quartile)
[3]n (%) excludes 'Unknown'

5.4.2 Long-term mortality

Allocation to tocilizumab was associated with a significant improvement in the primary efficacy outcome of all-cause mortality at 6 months, compared with usual care. 694/2022 (34%) of participants in the tocilizumab group and 816/2094 (39%) of participants in the usual care group died within 6 months of randomisation (RR 0.87 [95% CI 0.79–0.96], p=0.007) (Table 5-8, Figure 5-11).

An exploratory analysis of all-cause mortality at 2 years after randomisation showed a stable treatment effect estimate, with a preserved significant reduction in mortality with tocilizumab treatment (RR 0.87 [95% CI 0.79 – 0.96], p=0.007) (Figure 5-12). A further 251 participants in the treatment comparison died between 28-day and 2-year follow-up points, an increase in event numbers of 19% compared to follow-up at 28 days (Figure 5-13).

Table 5-8: Effect of allocation to tocilizumab on primary long-term follow-up outcomes.

	Tocilizumab (n=2022)	Usual Care (n=2094)	Rate or Risk Ratio (95% CI)	p-value
Primary outcomes				
Mortality within 6 months	694 (34%)	816 (39%)	0.87 (0.79 - 0.96)	0.007
Major non-COVID infection within 28 days	270 (13%)	311 (15%)	0.88 (0.75 - 1.03)	0.12
Major non-COVID infection within 6 months	382 (19%)	412 (20%)	0.93 (0.81 - 1.07)	0.28

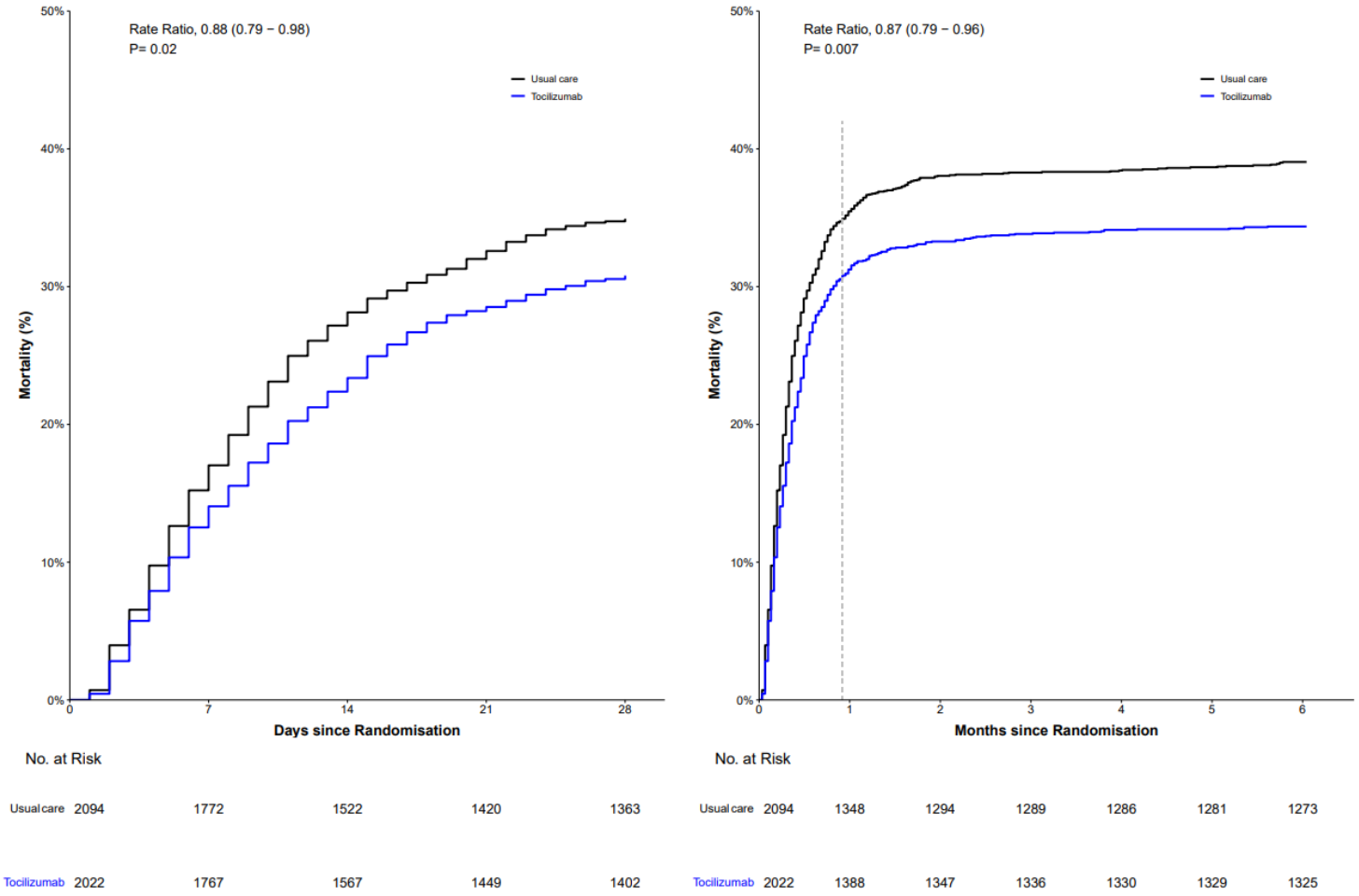


Figure 5-11: Effect of allocation to tocilizumab on all-cause mortality in the RECOVERY tocilizumab comparison.
Left panel: 28-day mortality. Right panel: 6-month mortality.
The Kaplan-Meier curves have not been adjusted for age and respiratory support group. The rate ratios have been adjusted for age and respiratory support group at randomisation.

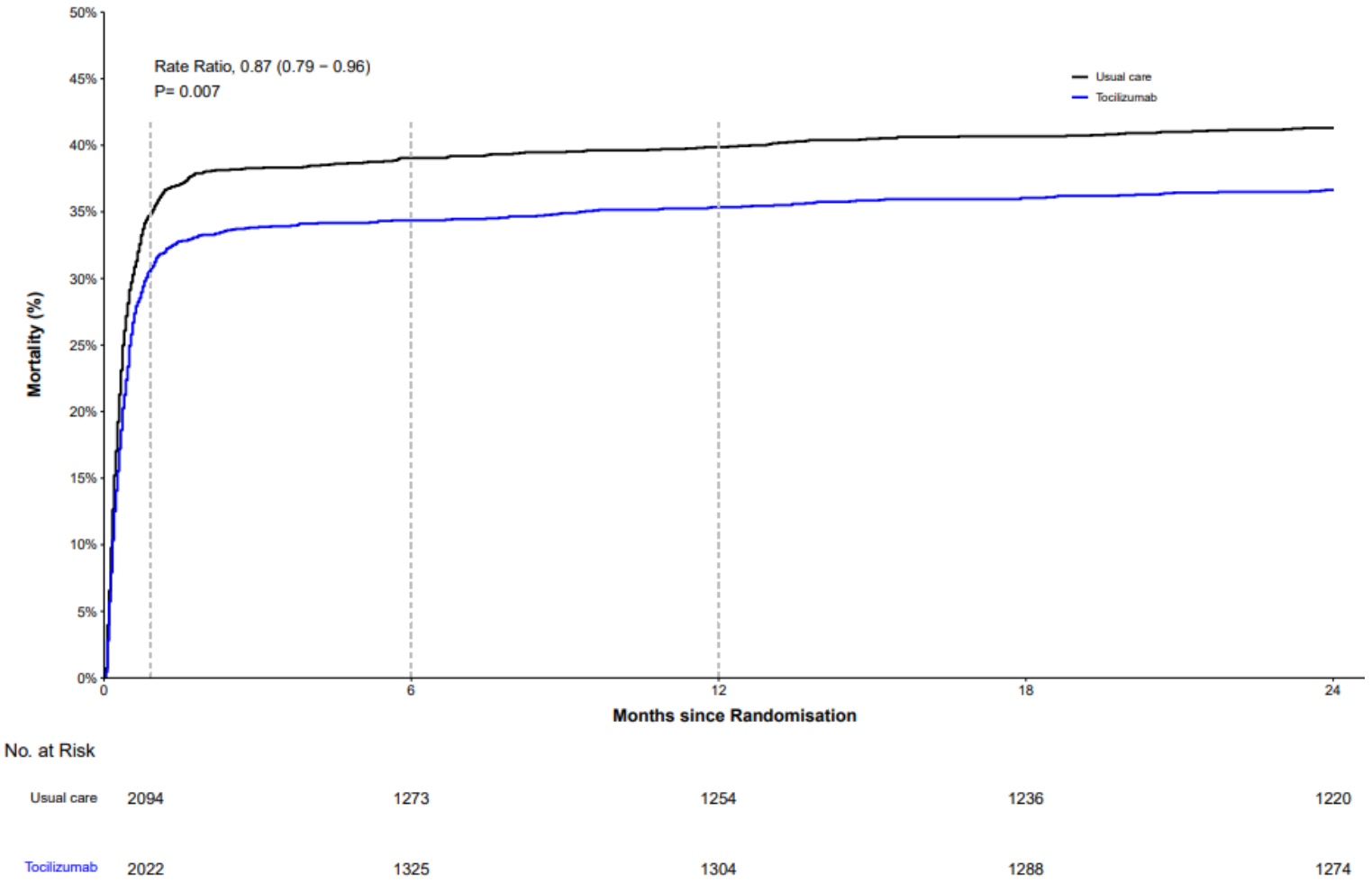


Figure 5-12: Effect of allocation to tocilizumab on 2-year mortality in the RECOVERY tocilizumab comparison.
The Kaplan-Meier curves have not been adjusted for age and respiratory support group. The rate ratios have been adjusted for age and respiratory support group at randomisation.

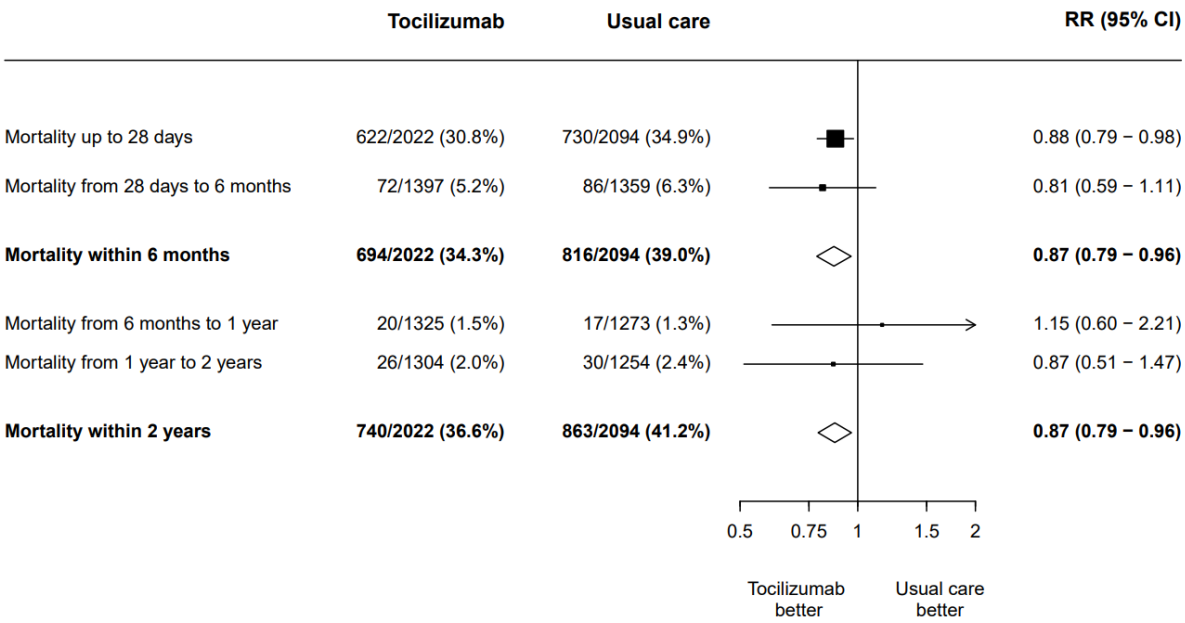


Figure 5-13: Mortality in the all participants in the RECOVERY tocilizumab comparison, stratified by follow-up time period.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group and randomisation.

Categorisation of diagnoses leading to death within 6 months was consistent with a tocilizumab treatment benefit on mortality relating to COVID-19 (Supplementary Table 29).

5.4.3 Non-COVID infection

There was no significant difference seen between the tocilizumab group and the usual care group in the primary safety outcome of major non-COVID infection (Figure 5-14, Figure 5-15 and Table 5-8). Within 28 days, 270/2022 (13%) in the tocilizumab group and 311/2094 (15%) in the usual care group experienced this outcome (RR 0.88 [95% CI 0.75–1.03], p=0.12). At 6 months, this had become 382 (19%) of participants allocated tocilizumab and 412 (20%) of participants allocated usual care (RR 0.93 [95% CI 0.81 – 1.07], p=0.28).

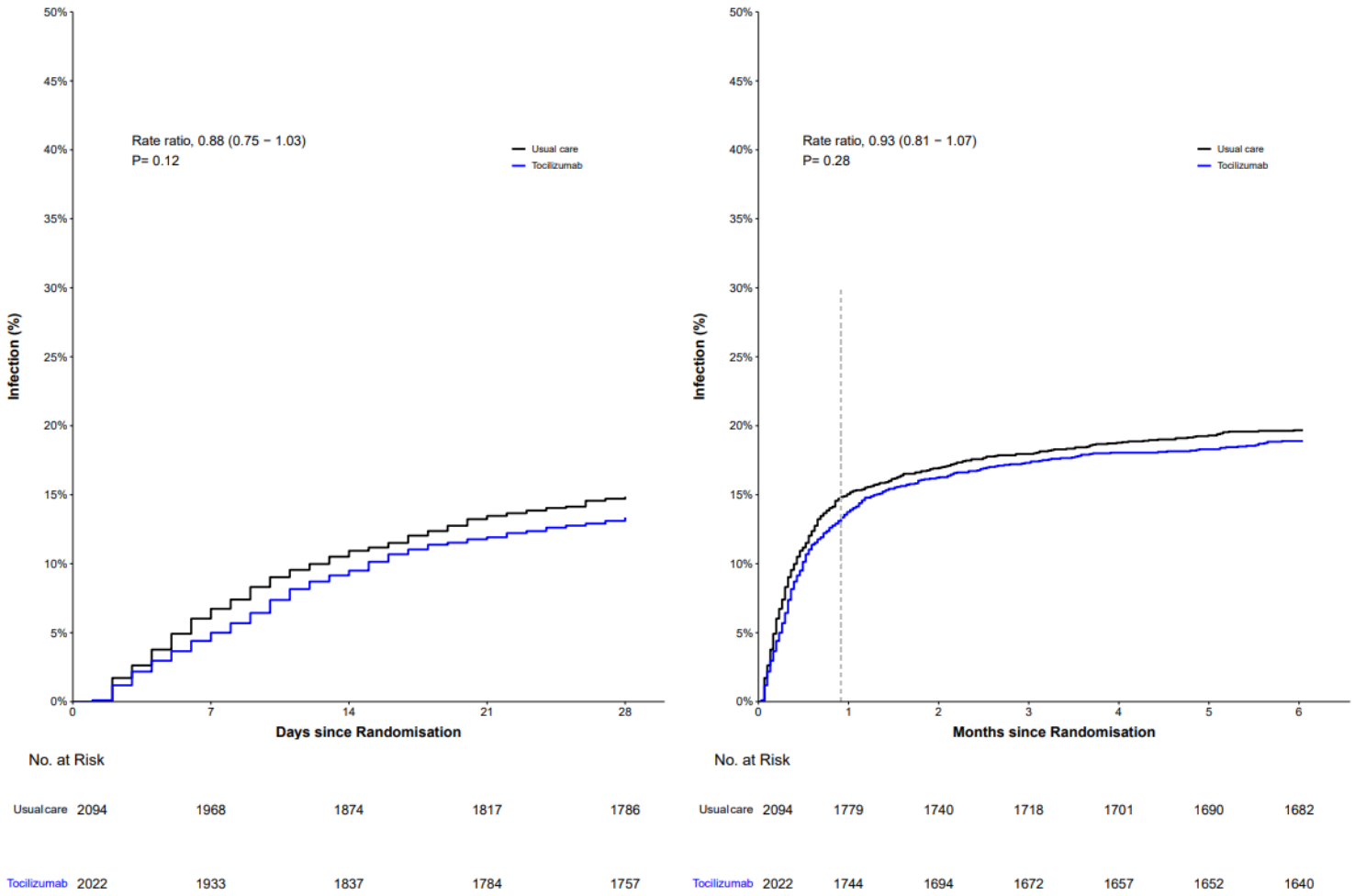


Figure 5-14: Effect of allocation to tocilizumab on major non-COVID infection in the RECOVERY tocilizumab comparison.
Left panel: Major non-COVID infection within 28 days. Right panel: Major non-COVID infection within 6 months.
The Kaplan-Meier curves have not been adjusted for age and respiratory support group. The rate ratios have been adjusted for age and respiratory support group at randomisation.

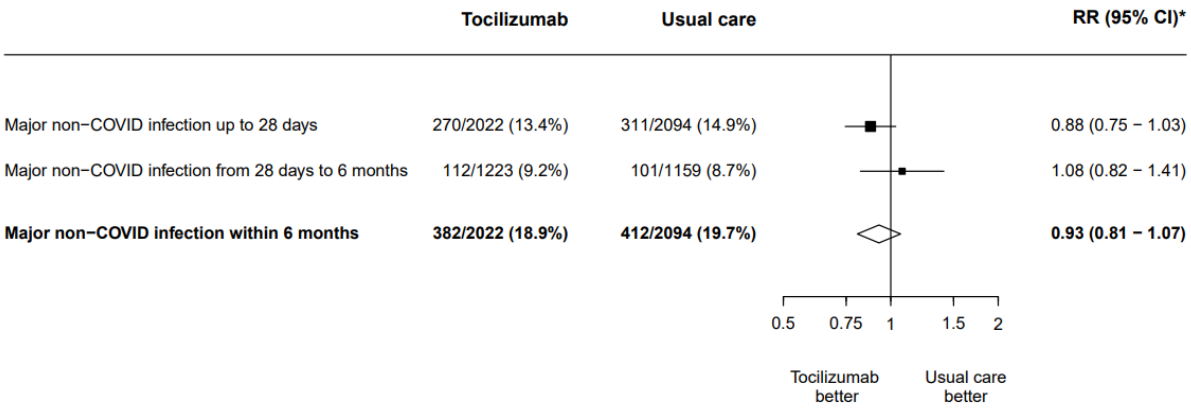


Figure 5-15: Major non-COVID infection in the RECOVERY tocilizumab comparison stratified by follow-up time period.
**RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.*

Amongst the identified major non-COVID infection events, the most commonly identified type of organism was bacterial, making up approximately two thirds of events (Table 5-9). The most common anatomical site was the lower respiratory tract (just over half of identified events), followed by bloodstream and urinary tract infections. Two thirds of the total events at 6-month follow-up occurred within 3 weeks of randomisation. At 28-day follow-up, over 90% of events had occurred during the index hospitalisation, falling to around three quarters of events at 6-month follow-up. Fungal infection and tuberculosis appeared rare in both treatment groups.

Table 5-9: Major non-COVID infection event details by randomised treatment allocation in the RECOVERY tocilizumab comparison.

	Major non-COVID infection within 28 days		Major non-COVID infection within 6 months	
	Tocilizumab (n=2022)*	**Usual Care (n=2094)***	**Tocilizumab (n=2022)***	**Usual Care (n=2094)***
Organism				
Bacterial	193 (9.5)	211 (10)	255 (13)	266 (13)
Fungal	38 (1.9)	35 (1.7)	51 (2.5)	49 (2.3)
Viral (not SARS-CoV-2)	4 (0.2)	8 (0.4)	5 (0.2)	13 (0.6)
Tuberculosis	0 (0)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Other organism	1 (<0.1)	1 (<0.1)	2 (<0.1)	2 (<0.1)
Unspecified organism	54 (2.7)	71 (3.4)	99 (4.9)	110 (5.3)
Anatomical site				
Pneumonia/Lower respiratory tract	146 (7.2)	172 (8.2)	213 (11)	251 (12)
Bloodstream	85 (4.2)	82 (3.9)	100 (4.9)	108 (5.2)
Urinary tract	24 (1.2)	33 (1.6)	51 (2.5)	62 (3.0)
Intra-abdominal	9 (0.4)	6 (0.3)	20 (1.0)	20 (1.0)
Skin and soft tissue	5 (0.2)	8 (0.4)	27 (1.3)	20 (1.0)
Bone and joint	2 (<0.1)	0 (0)	7 (0.3)	7 (0.3)
Upper respiratory tract	3 (0.1)	3 (0.1)	4 (0.2)	4 (0.2)
Other anatomical site	24 (1.2)	29 (1.4)	32 (1.6)	45 (2.1)
Unspecified anatomical site	30 (1.5)	31 (1.5)	33 (1.6)	32 (1.5)
Event timing				
Median event study day (IQR)	10 (5, 15)	9 (4, 15)	14 (7, 34)	12 (6, 28)
Occurred during index hospitalisation	243 (12)	288 (14)	264 (13)	315 (15)
Data source				
Hospital admission datasets	159 (7.9)	186 (8.9)	272 (13)	286 (14)
Microbiology dataset	129 (6.4)	134 (6.4)	148 (7.3)	167 (8.0)
Death datasets	29 (1.4)	34 (1.6)	42 (2.1)	41 (2.0)
Total				
Major non-COVID infection	270 (13)	311 (15)	382 (19)	412 (20)

**n (%)*
IQR = Interquartile range

No significant differences were observed in secondary and tertiary non-COVID infection outcomes (Table 5-10).

Sensitivity analyses of the major non-COVID infection outcome and non-COVID infection secondary outcome resulted in similar findings (Supplementary Table 30).

Tabulations of all infection outcomes by event type, timing, and data sources, are presented in Supplementary Table 31 to Supplementary Table 36.

Table 5-10: Effect of allocation to tocilizumab on secondary and tertiary infection outcomes.

	Tocilizumab (n=2022)	Usual Care (n=2094)	Rate or Risk Ratio (95% CI)	p-value
Secondary outcomes				
Any non-COVID infection within 28 days	372 (18%)	394 (19%)	1.00 (0.88 - 1.13)	0.96
Any non-COVID infection within 6 months	606 (30%)	612 (29%)	1.03 (0.94 - 1.14)	0.48
Microbiologically confirmed non-COVID infection within 28 days	129 (6.4%)	134 (6.4%)	1.00 (0.79 - 1.28)	0.98
Microbiologically confirmed non-COVID infection within 6 months	148 (7.3%)	167 (8.0%)	0.91 (0.73 - 1.14)	0.43
Bloodstream infection within 28 days	85 (4.2%)	82 (3.9%)	1.09 (0.80 - 1.47)	0.59
Bloodstream infection within 6 months	100 (4.9%)	108 (5.2%)	0.96 (0.73 - 1.26)	0.78
Tertiary outcomes				
Bacterial infection within 28 days	286 (14%)	287 (14%)	1.05 (0.91 - 1.22)	0.51
Bacterial infection within 6 months	498 (25%)	486 (23%)	1.07 (0.96 - 1.19)	0.21
Fungal infection within 28 days	42 (2.1%)	44 (2.1%)	1.00 (0.66 - 1.52)	0.99
Fungal infection within 6 months	61 (3.0%)	70 (3.3%)	0.90 (0.64 - 1.27)	0.56

5.4.4 Other clinical benefits

Participants allocated tocilizumab were significantly more likely to be discharged alive from hospital within 6 months compared to those allocated usual care (1370 (68%) vs 1294 (62%), RR 1.18 [95% CI 1.09–1.27], p <0.001) (Figure 5-16, Table 5-11).

There was no difference observed between treatment groups in the occurrence of long COVID or the ability to self-care at hospital discharge (Table 5-11).

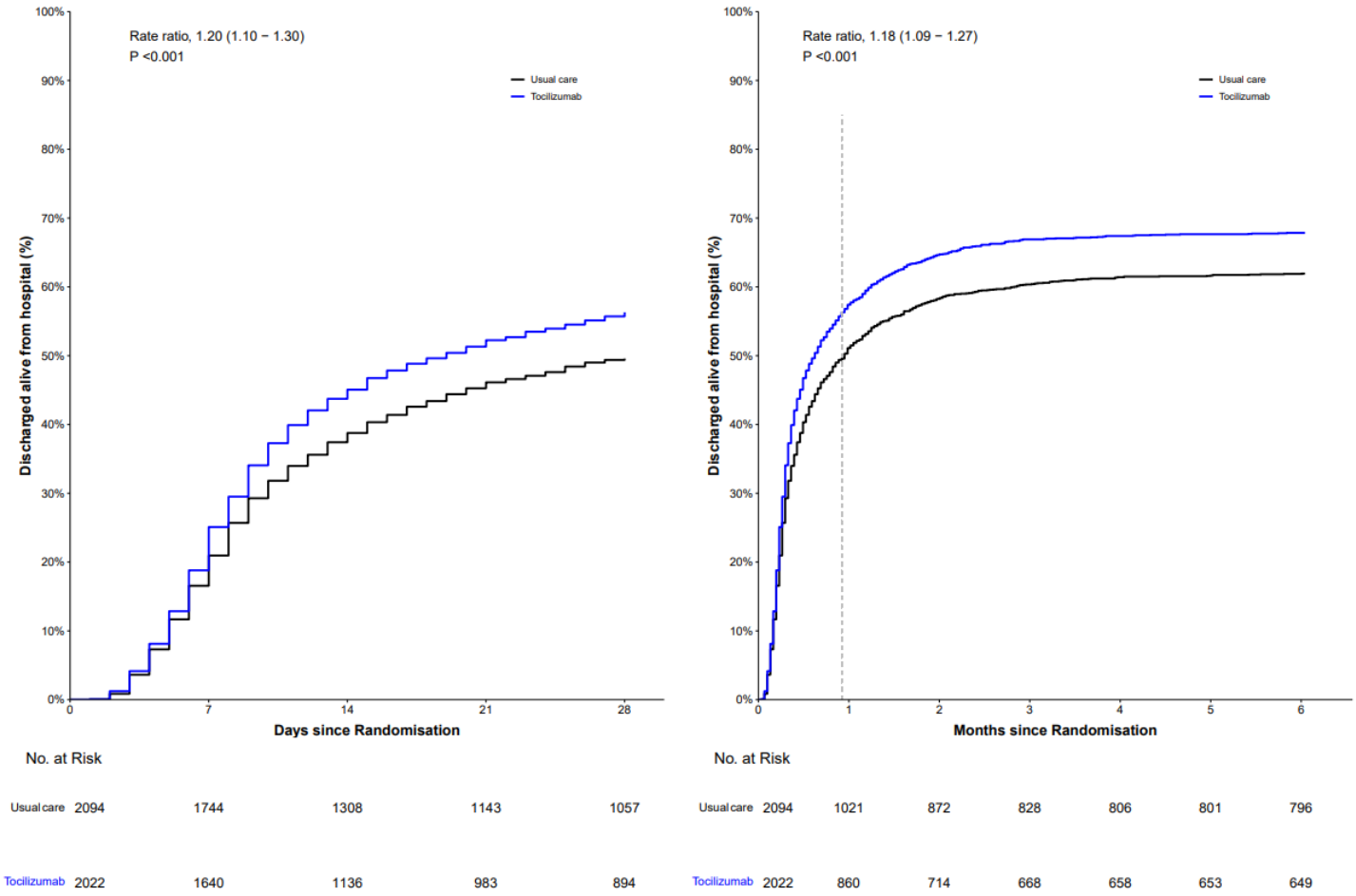


Figure 5-16: Effect of allocation to tocilizumab on discharge alive from hospital in the RECOVERY tocilizumab comparison.
Left panel: Discharged alive within 28 days. Right panel: Discharged alive within 6 months.
The Kaplan-Meier curves have not been adjusted for age and respiratory support group. The rate ratios have been adjusted for age and respiratory support group at randomisation.

Table 5-11: Effect of allocation to tocilizumab on other clinical benefits.

	Tocilizumab (n=2022)	Usual Care (n=2094)	Rate or Risk Ratio (95% CI)	p-value
Secondary outcomes				
Discharged alive from hospital within 6 months	1,370 (68%)	1,294 (62%)	1.18 (1.09 - 1.27)	<0.001
Long COVID within 18 months	146 (7.2%)	165 (7.9%)	0.85 (0.68 - 1.06)	0.15
Tertiary outcomes				
Preserved ability to self-care at hospital discharge[1]	463/610 (76%)	400/516 (78%)	0.89 (0.67 - 1.19)	0.44
[1]Assessed in participants in the RECOVERY-ISARIC tocilizumab comparison population who were discharged alive from hospital and had an assessment recorded.				

5.4.5 Other potential treatment-related harms

There were no significant differences consistent with harm observed in other secondary and tertiary outcomes; including GI complications and liver injury (Table 5-12). There may have been a higher rate of neutropenia in those randomised to tocilizumab in an analysis with very small event numbers (Table 5-12). No differences were seen in other exploratory outcomes. Tabulations of all outcomes by event type, timing and data sources are presented in Supplementary Table 37 to Supplementary Table 44.

Sensitivity analyses of secondary outcomes produced similar results to the main analysis (Supplementary Table 45).

Table 5-12: Effect of allocation to tocilizumab on potential treatment-related harms.

	Tocilizumab (n=2022)	Usual Care (n=2094)	Rate or Risk Ratio (95% CI)	p-value
Secondary outcomes				
Gastrointestinal complication within 28 days	23 (1.1%)	16 (0.8%)	1.46 (0.77 - 2.76)	0.25
Gastrointestinal complication within 6 months	28 (1.4%)	28 (1.3%)	1.00 (0.59 - 1.69)	>0.99
Venous thromboembolism within 28 days	70 (3.5%)	80 (3.8%)	0.88 (0.64 - 1.21)	0.43
Venous thromboembolism within 6 months	95 (4.7%)	107 (5.1%)	0.88 (0.67 - 1.16)	0.36
Tertiary outcomes				
Metabolic complication within 28 days	18 (0.9%)	35 (1.7%)	0.52 (0.29 - 0.92)	0.02
Metabolic complication within 6 months	39 (1.9%)	50 (2.4%)	0.78 (0.51 - 1.18)	0.24
Incident diabetes within 12 months[1]	22/1,262 (1.7%)	22/1,321 (1.7%)	1.06 (0.59 - 1.92)	0.84
Fracture within 28 days	2 (<0.1%)	3 (0.1%)	0.70 (0.12 - 4.23)	0.70
Fracture within 6 months	8 (0.4%)	7 (0.3%)	1.08 (0.39 - 3.00)	0.88
Psychiatric complication within 28 days	33 (1.6%)	52 (2.5%)	0.67 (0.43 - 1.03)	0.07
Psychiatric complication within 6 months	58 (2.9%)	74 (3.5%)	0.83 (0.59 - 1.16)	0.27
Clinically-defined liver injury within 28 days	27 (1.3%)	30 (1.4%)	0.90 (0.54 - 1.52)	0.69
Clinically-defined liver injury within 6 months	36 (1.8%)	38 (1.8%)	0.94 (0.60 - 1.48)	0.79
Exploratory outcomes				
Hyperglycaemia within 28 days[2]	70/1,215 (5.8%)	60/1,125 (5.3%)	1.07 (0.76 - 1.51)	0.70
Acute kidney injury within 28 days[2,3]	36/1,215 (3.0%)	36/1,125 (3.2%)	0.93 (0.57 - 1.47)	0.75
Neutropenia within 28 days[2]	16/1,215 (1.3%)	6/1,125 (0.5%)	2.39 (0.93 – 6.11)	0.07
Biochemically-defined liver injury within 28 days[2]	20/1,215 (1.6%)	16/1,125 (1.4%)	1.17 (0.61 - 2.26)	0.64
Viral clearance within 28 days[4]	111/246 (45%)	101/253 (40%)	1.13 (0.86 - 1.48)	0.37

[1]Assessed in participants with no evidence of diabetes mellitus at baseline
[2]Assessed in participants in the RECOVERY-ISARIC tocilizumab comparison population.
[3] Acute kidney injury was defined as a ≥1.5x increase in serum creatinine from baseline.
[4]Assessed in participants in the RECOVERY-ISARIC tocilizumab comparison population who had a repeat SARS-CoV-2 test recorded within 28 days.

The pre-specified exploratory analysis of hospital-recorded diagnoses did not suggest any tocilizumab-related safety signals (Supplementary Table 46).

5.4.6 Subgroup analyses

Subgroup analyses of mortality at 6 months suggested possible heterogeneity of treatment effect according to immunosuppression status and treatment with

corticosteroids (Figure 5-17). Findings were consistent with those for 28-day mortality (Supplementary Figure 16).

Subgroup analyses of the primary infection outcome are presented in Figure 5-18 and Figure 5-19. There was no evidence that tocilizumab increased infection risk in those also receiving corticosteroids.

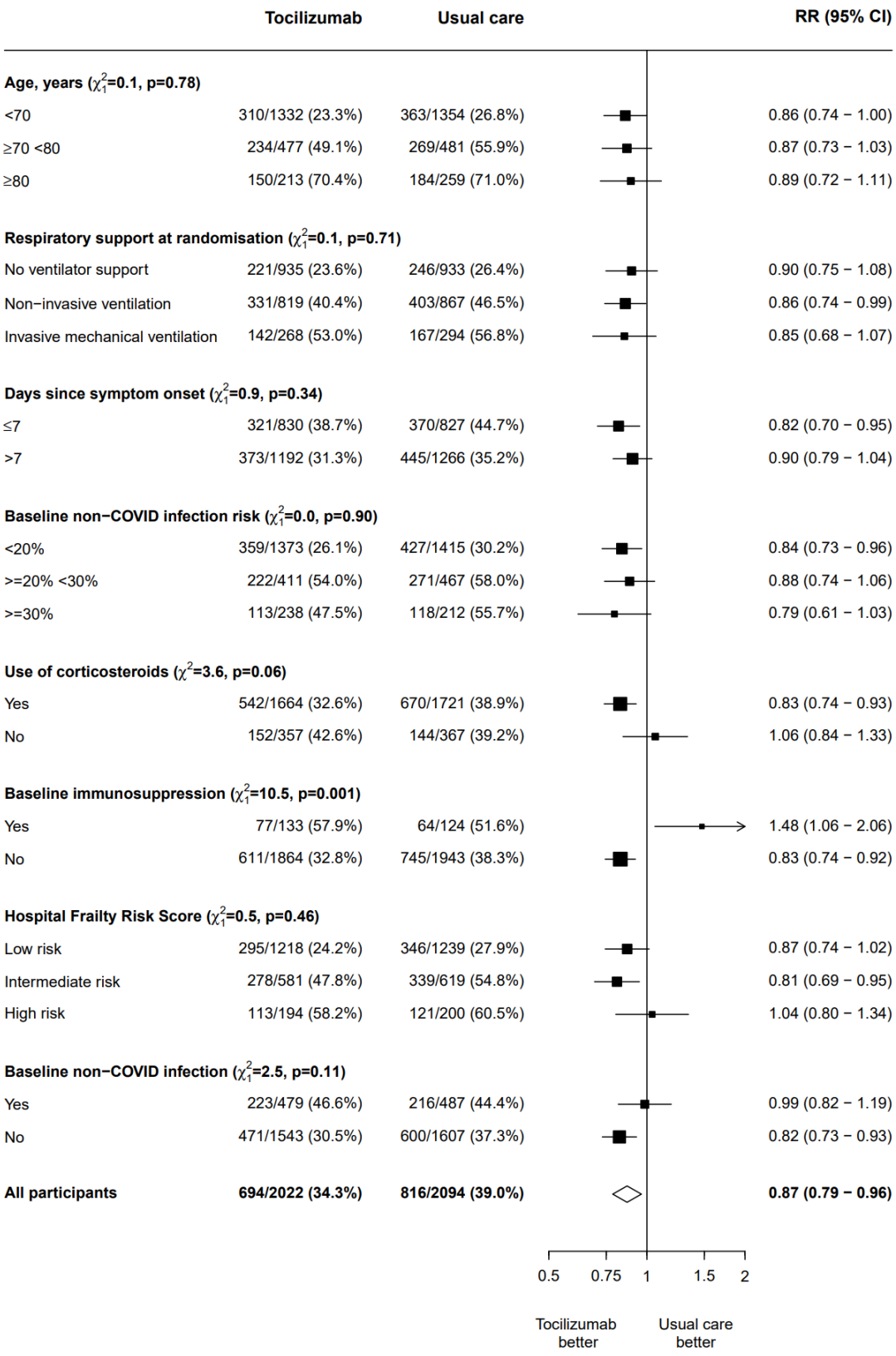


Figure 5-17: Subgroup analysis of effect of allocation to tocilizumab on all-cause mortality within 6 months.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.

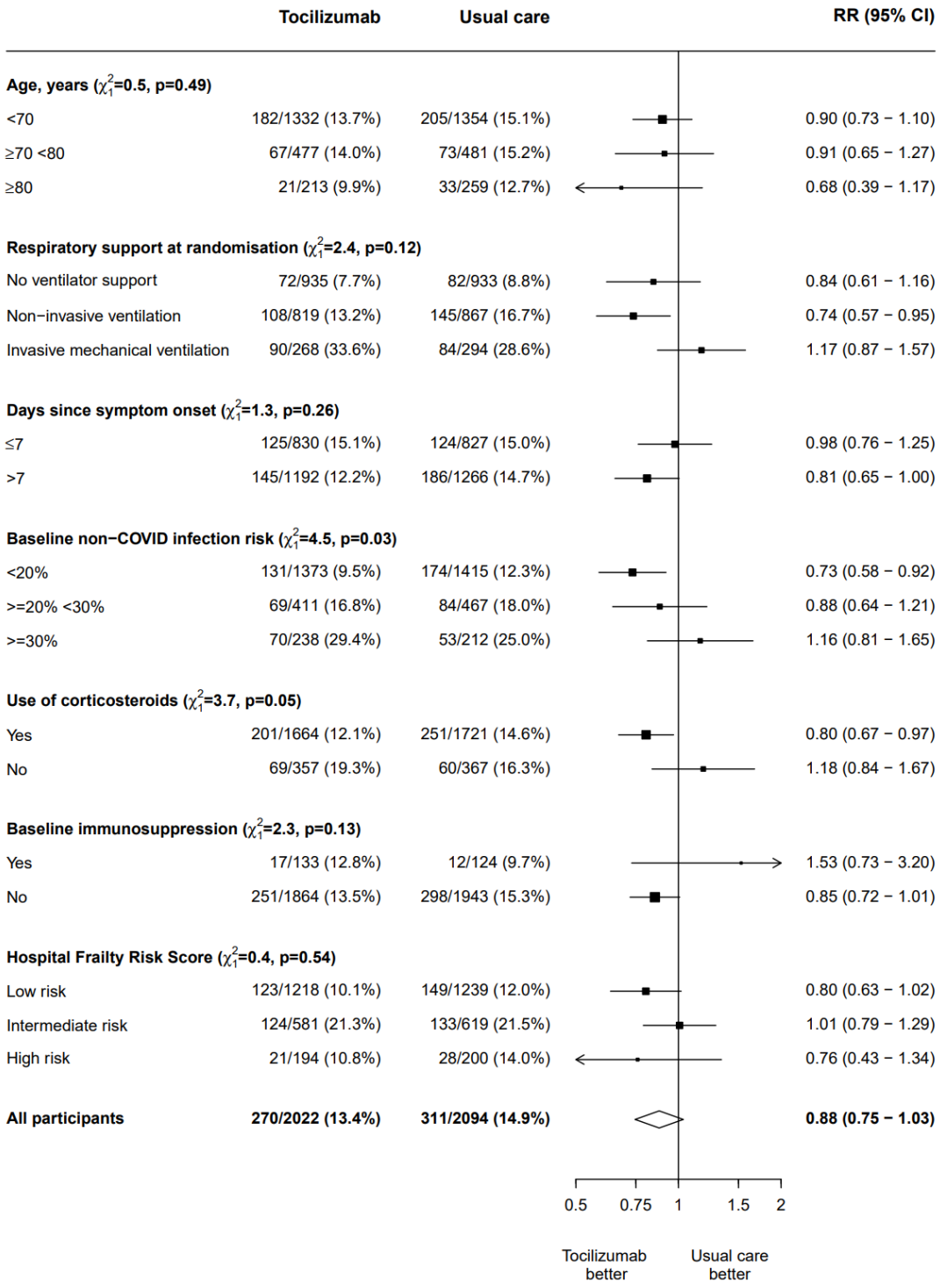


Figure 5-18: Subgroup analysis of effect of allocation to tocilizumab on major non-COVID infection within 28 days.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.

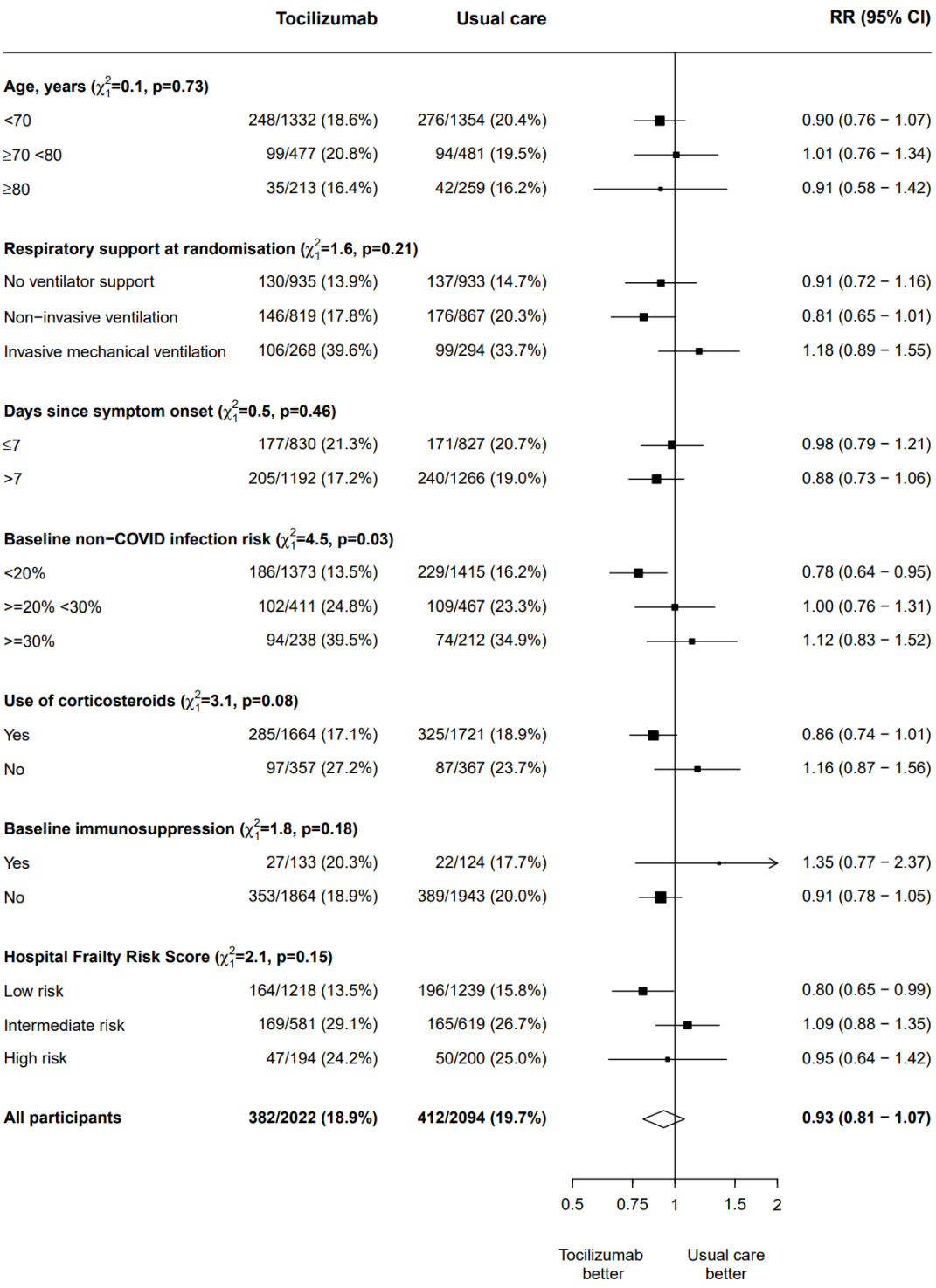


Figure 5-19: Subgroup analysis of effect of allocation to tocilizumab on major non-COVID infection within 6 months.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.

5.5 Baricitinib Randomised Comparisons

5.5.1 Baseline characteristics

Participants who were allocated baricitinib were a mean of 0.8 years older than those allocated usual care. Other characteristics, including newly derived baseline characteristics for the extended analysis, were well-matched at randomisation (Table 5-13).

Table 5-13: Baseline characteristics according to randomised treatment allocation for participants in the RECOVERY baricitinib comparison

	Baricitinib (N=4148)	Usual Care (N=4008)
Demographics		
Age[1]	58.5 (15.4)	57.7 (15.5)
Age Group		
Age <70	3,142 (76%)	3,086 (77%)
Age >=70 <80	665 (16%)	654 (16%)
Age >=80	341 (8.2%)	268 (6.7%)
Sex		
Female	1,408 (34%)	1,370 (34%)
Male	2,740 (66%)	2,638 (66%)
Acute illness features		
Time since symptom onset		
Time of onset <=7 days	1,495 (36%)	1,451 (36%)
Time of onset >7 days	2,649 (64%)	2,556 (64%)
Days since admission to hospital[2]	1 (1, 3)	1 (1, 2)
Respiratory support		
No oxygen or ventilation	228 (5.5%)	237 (5.9%)
Oxygen requirement with no ventilation	2,770 (67%)	2,743 (68%)
Non-invasive ventilation	1,016 (24%)	911 (23%)
Mechanical ventilation or ECMO	134 (3.2%)	117 (2.9%)
Baseline non-COVID infection	791 (19%)	811 (20%)
Laboratory measurements		
C-reactive protein, mg/L[2]	84 (42, 146)	87 (44, 143)
Creatinine, µmol/L[2]	76 (63, 93)	76 (62, 92)
Baseline co-morbidities		
Diabetes	961 (23%)	941 (24%)
Heart disease	782 (19%)	706 (18%)
Chronic lung disease	882 (21%)	783 (20%)
Tuberculosis	0 (0%)	0 (0%)
HIV	13 (0.3%)	9 (0.2%)
Severe liver disease	33 (0.8%)	33 (0.8%)
Severe kidney impairment	101 (2.4%)	79 (2.0%)
Severe mental illness	693/3,960 (18%)	707/3,836 (18%)
Immunosuppression	210/3,963 (5.3%)	199/3,840 (5.2%)
Charlson score[2]	2 (1, 4)	2 (1, 4)
Hospital Frailty Risk Score group[3]		
Low risk (<5)[3]	2,849 (72%)	2,735 (72%)
Intermediate risk (5-15)[3]	850 (22%)	847 (22%)
High risk (>15)[3]	247 (6.3%)	242 (6.3%)
Unknown	202 (4.9%)	184 (4.6%)

Other treatments		
Corticosteroids	3,962 (96%)	3,809 (95%)
Tocilizumab	1,342 (32%)	1,286 (32%)
[1]Mean (Standard Deviation) *[2]Median (Lower quartile, Upper quartile)* *[3]n (%) excludes 'Unknown'*		

5.5.2 Long-term mortality

Allocation to baricitinib was associated with a nominally significant improvement in the primary efficacy outcome of all-cause mortality at 6 months compared with usual care: 651/4148 (16%) of participants in the baricitinib group and 664/4008 (17%) of participants in the usual care group died within 6 months of randomisation (RR 0.88 [95% CI 0.79 – 0.98], p=0.03) (Table 5-14, Figure 5-20). An exploratory analysis of all-cause mortality at 2 years after randomisation showed a stable baricitinib treatment effect in reducing mortality (RR 0.89 [95% CI 0.80 – 0.99], p=0.03) (Figure 5-21). A further 405 participants in the treatment comparison died between 28-day and 2-year follow-up end points, an increase in event numbers of 38% compared to initial follow-up at 28 days (Figure 5-22).

Table 5-14: Effect of allocation to baricitinib on primary long-term follow-up outcomes.

	Baricitinib (n=4148)	**Usual Care (n=4008)**	**Rate or Risk Ratio (95% CI)**	**p-value**
Primary outcomes				
Mortality within 6 months	651 (16%)	664 (17%)	0.88 (0.79 - 0.98)	0.03
Major non-COVID infection within 28 days	664 (16%)	630 (16%)	0.99 (0.87 - 1.11)	0.82
Major non-COVID infection within 6 months	853 (21%)	784 (20%)	1.03 (0.92 - 1.15)	0.59

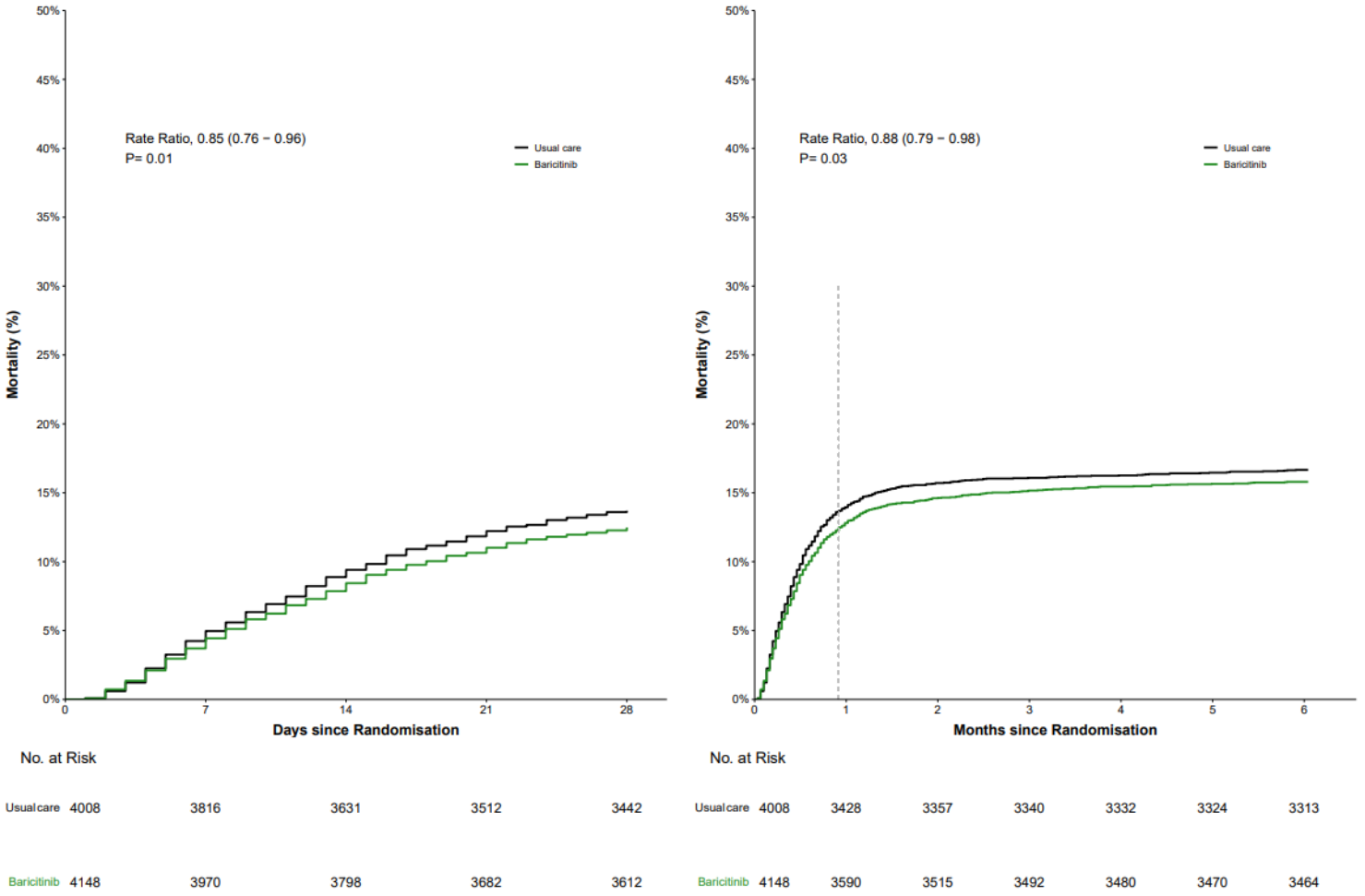


Figure 5-20: Effect of allocation to baricitinib on all-cause mortality in the RECOVERY baricitinib comparison.
Left panel: 28-day mortality. Right panel: 6-month mortality.
The Kaplan-Meier curves have not been adjusted for age and respiratory support group. The rate ratios have been adjusted for age and respiratory support group at randomisation.

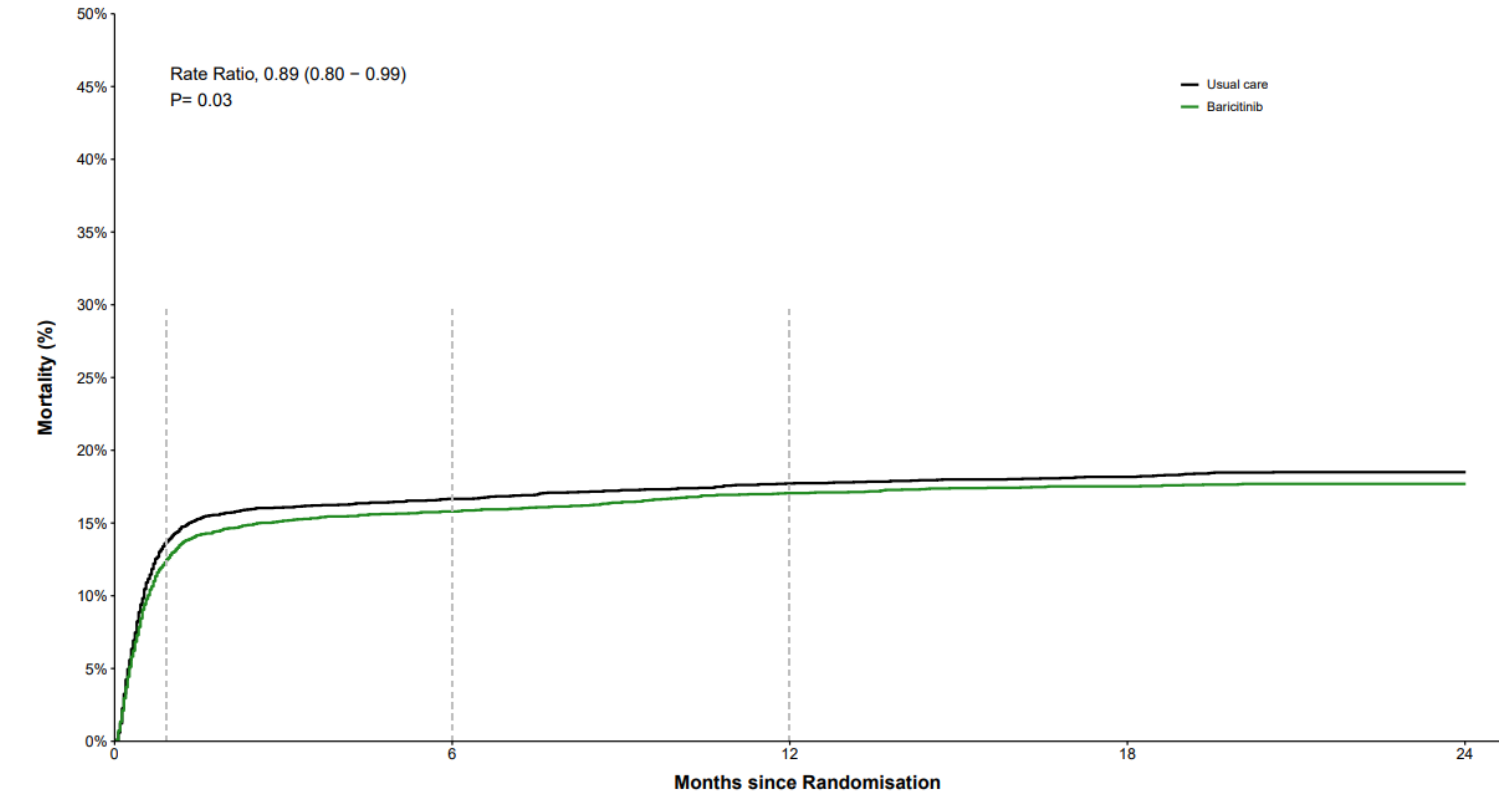


Figure 5-21: Effect of allocation to baricitinib on 2-year mortality in the RECOVERY baricitinib comparison.
The Kaplan-Meier curves have not been adjusted for age and respiratory support group. The rate ratios have been adjusted for age and respiratory support group at randomisation.

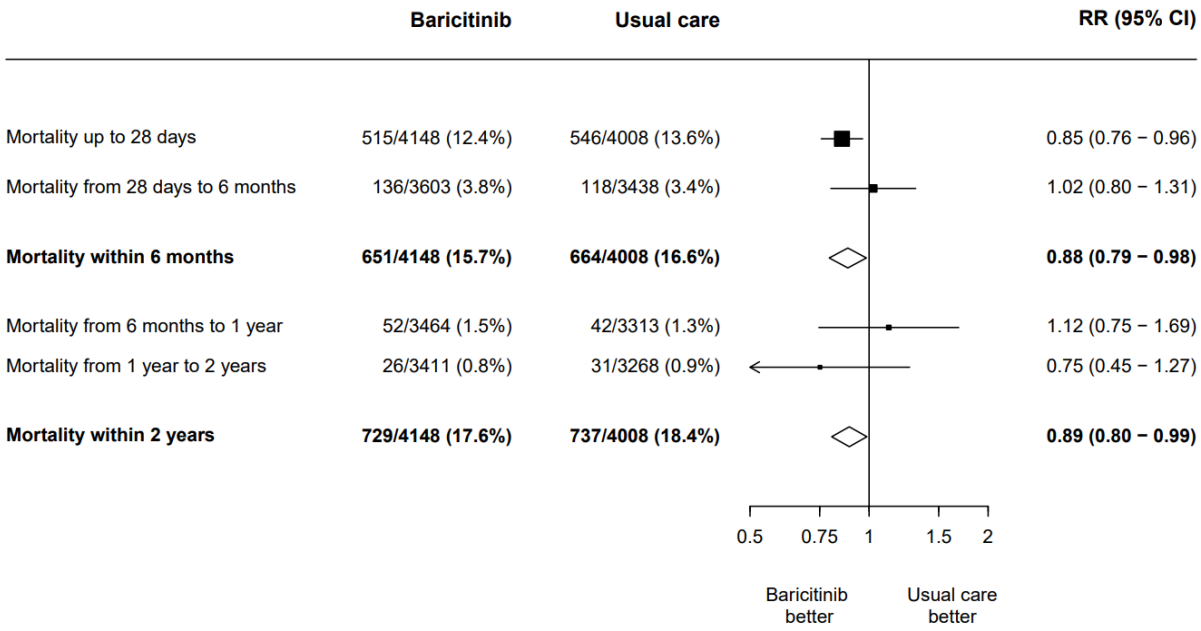


Figure 5-22: All-cause mortality in all participants in the RECOVERY baricitinib comparison, stratified by follow-up time period.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.

Exploratory analyses of diagnoses leading to death within 6 months, was consistent with a baricitinib treatment benefit on mortality relating to COVID-19, but not for other causes (Supplementary Table 47).

5.5.3 Non-COVID infection

There was no statistically significant difference between treatment groups in the primary safety outcome of major non-COVID infection (Table 5-14, Figure 5-23). At 28 days, 664 (16%) of participants allocated baricitinib and 630 (16%) of participants allocated usual care experienced the outcome (RR 0.99 [95% CI 0.87 – 1.11], p=0.82). At 6 months, this was 853 (21%) in the baricitinib group and 784 (20%) in the usual care group (RR 1.03 [95% CI 0.92 – 1.15], p=0.59).

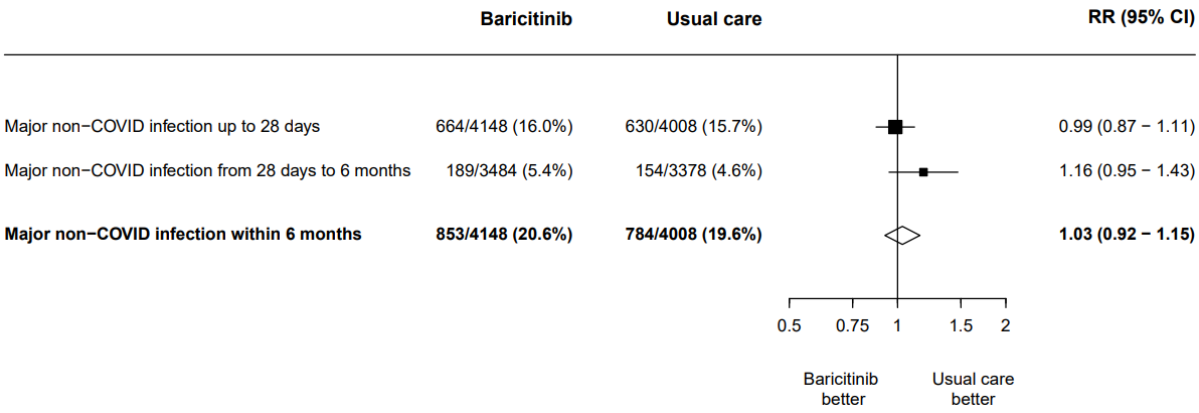


Figure 5-23: Major non-COVID infection in the RECOVERY baricitinib comparison stratified by follow-up time period.
**RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.*

The baricitinib comparison used available follow-up CRF diagnoses of major non-COVID infection, combined with those derived from RCD. Putative organism type was most commonly unspecified, followed by bacterial (Table 5-15). The lower respiratory tract was the most common anatomical site of infection, followed by urinary tract and bloodstream infections. 60% of the RCD-derived events identified occurred within 3 weeks of randomisation. At 28-day follow-up, approximately 90% of events had occurred during the index hospitalisation, falling to around three quarters of identified events at 6 month follow-up. Events were most commonly identified from the follow-up CRF data at 28-day follow-up, followed by the hospital admission datasets. At 6-month follow-up the hospital admission datasets had become the most common event data source (follow-up CRF data was not collected beyond 28 day follow-up).

Table 5-15: Major non-COVID infection event details by randomised treatment allocation in the RECOVERY baricitinib comparison.

	Major non-COVID infection within 28 days		Major non-COVID infection within 6 months	
	Baricitinib (n=4148)*	**Usual Care (n=4008)***	**Baricitinib (n=4148)***	**Usual Care (n=4008)***
Organism				
Bacterial	240 (5.8)	250 (6.2)	344 (8.3)	347 (8.7)
Fungal	89 (2.1)	99 (2.5)	115 (2.8)	106 (2.6)
Viral (not SARS-CoV-2)	15 (0.4)	16 (0.4)	29 (0.7)	23 (0.6)
Tuberculosis	0 (0)	1 (<0.1)	0 (0)	1 (<0.1)
Other organism	18 (0.4)	13 (0.3)	19 (0.5)	15 (0.4)
Unspecified organism	364 (8.8)	319 (8.0)	446 (11)	381 (9.5)
Anatomical site				
Pneumonia/Lower respiratory tract	433 (10)	389 (9.7)	572 (14)	509 (13)
Bloodstream	117 (2.8)	121 (3.0)	134 (3.2)	144 (3.6)
Urinary tract	100 (2.4)	101 (2.5)	147 (3.5)	138 (3.4)
Intra-abdominal	14 (0.3)	14 (0.3)	33 (0.8)	36 (0.9)
Skin and soft tissue	41 (1.0)	39 (1.0)	66 (1.6)	73 (1.8)
Bone and joint	3 (<0.1)	4 (<0.1)	11 (0.3)	12 (0.3)
Upper respiratory tract	5 (0.1)	4 (<0.1)	10 (0.2)	10 (0.2)
Other anatomical site	107 (2.6)	131 (3.3)	131 (3.2)	146 (3.6)
Unspecified anatomical site	27 (0.7)	39 (1.0)	46 (1.1)	40 (1.0)
Event timing				
Median event study day (IQR)	9 (5, 16)	10 (4, 16)	17 (7, 43)	16 (7, 38)
Occurred during index hospitalisation	582 (14)	569 (14)	608 (15)	587 (15)
Data source				
Hospital admission datasets	269 (6.5)	267 (6.7)	485 (12)	455 (11)
Microbiology dataset	186 (4.5)	190 (4.7)	222 (5.4)	222 (5.5)
Death datasets	30 (0.7)	21 (0.5)	58 (1.4)	42 (1.0)
Follow-up case report form	412 (9.9)	399 (10.0)	412 (9.9)	399 (10.0)
Total				
Major non-COVID infection	664 (16)	630 (16)	853 (21)	784 (20)

** n (%)*
IQR = Interquartile range

No significant differences were observed in secondary and tertiary non-COVID infection outcomes (Table 5-16). Tabulations of all infection outcomes by event type, timing and data sources are presented in Supplementary Table 48 to Supplementary Table 53.

Sensitivity analyses of the major non-COVID infection and non-COVID infection outcomes resulted in similar findings (Supplementary Table 54).

Table 5-16: Effect of allocation to baricitinib on secondary and tertiary infection outcomes.

	Baricitinib (n=4148)	Usual Care (n=4008)	Rate or Risk Ratio (95% CI)	p-value
Secondary outcomes				
Any non-COVID infection within 28 days	886 (21%)	852 (21%)	0.98 (0.88 - 1.09)	0.71
Any non-COVID infection within 6 months	1,404 (34%)	1,321 (33%)	1.02 (0.93 - 1.12)	0.64
Microbiologically confirmed non-COVID infection within 28 days	186 (4.5%)	190 (4.7%)	0.92 (0.77 - 1.11)	0.40
Microbiologically confirmed non-COVID infection within 6 months	222 (5.4%)	222 (5.5%)	0.94 (0.79 - 1.11)	0.46
Bloodstream infection within 28 days	117 (2.8%)	121 (3.0%)	0.88 (0.67 - 1.15)	0.35
Bloodstream infection within 6 months	134 (3.2%)	144 (3.6%)	0.87 (0.69 - 1.08)	0.21
Tertiary outcomes				
Bacterial infection within 28 days	467 (11%)	469 (12%)	0.95 (0.84 - 1.07)	0.40
Bacterial infection within 6 months	973 (23%)	950 (24%)	0.98 (0.91 - 1.06)	0.67
Fungal infection within 28 days	99 (2.4%)	109 (2.7%)	0.85 (0.65 - 1.10)	0.21
Fungal infection within 6 months	141 (3.4%)	134 (3.3%)	0.98 (0.78 - 1.24)	0.89

5.5.4 Other clinical benefits

The proportion of participants discharged from hospital alive within 6 months was significantly higher in the baricitinib group compared with the usual care group (85% vs 84%, RR 1.12 [95% CI 1.07–1.17], p <0.001) (Figure 5-24, Table 5-17).

There was no difference observed between treatment groups in the occurrence of long COVID or the ability to self-care at hospital discharge (Table 5-17).

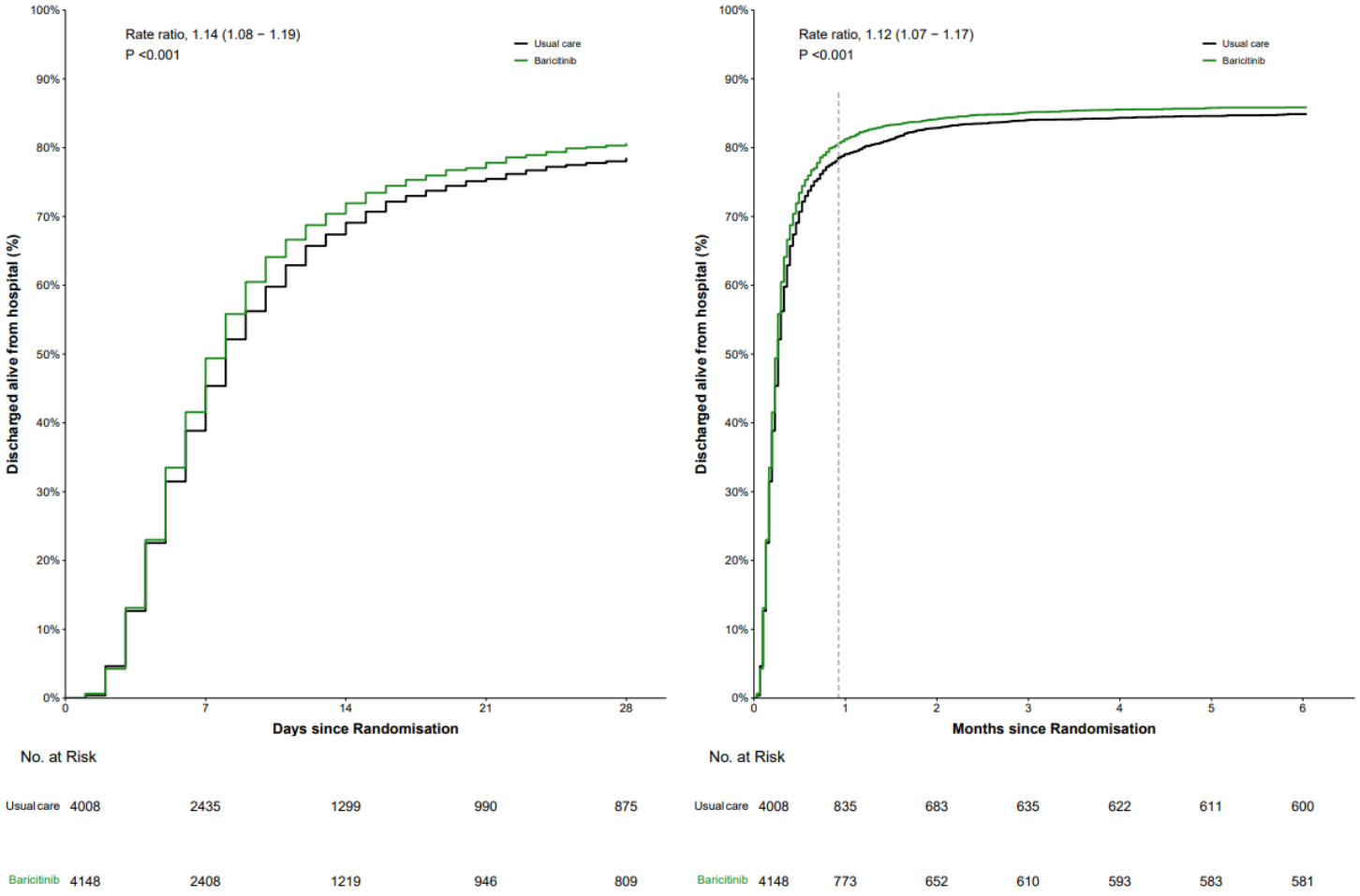


Figure 5-24: Effect of allocation to baricitinib on discharge alive from hospital in the RECOVERY baricitinib comparison.
Left panel: Discharged alive within 28 days. Right panel: Discharged alive within 6 months.
The Kaplan-Meier curves have not been adjusted for age and respiratory support group. The rate ratios have been adjusted for age and respiratory support group at randomisation.

Table 5-17: Effect of allocation to baricitinib on other clinical benefits.

	Baricitinib (n=4148)	Usual Care (n=4008)	Rate or Risk Ratio (95% CI)	p-value
Secondary outcomes				
Discharged alive from hospital within 6 months	3,538 (85%)	3,382 (84%)	1.12 (1.07 - 1.17)	<0.001
Long COVID within 18 months	373 (9.0%)	325 (8.1%)	1.11 (0.95 - 1.28)	0.18
Tertiary outcomes				
Preserved ability to self-care at hospital discharge[1]	954/1,115 (86%)	941/1,095 (86%)	1.00 (0.78 - 1.28)	1.00
[1]Assessed in participants in the RECOVERY-ISARIC baricitinib comparison population who were discharged alive from hospital and had assessment recorded.				

5.5.5 Other potential treatment-related harms

GI complications may have been more frequent in the baricitinib group (Table 5-18). Approximately 80% of GI complications were recorded as GI bleeding events (Supplementary Table 55).

No signal of harm was observed in the other secondary, tertiary and exploratory outcomes; including VTE and liver injury (Table 5-18). Tabulations of all outcomes by event type, timing and data sources are presented in Supplementary Table 55 to Supplementary Table 62.

Sensitivity analyses of secondary outcomes produced similar results to the main analysis (Supplementary Table 63).

Table 5-18: Effect of allocation to baricitinib on potential treatment-related harms.

	Baricitinib (n=4148)	Usual Care (n=4008)	Rate or Risk Ratio (95% CI)	p-value
Secondary outcomes				
Gastrointestinal complication within 28 days	43 (1.0%)	27 (0.7%)	1.49 (0.93 - 2.43)	0.11
Gastrointestinal complication within 6 months	71 (1.7%)	40 (1.0%)	1.66 (1.14 - 2.46)	0.01
Venous thromboembolism within 28 days	220 (5.3%)	227 (5.7%)	0.93 (0.77 - 1.11)	0.40
Venous thromboembolism within 6 months	247 (6.0%)	266 (6.6%)	0.89 (0.75 - 1.05)	0.16
Tertiary outcomes				
Metabolic complication within 28 days	57 (1.4%)	52 (1.3%)	1.04 (0.71 - 1.51)	0.86
Metabolic complication within 6 months	108 (2.6%)	88 (2.2%)	1.16 (0.87 - 1.53)	0.31
Incident diabetes within 12 months[1]	52/2,879 (1.8%)	45/2,766 (1.6%)	1.11 (0.74 - 1.65)	0.62
Fracture within 28 days	6 (0.1%)	6 (0.1%)	0.88 (0.28 - 2.75)	0.83
Fracture within 6 months	22 (0.5%)	23 (0.6%)	0.87 (0.49 - 1.57)	0.65
Psychiatric complication within 28 days	54 (1.3%)	47 (1.2%)	1.08 (0.73 - 1.59)	0.71
Psychiatric complication within 6 months	90 (2.2%)	91 (2.3%)	0.93 (0.70 - 1.24)	0.61
Clinically-defined liver injury within 28 days	59 (1.4%)	77 (1.9%)	0.73 (0.52 - 1.03)	0.07
Clinically-defined liver injury within 6 months	73 (1.8%)	101 (2.5%)	0.69 (0.51 - 0.93)	0.01
Exploratory outcomes				
Hyperglycaemia within 28 days[2]	39/1,825 (2.1%)	45/1,775 (2.5%)	0.85 (0.55 - 1.31)	0.46
Acute kidney injury within 28 days[2,3]	10/1,825 (0.5%)	20/1,775 (1.1%)	0.49 (0.23 - 1.05)	0.07
Neutropenia within 28 days[2]	4/1,825 (0.2%)	6/1,775 (0.3%)	0.69 (0.19 - 2.43)	0.56
Biochemically-defined liver injury within 28 days[2]	14/1,825 (0.8%)	16/1,775 (0.9%)	0.86 (0.42 - 1.76)	0.67
Viral clearance within 28 days[4]	98/251 (39%)	87/250 (35%)	1.13 (0.84 - 1.50)	0.42

[1]Assessed in participants with no evidence of diabetes mellitus at baseline.
[2]Assessed in participants in the RECOVERY-ISARIC baricitinib comparison population.
[3]Acute kidney injury was defined as a ≥1.5 fold increase in serum creatinine from baseline.
[4]Assessed in participants in the RECOVERY-ISARIC baricitinib comparison population who had a repeat SARS-CoV-2 test recorded within 28 days.

A pre-specified exploratory analysis of primary hospital-recorded diagnoses was consistent with a higher rate of GI bleed or perforation diagnoses recorded in the baricitinib group compared with the usual care group, but event numbers were small (18 diagnoses vs 5 diagnoses) (Supplementary Table 64).

5.5.6 Subgroup analyses

Subgroup analyses of mortality at 6 months did not demonstrate any significant heterogeneity according to the defined subgroups (Figure 5-25). This was consistent with the findings at 28-day follow-up (Supplementary Figure 17).

Subgroup analyses of major non-COVID infection at 28 days and 6 months did not demonstrate any significant heterogeneity. There was no evidence that baricitinib increased infection risk in those also receiving other immunomodulatory therapies, including corticosteroids, tocilizumab, and both in combination (Figure 5-26, Figure 5-27).

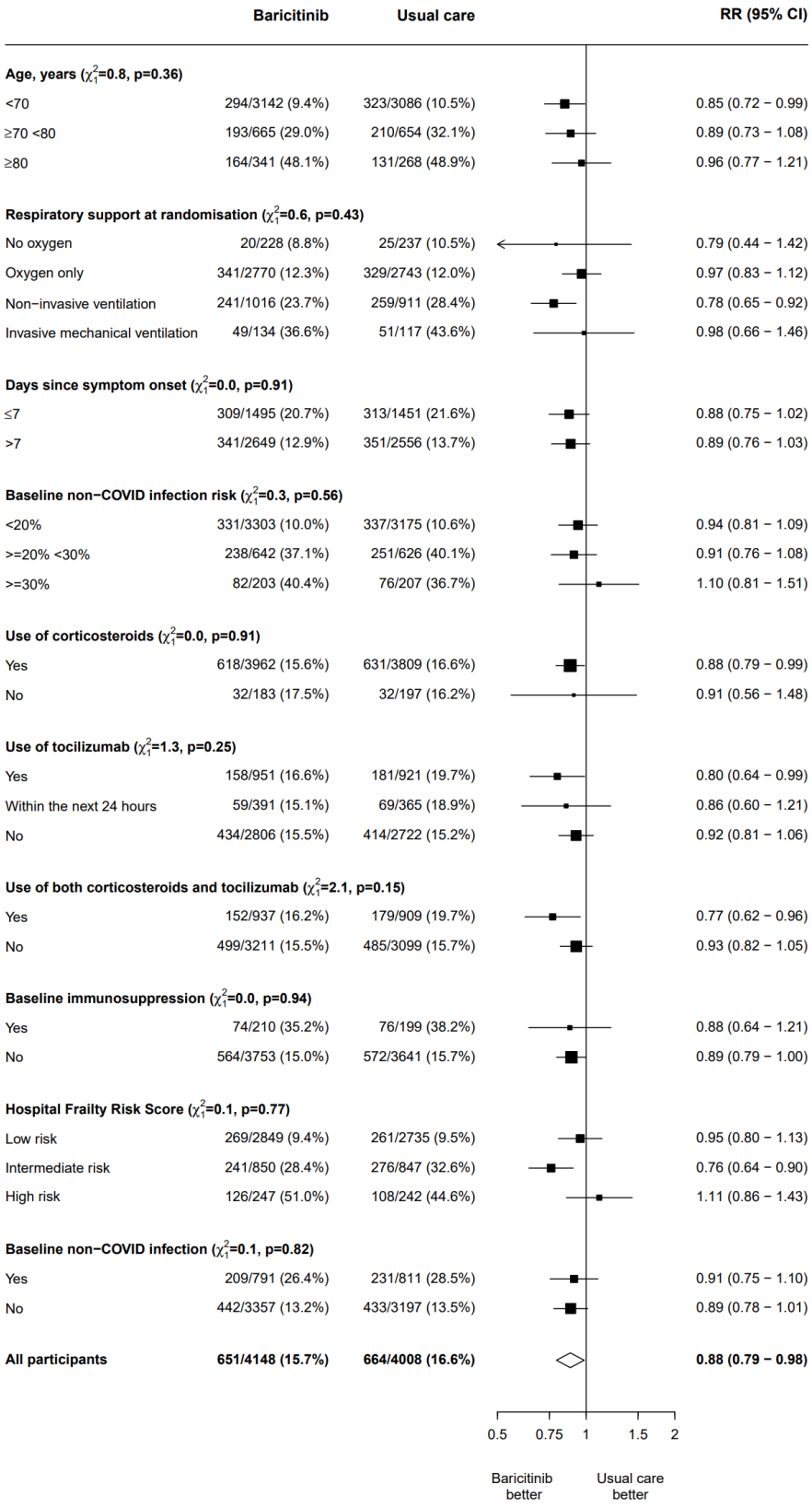


Figure 5-25: Subgroup analysis of effect of allocation to baricitinib on all-cause mortality within 6 months.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.

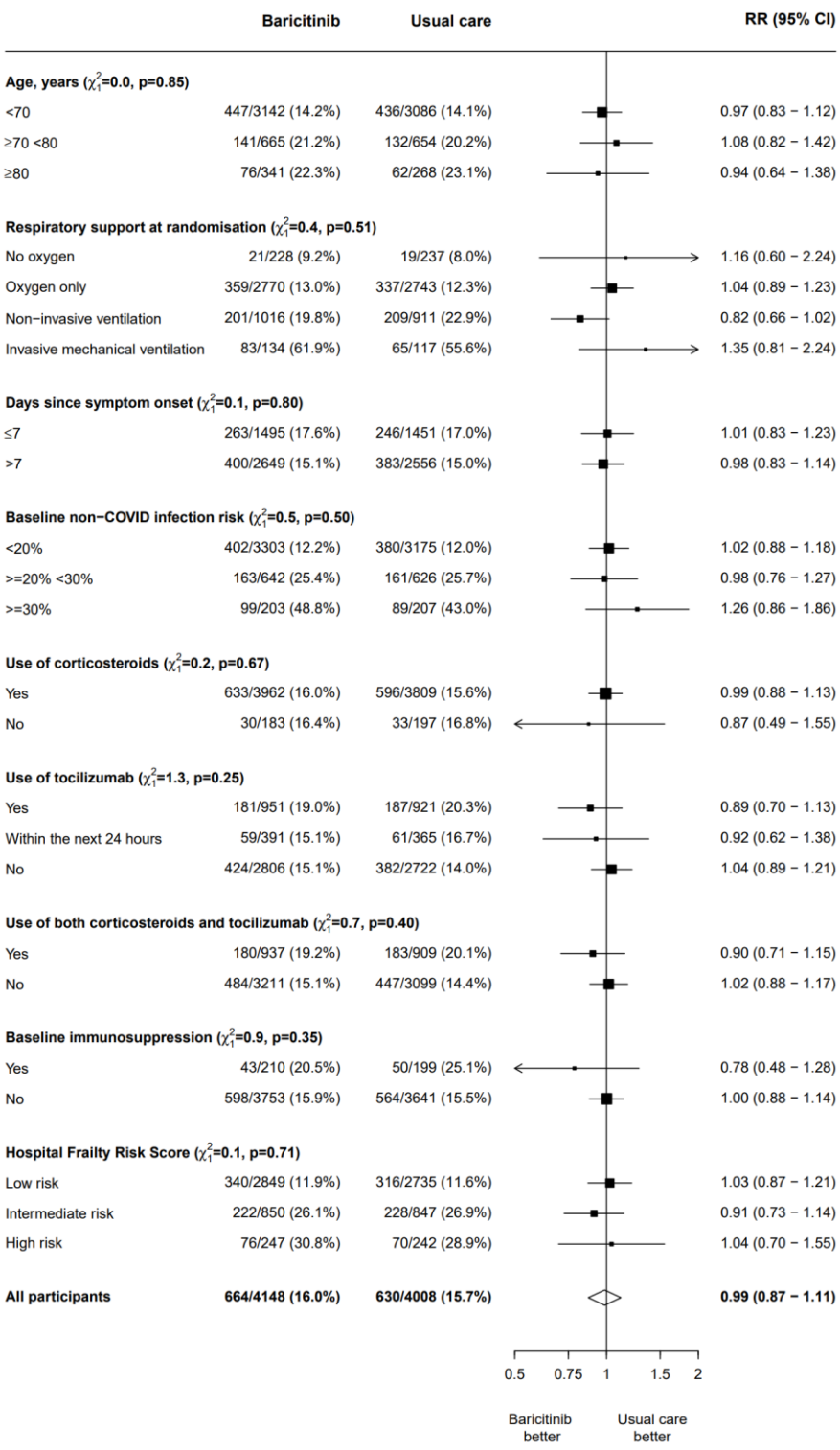


Figure 5-26: Subgroup analysis of effect of allocation to baricitinib on major non-COVID infection within 28 days.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.

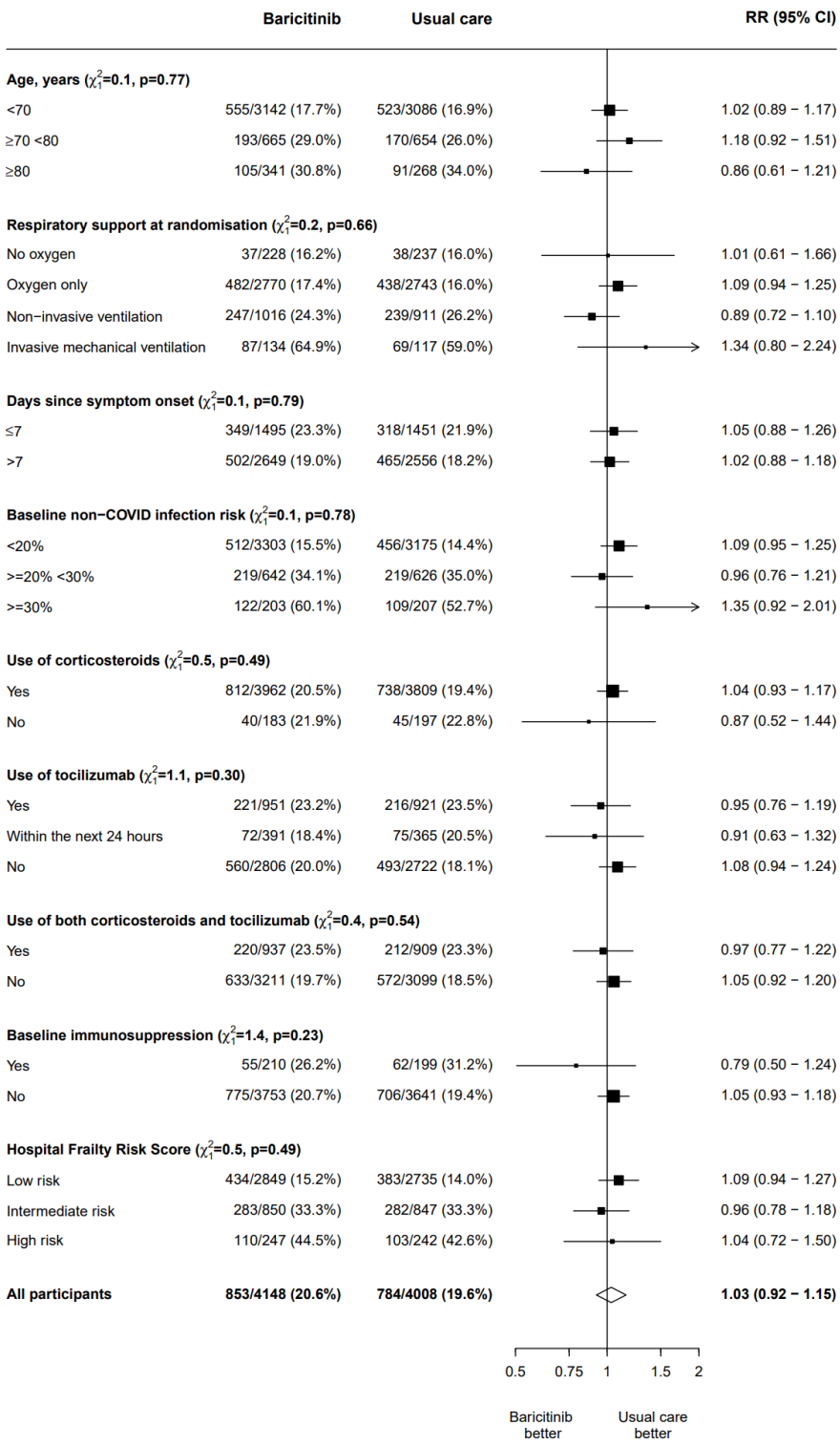


Figure 5-27: Subgroup analysis of effect of allocation to baricitinib on major non-COVID infection within 6 months.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.

5.6 Higher Dose Dexamethasone Randomised Comparisons

5.6.1 Baseline characteristics

In the completed subgroup of the RECOVERY higher dose dexamethasone comparison (those who were hypoxic but not on ventilatory support at randomisation), participants in the higher dose dexamethasone treatment group were a mean of 1.9 years younger than in the usual care group (Table 5-19). Usual care included high rates of standard dose dexamethasone use (as anticipated). Other baseline characteristics were well-matched between treatment groups. The derivation of HFRS from RCD was only possible for participants who had been recruited in the UK.

Table 5-19: Baseline characteristics according to randomised treatment allocation for participants who were hypoxic but not requiring ventilatory support at randomisation in the RECOVERY higher dose dexamethasone comparison.

	Higher dose Dexamethasone (N=659)	**Usual Care (N=613)**
Demographics		
Age[1]	60.2 (18.3)	62.1 (16.6)
Age Group		
Age <70	426 (65%)	395 (64%)
Age >=70 <80	128 (19%)	123 (20%)
Age >=80	105 (16%)	95 (15%)
Sex		
Female	266 (40%)	236 (39%)
Male	393 (60%)	376 (61%)
Region		
Africa	12 (1.8%)	3 (0.5%)
Asia	398 (60%)	347 (57%)
UK	249 (38%)	263 (43%)
Acute illness features		
Time since symptom onset		
Time of onset <=7 days	384 (58%)	346 (56%)
Time of onset >7 days	275 (42%)	267 (44%)
Days since admission to hospital[2]	1 (0, 2)	1 (1, 2)
Respiratory support		
No oxygen or ventilation	5 (0.8%)	3 (0.5%)
Oxygen requirement with no ventilation	654 (99%)	610 (100%)
Baseline non-COVID infection	82 (12%)	72 (12%)
Laboratory measurements		
C-reactive protein, mg/L[2]	68 (26, 119)	64 (26, 129)
Creatinine, µmol/L[2]	79 (63, 98)	79 (64, 97)
Baseline co-morbidities		
Diabetes	129 (20%)	119 (20%)
Heart disease	186 (29%)	165 (27%)
Chronic lung disease	135 (21%)	134 (22%)
Tuberculosis	5 (0.8%)	5 (0.8%)

HIV	3 (0.5%)	3 (0.5%)
Severe liver disease	5 (0.8%)	7 (1.1%)
Severe kidney impairment	22 (3.3%)	18 (3.0%)
Severe mental illness	50 (7.6%)	51 (8.3%)
Immunosuppression	68 (10%)	60 (9.8%)
Charlson score[2]	5 (3, 7)	5 (3, 7)
Hospital Frailty Risk Score group		
Low risk (<5)[3]	120 (49%)	129 (50%)
Intermediate risk (5-15)[3]	79 (33%)	81 (32%)
High risk (>15)[3]	44 (18%)	47 (18%)
Unknown	416 (63%)	356 (58%)
Other treatments		
Low dose corticosteroids	604 (92%)	574 (94%)
Tocilizumab	83 (13%)	72 (12%)

[1]Mean (Standard Deviation)
[2]Median (Lower quartile, Upper quartile)
[3]n (%) excludes 'Unknown'

5.6.2 Long-term mortality

Allocation to higher dose dexamethasone was associated with a significant hazard in the primary efficacy outcome of all-cause mortality at 6 months, compared with usual care: 146/659 (22%) of participants in the higher dose dexamethasone group and 108/613 (18%) of participants in the usual care group died within 6 months of randomisation (RR 1.35 [95% CI 1.05 – 1.73], p=0.02) (Table 5-20, Figure 5-28).

Table 5-20: Effect of allocation to higher dose dexamethasone on primary long-term follow-up outcomes.

	Higher dose Dexamethasone (n=659)	Usual Care (n=613)	Rate or Risk Ratio (95% CI)	p-value
Primary outcomes				
Mortality within 6 months	146 (22%)	108 (18%)	1.35 (1.05 - 1.73)	0.02
Major non-COVID infection within 28 days	111 (17%)	88 (14%)	1.17 (0.91 - 1.51)	0.23
Major non-COVID infection within 6 months	142 (22%)	117 (19%)	1.11 (0.90 - 1.38)	0.33

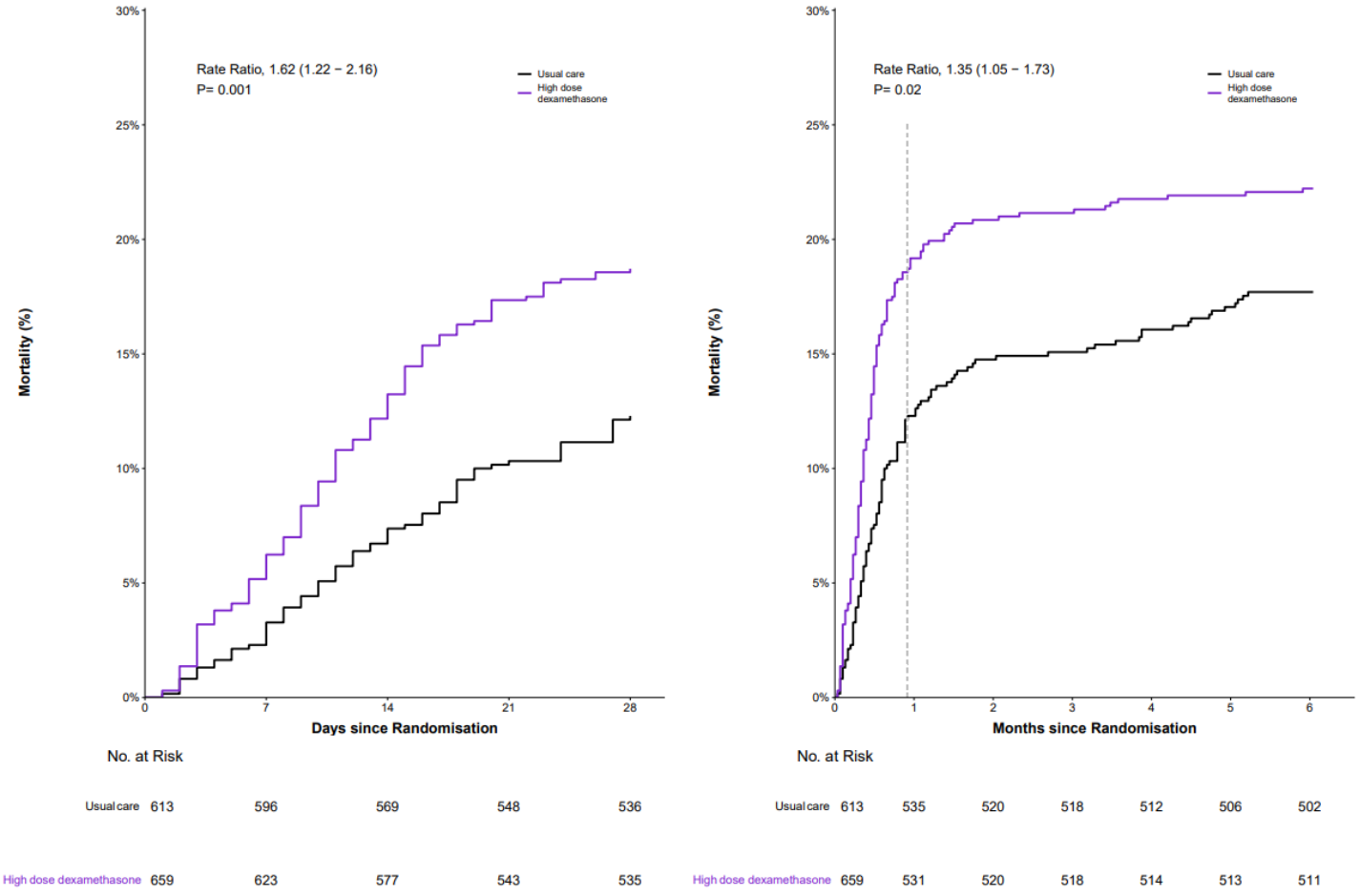


Figure 5-28: Effect of allocation to higher dose dexamethasone on all-cause mortality in participants who were hypoxic but not requiring ventilatory support in the RECOVERY higher dose dexamethasone comparison.
Left panel: 28-day mortality. Right panel: 6-month mortality.
The Kaplan-Meier curves have not been adjusted for age and respiratory support group. The rate ratios have been adjusted for age and respiratory support group at randomisation.

Stratifying the treatment effect estimate by follow-up period suggested a possible reduction in the magnitude of the hazard observed in the post-28-day time period but still an overall treatment effect estimate most consistent with harm from higher dose dexamethasone in this subgroup (Figure 5-29). A further 56 participants in the completed subgroup of the treatment comparison died between the 28-day and 6-month follow-up end points, an increase of 28% in event numbers compared to initial follow-up at 28 days.

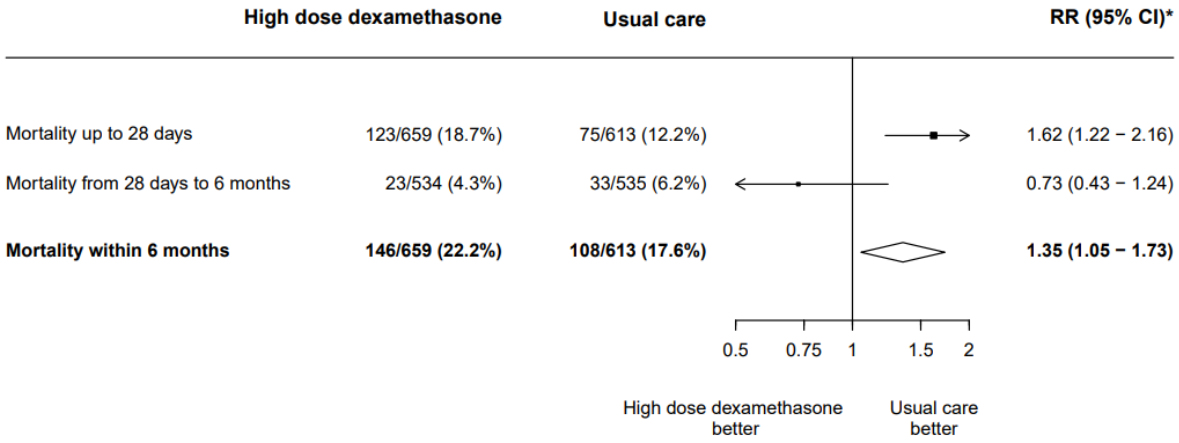


Figure 5-29: Mortality in participants who were hypoxic but not requiring ventilatory support in the RECOVERY higher dose dexamethasone comparison, stratified by follow-up time period.

Exploratory analyses of diagnoses leading to death, suggested most deaths were still considered to be related to COVID-19 (Supplementary Table 65).

5.6.3 Non-COVID infection

There was no significant difference between treatment groups in the primary safety outcome of major non-COVID infection (Table 5-20, Figure 5-30). At 28 days, 111 (17%) of participants allocated high dose dexamethasone and 88 (14%) allocated usual care experienced the outcome (RR 1.17 [95% CI 0.91 – 1.51], p=0.23). At 6 months, this was

142 (22%) in the dexamethasone group and 117 (19%) in the usual care group (RR 1.11 [95% CI 0.90 – 1.38], p=0.33).

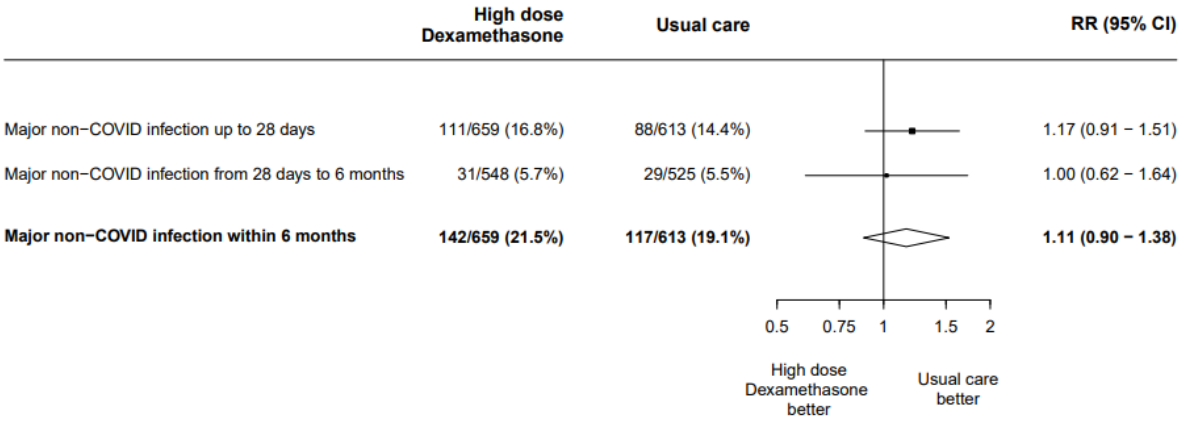


Figure 5-30: Major non-COVID infection in the completed subgroup of the RECOVERY high dose dexamethasone comparison stratified by follow-up time period.

Similarly to the other treatment comparisons, the most commonly identified major non-COVID infection events were putatively bacterial and at the lower respiratory tract anatomical site (Table 5-21). Most events had occurred during the index hospitalisation and were identified from the RECOVERY follow-up CRF data and the hospital admission RCD datasets.

Table 5-21: Major non-COVID infection event details by randomised treatment allocation in the completed subgroup of the RECOVERY high dose dexamethasone comparison.

	Major non-COVID infection within 28 days		Major non-COVID infection within 6 months	
	High dose Dexamethasone (n=659)	Usual Care (n=613)	High dose Dexamethasone (n=659)	Usual Care (n=613)
Organism				
Bacterial	75 (11)	60 (9.8)	94 (14)	79 (13)
Fungal	9 (1.4)	7 (1.1)	11 (1.7)	16 (2.6)
Viral (not SARS-CoV-2)	2 (0.3)	1 (0.2)	7 (1.1)	3 (0.5)
Tuberculosis	0 (0)	0 (0)	0 (0)	2 (0.3)
Other organism	1 (0.2)	3 (0.5)	1 (0.2)	5 (0.8)
Unspecified organism	29 (4.4)	28 (4.6)	43 (6.5)	38 (6.2)
Anatomical site				
Pneumonia/Lower respiratory tract	86 (13)	55 (9.0)	104 (16)	86 (14)
Bloodstream	9 (1.4)	4 (0.7)	11 (1.7)	6 (1.0)
Urinary tract	14 (2.1)	16 (2.6)	19 (2.9)	26 (4.2)
Intra-abdominal	1 (0.2)	2 (0.3)	3 (0.5)	5 (0.8)
Skin and soft tissue	3 (0.5)	7 (1.1)	10 (1.5)	16 (2.6)
Bone and joint	0 (0)	2 (0.3)	1 (0.2)	2 (0.3)
Upper respiratory tract	0 (0)	1 (0.2)	1 (0.2)	3 (0.5)
Other anatomical site	11 (1.7)	14 (2.3)	13 (2.0)	20 (3.3)
Unspecified anatomical site	15 (2.3)	12 (2.0)	20 (3.0)	14 (2.3)
Event timing				
Median event study day (IQR)	11 (8, 17)	9 (5, 16)	26 (11, 65)	21 (8, 46)
Occurred during index hospitalisation	96 (15)	74 (12)	99 (15)	78 (13)
Data Source				
Hospital admission datasets	30 (4.6)	39 (6.4)	64 (9.7)	74 (12)
Microbiology dataset	4 (0.6)	5 (0.8)	8 (1.2)	8 (1.3)
Death datasets	9 (1.4)	5 (0.8)	15 (2.3)	17 (2.8)
Follow-up case report form	81 (12)	58 (9.5)	83 (13)	58 (9.5)
Total				
Non-COVID infection	111 (17)	88 (14)	142 (22)	117 (19)

** n (%)*
IQR = Interquartile range

There was no difference between treatment groups in other secondary and tertiary infection outcomes (Table 5-22). Categorisations of all infection outcomes are presented in Supplementary Table 66 to Supplementary Table 71.

Table 5-22: Effect of allocation to higher dose dexamethasone on secondary and tertiary infection outcomes.

	Higher dose Dexamethasone (n=659)	Usual Care (n=613)	Rate or Risk Ratio (95% CI)	p-value
Secondary outcomes				
Any non-COVID infection within 28 days	138 (21%)	109 (18%)	1.17 (0.94 - 1.47)	0.17
Any non-COVID infection within 6 months	183 (28%)	158 (26%)	1.06 (0.89 - 1.27)	0.49
Microbiologically confirmed non-COVID infection within 28 days	10 (1.5%)	8 (1.3%)	1.17 (0.46 - 3.04)	0.74
Microbiologically confirmed non-COVID infection within 6 months	14 (2.1%)	11 (1.8%)	1.19 (0.54 - 2.65)	0.67
Bloodstream infection within 28 days	9 (1.4%)	4 (0.7%)	2.13 (0.69 - 7.90)	0.21
Bloodstream infection within 6 months	11 (1.7%)	6 (1.0%)	1.71 (0.65 - 4.94)	0.29
Tertiary outcomes				
Bacterial infection within 28 days	95 (14%)	81 (13%)	1.09 (0.83 - 1.44)	0.53
Bacterial infection within 6 months	137 (21%)	129 (21%)	0.99 (0.80 - 1.22)	0.91
Fungal infection within 28 days	11 (1.7%)	9 (1.5%)	1.14 (0.47 - 2.80)	0.78
Fungal infection within 6 months	15 (2.3%)	19 (3.1%)	0.73 (0.37 - 1.42)	0.36

5.6.4 Other clinical effects

The proportion of participants discharged from hospital alive within 6 months may have been lower in the higher dose dexamethasone group compared with the usual care group (83% vs 87%, RR 0.90 [95% CI 0.80 – 1.01], p=0.07), with a treatment effect estimate similar to at 28 days (Figure 5-31, Table 5-23).

The analyses suggested there may have been a lower occurrence of long COVID in the higher dose dexamethasone treatment group (Table 5-23). However, this analysis had low event numbers and was subject to potential survivor bias.

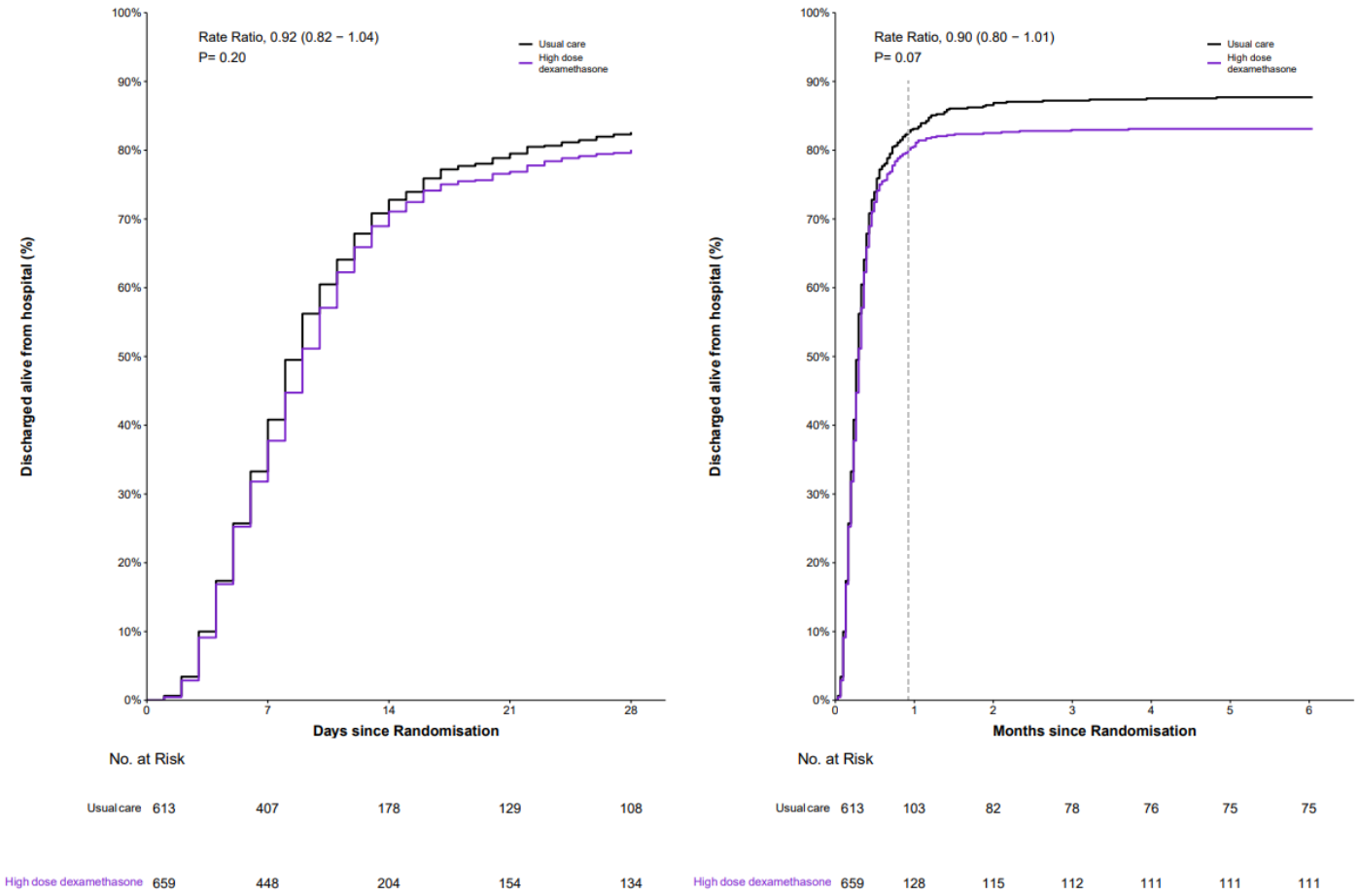


Figure 5-31: Discharge alive from hospital in participants who were hypoxic but not requiring ventilatory support at randomisation in the RECOVERY higher dose dexamethasone comparison.
Left panel: Discharged alive within 28 days. Right panel: Discharged alive within 6 months.
The Kaplan-Meier curves have not been adjusted for age and respiratory support group. The rate ratios have been adjusted for age and respiratory support group at randomisation.

Metabolic complications were more frequent in the higher dose dexamethasone treatment group (22% vs 15% within 28 days, RR 1.53 [95% CI 1.21 – 1.95], p <0.001) (Table 5-23). Over 95% of identified events were of hyperglycaemia with no events of diabetic ketoacidosis (Supplementary Table 72). Approximately 40% of metabolic complication events occurred in participants with existing evidence of diabetes mellitus at randomisation.

No significant evidence of harm was observed in other secondary and tertiary outcomes, including GI complications, VTE, long bone or vertebral fractures, and psychiatric complications (Table 5-23). Categorisations of all outcomes by event type, timing and data sources are presented in Supplementary Table 72 to Supplementary Table 79.

Table 5-23: Effect of allocation to higher dose dexamethasone on other clinical effects.

	Higher dose Dexamethasone (n=659)	Usual Care (n=613)	Rate or Risk Ratio (95% CI)	p-value
Secondary outcomes				
Discharged alive from hospital within 6 months	546 (83%)	535 (87%)	0.90 (0.80 - 1.01)	0.07
Gastrointestinal complication within 28 days	3 (0.5%)	6 (1.0%)	0.47 (0.10 - 1.76)	0.28
Gastrointestinal complication within 6 months	5 (0.8%)	10 (1.6%)	0.47 (0.15 - 1.30)	0.16
Venous thromboembolism within 28 days	13 (2.0%)	18 (2.9%)	0.66 (0.32 - 1.34)	0.26
Venous thromboembolism within 6 months	15 (2.3%)	22 (3.6%)	0.63 (0.32 - 1.19)	0.16
Long COVID within 18 months	4 (0.6%)	13 (2.1%)	0.30 (0.10 - 0.92)	0.03
Tertiary outcomes				
Metabolic complication within 28 days	148 (22%)	90 (15%)	1.53 (1.21 - 1.95)	<0.001
Metabolic complication within 6 months	150 (23%)	96 (16%)	1.46 (1.16 - 1.84)	0.001
Incident diabetes within 12 months[1]	2/506 (0.4%)	1/476 (0.2%)	1.87 (0.18 - 40.51)	0.61
Fracture within 28 days	2 (0.3%)	1 (0.2%)	2.03 (0.18 - 22.38)	0.56
Fracture within 6 months	5 (0.8%)	2 (0.3%)	2.57 (0.50 - 13.24)	0.26
Psychiatric complication within 28 days	2 (0.3%)	4 (0.7%)	0.47 (0.06 - 2.43)	0.39
Psychiatric complication within 6 months	7 (1.1%)	18 (2.9%)	0.36 (0.14 - 0.83)	0.02
Clinically-defined liver injury within 28 days	6 (0.9%)	4 (0.7%)	1.39 (0.40 - 5.41)	0.61
Clinically-defined liver injury within 6 months	7 (1.1%)	9 (1.5%)	0.72 (0.26 - 1.92)	0.51
[1]Assessed in participants with no evidence of diabetes mellitus at baseline				

The exploratory analysis of hospital-recorded diagnoses is presented in Supplementary Table 80.

5.6.5 Subgroup analyses

Pre-defined subgroup analyses of mortality at 6 months, and major non-COVID infection at 28 days and 6 months, did not support any significant heterogeneity in higher dose dexamethasone treatment effect, though event numbers were very small in many subgroups (Figure 5-32, Figure 5-33 and Figure 5-34).

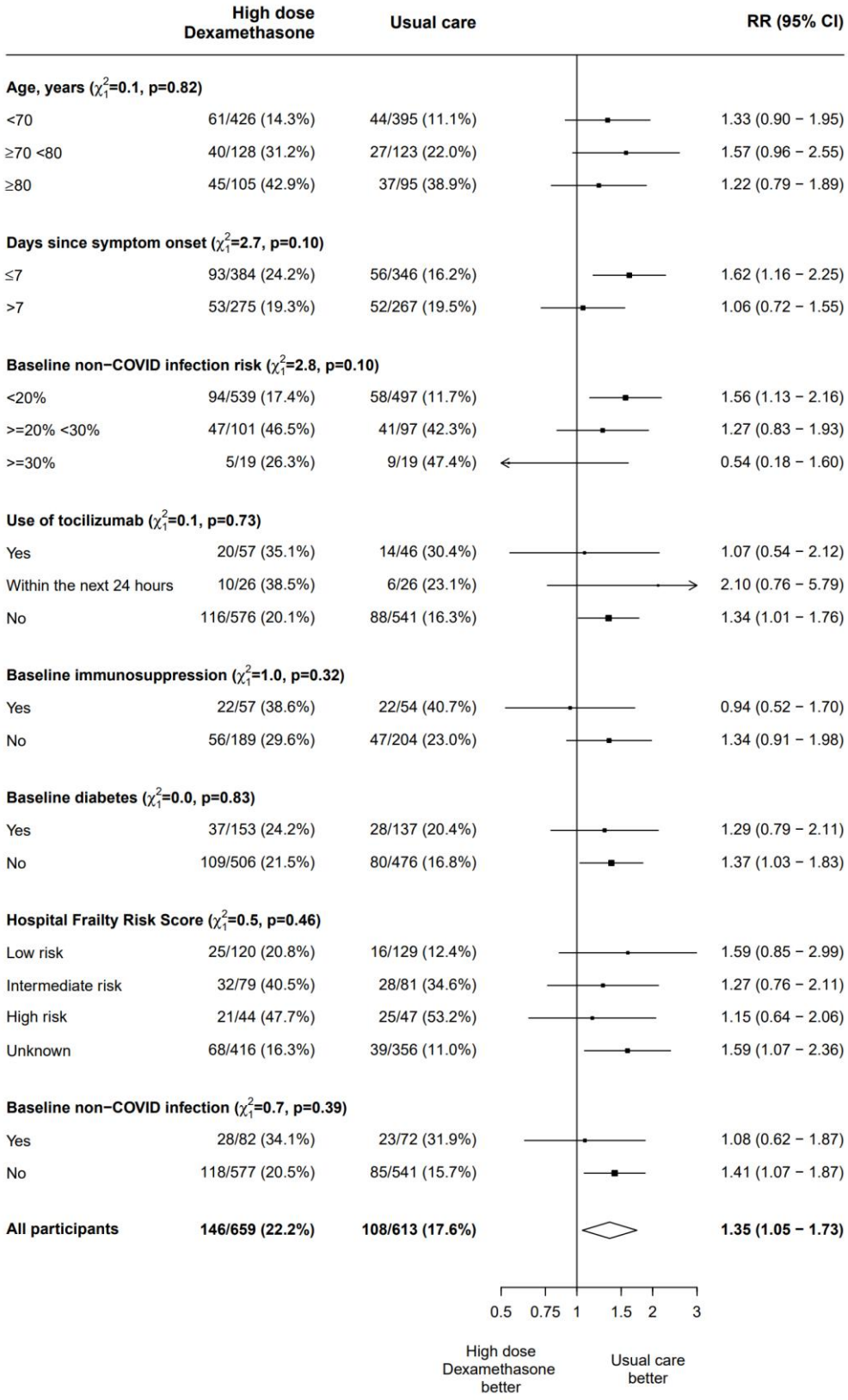


Figure 5-32: Subgroup analysis of effect of allocation to higher dose dexamethasone on all-cause mortality within 6 months.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.

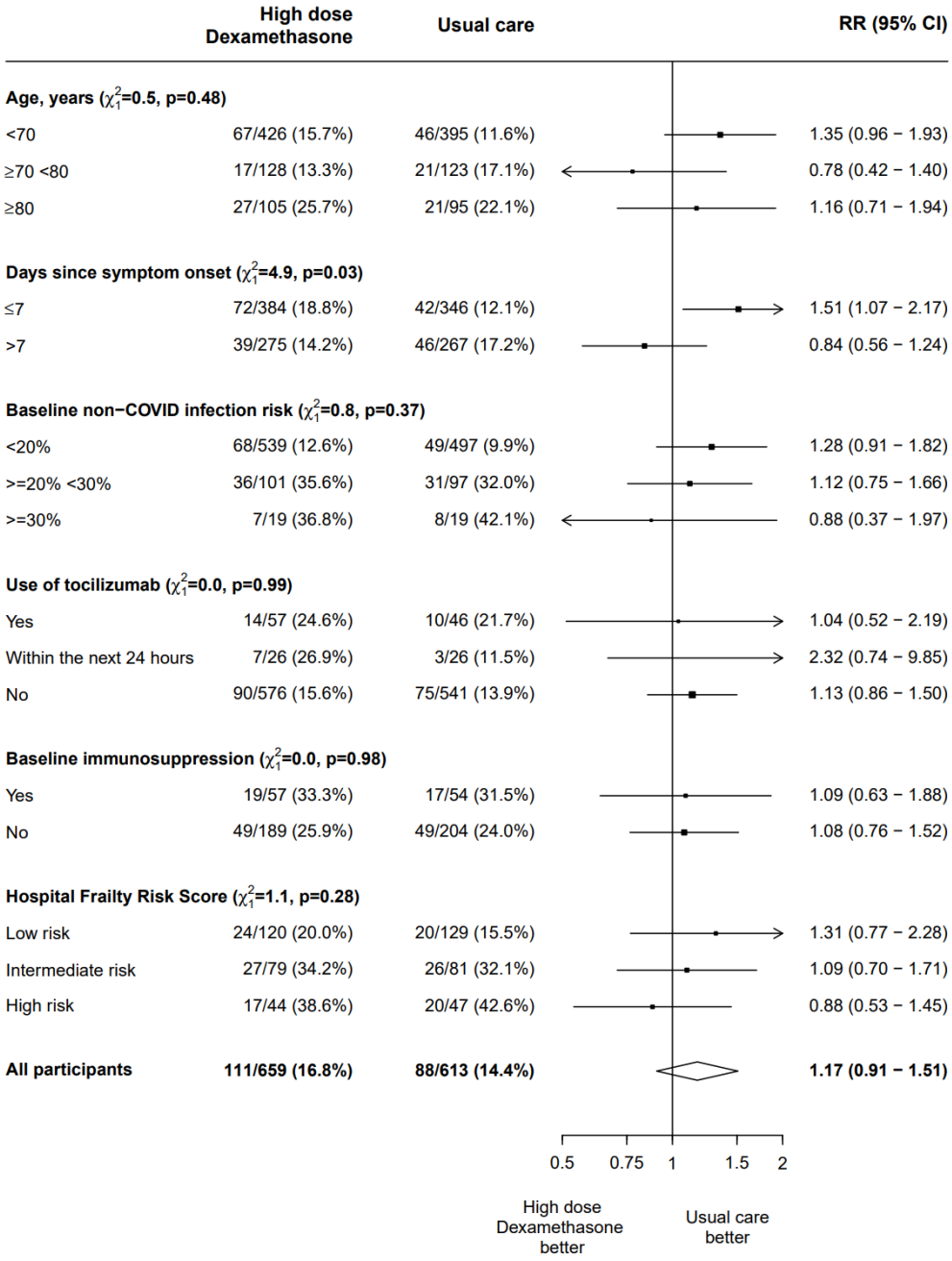


Figure 5-33: Subgroup analysis of effect of allocation to higher dose dexamethasone on major non-COVID infection within 28 days.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.

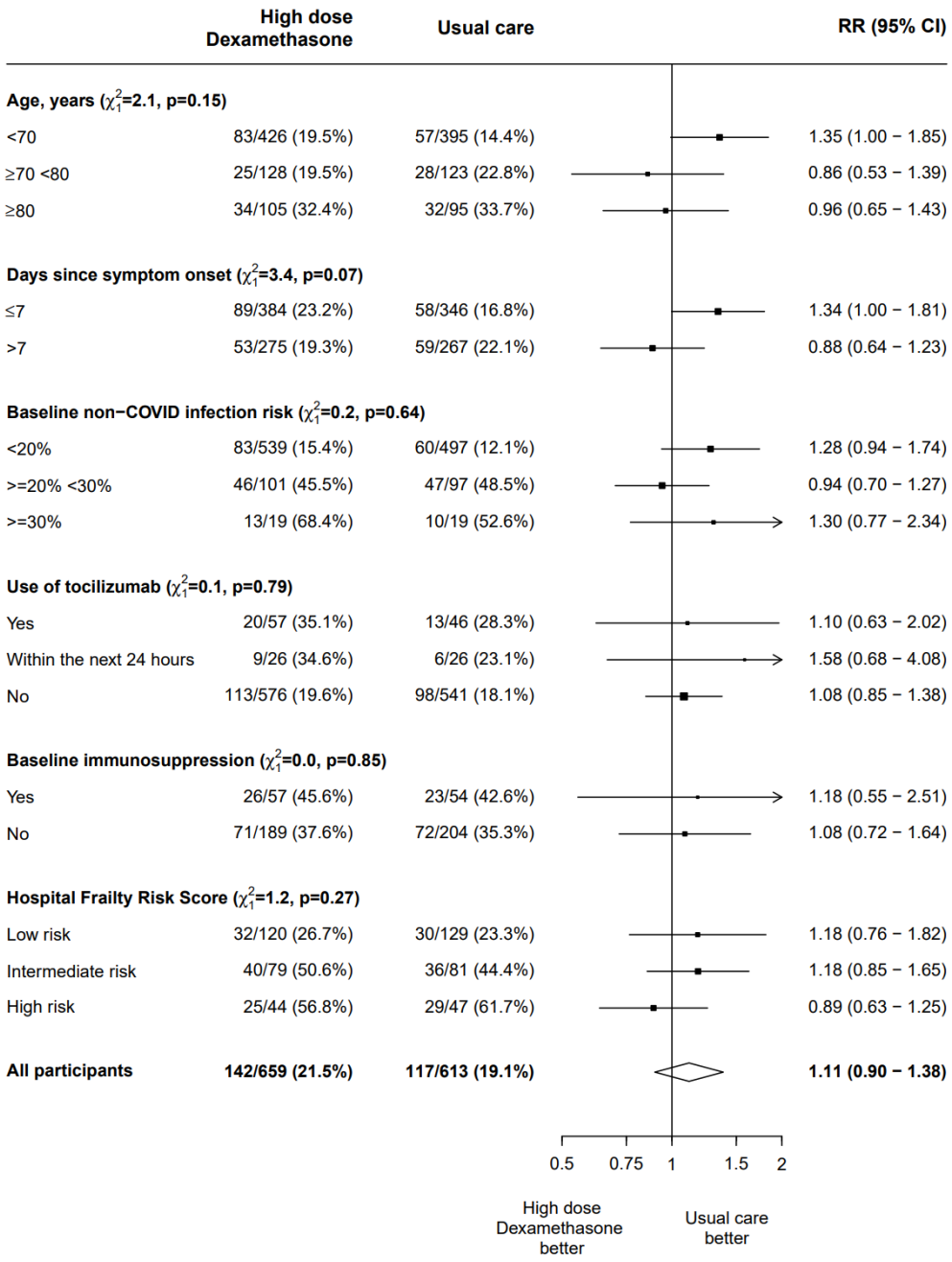


Figure 5-34: Subgroup analysis of effect of allocation to higher dose dexamethasone on major non-COVID infection within 6 months.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.

Chapter 6

Exploratory Analysis Results

6.1 Chapter Summary

This is the second of two chapters detailing the results of the extended analysis. This chapter includes exploratory analyses of the heterogeneity of dexamethasone treatment effect, and randomised comparisons of biological measurements. These results correspond to the fifth and sixth aims of the thesis (Section 1.4).

The chapter begins with an evaluation of the representativeness of the subset of the RECOVERY populations who have linked ISARIC4C data, compared with the full RECOVERY populations. This serves to understand any differences in participants who were also included in ISARIC4C, and to demonstrate the validity of randomised comparisons in the RECOVERY-ISARIC treatment comparison populations. Additional subgroup analyses of interest in the dexamethasone comparison (respiratory support and frailty) are then explored, based on the results from Chapter 5 (Section 5.3.6). The remainder of the chapter explores the biological measurements, including randomised comparisons of dexamethasone treatment effects on an ordinal scale of oxygen requirement, commonly-measured blood biomarkers, such as CRP, and differential gene expression analyses.

6.2 RECOVERY-ISARIC Representativeness

6.2.1 All treatment comparisons

Across all treatment comparisons, RECOVERY participants who were also included in ISARIC4C were slightly older (63.6 vs 61.2 years) and more likely to be male, and a higher proportion required mechanical ventilation or ECMO at randomisation (8% vs. 5%), compared with RECOVERY participants who were not in ISARIC4C (Table 6-1). Rates of co-morbidities and frailty were also generally slightly higher amongst those included in ISARIC4C and a lower proportion of patients were treated with corticosteroids (68% vs 81%). These differences in baseline characteristics may have contributed to the higher 28-day mortality seen in participants who were also in ISARIC4C.

Table 6-1: Baseline characteristics and 28-day mortality according to linkage with ISARIC4C for all RECOVERY participants.

	In ISARIC4C, N=25,061	Not in ISARIC4C, N=23,256	p-value
Demographics			
Age[1]	63.6 (15.3)	61.2 (16.5)	<0.001
Age Group			<0.001
Age <70	15,948 (64%)	15,808 (68%)	
Age >=70 <80	5,251 (21%)	4,449 (19%)	
Age >=80	3,861 (15%)	2,938 (13%)	
Sex			0.005
Female	9,144 (36%)	8,750 (38%)	
Male	15,915 (64%)	14,443 (62%)	
Acute illness features			
Time since symptom onset			0.62
Time of onset <=7 days	10,057 (40%)	9,268 (40%)	
Time of onset >7 days	14,959 (60%)	13,912 (60%)	
Days since admission to hospital[2]	2 (1, 3)	1 (1, 3)	<0.001
Respiratory support			<0.001
No oxygen or ventilation	3,377 (13%)	2,742 (12%)	
Oxygen or non-invasive ventilation	19,671 (78%)	19,210 (83%)	
Mechanical ventilation or ECMO	2,012 (8.0%)	1,243 (5.4%)	
Baseline laboratory measurements			
C-reactive protein, mg/L[2]	86 (45, 146)	88 (43, 149)	0.94
Creatinine, µmol/L[2]	77 (63, 96)	77 (63, 97)	0.60
Baseline co-morbidities			
Diabetes	6,633 (27%)	5,701 (25%)	<0.001
Heart disease	5,991 (24%)	5,036 (22%)	<0.001
Chronic lung disease	5,741 (23%)	4,927 (21%)	<0.001

Tuberculosis	75 (0.3%)	79 (0.4%)	0.41
HIV	88 (0.4%)	107 (0.5%)	0.06
Severe liver disease	313 (1.3%)	272 (1.2%)	0.47
Severe kidney impairment	1,397 (5.6%)	1,217 (5.3%)	0.13
Severe mental illness	4,443/25,041 (18%)	3,312/19,981 (17%)	0.001
Immunosuppression	1,802/25,044 (7.2%)	1,468/20,016 (7.3%)	0.57
Charlson score[2]	3 (2, 6)	3 (1, 5)	<0.001
Hospital Frailty Risk Score group			<0.001
Low risk (<5)[3]	14,197 (57%)	12,197 (62%)	
Intermediate risk (5-15)[3]	7,026 (28%)	5,309 (27%)	
High risk (>15)[3]	3,744 (15%)	2,316 (12%)	
Unknown	94 (0.4%)	3434 (15%)	
COVID-19 treatments			
Corticosteroids	16,938 (68%)	18,816 (81%)	<0.001
Tocilizumab	1,834 (7.3%)	2,259 (9.8%)	<0.001
Primary study outcome			
Mortality within 28 days	5,743 (23%)	4,309 (19%)	<0.001

[1] Mean (Standard Deviation)
[2] Median (Lower quartile, Upper quartile)
[3] n (%) excludes 'Unknown'

The baseline characteristic differences could have been partially attributable to the high rates of recruitment into ISARIC4C during the first wave of the COVID-19 pandemic in the UK (March to June 2020) (Figure 6-1). 35% of RECOVERY-ISARIC participants were recruited in this period, compared with 25% of all RECOVERY participants.

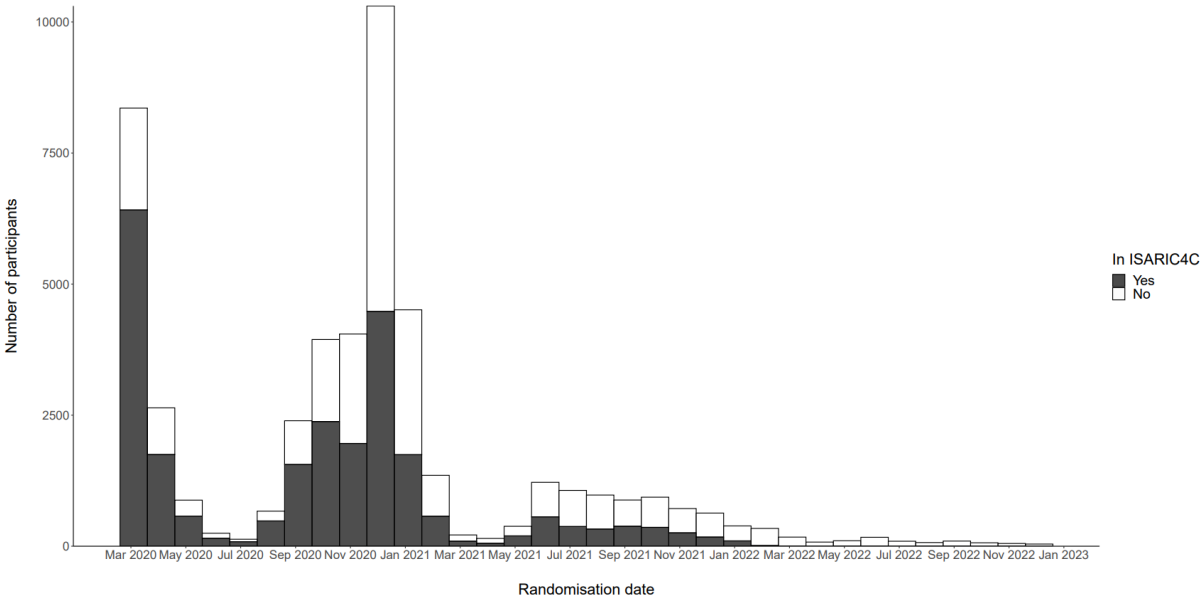


Figure 6-1: Proportion of RECOVERY participants included in ISARIC4C over time.

However, within the dexamethasone treatment comparison (which was entirely recruited within the March to June 2020 period), many of the observed differences in baseline characteristics were broadly similar, although some were of smaller magnitude, such as mean age (Table 6-2). The difference in 28-day mortality remained.

Table 6-2: Baseline characteristics and 28-day mortality according to linkage with ISARIC4C for RECOVERY dexamethasone comparison participants.

	In ISARIC4C, N=4,797	Not in ISARIC4C, N=1,628	p-value
Demographics			
Age[1]	66.5 (15.5)	65.0 (16.2)	0.005
Age Group			0.03
Age <70	2,677 (56%)	969 (60%)	
Age >=70 <80	1,014 (21%)	315 (19%)	
Age >=80	1,106 (23%)	344 (21%)	
Sex			0.04
Female	1,710 (36%)	626 (38%)	
Male	3,087 (64%)	1,002 (62%)	
Acute illness features			
Time since symptom onset			<0.001
Time of onset <=7 days	1,970 (41%)	747 (46%)	
Time of onset >7 days	2,810 (59%)	881 (54%)	
Time of onset unknown	17 (0.4%)	0 (0%)	
Days since admission to hospital[2]	2 (1, 5)	2 (1, 3)	<0.001
Respiratory support			<0.001
No oxygen or ventilation	1,103 (23%)	432 (27%)	
Oxygen or non-invasive ventilation	2,893 (60%)	990 (61%)	
Mechanical ventilation or ECMO	801 (17%)	206 (13%)	
Baseline co-morbidities			
Diabetes	1,180 (25%)	366 (22%)	0.21
Heart disease	1,330 (28%)	427 (26%)	0.26
Chronic lung disease	1,023 (21%)	323 (20%)	0.33
Tuberculosis	17 (0.4%)	8 (0.5%)	0.32
HIV	18 (0.4%)	14 (0.9%)	0.02
Severe liver disease	79 (1.6%)	40 (2.5%)	0.06
Severe kidney impairment	376 (7.8%)	148 (9.1%)	0.12
Severe mental illness	822/4,793 (17%)	254/1,494 (17%)	0.89
Immunosuppression	334/4,793 (7.0%)	100/1,498 (6.7%)	0.70
Charlson score[2]	4 (2, 6)	4 (2, 6)	0.13
Hospital Frailty Risk Score group			0.003
Low risk (<5)[3]	2,125 (44%)	731 (49%)	
Intermediate risk (5-15)[3]	1,564 (33%)	462 (31%)	
High risk (>15)[3]	1,087 (23%)	291 (20%)	
Unknown	21 (0.4%)	144 (8.8%)	
COVID-19 treatments			
Corticosteroids	1,582 (33%)	522 (32%)	0.50
Tocilizumab	143 (3.0%)	45 (2.8%)	0.65
Primary study outcome			
Mortality within 28 days	1,256 (26%)	335 (21%)	<0.001

[1]Mean (Standard Deviation)
[2]Median (Lower quartile, Upper quartile)
[3]n(%) exclude 'Unknown'

RECOVERY-ISARIC participants were recruited to ISARIC4C a median of 1 day after their date of randomisation in RECOVERY (IQR 1 day before to 15 days after). For participants who were recruited to ISARIC4C after randomisation, the decision to include in ISARIC4C could have been influenced by post-randomisation events (such as ICU admission or a longer duration of hospital stay), potentially accounting for some of the findings of increased disease severity and mortality within the RECOVERY-ISARIC population.

6.2.2 Dexamethasone

6.2.2.1 Baseline characteristics

In the RECOVERY-ISARIC dexamethasone comparison population, baseline characteristics between randomised groups remained well-matched (Table 6-3). The mean age was 1 year greater in the dexamethasone group (similar to the 1.1 year difference in the whole RECOVERY dexamethasone comparison population).

Table 6-3: Baseline characteristics according to randomised treatment group in the RECOVERY-ISARIC dexamethasone comparison population.

	Dexamethasone N=1582/2104 (75%)	**Usual care N=3215/4321 (74%)**
Demographics		
Age[1]	67.2 (15.2)	66.2 (15.6)
Age group		
Age <70	848 (54%)	1,829 (57%)
Age >=70 <80	360 (23%)	654 (20%)
Age >=80	374 (24%)	732 (23%)
Sex		
Female	560 (35%)	1,150 (36%)
Male	1,022 (65%)	2,065 (64%)
Acute illness features		
Time since symptom onset		
Time of onset <=7 days	665 (42%)	1,305 (41%)
Time of onset >7 days	913 (58%)	1,897 (59%)
Days since admission to hospital[2]	3 (1, 5)	2 (1, 5)
Respiratory support		
No oxygen or ventilation	345 (22%)	758 (24%)
Oxygen or non-invasive ventilation	977 (62%)	1,916 (60%)
Mechanical ventilation or ECMO	260 (16%)	541 (17%)
Baseline non-COVID infection	482 (30%)	961 (30%)
Baseline laboratory measurements		
C-reactive protein, mg/L[2]	118 (61, 206)	121 (62, 205)
Creatinine, µmol/L[2]	83 (65, 105)	83 (68, 108)

Baseline co-morbidities		
Diabetes	401 (25%)	779 (24%)
Heart disease	456 (29%)	874 (27%)
Chronic lung disease	318 (20%)	705 (22%)
Tuberculosis	5 (0.3%)	12 (0.4%)
HIV	6 (0.4%)	12 (0.4%)
Severe liver disease	28 (1.8%)	51 (1.6%)
Severe kidney impairment	116 (7.4%)	260 (8.1%)
Severe mental illness	265/1,580 (17%)	557/3,213 (17%)
Immunosuppression	105/1,580 (6.6%)	229/3,213 (7.1%)
Charlson score[2]	4 (2, 6)	4 (2, 6)
Hospital Frailty Risk Score group		
Low risk (<5)[3]	690 (44%)	1,435 (45%)
Intermediate risk (5-15)[3]	531 (34%)	1,033 (32%)
High risk (>15)[3]	353 (22%)	734 (23%)
Unknown	8 (0.5%)	13 (0.4%)
Other treatments		
Tocilizumab	38 (2.4%)	105 (3.3%)
[1]Mean (Standard Deviation)		
[2]Median (Lower quartile, Upper quartile)		
[3]n (%) excludes 'Unknown'		

6.2.2.2 Outcomes

A comparison of the RECOVERY trial primary outcome of 28-day mortality between the subgroups of participants with data in ISARIC4C, and those without data in ISARIC4C, showed no significant heterogeneity in the dexamethasone treatment effect estimate (Figure 6-2). The absolute mortality for those in ISARIC4C was higher.

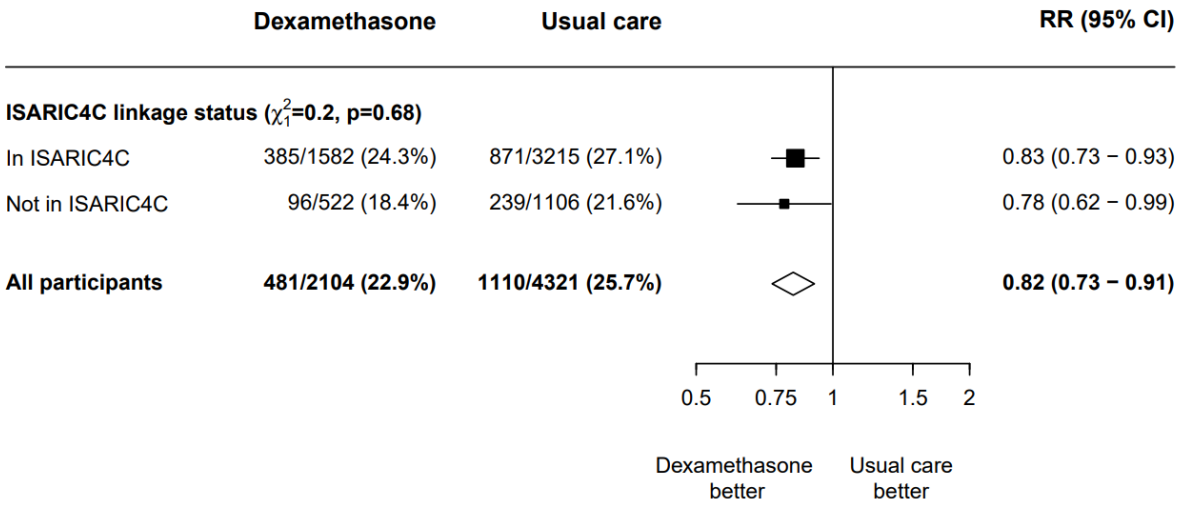


Figure 6-2: Subgroup analysis of 28-day mortality in the RECOVERY dexamethasone comparison by ISARIC4C linkage status.

6.2.3 Tocilizumab

6.2.3.1 Baseline characteristics

In the RECOVERY-ISARIC tocilizumab comparison population, baseline characteristics between randomised groups remained well-matched (Table 6-4).

Table 6-4: Baseline characteristics according to randomised treatment group in the RECOVERY-ISARIC tocilizumab comparison population.

	Tocilizumab N=1216/2022 (60%)	**Usual care N=1125/2094 (54%)**
Demographics		
Age[1]	63.4 (13.8)	64.1 (13.5)
Age group		
Age <70	791 (65%)	725 (64%)
Age >=70 <80	295 (24%)	250 (22%)
Age >=80	130 (11%)	150 (13%)
Sex		
Female	426 (35%)	343 (30%)
Male	790 (65%)	782 (70%)
Acute illness features		
Time since symptom onset		
Time of onset <=7 days	521 (43%)	465 (41%)
Time of onset >7 days	695 (57%)	660 (59%)
Days since admission to hospital[2]	1 (1, 2)	1 (1, 2)
Respiratory support		
No ventilator support	558 (46%)	506 (45%)
Non-invasive ventilation	487 (40%)	443 (39%)
Mechanical ventilation or ECMO	171 (14%)	176 (16%)
Baseline non-COVID infection	294 (24%)	268 (24%)
Baseline laboratory measurements		
C-reactive protein, mg/L[2]	143 (106, 203)	145 (105, 203)
Creatinine, µmol/L[2]	76 (60, 97)	76 (62, 98)
Baseline co-morbidities		
Diabetes	361 (30%)	335 (30%)
Heart disease	272 (23%)	279 (25%)
Chronic lung disease	307 (25%)	290 (26%)
Tuberculosis	1 (<0.1%)	2 (0.2%)
HIV	5 (0.5%)	3 (0.3%)
Severe liver disease	8 (0.7%)	5 (0.4%)
Severe kidney impairment	66 (5.5%)	50 (4.5%)
Severe mental illness	190/1,214 (16%)	168/1,124 (15%)
Immunosuppression	85/1,214 (7.0%)	71/1,124 (6.3%)
Charlson score[2]	3 (2, 5)	3 (2, 5)
Hospital Frailty Risk Score group		
Low risk (<5)[3]	728 (60%)	663 (59%)
Intermediate risk (5-15)[3]	364 (30%)	336 (30%)
High risk (>15)[3]	120 (9.9%)	124 (11%)
Unknown	4 (0.3%)	2 (0.2%)
Other treatments		
Corticosteroids	953 (78%)	874 (78%)

[1]Mean (Standard Deviation)
[2]Median (Lower quartile, Upper quartile)
[3]n (%) excludes 'Unknown'

6.2.3.2 Outcomes

A comparison of 28-day mortality between the subgroups of participants with data in ISARIC4C, and those without data in ISARIC4C, did not demonstrate significant statistical heterogeneity in the tocilizumab treatment effect observed (p=0.08) (Figure 6-3). The difference seen remained compatible with chance but was not as convincing as the evaluation for the other immunomodulatory treatment comparisons. Absolute mortality was slightly higher in those in ISARIC4C.

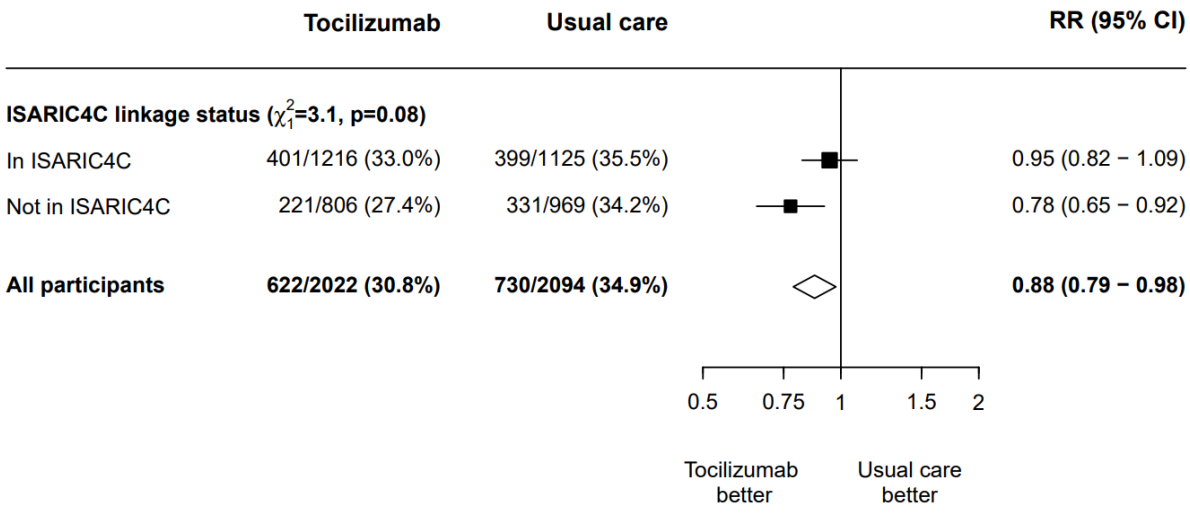


Figure 6-3: Subgroup analysis of 28-day mortality in the RECOVERY tocilizumab comparison by ISARIC4C linkage status.

6.2.4 Baricitinib

6.2.4.1 Baseline characteristics

In the RECOVERY-ISARIC baricitinib comparison population, baseline characteristics between randomised groups remained well-matched (Table 6-5). The mean age was 1.2 years older in the baricitinib group (similar to the 0.8 years difference observed in the whole RECOVERY baricitinib comparison population).

Table 6-5: Baseline characteristics according to randomised treatment group in the RECOVERY-ISARIC baricitinib comparison population.

	Baricitinib N=1826/4148 (44%)	**Usual care N=1776/4008 (44%)**
Demographics		
Age[1]	58.6 (15.6)	57.4 (15.5)
Age group		
Age <70	1,358 (74%)	1,373 (77%)
Age >=70 <80	316 (17%)	285 (16%)
Age >=80	152 (8.3%)	118 (6.6%)
Sex		
Female	636 (35%)	580 (33%)
Male	1,190 (65%)	1,196 (67%)
Acute illness features		
Time since symptom onset		
Time of onset <=7 days	700 (38%)	645 (36%)
Time of onset >7 days	1,125 (62%)	1,130 (64%)
Days since admission to hospital[2]	1 (1, 2)	1 (1, 2)
Respiratory support		
No oxygen or ventilation	94 (5.1%)	103 (5.8%)
Oxygen requirement with no ventilation	1,217 (67%)	1,181 (66%)
Non-invasive ventilation	465 (25%)	433 (24%)
Mechanical ventilation or ECMO	50 (2.7%)	59 (3.3%)
Baseline non-COVID infection	370 (20%)	372 (21%)
Laboratory measurements		
C-reactive protein, mg/L[2]	83 (42, 142)	87 (43, 143)
Creatinine, µmol/L[2]	76 (64, 94)	75 (62, 93)
Baseline co-morbidities		
Diabetes	428 (24%)	431 (24%)
Heart disease	347 (19%)	318 (18%)
Chronic lung disease	393 (22%)	338 (19%)
Tuberculosis	0 (0%)	0 (0%)
HIV	5 (0.3%)	4 (0.3%)
Severe liver disease	17 (0.9%)	16 (0.9%)
Severe kidney impairment	46 (2.5%)	31 (1.7%)
Severe mental illness	336 (18%)	337 (19%)
Immunosuppression	88 (4.8%)	109 (6.2%)
Charlson score[2]	2 (1, 4)	2 (1, 4)
Hospital Frailty Risk Score group		
High risk (>15)[3]	117 (6.4%)	109 (6.2%)
Intermediate risk (5-15)[3]	385 (21%)	389 (22%)
Low risk (<5)[3]	1,316 (72%)	1,268 (72%)
Unknown	8 (0.4%)	10 (0.6%)
Other treatments		
Corticosteroids	1,753 (96%)	1,682 (95%)
Tocilizumab	617 (34%)	600 (34%)

[1]Mean (Standard Deviation)
[2]Median (Lower quartile, Upper quartile)
[3]n (%) excludes 'Unknown'

6.2.4.2 Outcomes

A comparison of 28-day mortality between the subgroups of participants with data in ISARIC4C and those without data in ISARIC4C, showed no evidence of heterogeneity in the baricitinib treatment effect estimate (Figure 6-4). The absolute mortality for those in ISARIC4C remained slightly higher – as has been observed in the other treatment comparisons.

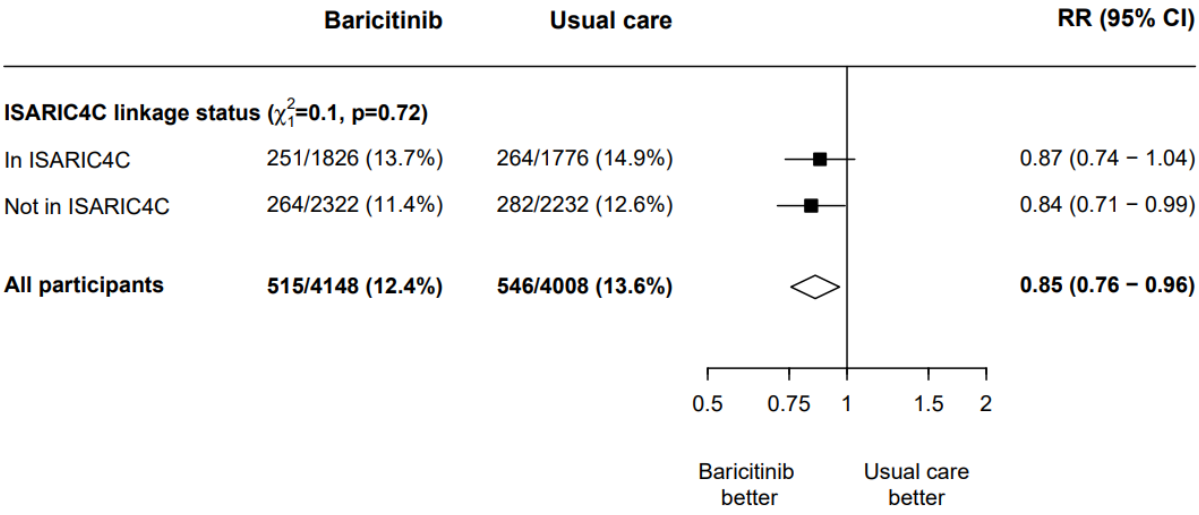


Figure 6-4: Subgroup analysis of 28-day mortality in the RECOVERY baricitinib comparison by ISARIC4C linkage status.

6.3 Exploration of the Heterogeneity of Dexamethasone Treatment Effect

6.3.1 Rationale

The subgroup analyses of mortality presented in Chapter 5 showed significant heterogeneity in dexamethasone treatment effect according to subgroups of respiratory support, HFRS, days since symptom onset; and possibly baseline non-COVID infection and age group (Section 5.3.6). Respiratory support and HFRS were taken forward for further exploration due to the strength of the evidence of heterogeneity and their clinical relevance. Those requiring mechanical ventilation at randomisation and those with a low frailty risk score appeared to experience a greater dexamethasone treatment benefit, while those not requiring oxygen at randomisation and those with a high frailty risk score may have experienced no benefit or harm from dexamethasone. Respiratory support represents a measure of acute disease stage and severity and HFRS represents a measure of a patient's general underlying health status. A post-hoc subgroup analysis of 28-day mortality by Charlson Co-morbidity Index score displayed similar results to that of HFRS, supporting the concept that general health status appeared to be a relevant determinant of the heterogeneity of dexamethasone treatment effect (Supplementary Figure 19). The following analyses aimed to gain further insight into how these factors contribute to the differences in dexamethasone treatment effect observed.

6.3.2 Extended respiratory support subgroups

Analysis Purpose: Use the linked ISARIC4C data to increase granularity of the measurement of baseline respiratory support status in the broad 'oxygen' subgroup of the dexamethasone comparison. Evaluate these extended respiratory support subgroups as a determinant of the heterogeneity of dexamethasone treatment effect (see Section 3.5.5.2).

Extended respiratory support subgroups derived from ISARIC4C data allowed the 'oxygen' subgroup (which included non-invasive ventilation) in the RECOVERY dexamethasone comparison to be further split into 'low or moderate oxygen' (FiO_2 <0.5), 'high oxygen' (FiO2 ≥0.5), and 'non-invasive ventilation' groups (see Section 1.3.4 and Section 3.5.5.2).

The subgroup analysis of 28-day mortality in the RECOVERY-ISARIC dexamethasone treatment comparison by baseline extended respiratory support subgroups demonstrated significant heterogeneity in dexamethasone treatment effect (Figure 6-5). A relatively linear trend in treatment effect estimate across the hierarchy of respiratory support groups was observed. Those requiring higher levels of respiratory support appeared to experience a larger proportional benefit from dexamethasone treatment, and those requiring lower levels of respiratory support appeared to experience a smaller proportional benefit from dexamethasone treatment.

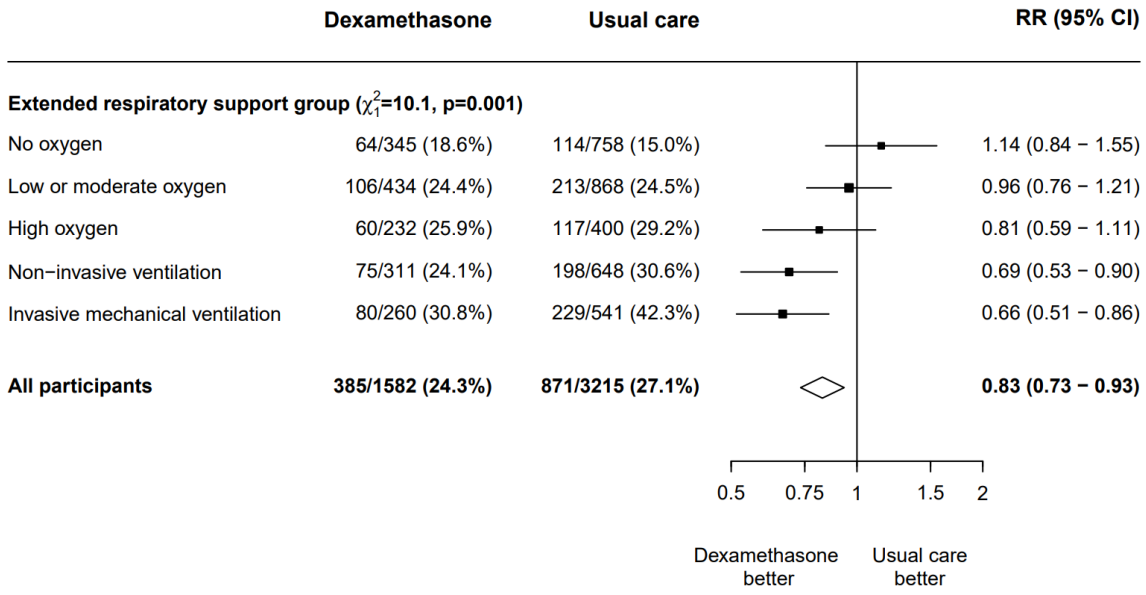


Figure 6-5: Subgroup analysis of effect of allocation to dexamethasone on all-cause mortality within 28 days, by subgroups defined by extended respiratory support group at randomisation in the RECOVERY-ISARIC dexamethasone comparison population.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age group at randomisation.

6.3.3 Effect on secondary efficacy outcomes

Analysis Purpose: Evaluate the robustness of the respiratory support and HFRS subgroup effects by evaluating in the RECOVERY trial secondary efficacy outcomes.

The heterogeneity of treatment effect by both respiratory support group and HFRS at randomisation persists in subgroup analyses of discharge alive from hospital within 28 days (Figure 6-6), and invasive mechanical ventilation or death within 28 days (the latter assessed amongst patients who were not receiving invasive mechanical ventilation at randomisation) (Figure 6-7).

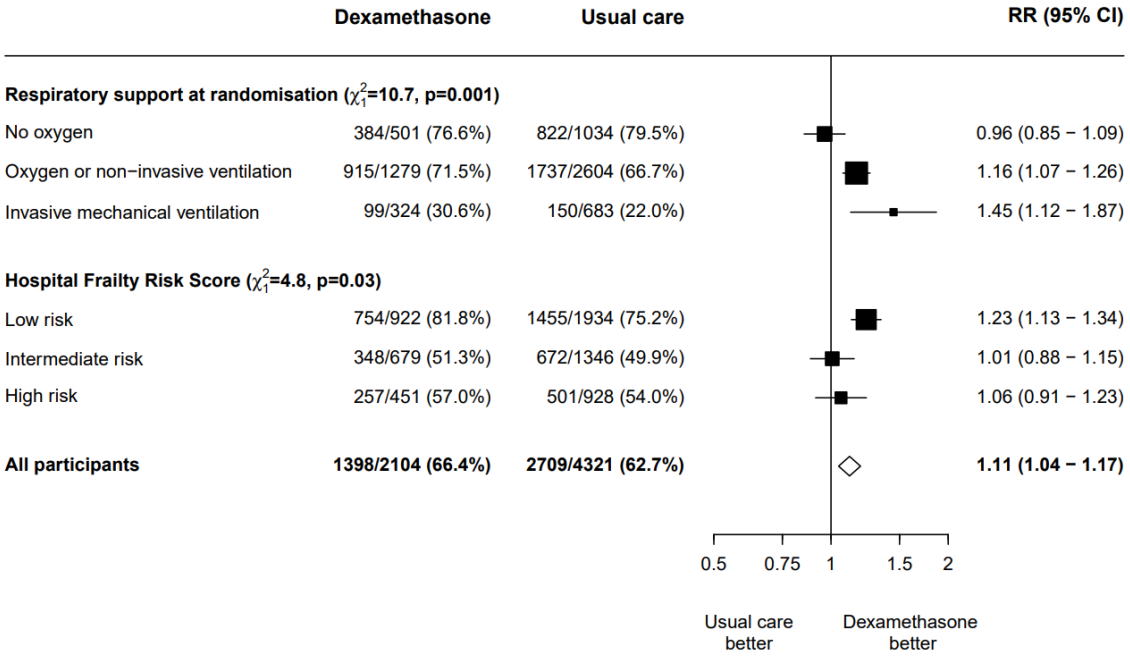


Figure 6-6: Subgroup analysis of effect of allocation to dexamethasone on discharge alive from hospital within 28 days in the RECOVERY dexamethasone comparison.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age ± respiratory support group at randomisation.

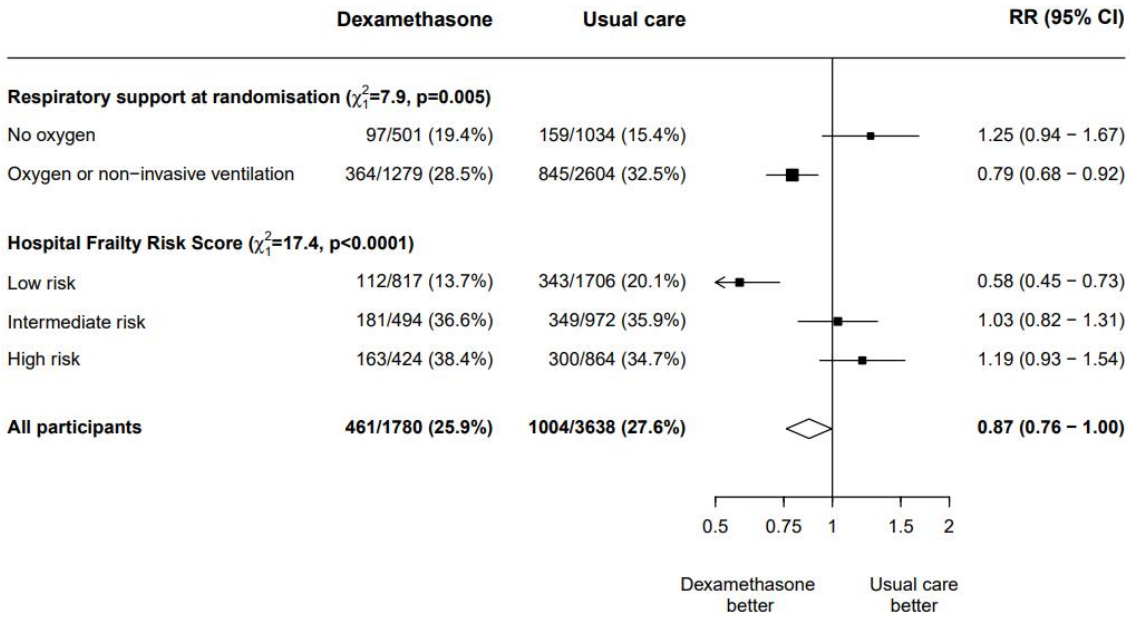


Figure 6-7: Subgroup analysis of effect of allocation to dexamethasone on invasive mechanical ventilation or death within 28 days in the RECOVERY dexamethasone comparison. Assessed in participants who were not on invasive mechanical ventilation at randomisation. RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.

6.3.4 Interactions between respiratory support and frailty subgroups

Analysis Purpose: Evaluate whether the respiratory support and HFRS subgroups are correlated at baseline, and whether both subgroups appear to be important independent determinants of the heterogeneity of dexamethasone treatment effect when considering any correlation.

There were correlations between the baseline characteristics that might mediate the heterogeneity of dexamethasone treatment effect, including between respiratory support group and HFRS. This raises the possibility that the multiple marginal subgroup analyses were replicating the same effect through confounding rather than delineating independent determinants of treatment effect heterogeneity. It is therefore important to undertake further analyses to explore whether the effects were independent of each other.

Within respiratory support subgroups, those in the ‘no oxygen’ group were oldest, had the shortest time since symptom onset and were the most likely to have a high frailty risk

score (Table 6-6). Those in the ‘oxygen’ group were of intermediate age and symptom duration and were the most likely to have a low frailty risk score. Those in the ‘mechanical ventilation’ group were youngest, had the longest duration of symptoms and were the most likely to have an intermediate frailty risk score.

Table 6-6: Baseline characteristics according to respiratory support groups in the RECOVERY dexamethasone comparison.

	Respiratory support group		
	No oxygen or ventilation (N=1535)	**Oxygen or non-invasive ventilation (N=3883)**	**Mechanical ventilation or ECMO (N=1007)**
Demographics			
Age[1]	69.4 (17.5)	66.7 (15.3)	59.1 (11.4)
Age Group			
Age <70	659 (43%)	2,149 (55%)	838 (83%)
Age >=70 <80	338 (22%)	838 (22%)	153 (15%)
Age >=80	538 (35%)	896 (23%)	16 (1.6%)
Sex			
Female	643 (42%)	1,420 (37%)	273 (27%)
Male	892 (58%)	2,463 (63%)	734 (73%)
Acute illness features			
Time since symptom onset			
Time of onset <=7 days	901 (59%)	1,603 (41%)	213 (21%)
Time of onset >7 days	631 (41%)	2,269 (59%)	791 (79%)
Days since admission to hospital[2]	2 (1, 5)	2 (1, 4)	5 (3, 9)
Baseline non-COVID infection	453 (30%)	1,068 (28%)	377 (37%)
Baseline co-morbidities			
Diabetes	342 (22%)	950 (25%)	254 (25%)
Heart disease	519 (34%)	1,074 (28%)	164 (17%)
Chronic lung disease	351 (23%)	883 (23%)	112 (11%)
Tuberculosis	8 (0.5%)	11 (0.3%)	6 (0.6%)
HIV	5 (0.4%)	21 (0.6%)	6 (0.6%)
Severe liver disease	32 (2.1%)	72 (1.9%)	15 (1.5%)
Severe kidney impairment	119 (7.8%)	253 (6.5%)	152 (15%)
Severe mental illness	299/1,487 (20%)	666/3,810 (17%)	112/990 (11%)
Immunosuppression	104/1,489 (7.0%)	287/3,814 (7.5%)	44/990 (4.4%)
Charlson score[2]	5 (3, 7)	4 (2, 6)	2 (1, 4)
Hospital Frailty Risk Score group			
Low risk (<5)	518 (34%)	2,005 (52%)	333 (33%)
Intermediate risk (5-15)	397 (26%)	1,069 (28%)	559 (56%)
High risk (>15)	567 (37%)	721 (19%)	91 (9.0%)
Unknown	53 (3.5%)	88 (2.3%)	24 (2.4%)
Other treatments			
Tocilizumab	10 (0.7%)	143 (3.7%)	35 (3.5%)

[1]Mean (Standard Deviation)

[2]Median (Lower quartile, Upper quartile)

Within HFRS subgroups, those who had a low frailty risk score were youngest, had the longest time since symptom onset and were the most likely to require oxygen at randomisation (Table 6-7). Those in the intermediate frailty risk score group were of intermediate age and symptom duration and were the most likely to require mechanical ventilation at randomisation. Those in the high frailty risk score group were oldest, had the shortest duration of symptoms and were the most likely to not require oxygen at randomisation.

Table 6-7: Baseline characteristics according to Hospital Frailty Risk Score groups.

	Hospital Frailty Risk Score group[1]		
	Low risk (N=2856)	**Intermediate risk (N=2025)**	**High risk (N=1379)**
Demographics			
Age[2]	59.7 (14.1)	68.1 (14.3)	77.2 (13.1)
Age Group			
Age <70	2,164 (76%)	1,036 (51%)	333 (24%)
Age >=70 <80	443 (16%)	519 (26%)	343 (25%)
Age >=80	249 (8.7%)	470 (23%)	703 (51%)
Sex			
Female	999 (35%)	697 (34%)	578 (42%)
Male	1,857 (65%)	1,328 (66%)	801 (58%)
Acute illness features			
Time since symptom onset			
Time of onset <=7 days	933 (33%)	820 (41%)	876 (64%)
Time of onset >7 days	1,918 (67%)	1,198 (59%)	498 (36%)
Days since admission to hospital[3]	2 (1, 3)	3 (1, 7)	3 (1, 7)
Respiratory support			
No oxygen or ventilation	518 (18%)	397 (20%)	567 (41%)
Oxygen or non-invasive ventilation	2,005 (70%)	1,069 (53%)	721 (52%)
Mechanical ventilation or ECMO	333 (12%)	559 (28%)	91 (6.6%)
Baseline non-COVID infection	537 (19%)	802 (40%)	558 (40%)
Baseline co-morbidities			
Diabetes	582 (20%)	533 (26%)	401 (29%)
Heart disease	473 (17%)	598 (30%)	654 (48%)
Chronic lung disease	471 (17%)	485 (24%)	362 (26%)
Tuberculosis	10 (0.4%)	6 (0.3%)	6 (0.5%)
HIV	15 (0.6%)	2 (0.1%)	1 (<0.1%)
Severe liver disease	35 (1.2%)	45 (2.2%)	33 (2.4%)
Severe kidney impairment	80 (2.8%)	228 (11%)	205 (15%)
Severe mental illness	332 (12%)	339 (17%)	405 (29%)
Immunosuppression	134 (4.7%)	190 (9.4%)	111 (8.0%)
Charlson score[3]	2 (1, 4)	4 (2, 6)	7 (5, 9)
Other treatments			
Tocilizumab	93 (3.3%)	64 (3.2%)	27 (2.0%)

[1]165 participants with an 'Unknown' Hospital Frailty Risk Score are not included.
[2]Mean (Standard Deviation)
[3]Median (Lower quartile, Upper quartile)

The correlation observed between disease severity and frailty may be explained by both physiological and contextual reasons. Those with higher levels of frailty are at higher risk of developing severe illness. They are also more likely to have a lower threshold to be admitted to hospital and less likely to be offered escalation of care in hospital to interventions such as invasive mechanical ventilation.

An analysis approach to attempt to mitigate for the potential for confounding in the HFRS and respiratory subgroups as determinants of dexamethasone treatment heterogeneity was that including interactions with other key subgroups and standardisation (Section 3.6.7.2). In these analyses, Cox regression models were constructed including interaction terms between treatment assignment and each of the two correlated baseline subgroups of interest. Hazard ratio estimates within one subgroup of interest were then standardised to the overall distribution of the other factor of interest, such that the distribution of the second factor was the same in each of the subgroups of the first factor. These analyses demonstrated significant heterogeneity according to both respiratory support and frailty risk score groups (Figure 6-8). The contrast matrix for these models prior to standardisation and absolute numbers of participants and deaths according to both subgroups can be found in Supplementary Table 81 and Supplementary Table 82.

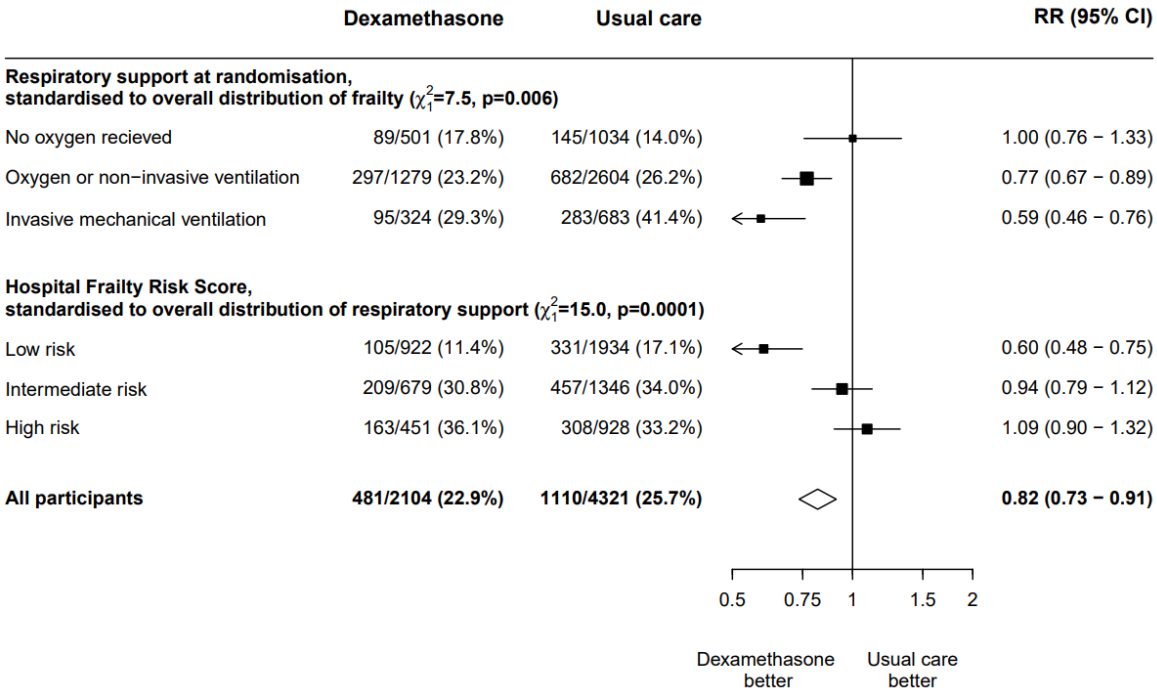


Figure 6-8: Subgroup analysis of 28-day mortality in the RECOVERY dexamethasone comparison after considering interactions with other key subgroups with standardisation.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age group at randomisation.

6.3.5 Effect on potential treatment-related harms

Analysis Purpose: Evaluate whether respiratory support and HFRS subgroups were important determinants of potential treatment-related harms.

Based on biological plausibility and the results from the long-term follow-up analysis for dexamethasone and the completed subgroup of higher dose dexamethasone, the most probable specific corticosteroid treatment-related harms that may have contributed to the unfavourable mortality treatment effect estimates in the 'no oxygen' and high frailty risk score groups were anticipated to be hyperglycaemia or non-COVID infection, although harm may well be multifactorial.

In the long-term follow-up subgroup analysis results in Chapter 5, there was no clear evidence of statistical heterogeneity in the subgroups defined by respiratory support or HFRS on the outcome of major non-COVID infection (Figure 5-9, Figure 5-10).

For the outcome of hyperglycaemia within 28 days, there was also no evidence of heterogeneity according to respiratory support or HFRS, though event numbers were small in some subgroups (Figure 6-9).

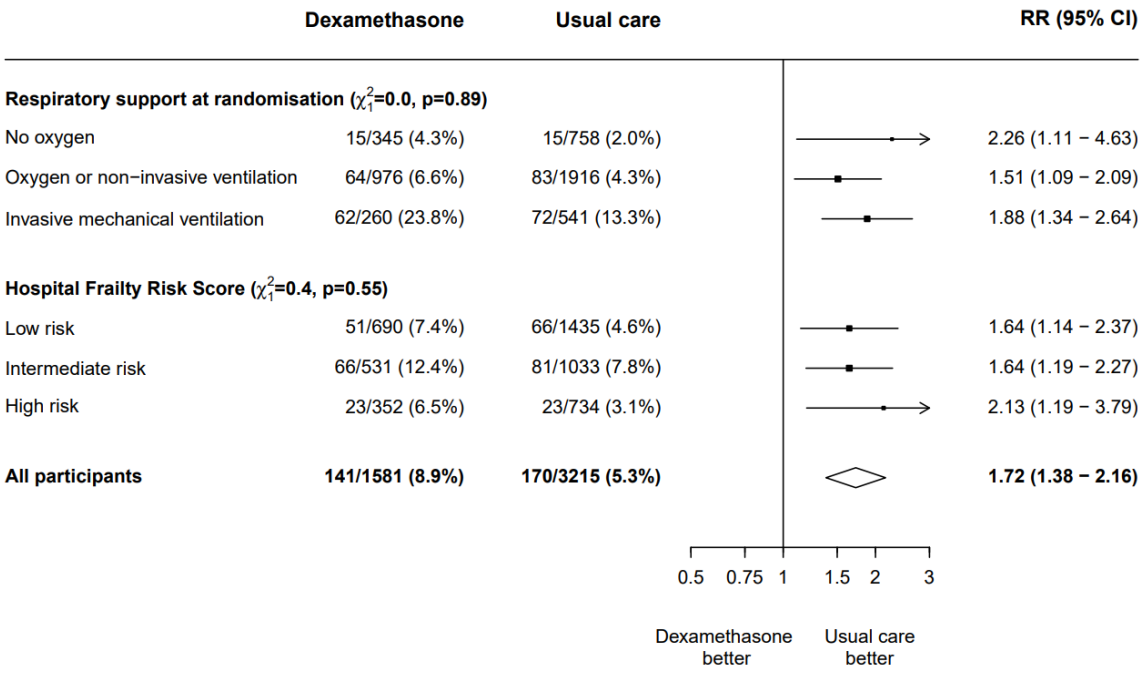


Figure 6-9: Subgroup analysis of effect of allocation to dexamethasone on hyperglycaemia within 28 days, assessed in the RECOVERY-ISARIC dexamethasone comparison.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age ± respiratory support group at randomisation.

6.3.6 Clinical trajectory in the dexamethasone 'no oxygen' subgroup

Analysis Purpose: Gain insight into likely contributors to death in the dexamethasone 'no oxygen' subgroup by describing the oxygenation and CRP trajectories of participants in this subgroup.

In the 'no oxygen' subgroup of the RECOVERY dexamethasone population, >80% of deaths within 28 days were attributed to COVID-19 (Table 6-8).

Table 6-8: Categorisation of diagnoses leading to death within 28 days in the 'no oxygen' subgroup of the RECOVERY dexamethasone comparison.

	Dexamethasone[1] N=89/501 (18%)	**Usual Care[1] N=145/1034 (14%)**
Category		
COVID-19	71 (80)	122 (84)
Other infection	6 (6.7)	9 (6.2)
Cardiac	2 (2.2)	6 (4.1)
Stroke	4 (4.5)	6 (4.1)
Other vascular	2 (2.2)	5 (3.4)
Medical	13 (15)	14 (9.7)
External	0 (0)	2 (1.4)
Unknown (No formal diagnosis recorded)	2 (2.2)	6 (4.1)
Total		
Any death diagnosis	89 (100)	145 (100)
[1]n (%). *Denominators represent total deaths in each treatment arm of the 'no oxygen' subgroup of the RECOVERY dexamethasone comparison*		

In the 'no oxygen' subgroup of the RECOVERY-ISARIC dexamethasone comparison population, those who died developed worsening oxygenation (an increasing modified ordinal scale score) prior to death compared to those who survived (Table 6-9, Figure 6-10). There was a suggestion of a deterioration in levels of inflammatory markers (CRP) (Table 6-9, Figure 6-11).

Table 6-9: Daily rate of change in biological measurements in the first 7 days after randomisation by vital status in the 'no oxygen' subgroup of the RECOVERY-ISARIC dexamethasone comparison population.

Daily rate of change in biological measurement	**Vital status at 28 days**		**Difference in adjusted means (95% CI)[1]**
	Died (n=178), mean (SE)	**Survived (n=925), mean (SE)**	
Modified ordinal scale score (categories)*	0.80 (0.11)	0.49 (0.06)	0.31 (0.08, 0.55)
C-reactive protein (mg/L)	2.3 (5.7)	-9.5 (2.6)	11.8 (-0.4, 24.0)
**Modified ordinal scale score excluded category 1 (discharged alive) and category 8 (death)* *[1]Adjusted for age group at randomisation*			

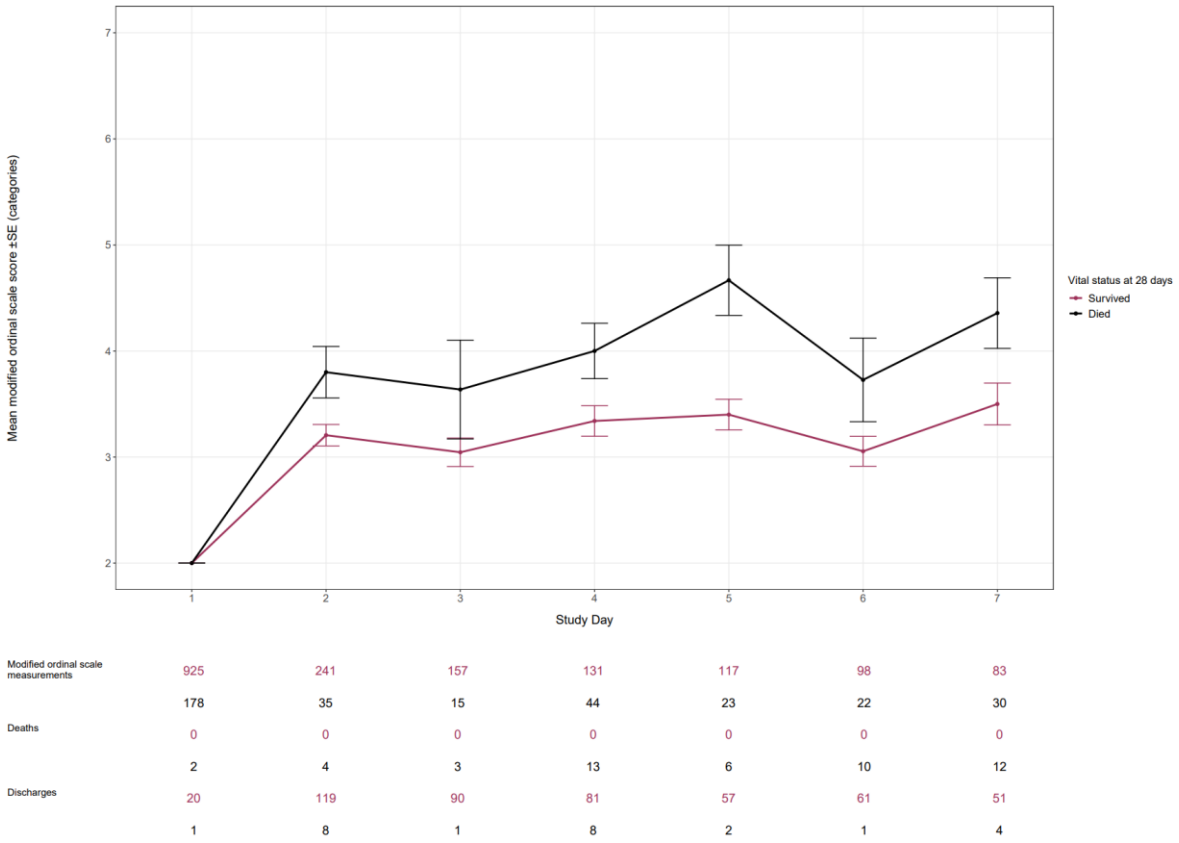


Figure 6-10: Mean modified ordinal scale score per study day according to vital status at 28 days for participants in the 'no oxygen' subgroup of the RECOVERY-ISARIC dexamethasone comparison population.
Points represent group mean (± Standard Error) for all participants with an available measurement on that study day.
Modified ordinal scale score excludes category 1 (discharged alive) and category 8 (death).

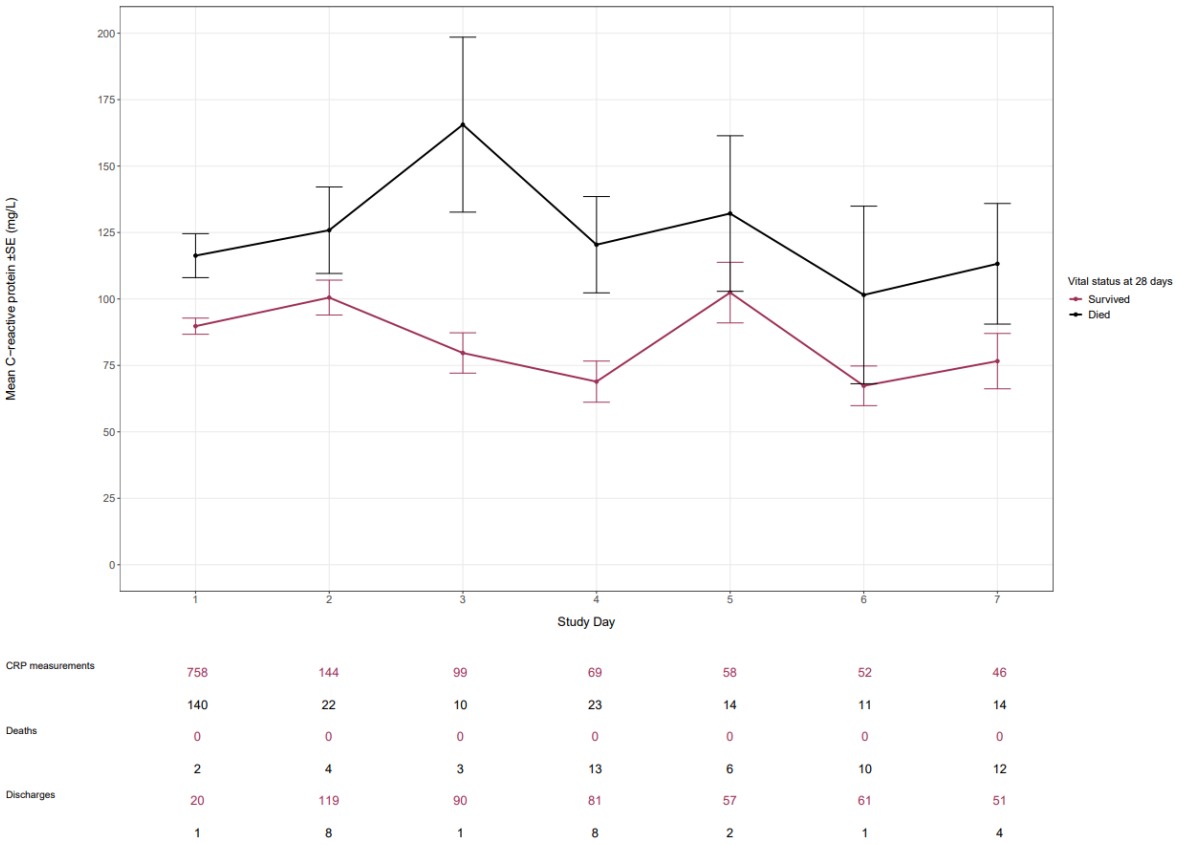


Figure 6-11: Mean C-reactive protein per study day according to vital status at 28 days for participants in the 'no oxygen' subgroup of the RECOVERY-ISARIC dexamethasone comparison population.
Points represent group mean (± Standard Error) for all participants with an available measurement on that study day.

These results appear consistent with a clinical trajectory of worsening COVID-19 in those who died in the 'no oxygen' subgroup, despite dexamethasone treatment and the relatively lower baseline disease severity.

6.4 Randomised Comparisons of Biological Measurements

The results of the randomised comparisons of biological measurements in the dexamethasone comparison are presented here. Results of the tocilizumab and baricitinib comparisons can be found in Supplementary Table 84 to Supplementary Table 87 and Supplementary Figure 23 to Supplementary Figure 27.

6.4.1 Ordinal scale score

There was a suggestion of a greater decrease in the mean daily rate of change in ordinal scale score in the dexamethasone group, compared with the usual care group, during the first 7 days after randomisation (-0.06 vs 0.01 categories; difference in adjusted means, -0.08 categories [95% CI -0.15, 0.00], p=0.04) (Figure 6-12, Figure 6-13 and Table 6-10). A negative daily rate of change corresponds to an improvement in respiratory support requirements and the magnitude of this treatment effect point estimate corresponds to an approximate average reduction of one ordinal scale score category per twelve days in those treated with dexamethasone. This result was nominally statistically significant despite the convincing mortality treatment benefit seen in the RECOVERY-ISARIC dexamethasone comparison population (Figure 6-2).

Table 6-10: Exploratory outcomes of daily rate of change in biological measurements in the first 7 days after randomisation in the RECOVERY-ISARIC dexamethasone comparison population.

Daily rate of change in biological measurement	Dexamethasone (N=1582), mean (SE)	Usual Care (N=3215), mean (SE)	Difference in adjusted means[1] (95% CI)	p-value
Ordinal scale score (categories)	-0.06 (0.03)	0.01 (0.02)	-0.08 (-0.15 , 0.00)	0.04
C-reactive protein (mg/L)	-21.6 (1.6)	-3.4 (1.2)	-18.2 (-22.0 , -14.4)	<0.0001
Neutrophil:lymphocyte ratio	0.77 (0.18)	-0.39 (0.13)	1.17 (0.72 , 1.62)	<0.0001
Glucose (mmol/L)	0.95 (0.21)	0.22 (0.12)	0.73 (0.23 , 1.23)	0.005
Creatinine (µmol/L)	-2.0 (1.4)	-2.6 (1.2)	0.6 (-2.7 , 4.0)	0.72
Alanine aminotransferase (IU/L)	6.1 (1.3)	6.6 (1.1)	-0.5 (-4.0 , 3.1)	0.79

SE = Standard Error
95% CI = 95% Confidence Interval
[1]Adjusted for age and respiratory support group at randomisation

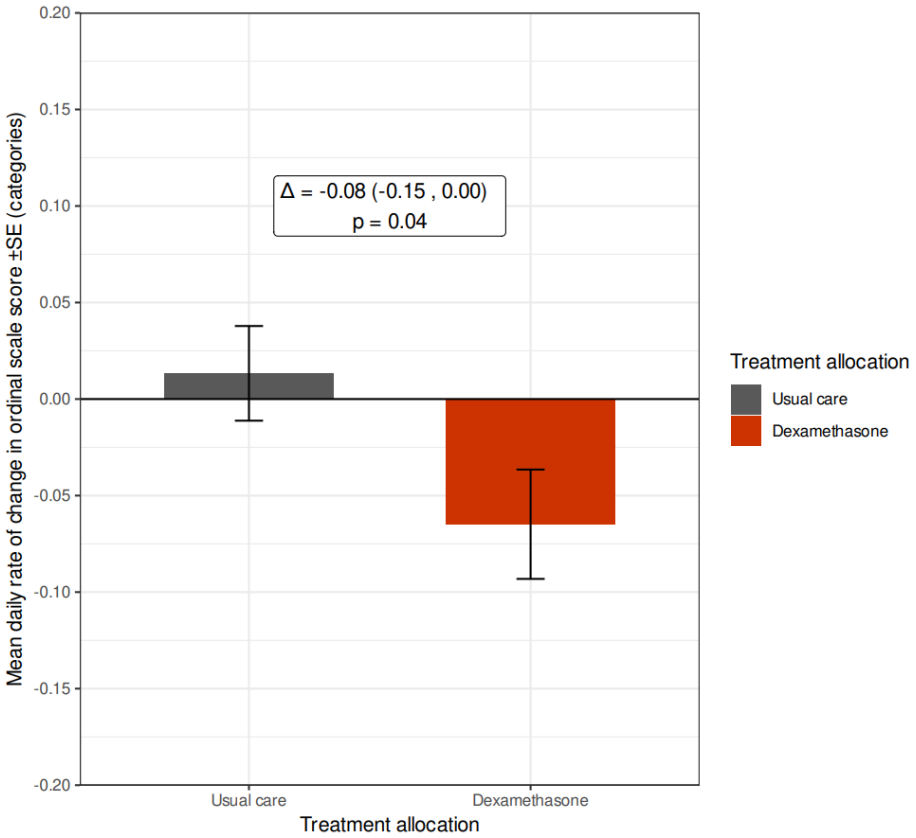


Figure 6-12: Daily rate of change in ordinal scale score within the first 7 days after randomisation, by treatment allocation in the RECOVERY-ISARIC dexamethasone comparison population.
SE = Standard Error

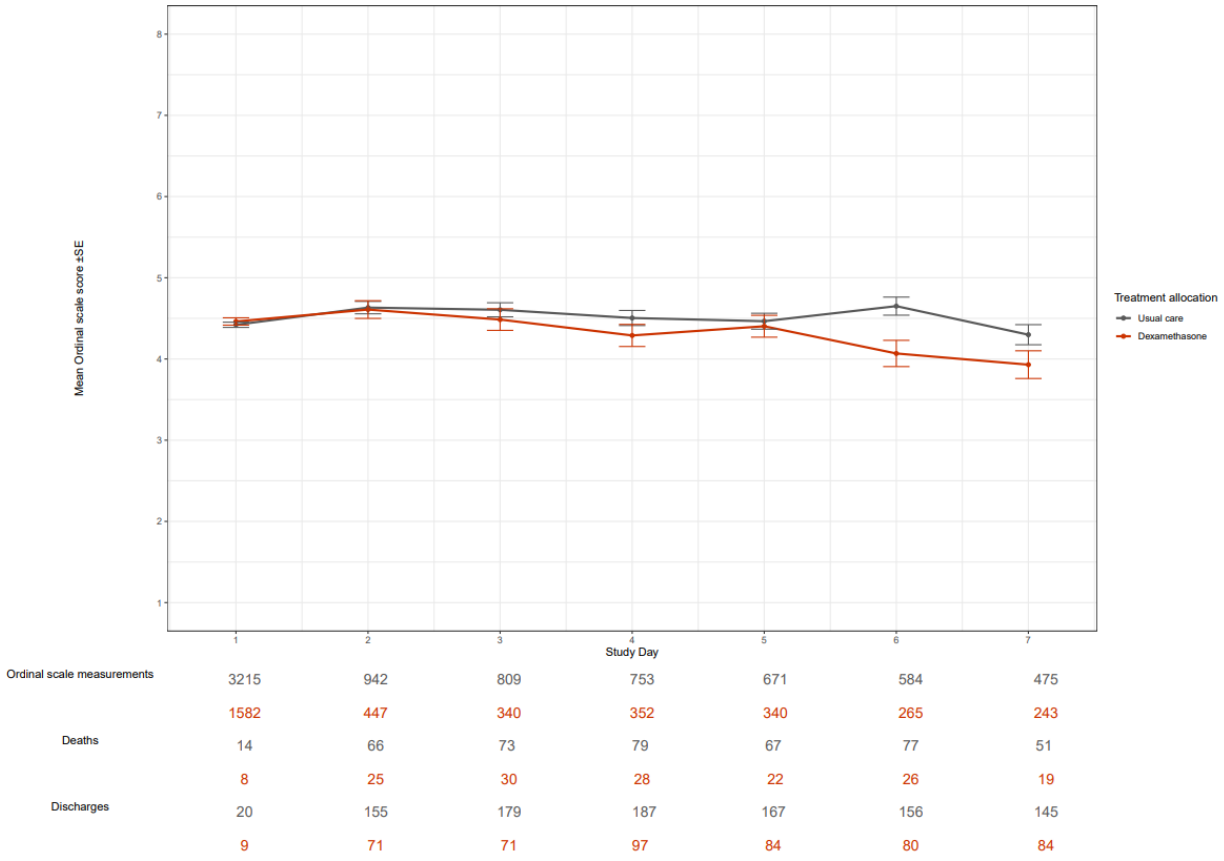


Figure 6-13: Mean ordinal scale score per study day according to randomised allocation for participants in the dexamethasone RECOVERY-ISARIC population.
Points represent group mean (± Standard Error) for all participants with an available measurement on that study day.

Sensitivity analyses varying the follow-up time and using complete case analysis displayed similar results to the main analysis (Supplementary Table 83).

In the proportional odds model for ordinal scale score, participants in the dexamethasone group had significantly improved odds of a lower ordinal scale score at day 5 (an improvement in oxygenation status), compared with the usual care group (Common odds ratio 0.84 [95% CI 0.73 – 0.97], p=0.02) (Figure 6-14, Supplementary Figure 20).

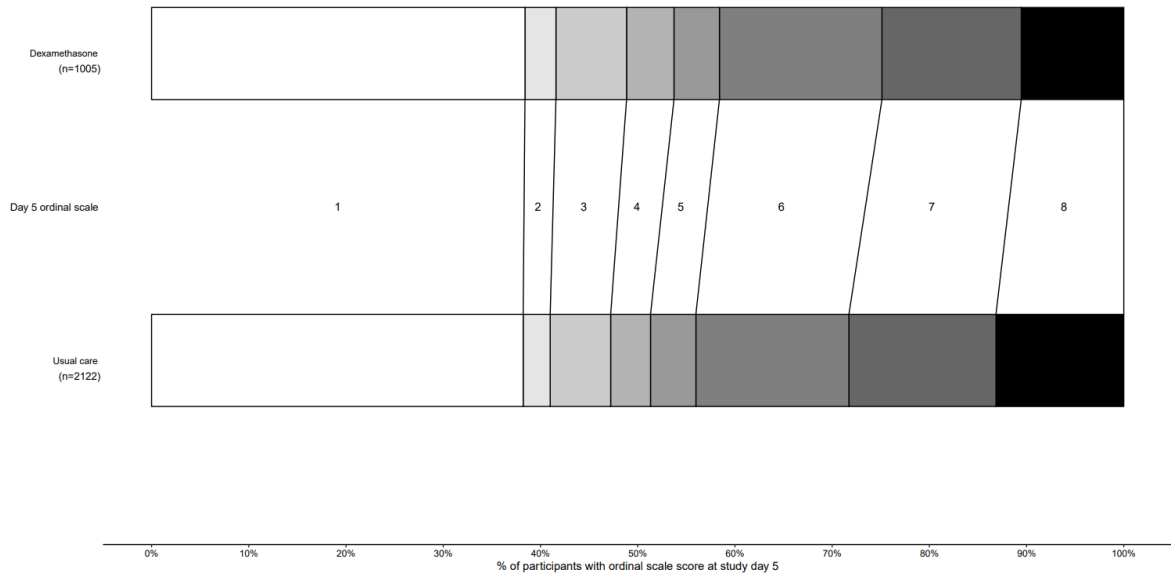


Figure 6-14: Distribution of ordinal scale score at 5 days by randomised allocation in the RECOVERY-ISARIC dexamethasone comparison.

6.4.2 Commonly-measured blood biomarkers

The daily rate of change in CRP showed a significantly greater mean reduction in the dexamethasone group compared with the usual care group (-21.6 vs -3.4 mg/L; difference in adjusted means, -18.2 mg/L [95% CI -22.0, -14.4], p<0.0001) (Figure 6-15, Figure 6-16 and Table 6-10). This corresponds to a dexamethasone treatment-related difference in CRP of approximately 125mg/L across the first 7 days after randomisation.

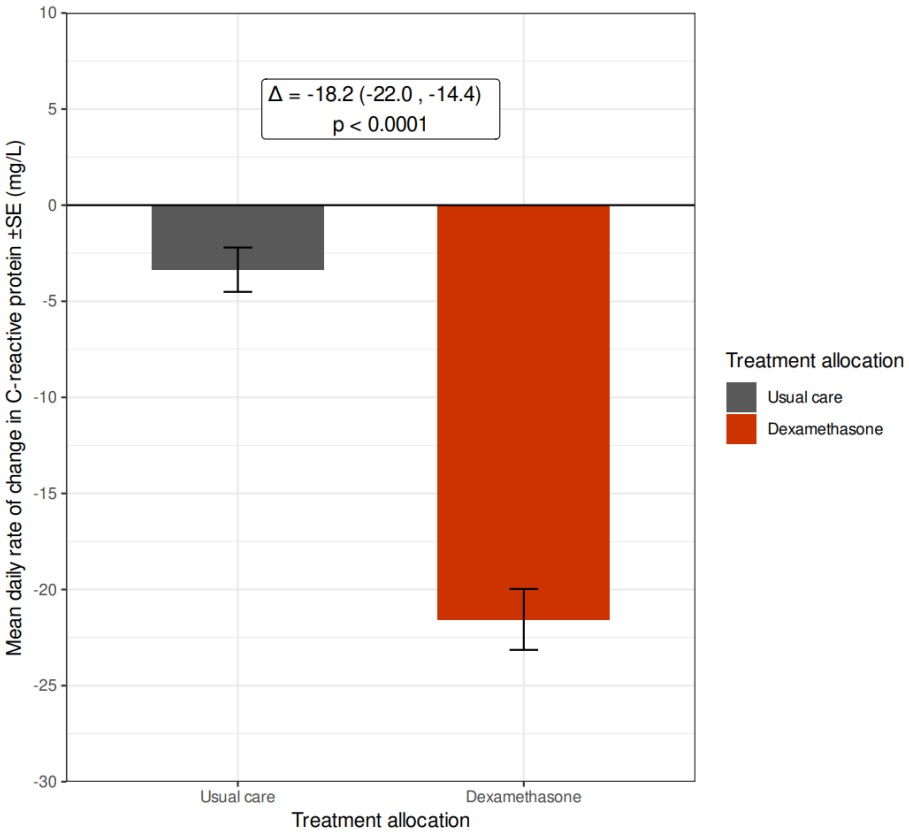


Figure 6-15: Daily rate of change in C-reactive protein within the first 7 days after randomisation, by treatment allocation in the RECOVERY-ISARIC dexamethasone comparison population.
SE = Standard Error

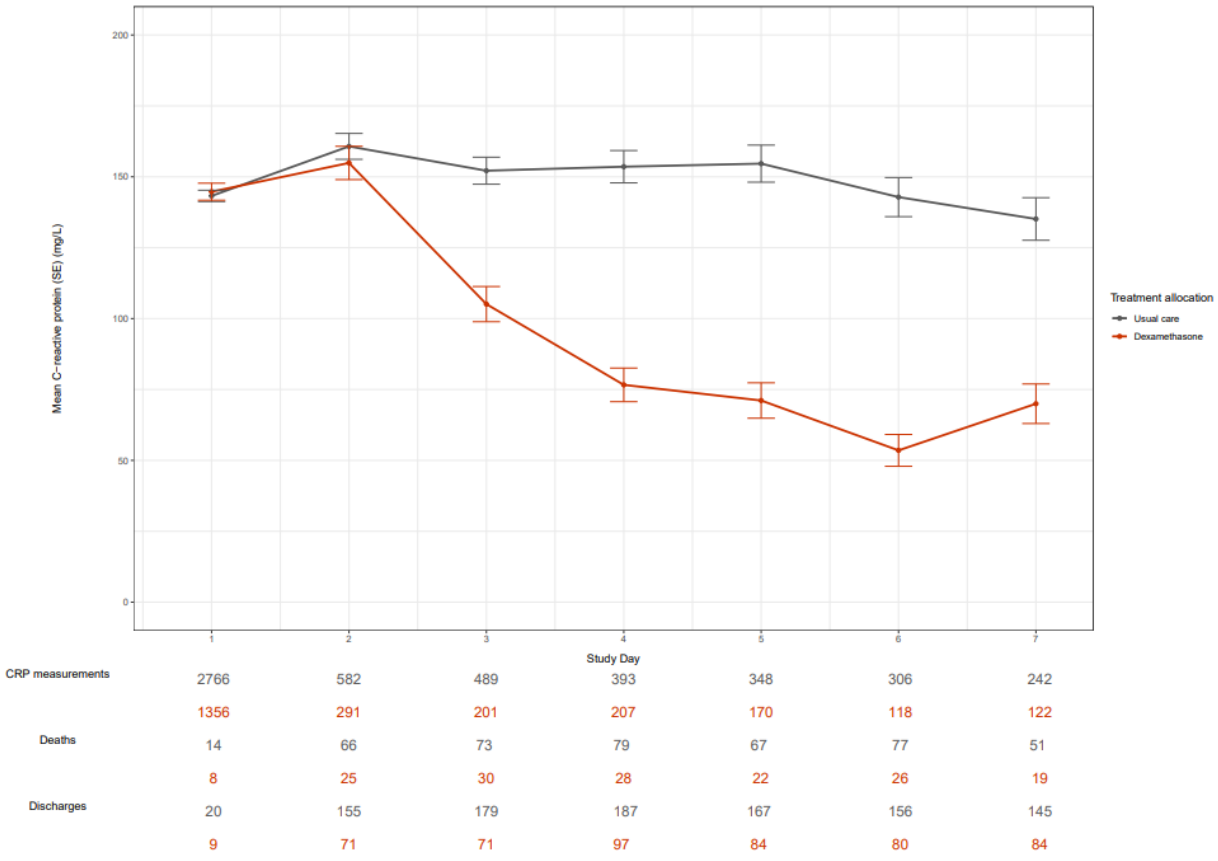


Figure 6-16: Mean C-reactive protein per study day according to randomised allocation for participants in the RECOVERY-ISARIC dexamethasone comparison population.
Points represent group mean (± Standard Error) for all participants with an available measurement on that study day.

The mean daily rate of change in glucose was significantly greater in those allocated dexamethasone (0.95 vs 0.22 mmol/L; difference in adjusted means, 0.73 mmol/L [95% CI 0.23, 1.23], p=0.005) (Table 6-10, Figure 6-17 and Figure 6-18). This corresponds to a dexamethasone treatment-related difference in glucose of approximately 5 mmol/L across the first 7 days after randomisation.

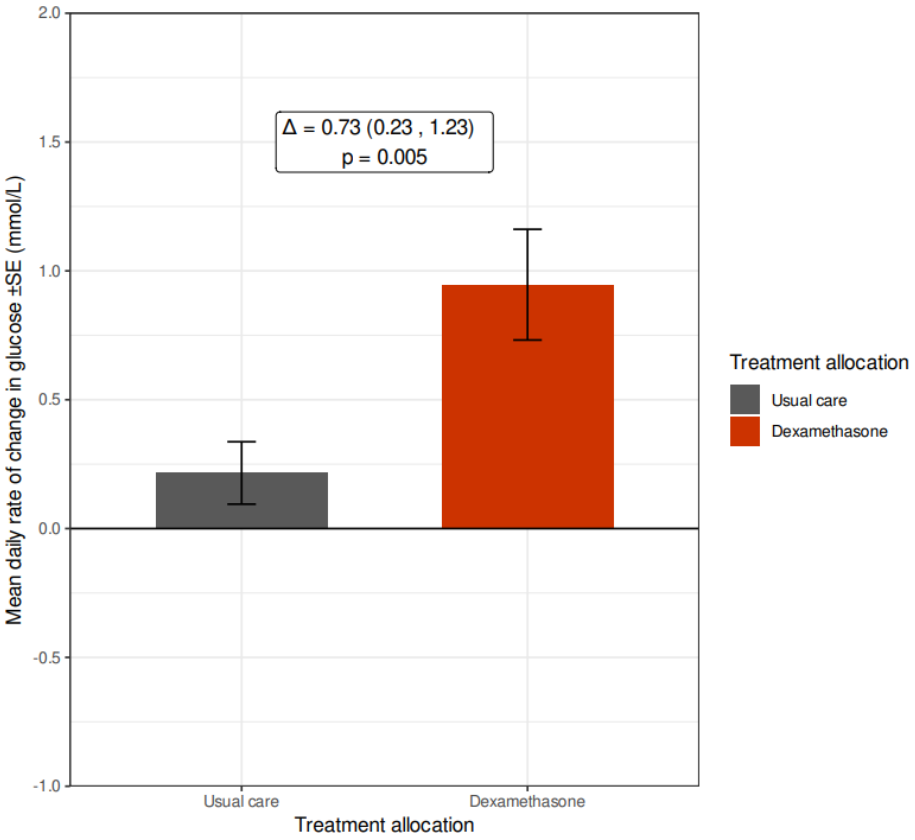


Figure 6-17: Daily rate of change in glucose within the first 7 days after randomisation, by treatment allocation in the RECOVERY-ISARIC dexamethasone comparison population. SE = Standard Error.



Figure 6-18: Mean glucose per study day according to randomised allocation for participants in the RECOVERY-ISARIC dexamethasone comparison population.
Points represent group mean (± Standard Error) for all participants with an available measurement on that study day.

The mean daily rate of change in neutrophil:lymphocyte ratio (NLR) was significantly greater in the dexamethasone treatment group (Table 6-10, Figure 6-19 and Figure 6-20). No differences between treatment groups were found in the daily rate of change in creatinine or ALT (Table 6-10).

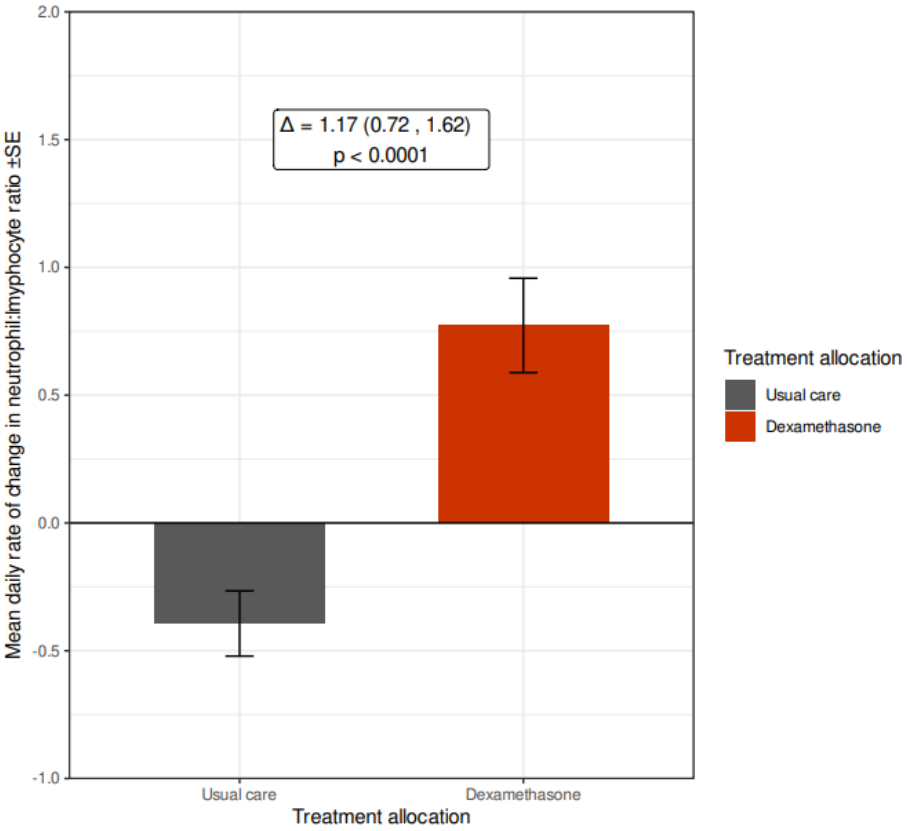


Figure 6-19: Daily rate of change in Neutrophil:lymphocyte ratio within the first 7 days after randomisation, by treatment allocation in the RECOVERY-ISARIC dexamethasone comparison population.
SE = Standard Error.

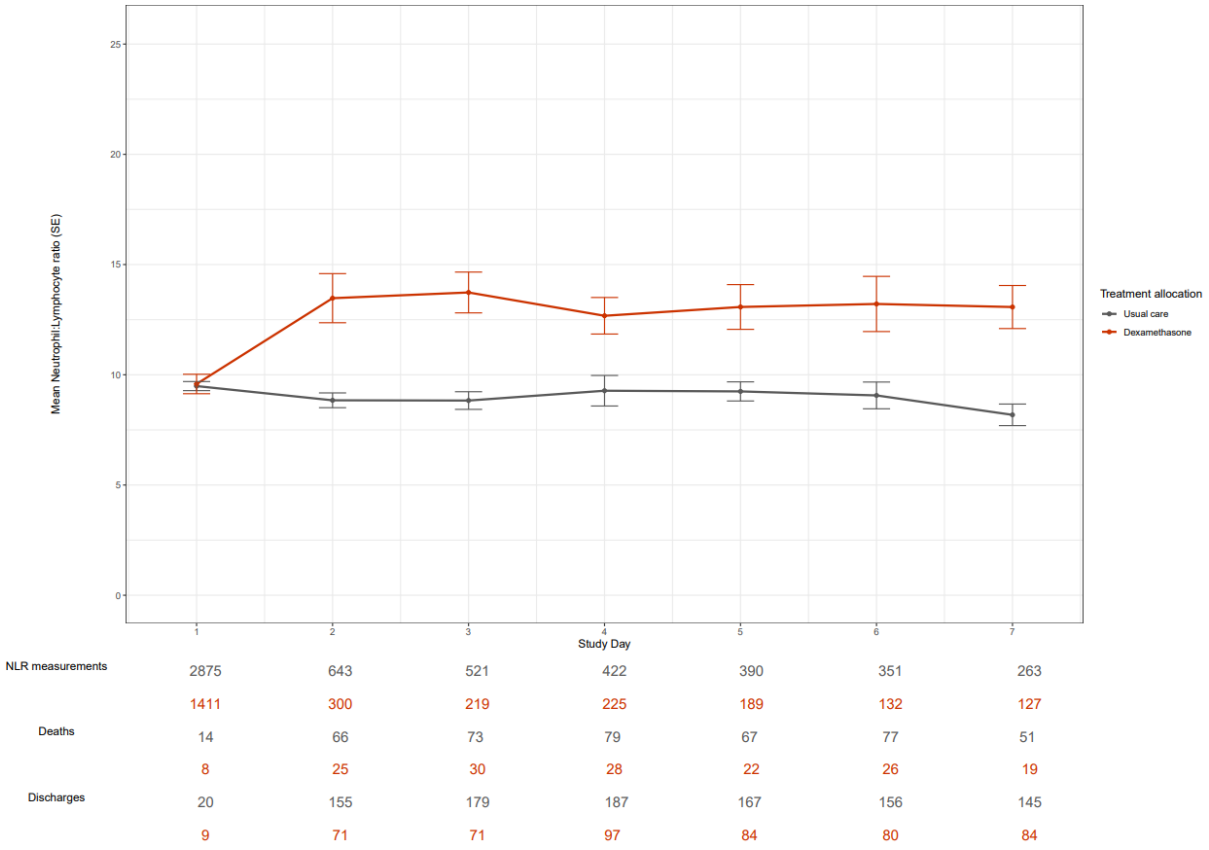


Figure 6-20: Mean Neutrophil:lymphocyte ratio per study day according to randomised allocation for participants in the RECOVERY-ISARIC dexamethasone comparison population.
Points represent group mean (± Standard Error) for all participants with an available measurement on that study day.

Sensitivity analyses varying the follow-up time and using complete case analysis displayed similar results to the main analysis (Supplementary Table 83).

6.4.3 Subgroup analyses of biological measurements

There was no evidence of heterogeneity of dexamethasone treatment effect according to subgroups of respiratory support or HFRS group on the daily rate of change in ordinal scale score, CRP, or glucose in the first 7 days after randomisation (Figure 6-21, Supplementary Figure 21, Supplementary Figure 22).

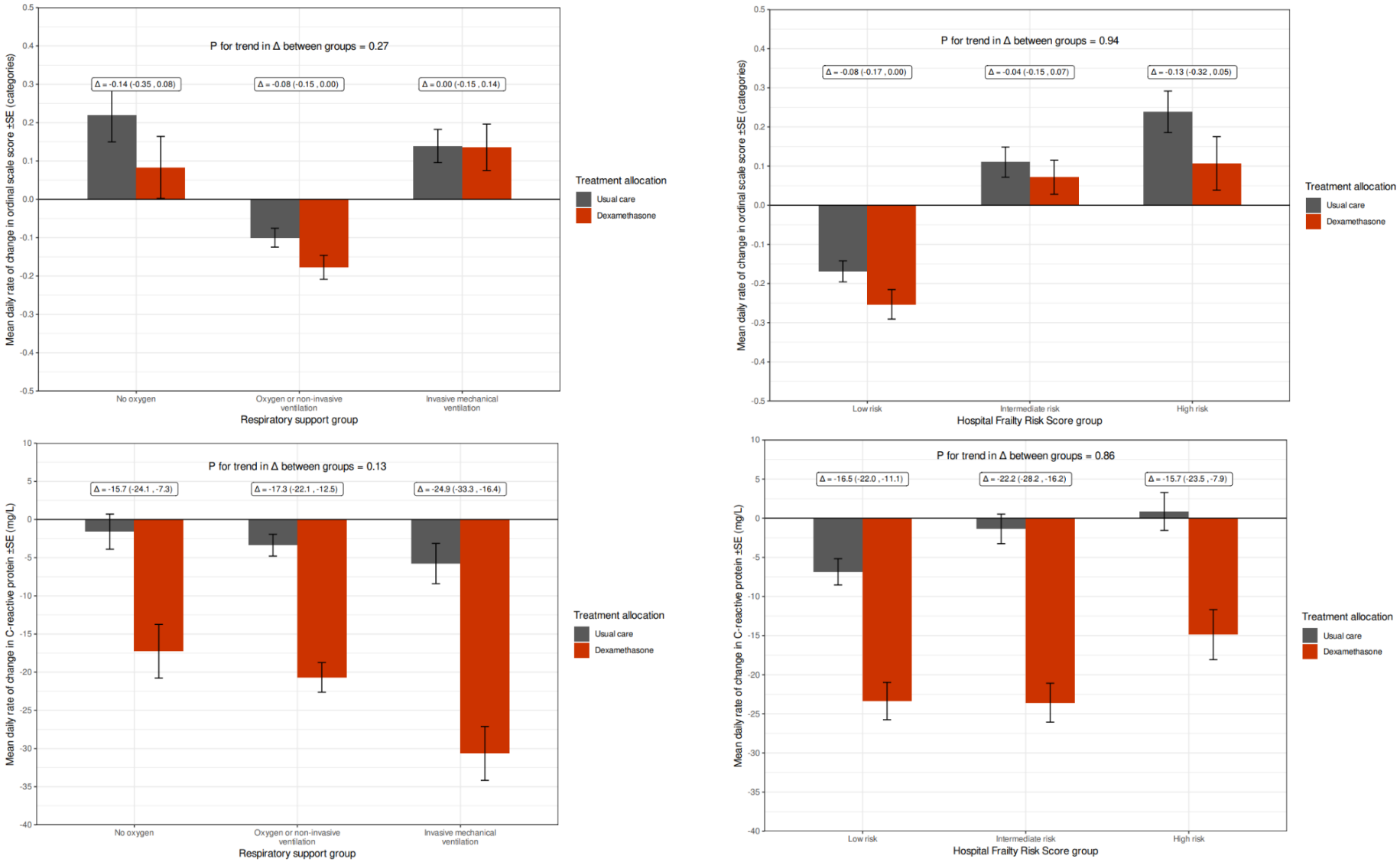


Figure 6-21: Subgroup analyses of daily rate of change in ordinal scale score and C-reactive protein within the first 7 days after randomisation in the RECOVERY-ISARIC dexamethasone comparison population.
Top left: Ordinal scale score by respiratory support group. Top right: Ordinal scale score by Hospital Frailty Risk Score group. Bottom left: C-reactive protein by respiratory support group. Bottom right: C-reactive protein by Hospital Frailty Risk Score group.

6.5 Randomised Comparisons of Gene Expression Data

6.5.1 Baseline characteristics

Gene expression data at day 3 after randomisation was available for 34 participants in the RECOVERY-ISARIC dexamethasone comparison. In this population, those randomised to dexamethasone were somewhat older and more likely to be female than those randomised to usual care, but were similar regarding baseline illness severity, co-morbidities, frailty, and 28-day clinical outcomes (Table 6-11).

Table 6-11: Baseline characteristics and outcomes by randomised allocation for participants in the RECOVERY-ISARIC dexamethasone comparison population with gene expression data available at day 3 of follow-up.

	Dexamethasone (N=8)	Usual Care (N=26)
Baseline characteristics		
Age Group		
Age <70	4 (50%)	19 (73%)
Age >=70 <80	2 (25%)	3 (12%)
Age >=80	2 (25%)	4 (15%)
Sex		
Female	6 (75%)	9 (35%)
Male	2 (25%)	17 (65%)
Respiratory support		
No oxygen or ventilation	3 (38%)	6 (23%)
Oxygen or non-invasive ventilation	4 (50%)	15 (58%)
Mechanical ventilation or ECMO	1 (13%)	5 (19%)
Any major comorbidity[1]	3 (38%)	9 (35%)
Hospital Frailty Risk Score		
Low risk (<5)	6 (75%)	21 (81%)
Intermediate risk (5-15)	1 (13%)	3 (12%)
High risk (>15)	1 (13%)	2 (8%)
Outcomes		
Died within 28 days	2 (25%)	6 (23%)
Discharged alive from hospital within 28 days	6 (75%)	16 (62%)
[1]Includes diabetes mellitus, heart disease, lung disease, tuberculosis, HIV, severe liver disease, severe kidney disease, severe mental illness or immunosuppression.		

6.5.2 Differential gene expression

6.5.2.1 Overview

There were 912 differentially expressed genes between the treatment groups in the dexamethasone treatment comparison population with gene expression data available at

day 3 after randomisation (Figure 6-22). 617 genes were upregulated with dexamethasone treatment and 295 genes were downregulated. The full list of differentially expressed genes (at an adjusted p-value threshold of <0.05 and log_2fold change of <-1 or >1), between treatment groups can be found in Supplementary Table 88.

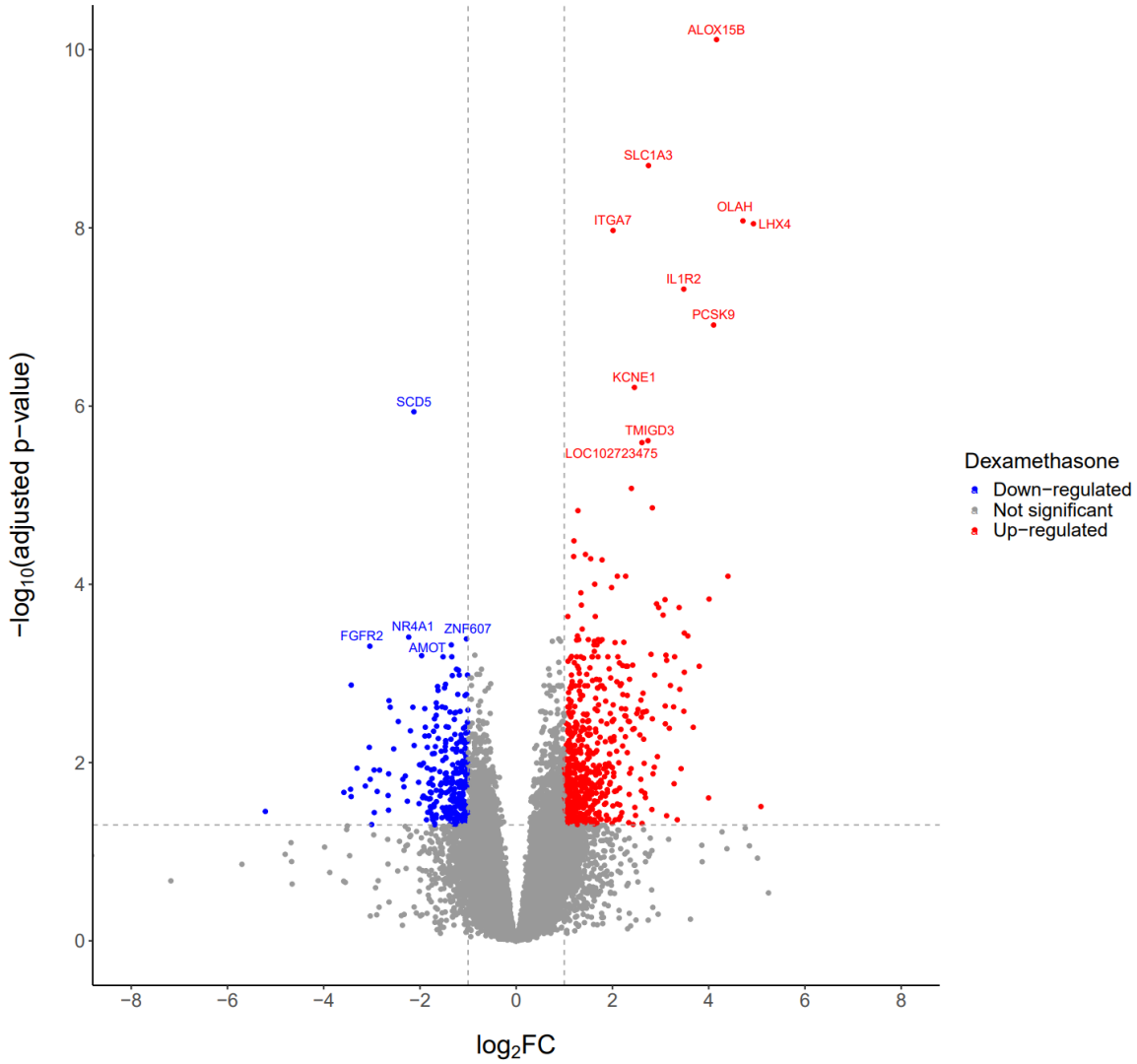


Figure 6-22: Volcano plot of differentially expressed genes at day 3 after randomisation according to dexamethasone treatment allocation.
Differential gene expression analysis models adjusted for age, sex and respiratory support group at randomisation.
Assessed in the 34 participants in the RECOVERY-ISARIC dexamethasone comparison population with gene expression data available at day 3 (±1 day) after randomisation.
log_2FC = log_2 Fold Change.

A heat map of these differentially expressed genes suggested some clustering of samples by randomised treatment allocation (Supplementary Figure 28).

6.5.2.2 Pathway enrichment analysis

Analysis Purpose: Determine the key biological processes over-represented in the differential gene expression analysis by randomised treatment allocation (see Section 3.5.4.2). Consider their relevance for understanding the effect of immunomodulatory treatment in COVID-19 and the implications for using this gene expression data in future research.

The planned pathway enrichment analysis using Gene Ontology Biological Processes reference data showed that the differentially expressed genes between dexamethasone and usual care were over-represented in some pathways of inflammatory and immune response, as well as general cell signalling (Figure 6-23). The full list of significantly over-represented Biological Processes, at an adjusted p-value threshold of <0.01, can be found in Supplementary Table 89.

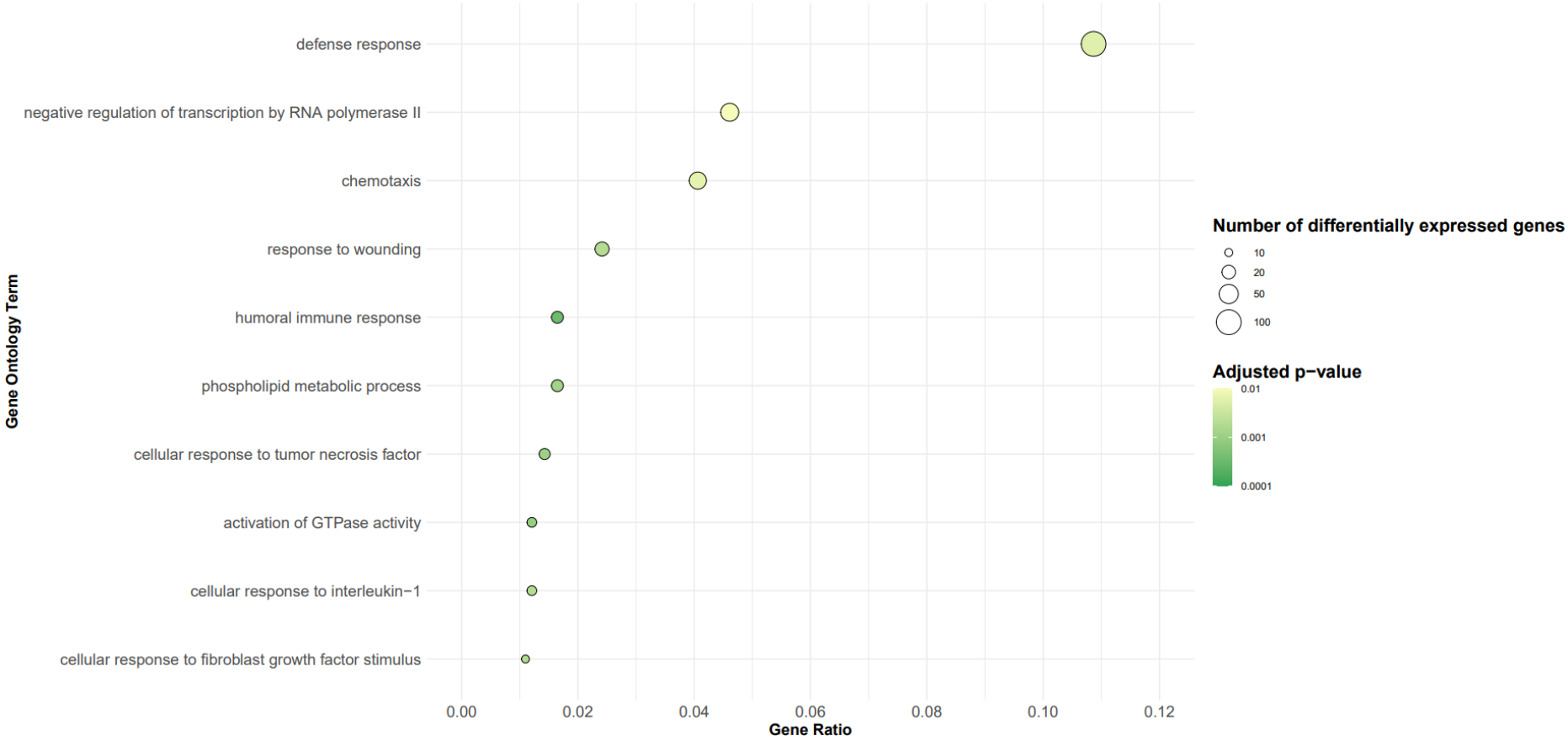


Figure 6-23: Top 10 differentially expressed Gene Ontology Biological Processes terms from pathway enrichment analysis of differentially expressed genes by dexamethasone randomised treatment allocation.
Gene ratio is calculated as the number of differentially expressed genes in the Biological Process term divided by the total number of differentially expressed genes.

6.5.2.3 Gene sets of interest

Analysis purpose: Assess whether randomised comparisons of the effect of dexamethasone on a priori identified gene sets could detect dexamethasone treatment effects in gene sets related to severe COVID-19 (see Section 3.5.4.2). Evaluate whether evidence of dexamethasone efficacy could be inferred from the effect on gene expression in genes putatively causally implicated in the development of severe COVID-19 (from Mendelian Randomisation and metaTWAS studies). Consider the implications for using this gene expression data in future research.

Expression of the positive control gene set of steroid treatment marker genes was significantly impacted by dexamethasone treatment, in the direction anticipated to be associated with corticosteroid treatment (Table 6-12).

Dexamethasone was not found to significantly alter the expression of genes identified in the primary assessment gene sets (those genes that were putatively causally related to the development of severe COVID-19).

There was a highly significant dexamethasone treatment effect on expression of genes identified from observational studies to be associated with increased COVID-19 severity. The direction of this effect was the opposite to that suggested to be non-causally associated with higher COVID-19 severity in the observational studies (potentially related to confounding in the identification of genes in those studies).

Table 6-12: Gene set enrichment analysis of dexamethasone treatment effect on gene sets of interest identified a priori.

Gene set	Number of genes	Normalised enrichment score*	Adjusted p-value
Positive control gene set			
Steroid treatment marker genes	51	2.00	<0.0001
Primary assessments			
Mendelian Randomisation candidate genes	25	0.95	0.52
metaTWAS candidate genes	269	-1.13	0.14
Exploratory assessments			
Disease severity genes A (COMBAT study)	820	1.81	<0.0001
Disease severity genes B (GEN-COVID study)	301	2.21	<0.0001
All genes	31819		

** Normalised enrichment score is computed from the highest (or lowest) running score for the ranked list of the gene set, normalised for the differences in the number of genes between gene sets. A positive enrichment score indicates genes were up-regulated in the dexamethasone group, whereas a negative enrichment score indicates genes were down-regulated in the dexamethasone group.*
metaTWAS = Transcriptome-wide association study with meta-analysis.

Chapter 7

Discussion

7.1 Chapter Summary

This chapter discusses the results from both the long-term follow-up (Chapter 5) and exploratory (Chapter 6) elements of the extended analysis. It contextualises the findings within the background literature and other components of the thesis, and considers implications for clinical practice and future research.

The chapter begins with an overview of the key results. It then takes each major aim of the thesis in turn and discusses how the aim has been addressed. In the interpretation of results, consideration is given to the following elements: biological plausibility; findings from other COVID-19 RCTs (Chapter 2) and other background literature where appropriate; the strengths and limitations of the analysis methods used (Chapter 3); the performance characteristics of the assessments derived from RCD (Chapter 4); and the potential implications for clinical practice and future research. The chapter then discusses the overarching strengths and limitations of the extended analysis, wider applications of the thesis work and potential future directions of research. The chapter and thesis is then closed through a Conclusions section, summarising the most important findings from the extended analysis.

7.2 Results Overview

7.2.1 Mortality

The immunomodulatory treatments of dexamethasone (at a standard dose of 6mg/day), tocilizumab and baricitinib all significantly reduced mortality in patients hospitalised with COVID-19 at 6-month follow-up and beyond. The previously known short-term mortality benefit of these treatments is maintained[29-31], supporting their ongoing use in clinical practice with increased certainty. The overall mortality benefits of immunomodulatory treatments clearly outweigh any potential risks within their current use in clinical practice.

Higher dose dexamethasone treatment (at an initial dose of 20 mg/day) in patients who are hypoxic but not requiring ventilatory support, increases all-cause mortality compared with usual care at 6-month follow-up - in line with conclusions of harm at short-term follow-up[44].

7.2.2 Other clinical benefits

Standard dose dexamethasone, tocilizumab and baricitinib significantly improved the rate at which participants were discharged alive from hospital at 6-month follow-up. By this time, almost all participants had died or been discharged from their initial hospital admission with COVID-19.

None of the immunomodulatory treatments demonstrated a beneficial impact on illness recovery. There were methodological caveats to these results (Section 7.3.3), but overall, the analyses found no evidence that immunomodulatory treatments improve illness recovery beyond the acute hospitalisation.

7.2.3 Non-COVID infection

No immunomodulatory treatment was definitively associated with an increased risk of non-COVID infection. Neither tocilizumab nor baricitinib showed any signal of a treatment-related risk in the primary outcome of major non-COVID infection nor in secondary or tertiary

outcomes or sensitivity analyses. The results for standard dose dexamethasone were still broadly reassuring; dexamethasone was not associated with a significant increased risk of non-COVID infection using the primary definition of major non-COVID infection. Findings were borderline for an increased risk in the secondary outcome of bloodstream infection and in some pre-specified exploratory and sensitivity analyses. A small excess infection risk was possible with standard dose dexamethasone, but treatment-related mortality benefits clearly outweighed this possibility overall. The interpretation of these findings is further discussed in Section 7.3.2.2.

7.2.4 Other potential treatment-related harms

Overall, any potential immunomodulatory treatment-related harms appeared small, even with systematic evaluation in each of the treatment comparisons.

Dexamethasone treatment was robustly associated with glycaemic complications, assessed through several different analysis approaches. This was further emphasised by the findings of increased risk of hyperglycaemia with higher dose dexamethasone. There was no evidence in these analyses that short-term dexamethasone treatment was associated with an adverse effect on GI complications, VTE, long bone or vertebral fractures, psychiatric complications, or long-term diabetes mellitus risk.

There was no evidence of a harmful effect of tocilizumab treatment on GI complications or liver injury. Neutropenia may have been more common with tocilizumab, but severe neutropenia appeared to occur very rarely. A possible signal of harm was observed in the subgroup of participants with immunosuppression who received tocilizumab, but the findings should be interpreted with caution – these results are discussed further in Section 7.3.1.2.

There was no evidence of a harmful effect of short-term baricitinib treatment on VTE, liver injury or neutropenia. An association with an increased rate of GI complications was possible (Section 7.3.2.5).

7.2.5 Heterogeneity of dexamethasone treatment effect

There was pre-existing evidence of heterogeneity of dexamethasone treatment effect according to respiratory support status at randomisation, with patients on higher levels of respiratory support experiencing greater treatment benefit and patients who did not require oxygen appearing unlikely to experience benefit from dexamethasone treatment. The extended analysis demonstrated that, even accounting for respiratory status, there was also evidence of heterogeneity of dexamethasone treatment effect according to patient frailty status. It is unclear if any subgroups of patients definitively experience harm from standard dose dexamethasone treatment, but an unfavourable risk-benefit balance was a possibility in patients not requiring oxygen support and with high frailty. It is likely that dexamethasone treatment confers some benefits and some harms, and the overall treatment effect may depend on a dynamic interplay between disease severity, drug dose and host vulnerability factors in individual patients.

7.2.6 Biological measurements

Exploratory analyses have provided unique, reliable data from a large, randomised comparison of the effect of the immunomodulatory treatments on biological measurements in COVID-19, with the potential to inform future research.

At short-term follow-up, participants treated with dexamethasone showed differential expression of genes involved in pathways of inflammatory and immune response and non-causally linked to severe COVID-19. Dexamethasone treatment-related gene expression changes were not demonstrated in gene sets thought causally related to the development of severe COVID-19. The interpretation of these findings is discussed in Section 7.3.5.

7.3 Application of Findings to Thesis Aims

This section evaluates the extended analysis findings directly against the stated thesis aims (Section 1.4), considering the interpretation and impact of the results in the context of other research; the thesis systematic review and meta-analysis (Chapter 2); and the thesis method development (Chapter 4). Thesis aim i) ('Provide an evaluation of the quality and quantity of current evidence relating to the efficacy and safety of the immunomodulatory treatments for hospitalised patients with COVID-19, through a systematic review and meta-analysis') is discussed in Chapter 2. The remaining five aims are discussed here.

7.3.1 Efficacy of immunomodulatory treatments at long-term follow-up

Thesis aim ii): Evaluate the efficacy of the RECOVERY immunomodulatory treatments at long-term follow-up.

7.3.1.1 Overview

The extended analysis results contribute valuable data that improves the certainty of evidence of the effect of corticosteroids, IL-6 RAs and JAKIs on longer-term efficacy, including mortality, for hospitalised patients with COVID-19. The known short-term mortality benefit of each of these treatments is sustained during long-term follow-up. Healthcare professionals can continue to use these immunomodulatory treatments for COVID-19 with greater confidence, benefitting patients.

In many cases, the contribution of the size of additional information from the extended analysis is large compared to the existing evidence from other COVID-19 RCTs. Compared with the totality of evidence found in the thesis systematic review and meta-analysis, longer-term (≥60 days) mortality event numbers are increased by more than 3-fold for corticosteroids, more than 2-fold for IL-6 RAs, and more than 5-fold for JAKIs.

The all-cause mortality outcome is objective and resistant to bias. Data is comprehensively collected from the RECOVERY trial follow-up CRFs and multiple supporting RCD datasets,

with high levels of data completeness. Recorded deaths are highly likely to be accurate and very few deaths should have been missed or incorrectly reported.

The extended analysis also included an evaluation of diagnoses leading to death, incorporating those recorded in part 1 of the death certificate. This showed a benefit of each immunomodulatory treatment on COVID-19 specific mortality and no clear effect on any other categorised causes of death, further supporting evidence of efficacy for COVID-19.

7.3.1.2 Treatment effect estimates on mortality

The magnitude of mortality benefits observed in the extended analysis were similar to RECOVERY 28-day follow-up and estimates from the meta-analyses of RCTs from Chapter 2 (Table 7-1). The compounded mortality benefit across all three beneficial immunomodulatory treatments in hypoxic patients in current clinical use is roughly a one third reduction in mortality at 6-month follow-up.

Table 7-1: Summary of immunomodulatory mortality treatment effect estimates from the extended analysis, RECOVERY 28-day follow-up and thesis meta-analyses.

Treatment	RECOVERY at 6 months RR (95% CI)	RECOVERY at 28 days RR (95% CI)	Meta-analysis at 90 days* RR (95% CI)	Meta-analysis at 28 days† RR (95% CI)
Standard dose dexamethasone	0.87 (0.79 – 0.96)	0.82 (0.73 – 0.91)	0.96 (0.71 – 1.29)	0.82 (0.74 – 0.90)
Tocilizumab	0.87 (0.79 – 0.96)	0.88 (0.79 – 0.98)	0.83 (0.71 – 0.98)	0.88 (0.81 – 0.96)
Baricitinib	0.88 (0.79 – 0.98)	0.85 (0.76 – 0.96)	0.74 (0.58 – 0.94)	0.79 (0.71 – 0.88)
Higher dose dexamethasone	1.35 (1.05 – 1.73)	1.62 (1.22 – 2.16)	0.95 (0.80 – 1.14)	0.99 (0.86 – 1.15)

**As presented in Chapter 2, does not include RECOVERY long-term follow-up.*
†As presented in Chapter 2, includes RECOVERY 28-day follow-up.

i) Dexamethasone

Standard dose dexamethasone reduced mortality by an estimated 13% compared with usual care at 6-month follow-up across all participants. A larger magnitude treatment benefit was

seen in participants requiring mechanical ventilation at randomisation – an estimated 31% proportional reduction in mortality.

Combining the extended analysis results with pre-existing evidence increases the certainty of evidence in the long-term follow-up benefits of corticosteroid treatment, by improving precision and reducing bias relating to missing outcome data (Figure 7-1, High certainty of evidence). The updated meta-analysis results are dominated by RECOVERY, with fewer than 300 death events from other trials contributing to the treatment effect estimate. Many other COVID-19 corticosteroid RCTs were stopped upon announcement of the RECOVERY dexamethasone results, as it was felt no longer justifiable to continue to randomise patients due to loss of clinical equipoise[91,101].

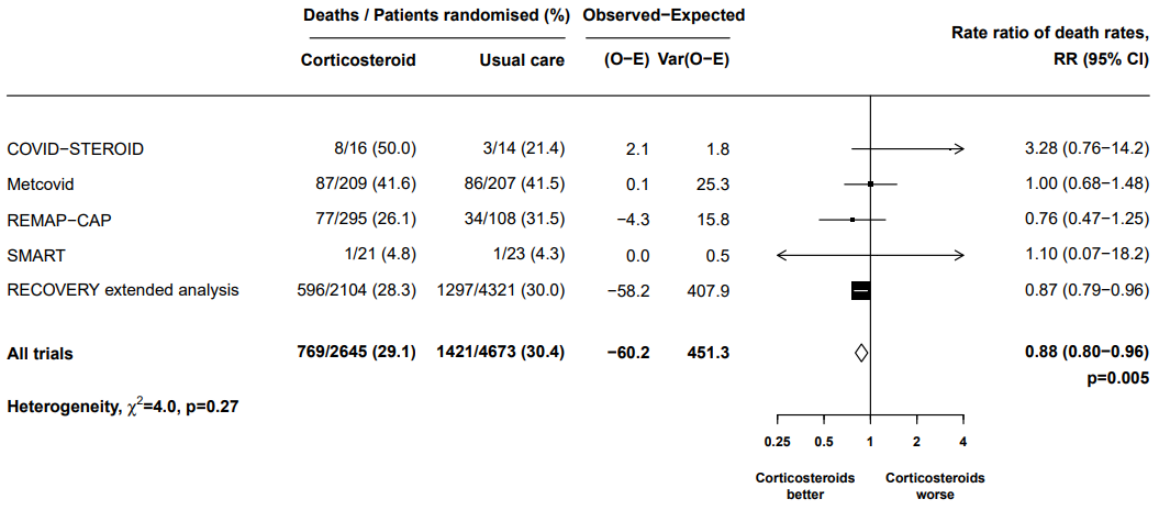


Figure 7-1: Meta-analysis of longer-term all-cause mortality in randomised controlled trials of systemic corticosteroids compared with no corticosteroids in hospitalised patients with COVID-19, updated to include results of the extended analysis.
Includes eligible RCTs with mortality data from 60 days to 6 months follow-up.

Compared with 28-day all-cause mortality, the proportional dexamethasone treatment effect estimate is slightly closer to 1 (Table 7-1). This is conceptualised to relate to the benefit of dexamethasone treatment being seen predominantly during early follow-up. This is then followed by a long-term follow-up period where the treatment confers neither benefit nor harm and the mortality difference between treatment groups in the later period is simply due

to chance. In this situation, the proportional risk benefit wanes slightly over time (due to the dilutional impact of later events not affected by treatment), bringing the treatment effect estimate slightly back towards 1. The relatively high rate of mortality in the long-term follow-up in the dexamethasone treatment comparison after 28 days compared with the other treatment comparisons suggests the dexamethasone comparison population had high baseline mortality risk, potentially due to recruitment during the first 'wave' of the pandemic in the UK during which older patients were particularly severely affected[382].

Clinical practice guidelines recommend giving standard dose corticosteroid treatment for patients requiring oxygen or ventilatory support, but not in those who do not require oxygen[25,26]. The heterogeneity in treatment effect according to respiratory support at randomisation that was demonstrated in the original 28-day RECOVERY follow-up[29], remains present at 6-month follow-up. Treatment benefits in subgroups of patients on invasive mechanical ventilation are larger than the overall treatment effect estimate; while patients not requiring oxygen at randomisation remain unlikely to derive benefit from dexamethasone treatment and may experience harm. Contributing factors to the heterogeneity of corticosteroid treatment effects are discussed further in Section 7.3.4.

ii) Tocilizumab

In the tocilizumab comparison, tocilizumab was associated with an estimated 13% proportional reduction in mortality at 6-month follow-up. The magnitude of treatment benefit was similar to the result at 28-day follow-up and that found in the meta-analyses (Table 7-1).

The extended analysis adds just over double the intervention group event numbers to the existing meta-analysis evidence regarding longer-term mortality, reducing bias relating to missing outcome data (Figure 7-2, High certainty of evidence).

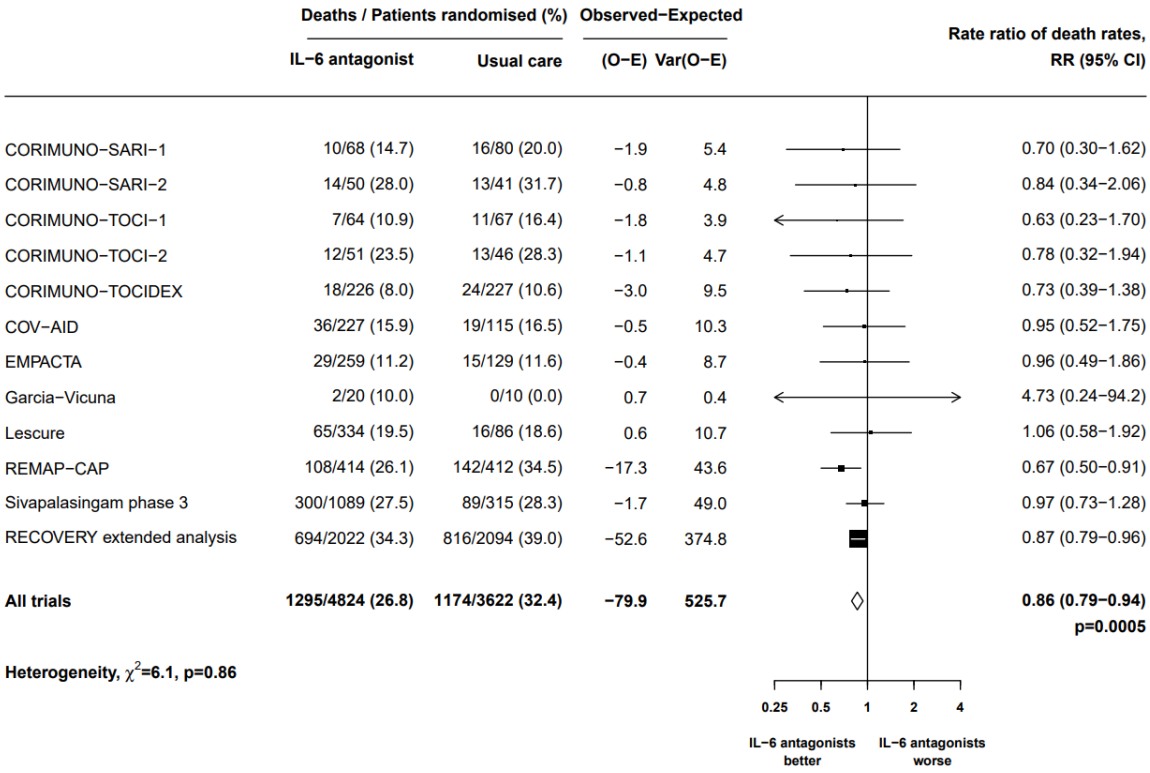


Figure 7-2: Meta-analysis of longer-term all-cause mortality in randomised controlled trials of interleukin-6 receptor antagonists compared with usual care/placebo in hospitalised patients with COVID-19, updated to include results of the extended analysis.
Includes eligible RCTs with mortality data from 60 days to 6 months follow-up.

Within the mortality subgroup analyses, there was a possibility of heterogeneity of treatment effect according to baseline immunosuppression status, with those who were immunosuppressed appearing to have higher mortality with tocilizumab compared with usual care (Section 5.4.6). Vigilance for complications (such as infections) in immunosuppressed patients receiving tocilizumab should be particularly high. However, certainty in this subgroup result is very low, and the findings should not drive changes in COVID-19 treatment at this time.

The immunosuppression subgroup analysis in this study was not pre-specified and was part of several simultaneous subgroup analyses, increasing the chance of a type 1 error (false positive). The overall number of deaths in this subgroup was small (77 deaths in the tocilizumab group in those with immunosuppression), increasing the propensity for random

error. The extended analysis found no evidence of heterogeneity in mortality treatment effect according to related subgroups of baseline non-COVID infection risk and no evidence that tocilizumab increased the risk of non-COVID infections in the overall population. The tocilizumab immunosuppression subgroup analysis of major non-COVID infection lacked statistical power and was not confirmatory of a hazard mediated via this mechanism, especially in the context of a null overall result for infection risk with tocilizumab. Over-interpretation of a trial subgroup analysis, may result in patients who should benefit from treatment being inappropriately excluded[383]. Subgroup analyses that give qualitatively different treatment effects (i.e. the direction of effect is reversed) in small subgroups are generally clinically implausible and subject to random error[77,384].

A published meta-analysis of randomised trials of immunomodulators in immunocompromised patients hospitalised with COVID-19 did not suggest any evidence of harm in this population, including on mortality, secondary infection, and within a subgroup analysis of IL-6 RA trials only[385]. However, power was limited as only 32 deaths occurred in immunocompromised participants in IL-6 RA trials. Many other larger IL-6 RA trials excluded immunosuppressed patients[105,106,108].

The baseline immunosuppression variable was derived from RCD with some thesis method development validation. It appeared to have good diagnostic performance compared to a reference standard of RECOVERY or ISARIC4C CRF immunosuppression status but is still likely to be imperfect compared to a ‘gold-standard’ data collection.

iii) Baricitinib

Baricitinib was associated with an estimated 12% proportional reduction in mortality at 6-month follow-up, similar to the estimated 15% observed at 28 days.

The extended analysis mortality data enhances the evidence of the overall benefit of baricitinib therapy at long-term follow-up, improving precision in the treatment effect estimate and reducing bias relating to missing outcome data (Figure 7-3, Moderate certainty of

evidence). Some of the published smaller trials of JAKIs may be subject to publication bias favouring dissemination of results demonstrating treatment benefit in small trials[386].

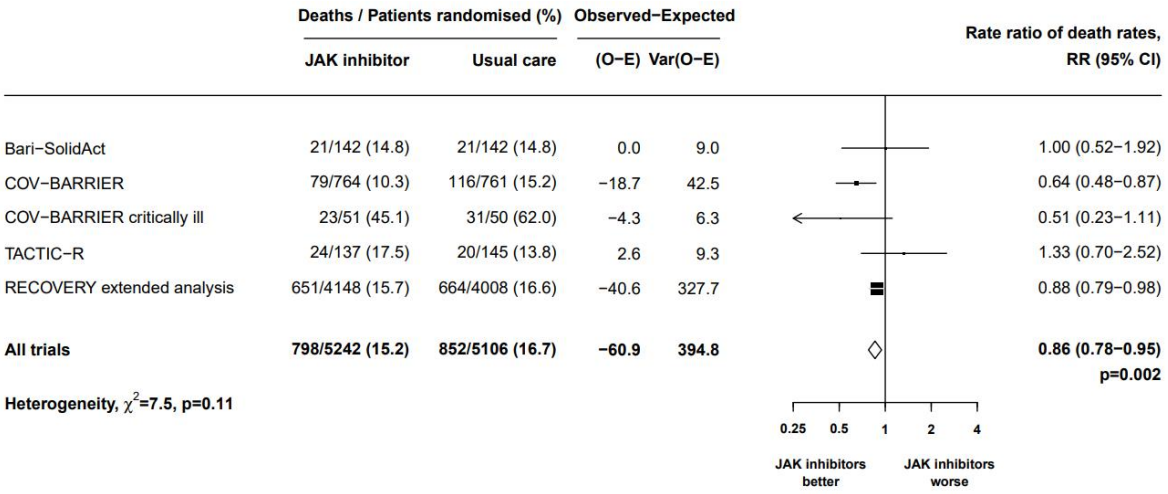


Figure 7-3: Meta-analysis of longer-term all-cause mortality in randomised controlled trials of Janus kinase inhibitors compared with usual care/placebo in hospitalised patients with COVID-19, updated to include results of the extended analysis.
Includes eligible RCTs with mortality data from 60 days to 6 months follow-up.

There was no evidence of significant heterogeneity in any subgroup evaluated for mortality in the baricitinib comparison.

iv) Higher dose dexamethasone

Higher dose dexamethasone increased mortality by approximately one third at 6-month follow-up in the subgroup of participants who were hypoxic but not requiring ventilation at randomisation. The estimated magnitude of harm at 6-month follow-up was smaller compared with 28 days, likely representing an over-estimate of treatment effect in a trial stopped early due to the observed hazard[44,387]. Higher dose dexamethasone should not be used in this population. Effects in patients requiring ventilation remain uncertain. The results of the RECOVERY evaluation in patients on ventilatory support at randomisation in RECOVERY are anticipated soon - recruitment to this comparison was stopped on 31 March 2024. However, there were only 477 participants in this comparison of whom 172 had died, meaning that its statistical power is limited.

7.3.1.3 Other assessments of efficacy

i) Discharge alive from hospital

At 28-day follow-up, 13% of participants in the dexamethasone comparison, 15% in the tocilizumab comparison and 8% in the baricitinib comparison, had neither died nor been discharged from hospital - leaving their outcome uncertain, and belonging to a group at high risk of death. By extending follow-up to 6 months this number reduces to <2% in all three treatment comparisons; giving a definitive outcome for almost all participants from their initial hospital admission with COVID-19.

The probability of being discharged alive from hospital within 6 months was improved with each of the three main immunomodulatory treatments, with high levels of certainty in the results. The magnitude of benefit was similar to that observed at 28 days in RECOVERY and in the thesis meta-analysis estimates from other RCTs, where this outcome was recorded.

ii) Renal outcomes

A reduced incidence of renal replacement therapy with dexamethasone treatment was observed in the RECOVERY 28-day follow-up[29]. In the extended analysis, standard dose dexamethasone appeared to reduce the incidence of biochemically-defined AKI (an increase in creatinine of ≥1.5 times from a participant's baseline value). The plausibility of this result is supported by the renal replacement therapy findings and suggests an overall treatment benefit of dexamethasone on short-term renal complications. This could relate to a direct renal effect of corticosteroid therapy[388], or from simply improving the severity of COVID-19, reducing end-organ complications associated with deteriorating physiology and critical illness.

7.3.2 Safety of immunomodulatory treatments

Thesis aim iii) Evaluate the safety of the RECOVERY immunomodulatory treatments at short-term and long-term follow-up.

7.3.2.1 Overview

The extended analysis has contributed vital data to the short- and long-term safety assessment of dexamethasone, tocilizumab and baricitinib in hospitalised patients with COVID-19. Pre-existing evidence was scant for many potential treatment-related harms in COVID-19 RCTs. Overall, the results from the extended analysis are reassuring. Any harms attributable to immunomodulatory treatments appeared small, even with systematic evaluation. It is clear the overall benefits of immunomodulatory treatment far outweigh any possible harms within their current use. Mitigation of plausible treatment-related harms should be targeted through vigilance and timely treatment for complications, rather than withholding immunomodulatory treatment.

Dexamethasone has the potential to cause harm if used in the wrong patient population. Higher dose dexamethasone increases mortality in patients not on ventilation. Hyperglycaemia and non-COVID pneumonia were demonstrable harms at short-term follow-up in this treatment comparison[44], although the overall hazard is likely to be multifactorial. Standard dose dexamethasone may cause harm in patients not requiring oxygen or with a high-risk frailty status. There is strong evidence that standard dose dexamethasone also increases the risk of hyperglycaemia compared with usual care – this analysis helps to quantify the risk and set it in the context of other potential treatment-related harms. Standard dose dexamethasone probably does not substantially increase the risk of non-COVID infection, but findings were not definitive. A small magnitude proportional risk increase remains plausible.

The safety profiles of tocilizumab and baricitinib were very reassuring overall. There was very weak evidence for a possible hazard in a subgroup analysis of immunosuppression in the tocilizumab comparison (discussed in Section 7.3.1.2), and for GI complications in patients receiving baricitinib (discussed in Section 7.3.2.5). The quality of evidence at this time precludes certainty in these findings but they may merit further evaluation in meta-

analysis in other COVID-19 trials, or in future randomised trials of these agents for any short-term indication. Tocilizumab and baricitinib are known to be associated with infections and GI complications with long-term use[45,46,389,390].

7.3.2.2 Non-COVID infection

Severely ill patients with COVID-19 are at high risk of other infective complications, which are associated with poor outcomes, including mortality[48,49]. Secondary infection risk could conceivably be exacerbated by immunomodulatory therapies resulting in reduced host immune defences. However, it is also feasible that optimising COVID-19 treatment could reduce the risk of secondary infections by reducing durations of invasive mechanical ventilation or hospitalisation and associated infection risks[391].

In this study, the association of immunomodulatory therapies with non-COVID infection was systematically evaluated using several different approaches – including defining the infections by seriousness, the presence or absence of laboratory diagnostic confirmation, and by putative organism. Most results were reassuring with regard to secondary infection risks from short-term COVID-19 immunomodulatory treatment, including no signals of infection risk with tocilizumab or baricitinib treatment. Combination immunomodulatory therapy with the addition of baricitinib to corticosteroids alone, or corticosteroids and IL-6 RAs, did not appear to confer any additional infection risk. The results for dexamethasone were more nuanced and the association with non-COVID infection displayed some uncertainties, which are explored further in the following section.

i) Dexamethasone

In the primary safety outcome of major non–COVID infection, there was no significant association between dexamethasone treatment and infection risk (RR 1.08 [95% CI 0.97 – 1.21], at 6 months). The lower bound of the 95% CI was close to 1 in this analysis, but the magnitude of any possible increased risk would appear small. The primary infection outcome

had 80% power to detect a risk increase of 21% in this outcome at 28 days and a risk increase of 16% at 6 months at a two-sided p-value threshold of 0.05 (Section 3.6.8).

Sensitivity analyses of the major non-COVID infection outcome suggested the treatment effect size estimate was quite stable with slight modifications in line with the anticipated effect of the sensitivity analyses. The point estimate for the 6-month follow-up slightly increased from 1.08 to 1.10 when only primary diagnostic position diagnoses were used (increased specificity). The treatment effect estimate slightly decreased from 1.08 to 1.05 at 6-month follow-up when peri-randomisation episode diagnoses were included (increased sensitivity).

In the secondary non-COVID infection outcomes, the effect of dexamethasone on bloodstream infection (BSI) was at the threshold for nominal statistical significance (p=0.05) and carries associated uncertainty. Type 1 error in this result is possible– no formal adjustment was made in the analyses for multiplicity of comparisons, and a significant finding at the 5% threshold in 1 of 7 secondary outcomes would be expected to occur in 30% of cases by chance alone. Any increased risk of infection occurs in the context of a clear overall mortality benefit of dexamethasone treatment. However, increasing awareness of risk could facilitate clinician awareness and optimal patient monitoring.

In the wider literature, secondary infection appears to be most common in critically ill patients with COVID-19[392]. Age and frailty are thought to be independent risk factors for hospitalisation for infection and associated poor clinical outcomes[393-395]. In the extended analysis subgroup analyses of the primary infection outcome, there was a possibility that participants who were older had an increased risk of infection relating to dexamethasone, but results were not definitive due to the overall null result in the primary outcome and the low event numbers precluding meaningful subgroup analysis in other related outcomes. Interestingly, there was no definitive evidence that frailty status, respiratory support group or baseline non-COVID infection risk group affected treatment-related risk of infection. Point

estimates for frailty and respiratory support were compatible with increased risk in subgroups with less treatment benefit (High frailty risk and 'No oxygen' subgroups) but did not show statistically significant heterogeneity. No other randomised trials could be found that evaluated the risk of non-COVID infection by relevant subgroups.

Validation and method development of the main infection outcomes suggest they should be reasonably resistant to bias in a randomised trial setting. The primary infection outcome had an estimated specificity of 0.956 when compared with RECOVERY CRF data, and 0.949 when compared with ISARIC4C CRF data. 91% of cases in a sample of the RECOVERY population were confirmed on manual medical record review. 80% of a sample of RECOVERY participants with the primary infection outcome present had a systemic anti-infective agent being administered at the time the diagnosis code was recorded – over twice the background proportion receiving anti-infectives. Diagnostic code-derived infection events had an estimated specificity of 0.968 from the wider literature review.

The BSI outcome represents an objective laboratory-confirmed diagnosis from a sterile body site and should not be subject to major bias in outcome ascertainment. Data quality monitoring from Public Health England suggested 94% of major BSIs are captured via this reporting route[193]. In method development for the extended analysis, BSI events had a high estimated specificity (0.987) and 95% of patients received systemic antimicrobials within 3 days of specimen collection, suggesting the events are likely to be "true" serious infections. In the remaining infection outcomes, all treatment effect point estimates were >1 but none reached the specified threshold of statistical significance.

An infection risk with dexamethasone is biologically plausible and consistent with some previous randomised evidence. Corticosteroids exert an immunosuppressive effect by acting on immune system cells, including reducing macrophage and T-cell activation, and inhibiting pro-inflammatory cytokines[396]. The largest published meta-analysis of 71 corticosteroid RCTs (for any indication), estimated a 60% proportional risk increase in infection with

corticosteroids compared with controls over a median of 21 days follow-up[397]. Risk appeared related to duration of exposure and steroid dose. In other acute severe diseases, such as acute respiratory distress syndrome, pneumonia, septic shock and traumatic brain injury, meta-analyses of RCTs of short-term corticosteroids have not demonstrated an increased secondary infection risk but with limited statistical power to exclude small magnitude, but still clinically important, effects[398-400]. Point estimates of treatment effect were typically of similar magnitude to those observed in the extended analysis. For example, a meta-analysis of RCTs of short-term corticosteroids for pneumonia reported an RR 1.19 [95% CI 0.73 – 1.93] for secondary infections in adults[171]. Combining the data from the extended analysis and other corticosteroid COVID-19 RCTs suggested corticosteroids were overall unlikely to be associated with an important secondary infection risk at short-term follow-up (Figure 7-4).

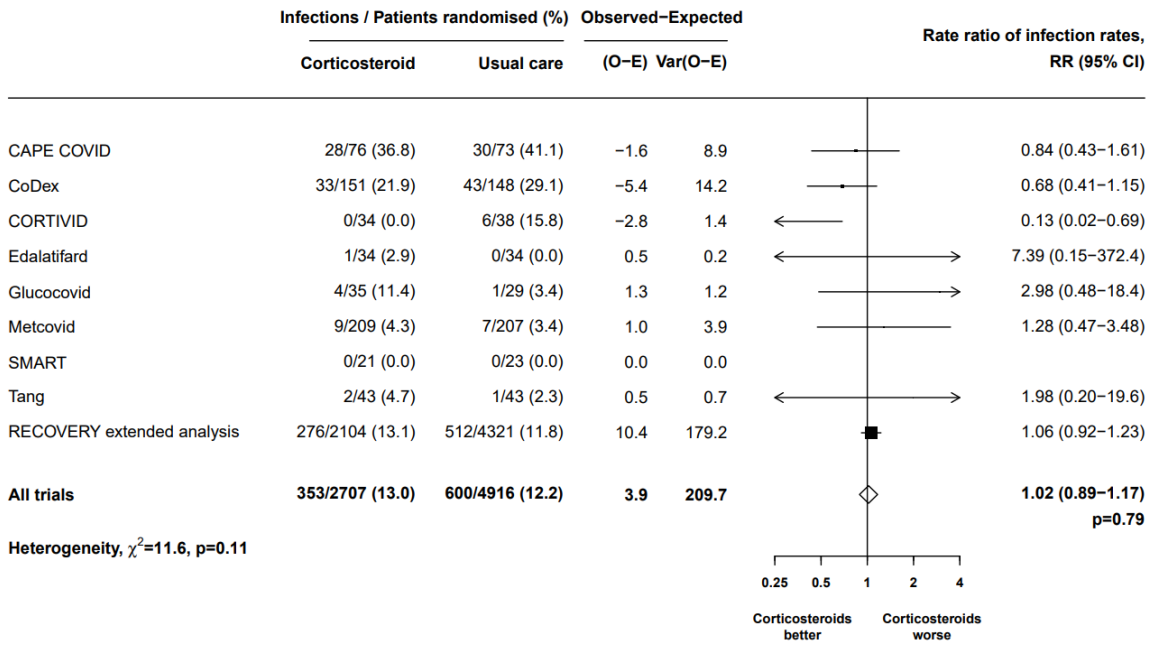


Figure 7-4: Meta-analysis of secondary infection within 28 days in randomised controlled trials of systemic corticosteroids compared with no corticosteroids in hospitalised patients with COVID-19, updated to include results of the extended analysis.

Findings were similar in the completed subgroup of the RECOVERY higher dose dexamethasone comparison. Higher dose dexamethasone treatment did not significantly affect the occurrence of overall major non-COVID infection compared to usual care in the

primary infection outcome (RR 1.17 [95% CI 0.91 – 1.51], at 28 days), although a small excess of non-COVID pneumonia at 28-day follow-up was reported from CRF data alone[44]. Again, all treatment effect estimates were >1 in primary and secondary non-COVID infection outcomes but conclusions were limited by statistical power.

Overall, it is possible there is no meaningful increased risk of non-COVID infection with dexamethasone treatment or that there is a small increased proportional risk, but findings are not definitive. If any risk is present, the magnitude is likely to be in the region of 10-15%, based on the assimilation of this study's outcomes and evidence from other trials. Standard dose dexamethasone reduces long-term mortality for patients hospitalised with COVID-19 and treatment benefits outweigh any possible non-COVID infection hazards.

ii) Tocilizumab

In the tocilizumab comparison, randomisation to tocilizumab was not associated with an increased risk of non-COVID infection in any evaluated outcome, compared with usual care. The upper bound of the 95% CI for the primary major non-COVID infection outcome was 1.06, suggesting even a moderate risk increase with treatment was improbable.

Non-COVID infection outcome results were consistent with the pre-existing data found in the systematic review. Incorporating the extended analysis non-COVID infection follow-up data increases intervention group event numbers by around 50% at short-term follow-up, further increasing confidence in this result. The updated meta-analysis for non-COVID infection within 28 days is now able to effectively exclude any increased risk of infection at short-term follow-up (Figure 7-5, High certainty of evidence). In totality, 90% of all participants randomised in IL-6 RA RCTs have now been evaluated in an assessment of secondary infection with no suggestion of a risk increase.

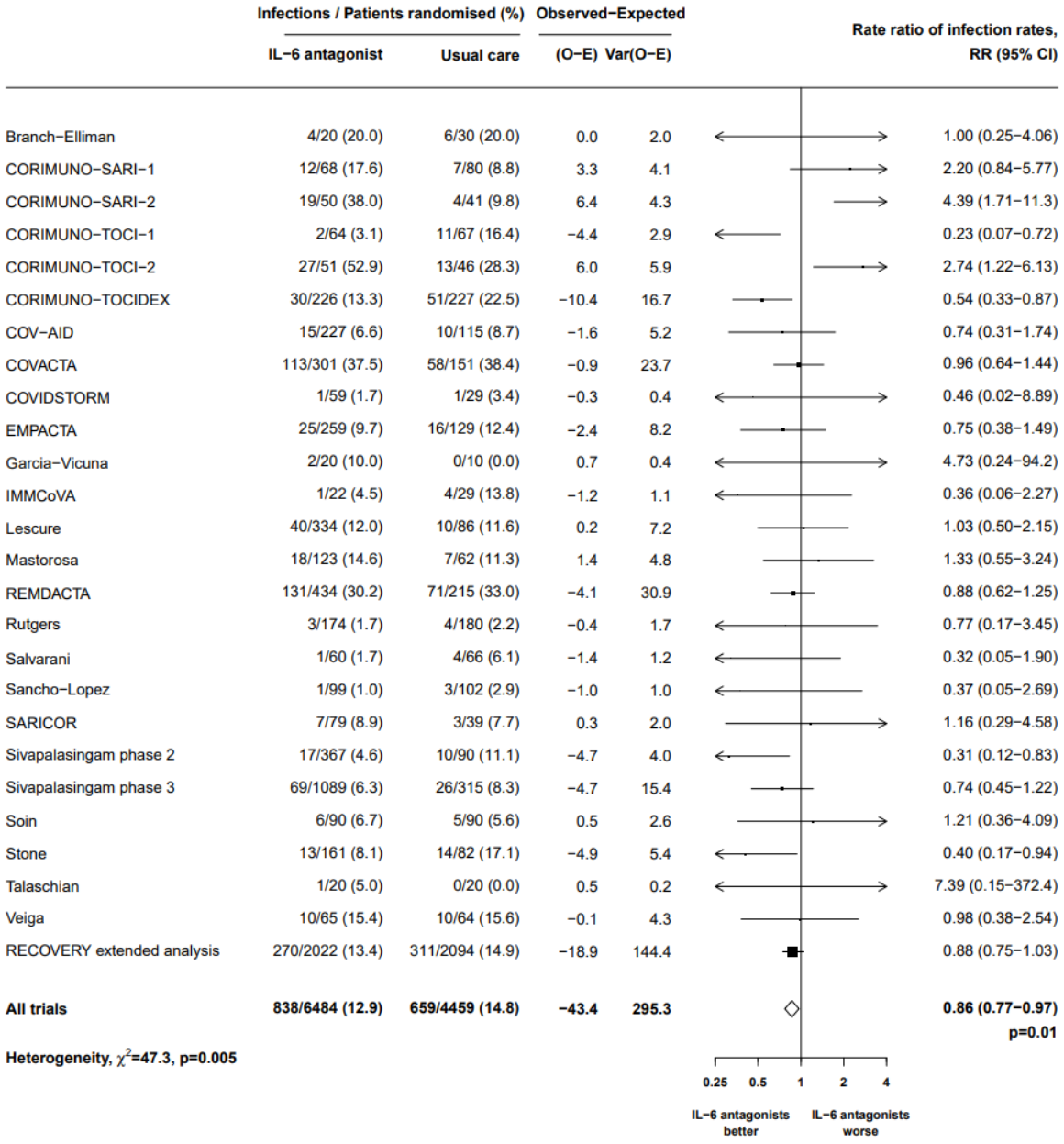


Figure 7-5: Meta-analysis of secondary infection within 28 days in randomised controlled trials of interleukin-6 receptor antagonist compared with usual care/placebo in hospitalised patients with COVID-19, updated to include results of the extended analysis.

Longer-term follow-up was also important as the elimination half-life of tocilizumab is 11-13 days and immunomodulatory effects may persist for months[401]. Inclusion of the extended analysis data suggests an increased risk of infection at longer-term follow-up is also unlikely (Figure 7-6, Moderate certainty of evidence).

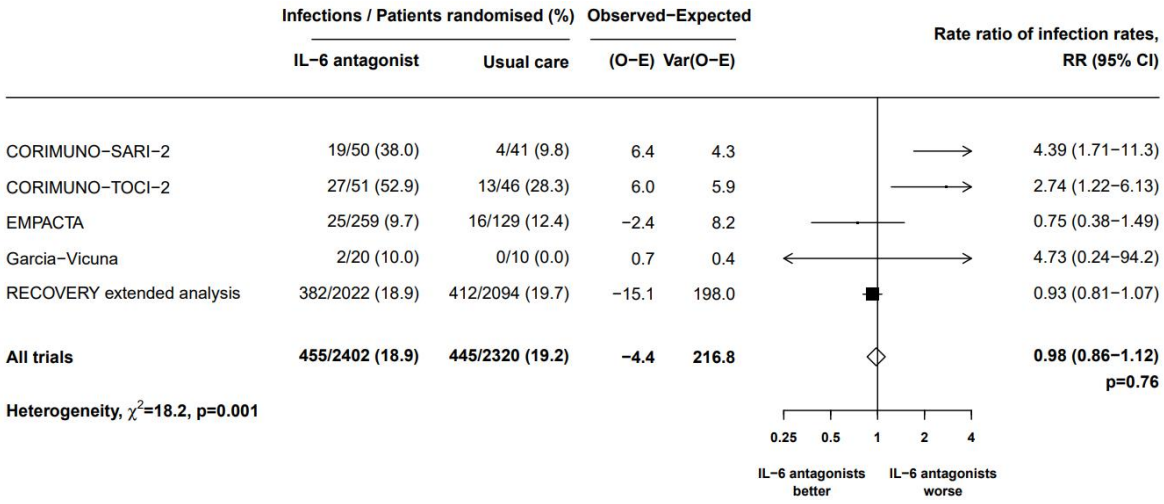


Figure 7-6: Meta-analysis of secondary infection at long-term follow-up in randomised controlled trials of interleukin-6 receptor antagonist compared with usual care/placebo in hospitalised patients with COVID-19, updated to include results of the extended analysis.
Includes eligible trials with secondary infection data from 60 days to 6 months follow-up.

In randomised studies outside of COVID-19, predominantly in rheumatoid arthritis, IL-6 RA treatment given for longer durations has been associated with an increased risk of infections[402,403], with an estimated magnitude of 18% compared with usual care in a meta-analysis of randomised trials assessed at 6 month follow-up[390]. The difference in the findings between the COVID-19 RCTs and those in other conditions could be explained by the shorter duration of treatment given (1 or 2 doses only for COVID-19, compared with monthly doses for 6 months for rheumatoid arthritis), or be representative of the altered risk-benefit balance dynamics in the setting of acute illness. For example, the reduction of infection risk from improving critical COVID-19 and the associated duration of medical interventions with tocilizumab in COVID-19 may outweigh a modest increase in infection susceptibility relating to short-term treatment.

iii) Baricitinib

In the baricitinib comparison, allocation to baricitinib was not associated with an increased risk of non-COVID infection in any infection outcome, compared with usual care. Results remained consistent amongst participants who were also receiving corticosteroids,

tocilizumab, or both. The upper bound of the 95% CI of the primary infection outcome at 6 months follow-up was 1.11, suggesting a substantial risk increase of infection was improbable. These results are consistent with the available data from the systematic review (meta-analysis estimate within 28 days, which included the RECOVERY CRF results at 28-day follow-up, RR 0.94 [95% CI 0.84 – 1.05]. These results increase certainty in the safety of baricitinib treatment for hospitalised patients with COVID-19 and increase confidence in the use of combination immunomodulatory treatment (such as dexamethasone, tocilizumab and baricitinib concurrently), with no evidence that adding baricitinib to other immunomodulatory treatments impacted secondary infection. This supports COVID-19 clinical guidelines that suggest combining immunomodulatory therapy in participants who may benefit from this – from the extended analysis results, the potential benefits seem likely to outweigh any harms[25,404].

In randomised trials of long-term JAKI treatment – in rheumatoid arthritis and atopic dermatitis - there appears to be an increased risk of infections, of a magnitude of approximately 25 -30%[389,405,406]. Similarly, to tocilizumab, the differences between this and the absence of infection risk in hospitalised patients with COVID-19 may be attributable to a shorter duration of therapy or effects mediated through the context of hospitalisation with an acute severe illness.

7.3.2.3 Metabolic complications

There was strong evidence that dexamethasone increased the risk of hyperglycaemia based on assessments using ISARIC4C and RCD data, and findings from the higher dose dexamethasone comparison. These results were further supported by other COVID-19 RCTs, and short-term corticosteroid RCTs in conditions outside of COVID-19. Dexamethasone was associated with an estimated risk increase of 70% in recorded hyperglycaemia compared with usual care in the RECOVERY-ISARIC sub-population. The daily rate of change in blood glucose in the first 7 days after randomisation was

approximately 5 mmol/L higher in the dexamethasone group compared with the usual care group (difference in adjusted means 0.73 mmol/L/day). In the metabolic complications outcome (using RCD diagnostic codes), a possible signal for an increased risk of metabolic complications within 28 days was also detected with an estimated magnitude of approximately 85%, though with wide CIs. In the higher dose dexamethasone comparison, the relative risk increase associated with higher dose dexamethasone for metabolic complications within 28 days was approximately 50%.

Corticosteroids are known to cause hyperglycaemia, principally by increasing insulin resistance[407]. Results from other trials in COVID-19 in the thesis systematic review and meta-analysis were consistent with the extended analysis findings; corticosteroids were associated with an estimated 50% increase in hyperglycaemia, compared with no corticosteroids at 28-day follow-up. The pooled estimate across all trials of higher versus lower dose dexamethasone was a 40% relative risk increase with a moderate level of certainty. In RCTs of short-term corticosteroids for pneumonia there is also a clear risk increase in hyperglycaemia with a treatment effect estimate RR of 1.68 [95% CI 1.30 – 2.16] in a meta-analysis including 458 events[171].

The results support glycaemic monitoring in hospitalised patients with COVID-19 receiving dexamethasone, including in non-diabetic patients[408]. Hyperglycaemia occurred more frequently in patients with diabetes, but around one third of events occurred in patients without a pre-existing diagnosis of diabetes. The dexamethasone treatment effect was similar in this group. In the higher dose dexamethasone comparison, two thirds of hyperglycaemia events in those randomised to higher dose dexamethasone occurred in patients with no known history of diabetes. The occurrence of severe metabolic complications such as diabetic ketoacidosis, appeared rare across both dexamethasone doses, although sensitivity of RCD diagnostic codes for these events were low.

Hyperglycaemia is associated with an increase in length of stay and mortality risk in COVID-19[66], as well as in other hospitalised patients[409,410]. Intensive blood glucose control in critically ill patients has been shown to reduce complications or mortality in some RCTs, although overall evidence remains uncertain[411-413]. Dexamethasone should be regarded to be an important contributor to glycaemic complications in hospitalised patients with COVID-19 and proactive measures to monitor and control blood glucose abnormalities should be in place. The knowledge that corticosteroids have this effect is not novel, but the extent and magnitude of the treatment-associated harm, as well as the broad patient population effected, should raise the profile of the importance of glycaemic monitoring in COVID-19 treatment[414-416].

The metabolic complication outcome used in this study had very low estimated sensitivity (0.06) but very high specificity (0.993) in method development testing. Overall event rates will be under-estimated for this outcome, but relative risk estimates should be preserved[344]. The limited sensitivity of the metabolic complications outcome is mitigated by the ability to assess direct blood glucose measurements in the RECOVERY-ISARIC population.

In the analysis of incident diabetes there was no evidence that short-term dexamethasone treatment increased the risk of diabetes in the subsequent 12 months, although conclusions were limited by imprecision. There were only 41 incident diabetes events in the dexamethasone comparison and the analysis had between 80 and 90% power to detect a 2-fold increase in diabetes risk - a very large effect size. The results are somewhat reassuring but cannot exclude a moderate effect on diabetes risk which would still be very important given the overall scale of patients treated with corticosteroids for COVID-19 worldwide (in the millions to date), meaning even a small effect could result in substantial health economic consequences. Long-term corticosteroids are known to increase the risk of diabetes[407,417].

The diabetes assessment itself derived from RCD had good diagnostic performance when evaluated as a baseline measurement. This assessment has the potential to have excellent

utility for baseline data or for long-term follow-up in other research studies, potentially using RCD only in place of study-specific data collection.

7.3.2.4 Venous thromboembolism

There was no convincing evidence of an increased risk of VTE for any of the immunomodulatory treatments.

JAKIs have been associated with an increased risk of VTE with long-term use[418], resulting in safety alerts being issued[419]. The rarity of events in RCTs (for any condition) have prevented meaningful randomised evaluation of VTE treatment effects[389]. In the baricitinib comparison of the extended analysis, baricitinib treatment did not appear to increase the risk of VTE with the upper bound of the 95% CI close to 1 in the main analysis and sensitivity analyses. This is reassuring that a short-term in-hospital course of 10 days baricitinib treatment is unlikely to confer an increased risk of VTE in COVID-19. COVID-19 is complicated by VTE in approximately 5% of cases[420]. JAKI treatment does not appear to be a contributing factor to that risk. This is also reassuring safety data for future studies assessing short-term JAKI therapy for other conditions.

In the dexamethasone comparison main analysis, dexamethasone treatment was not significantly associated with an increased risk of VTE. The sensitivity analysis of primary diagnostic position events only suggested the effect estimate may be unstable – with a higher specificity event definition resulting in an effect estimate that suggested a possible increased risk with dexamethasone treatment. There were, however, far fewer event numbers in this sensitivity analysis and so the potential for random error is more pronounced. The main analysis had 90% power to detect a risk increase of 50% within 6 months follow-up, and 80% power to detect a risk increase of 43%. In the method development validation, the specificity and PPV of primary diagnostic position events was slightly higher than for all diagnostic positions but not markedly so and is unlikely to fully explain the differences seen between analysis approaches. There is some biological

plausibility to a VTE risk increase with dexamethasone treatment with some observational studies suggesting an increase, but no randomised evidence[40,421]. Overall, the results of the sensitivity analysis bring some uncertainty, but there is no convincing evidence that dexamethasone is associated with an increased risk of VTE. Reassuringly, higher dose dexamethasone did not demonstrate any signal of an increased risk of VTE. In the systematic review, no other trials evaluated VTE risk with corticosteroids compared with no corticosteroids, but in higher dose corticosteroid trials, there was no signal of a treatment-related risk (RR 0.77 [95% CI 0.53 – 1.10]), supporting the null overall result as the most probable conclusion here.

The VTE outcome was robust for this analysis' purpose when evaluated in the method development testing. The assessment had an estimated specificity of 0.992, although a sensitivity of only 0.18, suggesting a high number of cases were missed, reducing the precision of treatment effect estimates. 97% of VTE cases were confirmed on manual medical record review and, in a population subset, 79% were on a systemic anticoagulant – more than 2.5 times the number without the outcome. In the broader RCD performance literature review, diagnostic code-derived VTE events retained an estimated specificity of 0.996.

7.3.2.5 Gastrointestinal complications

In the long-term follow-up analysis, baricitinib treatment may have been associated with an increased risk of GI complications (RR 1.66 [95% CI 1.14 – 2.46], at 6 months). The biological plausibility of this result is uncertain – most events were of 'unspecified GI bleeds'. Upper GI bleeds are not a known association with baricitinib therapy[46], although it is possible that diverticular bleeds could be contributing to the results. This result could be subject to random error given the relatively small event numbers (71 vs 40). In the original RECOVERY 28-day follow-up, there was also very weak evidence of increased GI bleeds from the CRF data only (18 vs 8 events), but again this could be consistent with chance[31]. There has been

no evidence of GI complication risk from long-term safety follow-up data of JAKI RCTs across all conditions[422]. Other COVID-19 trials in the thesis systematic review rarely gathered evidence of GI complications – with only 9 events across all other trials of JAKIs for COVID-19. Baricitinib does appear to have a risk of other GI complications, such as diverticulitis and perforation in wider long-term use[423]. At present, the possible increased risk in GI complications in patients randomised to short-term baricitinib treatment is of very low certainty. However, future randomised trials of JAKI treatment could record GI bleeding events as a safety outcome for further assessment.

In the dexamethasone comparison, there was no evidence of a treatment-related harm for GI complications. Point estimates were slightly >1 but with wide CIs. The analysis had 80% power to detect a treatment related risk increase of 56% in GI complications at 6 months. Sensitivity analyses that increased event derivation specificity moved the point estimate towards the null. With long-term corticosteroid use, a meta-analysis of randomised trials estimates a significant risk increase of approximately 40% for GI complications[424]. Overall, there is no evidence from this study that short-term corticosteroids for COVID-19 are associated with such a risk. A large risk increase (>60%) with dexamethasone treatment can be reasonably confidently excluded. In the thesis systematic review, there was no evidence of an increased risk with higher dose dexamethasone but with very small event numbers. Treatment effect point estimates were comparable to the findings here. Meta-analyses of GI complications from RCTs of short-term corticosteroids in pneumonia are also consistent with this conclusion[400].

Tocilizumab has been associated with a risk of GI perforation in observational studies[425]. In this analysis, there was no evidence of a treatment effect on GI complications. The analysis had 80% power to detect a 76% risk increase in GI complications in the tocilizumab comparison at 6-month follow-up. Small event numbers across this study and the meta-analysis in the systematic review chapter limit statistical power, but there is no evidence from

the available data of GI complication risk relating to short-term IL-6 RA treatment for COVID-19.

The GI complications outcome has some caveats. In the method development, the GI complications assessment had very high estimated specificity (0.997), although the events were rare. 80% of GI complications cases were found to be an active, current diagnosis in manual medical record review. In the broader literature review, no studies were found that evaluated RCD-coded GI complications in a whole study population, but events appeared to have reasonable PPV (0.72) in RCD diagnostic code-detected cases. GI complications were amongst the weaker evidence in terms of the diagnosis codes from the validation component of this study, mainly driven by difficulty distinguishing past medical history from active events in some cases.

7.3.2.6 Psychiatric complications

Corticosteroids have been associated with mood disturbances and delirium[426]. In this analysis, there was no evidence that dexamethasone (or any of the other immunomodulatory treatments) was associated with an increased risk of psychiatric complications. At 6-month follow-up the upper bound of the 95% CI was 1.26, making a large treatment-associated risk increase improbable. Most events recorded in the analysis were of delirium (75% of events recorded at 6-month follow-up). In the completed higher dose dexamethasone subgroup, a treatment-associated risk of psychiatric complications could be reasonably confidently excluded. The systematic review of psychiatric complications with higher dose versus lower dose corticosteroids was most consistent with no treatment effect, but with wide CIs. The analysis results were consistent with these findings, with no overall evidence that dexamethasone (at any dose) confers an increased risk of psychiatric complications when used for in-hospital treatment of COVID-19.

Confidence in the results is reduced by the limited method development data available to validate the psychiatric complications outcome. 96% of cases were confirmed on manual

medical record review and haloperidol use was 3.5 times more common in those with diagnostic codes, although with very small numbers of cases. The broader literature review suggested good estimated specificity (0.996) and poor sensitivity (0.11) of diagnostic codes for psychiatric complications (mainly delirium).

7.3.2.7 Liver injury

There was no evidence from this study that liver injury was increased with tocilizumab treatment in the clinically-defined events from linked RCD data, biochemically-defined events in linked ISARIC4C data, or daily rate of change in ALT in the RECOVERY-ISARIC population. Previous COVID-19 trials have suggested that tocilizumab was associated with an increased risk of elevated liver enzymes – with a meta-analysis RR estimate of 1.61 [95% CI 1.23 – 2.10]. With long-term use, tocilizumab has been associated with hepatic transaminase elevations in randomised trials when combined with methotrexate therapy for rheumatoid arthritis, compared with methotrexate therapy alone[403,427]. The most likely explanation for the discrepancy between the extended analysis results and that of the other RCTs is differences in event definitions. The extended analysis used a threshold of ALT >5 times the upper limit of normal while other studies appeared to collect information on any increase in hepatic transaminases above normal reference range. Overall, it is likely that IL-6 RA treatment is associated with modest increases in liver enzymes from evidence from other trials, but it does not appear to confer an increased risk of clinically significant liver injury.

Baricitinib has been associated with modest hepatic transaminase elevations with long-term use in randomised trials in patients with rheumatoid arthritis[406]. There was no evidence from the extended analysis that liver injury was increased with baricitinib COVID-19 treatment. The upper bound of the 95% CI at 28 days was at or very close to 1 in the clinically-defined events assessment, providing reassuring evidence for no increased risk of baricitinib-associated liver injury. Biochemically defined liver injury was not increased with baricitinib in the linked ISARIC data – though this time with wide CIs. These results are consistent with

the thesis systematic review and meta-analysis which showed no evidence of treatment effect on abnormal liver function events at 28 days with JAKIs (RR 0.90 [95% CI 0.66 – 1.22]).

7.3.2.8 AKI

There was evidence of potential benefit of dexamethasone treatment for acute renal complications (Section 7.3.1.3), and no evidence of a treatment-associated harm for biochemically-defined AKI events with tocilizumab or baricitinib.

7.3.2.9 Neutropenia

In these analyses, post-randomisation neutropenia events were very rare – with only 22 confirmed events in the tocilizumab comparison and 10 in the baricitinib comparison. It was possible that tocilizumab treatment was associated with neutropenia (RR 2.39 [95% CI 0.93 – 6.11]). In the thesis meta-analysis, tocilizumab was associated with neutropenia with a very large effect size, and these results remain consistent with that finding. Similarly to liver injury, it appears that most changes in neutrophil count are modest. In this analysis, only 5 events in the tocilizumab comparison (3 in the tocilizumab group) were of a neutrophil count of <1. The very low incidence of severe neutropenia suggests any treatment effect is likely to be of limited clinical significance.

7.3.2.10 Fractures

Corticosteroids are known to increase risk of osteoporosis with long-term use[428]. A treatment-related risk seems less plausible with short-term use, although an effect has been postulated in large observational studies[429]. There was no evidence from this study that long bone and vertebral fractures were increased at 6-month follow-up with standard dose dexamethasone, but event numbers were low. The analysis had 80% power to detect a two-thirds relative risk increase in fractures at 6 months. The results are slightly reassuring to rule out a very large risk increase. No other trials in the systematic review assessed fractures at long-term follow-up.

7.3.2.11 Viral clearance

There was no evidence that tocilizumab or baricitinib prolonged viral clearance, while results for dexamethasone were at the nominal threshold for statistical significance. However, this analysis was at high risk of survivor bias with repeat SARS-CoV-2 testing only occurring if you were alive (which was more likely with dexamethasone treatment). Any observed effect of delayed viral clearance occurs in the context of reduced mortality associated with standard dose dexamethasone and its clinical relevance is uncertain.

7.3.3 Effect of immunomodulatory treatments on illness recovery

Thesis aim iv) Evaluate the effects of the RECOVERY immunomodulatory treatments on long COVID and illness recovery.

7.3.3.1 Overview

There has been limited previous randomised evidence regarding the effect of short-term, in-hospital, immunomodulatory treatment on illness recovery or long COVID. The extended analysis does not demonstrate any evidence of efficacy for the immunomodulatory treatments for these outcomes. There were important methodological caveats associated with the long COVID outcome assessment for earlier treatment comparisons.

7.3.3.2 Illness recovery outcomes

None of the three main immunomodulatory treatments demonstrated a beneficial effect on the occurrence of long COVID at long-term follow-up or on a global assessment of functional status at hospital discharge. These findings make it less likely that immunomodulatory treatment aids illness recovery beyond the initial acute hospitalisation.

However, for the long COVID outcome, the diagnosis codes were not widely used until early 2021[212], meaning diagnoses occurring before this time could have been missed. This may particularly affect the earlier treatment comparisons of dexamethasone and tocilizumab. For example, in the dexamethasone comparison, there would be few long COVID diagnosis

codes used in the first 6 months of follow-up (of 18 months total) and no suitable alternatives were available.

Long COVID diagnoses from the primary care RCD appear to under-estimate the anticipated high population prevalence[69]. Many more people appear to self-report symptoms of long COVID – suggesting the sensitivity of this assessment may be low, although specificity should be reasonable because a healthcare professional has had to provide an assessment. Recorded events rely on participants presenting to primary care and an assessment and diagnosis being made and recorded. The long COVID diagnostic codes use different terminology ('post-COVID syndrome'), rather than the apparent patient-preferred terminology of long COVID[430] – this may impact the way they are utilised and coded. Validation was very limited given the absence of an available 'gold-standard' against which to compare.

For dexamethasone, the study had 80% power to detect a 44% relative risk reduction in long COVID. For tocilizumab, the analysis had 80% power to detect a 32% relative risk reduction in the occurrence of long COVID. For these treatments all but a modest treatment benefit is improbable. For baricitinib, the lower bound of the 95% CI from the analysis of the long COVID outcome was 0.95, making any meaningful treatment benefit unlikely. However, the limitations inherent in the RCD reduce confidence in definitive conclusions regarding the effect of immunomodulatory treatments on long COVID.

Among other RCTs that evaluated patient-centred outcomes, the Metcovid trial suggested a beneficial effect of corticosteroids on lung function tests but the clinical relevance was uncertain, as the benefits did not translate to differences in assessments of functional capacity[90]. REMAP-CAP evaluated health-related quality of life and disability at 180-day follow-up and found no meaningful difference between groups randomised to corticosteroids and no corticosteroids[92]. REMAP-CAP did suggest a small benefit in health-related quality of life at long-term follow-up with IL-6 RAs, but this did not extend to other measurements of similar outcomes, such as WHO Disability score. Outcome data collection was also

restricted to only a subset of sites. Ongoing RCTs of immunomodulatory treatments for symptomatic post-COVID syndromes will help elucidate any role for immunomodulatory therapy for this condition[431,432], but at present there is no signal of benefit from short-term immunomodulatory treatment given during acute hospital admission for COVID-19.

7.3.4 Exploration of the heterogeneity of corticosteroid treatment effects

Thesis aim v) Explore the heterogeneity of dexamethasone treatment effect observed in the RECOVERY trial.

7.3.4.1 Overview

In the extended analysis, there was clear evidence of heterogeneity of dexamethasone treatment effect that appeared to be determined by disease severity, drug dose and host vulnerability factors. There was no evidence to suggest fundamental biological differences in the action of corticosteroids in different subgroups. Instead, a dynamic risk-benefit balance may exist between these factors that determines the overall effect of corticosteroid treatment in COVID-19. Heterogeneity according to disease severity was well recognised from the 28-day follow-up of the RECOVERY dexamethasone comparison[29], and has influenced global treatment guidelines. The potential importance of host vulnerability factors is a novel finding for this thesis. Understanding of these factors has the potential to improve clinician awareness and monitoring for potential treatment-related harms and inform future research.

The increased mortality at long-term follow-up with higher dose dexamethasone in patients who were hypoxic but not requiring ventilatory support, suggests corticosteroids have the potential to cause meaningful harm in hospitalised patients with COVID-19, if used in the wrong patient population or dose.

7.3.4.2 Contributing factors and their interaction

Subgroup analyses of mortality in the standard dose dexamethasone comparison (Section 5.3.6) suggested there was important heterogeneity in dexamethasone treatment effect,

according to severity of COVID-19 illness (as measured by respiratory support requirement or duration of symptoms) and host vulnerability factors (as measured by HFRS or Charlson Co-morbidity Index score).

In the 6-month follow-up analyses, respiratory support remained an important determinant of heterogeneity, as seen in the 28-day follow-up findings. Those who required higher levels of respiratory support at randomisation appeared to experience the greatest benefit from dexamethasone treatment, while in those who did not require oxygen at randomisation the treatment effect estimate remained consistent with marginal benefit or meaningful harm.

There was also significant heterogeneity in dexamethasone treatment effect according to HFRS group at both 28-day and 6-month follow-up for mortality. Those with low frailty risk scores appeared to experience the greatest benefit from dexamethasone treatment, while those with high frailty risk scores may have experienced harm. Frailty has been defined as a "state of increased vulnerability" that is associated with physiological and function decline[433]. Frailty can be measured in a number of different ways, but is distinct from age and co-morbidities, and is robustly associated with poor health outcomes, including mortality[434,435]. The HFRS used in this analysis is a data-driven RCD-derived score measured using combinations of ICD-10 diagnostic codes that are weighted towards frailty determinants. It has shown good validity for predicting mortality, prolonged hospital length of stay and hospital readmission[220]. The HFRS showed correlation with other measures of frailty in method development for this study (Section 4.3.4.3). Here, it aimed to represent a global assessment of patient health and vulnerability – a general concept supported by replication of the heterogeneity findings in subgroups defined by Charlson Co-morbidity Index score in a sensitivity analysis.

Several approaches were taken in this study to try to delineate the most important determinants of heterogeneity in corticosteroid treatment effect:

i) Extended baseline respiratory group

The original RECOVERY respiratory support subgroup analyses were expanded by including a greater granularity of measurement of respiratory support at randomisation. Those in the 'oxygen or non-invasive ventilation' subgroup were split into low/moderate and high oxygen requirement groups (defined by FiO_2 requirement), and a non-invasive ventilation group. The subgroup analysis in these extended baseline respiratory support groups supported a spectrum of treatment effect magnitude, ranging from the highest levels of respiratory support (clear treatment benefit) to the lowest levels (absence of treatment benefit, possible harm) in a relatively linear relationship. These results increase the robustness of the finding of heterogeneity according to respiratory support and give further insight into the overall relationship between treatment effect and the disease severity spectrum.

ii) Effect on other outcomes

The heterogeneity according to frailty status and respiratory support group at randomisation remained present when assessed in the secondary efficacy outcomes of discharge alive from hospital and invasive mechanical ventilation or death – further supporting the robustness of the heterogeneity finding and the importance of these factors.

The proportional effects of standard dose dexamethasone on major non-COVID infection and hyperglycaemia were not convincingly different according to frailty or respiratory support groups, although the least favourable treatment effect estimates were found in those not on oxygen at randomisation and those with high-risk frailty scores. The findings of potential harm in some patients treated with corticosteroids is most consistent with multifactorial harm rather than a single treatment-related event type.

There was no evidence of heterogeneity in treatment effect on biological measurements – adjusted mean differences were very similar in CRP, ordinal scale score and glucose across all respiratory support and frailty subgroups. This suggests a broadly similar biological effect of dexamethasone, regardless of disease severity or host vulnerability.

iii) Interactions between respiratory support and frailty

There were correlations between baseline respiratory support and HFRS group, raising the possibility that confounding was accounting for the same finding across multiple marginal subgroup analyses[245]. Exploratory analyses attempted to account for the potential confounding and delineate the independent effect of each factor – in these, significant heterogeneity remained present in subgroups according to both respiratory support and HFRS group. These findings support the concept that both disease severity and host vulnerability are important contributors to the overall dynamic benefit-risk balance of corticosteroid treatment.

iv) Replication of findings in higher dose dexamethasone subgroup analyses

It is feasible that there is heterogeneity of higher dose dexamethasone treatment effect according to disease severity. The RECOVERY higher dose dexamethasone comparison was stopped in the subgroup of participants who did not require ventilatory support, while continuing in those who requiring ventilatory support at randomisation, despite the finding of harm in the former subgroup. The thesis meta-analysis (Section 2.3.5.1) also suggested there may be heterogeneity in higher dose corticosteroid treatment effect according to disease severity – although this was assessed at a trial population level, rather than at the level of the individual participant.

Subgroup analysis by frailty group in the completed RECOVERY higher dose dexamethasone sub-population did not demonstrate significant heterogeneity in treatment effect but was limited by statistical power and missing data - HFRS was available for <50% of the treatment comparison, as it was derived from RCD sources that were only available for participants randomised in the UK.

v) Conclusions

Disease severity (as measured by respiratory support), host vulnerability (as measured by HFRS), and drug dose all appear important determinants of the heterogeneity of dexamethasone treatment effect in COVID-19 and the risk-benefit balance of corticosteroid treatment for this indication. It is hypothesised that disease severity may predict corticosteroid treatment benefit, while frailty may predict corticosteroid treatment-related multifactorial harm.

7.3.4.3 Clinical trajectory of the RECOVERY dexamethasone 'no oxygen' subgroup

Mortality was more than 20% in both randomised groups at 6-month follow-up in the RECOVERY standard dose dexamethasone 'no oxygen' subgroup. The reasons why the death rate was high in this subgroup despite relatively low COVID-19 disease severity is poorly understood. The descriptive analyses from Section 6.3.6 suggest that participants who died in this subgroup went on to have worsening hypoxia after randomisation, most consistent with worsening COVID-19. This suggests that the patients not on oxygen at baseline were admitted to hospital at an earlier stage of COVID-19 disease but those who died followed a similar natural history until death as those with more severe disease at baseline. Despite this, dexamethasone treatment was not effective in the 'no oxygen' group, raising questions about timing of treatment. It is possible that the benefit-risk balance of corticosteroids in this subgroup may simply have not been favourable at the timing treatment was used. Harms from dexamethasone occurring early in treatment may have been sufficient to overcome any benefit of dexamethasone once patients became hypoxic. This promotes the question of optimal timing of corticosteroid treatment during the development of hypoxia, which requires further research[32].

7.3.4.4 Clinical implications

Current clinical guidelines recommend to treat patients with standard dose corticosteroids if they require oxygen or ventilatory support, and not if they require no oxygen[25,404]. The precise point at which corticosteroid treatment could be regarded as convincingly beneficial

is difficult to define and is hypothesised to relate to both disease severity and host vulnerability. Clinicians can utilise treatment with the greatest confidence in more critically unwell and less frail patients, and consider use with caution in those requiring lower levels of oxygen support or who are more frail with careful monitoring for complications. Results from the analyses are most consistent with multifactorial harm for which prevention for any one specific treatment-related complication is unlikely to be effective, although the most common are perhaps likely to be hyperglycaemia and non-COVID infections. A pragmatic approach may be to continue to treat all patients requiring oxygen but to have a high vigilance for potential complications in more frail patients.

There appears no discernible reason to alter global treatment guidelines based on the findings from these exploratory analyses – we appear to be broadly treating and not treating the correct patients. The extended analysis findings allow us to appreciate the greater nuance in treatment benefit-risk balance and supports the need for further randomised trials if assessing corticosteroids at different doses and durations. The findings may also have applications in understanding the use of corticosteroids in other acute respiratory infections.

7.3.5 Effects of immunomodulatory treatments on biological measurements

Thesis aim vi) Explore the effect of the RECOVERY immunomodulatory treatments on biological measurements, such as commonly-measured blood biomarkers and gene expression data.

7.3.5.1 Overview

In randomised comparisons, dexamethasone treatment was associated with changes in the trajectory of oxygenation status and inflammatory marker measurements that have been associated with mortality. Dexamethasone altered expression of genes non-causally linked to COVID-19 severity from observational studies, but the analysis could not demonstrate a treatment effect on gene expression thought to be causally related to the development of severe COVID-19.

The extended analysis evaluation of biological measurements provides reference data for further COVID-19 research involving immunomodulatory treatments. It has been evaluated with minimal bias through the randomised comparisons in the RECOVERY-ISARIC population and is unique - having only been achieved on this scale by the novel linkage of the large RECOVERY and ISARIC4C datasets. The biological measurement data could be of use when evaluating immunomodulatory treatments for acute severe respiratory infections in future research.

7.3.5.2 Oxygenation status

The ordinal scale score used was as a marker of oxygenation status with greater granularity in disease trajectory compared to binary death and discharged alive outcomes. Dexamethasone treatment conferred a greater improvement in ordinal scale score compared to usual care, whether assessed as a continuous or ordinal outcome. The magnitude of treatment effect was relatively small using this measurement. The difference in adjusted means between treatment groups was an estimated -0.08 categories/day in the dexamethasone main analysis, with the upper bound of the 95% CI close to 0. Patients improved an average of approximately half an ordinal scale category over the first 7 days after randomisation with dexamethasone treatment compared with usual care. Although assessed in the slightly smaller RECOVERY-ISARIC population (75% of the whole RECOVERY dexamethasone comparison), the results did not appear to provide more compelling or efficient evidence of benefit compared with the trial primary outcome analysis of 28-day mortality. The results were of nominal statistical significance despite being produced from an evaluation of a treatment that is known to have practice-defining mortality benefits. This suggests that the use of the ordinal scale outcome in future acute infectious respiratory disease trials may not be a particularly useful alternative, compared to the certainty provided by mortality assessment. Studies using ordinal scale scores as a primary outcome still need to be adequately powered to detect small differences associated with

treatment, as the small differences can equate to highly clinically significant benefits in mortality or hospital discharge. This needs to be considered in the design and interpretation of future research.

The ordinal scale score was treated as a continuous variable in the daily rate of change assessments. This is of uncertain validity as each step on the ordinal scale is unlikely to be equivalent. The use of the proportional odds model as a complimentary analysis method demonstrating similar results increases confidence in the overall findings of a general improvement in ordinal scale score associated with dexamethasone.

7.3.5.3 Inflammatory markers

Dexamethasone was associated with a highly significant reduction in the daily rate of change in CRP – resulting in a CRP that was an average of approximately 125mg/L lower at 7 days after randomisation with dexamethasone compared with usual care. CRP has been associated with mortality in large COVID-19 cohort studies[169,436]. In the systematic review, three other corticosteroids RCTs in COVID-19 found a significantly lower level of CRP in those randomised to receive corticosteroids, measured at a single follow-up point[96,98,100]. The average difference in reduction in CRP of approximately 50mg/L at day 3 or 4 after randomisation is consistent with the findings in the extended analysis of an estimated 18 mg/L/day difference. Several higher dose corticosteroid COVID-19 RCTs also found a reduction in CRP in those treated with higher-dose compared with lower dose corticosteroids[156,163]. In community-acquired pneumonia RCTs, corticosteroid treatment was associated with a greater reduction in CRP[437,438], where evidence of efficacy on clinical outcomes remains uncertain[172]. Change in CRP measurement is an outcome that appears to be able to detect corticosteroid treatment-related differences in small populations, but its validity as being representative of clinical outcomes is uncertain.

Conversely, dexamethasone treatment was also associated with a greater increase in the daily rate of change of NLR - in the opposite direction to observed correlations with

mortality[169,439]. This is likely related to the neutrophilia-inducing effects of corticosteroids due to increased migration of neutrophils from the bone marrow and increased survival through prevention of apoptosis[440]. This treatment-specific effect has implications for studies attempting to evaluate biomarker association with clinical outcomes in patients receiving corticosteroids. It limits the utility of NLR as a prognostic or predictive biomarker in COVID-19 research or any other corticosteroid-treated inflammatory condition. In a study comparing the association of NLR with mortality before and after the introduction of corticosteroid treatment, NLR was no longer associated with mortality after corticosteroids became standard care[441].

7.3.5.4 Gene expression data

Patients allocated to dexamethasone displayed differential expression of genes involved in a range of broadly clinically and biologically relevant inflammatory and immune pathways, compared with those allocated to usual care.

In the analysis of pre-specified gene sets of interest, dexamethasone appeared to have a measurable impact on gene expression relevant to severe COVID-19, but there was no evidence to support a causative conclusion of treatment efficacy from gene expression data alone. In the evaluation of gene sets putatively causally related to severe COVID-19 development (from Mendelian Randomisation and metaTWAS studies), dexamethasone did not demonstrate a significant treatment effect. These gene sets were identified as the primary assessments – where a demonstrable dexamethasone treatment effect would have had rationale to be interpreted as evidence of clinical efficacy based on the original study designs being regarded as capable of generating putatively causal evidence[442].

Dexamethasone also significantly impacted expression of gene sets that were non-causally associated with COVID-19 severity in two large independent observational studies[229,230]. Interestingly, dexamethasone effect was in the opposite direction to that observed with lower COVID-19 severity in the external study data – highlighting the difficulty in disentangling

causality in these observational studies. As a pilot analysis aiming to evaluate the feasibility of drawing meaningful conclusions from gene expression data in a randomised trial, the data showed some promise. Despite the small sample size, the differential gene expression analysis provided rich data with measurable impact on gene expression that was relevant to both drug and disease. Future randomised trials could consider integrating longitudinal transcriptomic sample collection to explore the potential of this data further.

The patients evaluated were only a very small subset of participants in the RECOVERY dexamethasone comparison and had some imbalances in baseline characteristics. It was not possible to comment on greater granularity of the involved immune pathways.

7.4 Strengths and Limitations

7.4.1 Study design

The main strengths of this study are that it is large, embedded in the randomised treatment comparisons of RECOVERY, and uses linked individual participant data from two comprehensive sources (RCD and ISARIC4C). This reduces random error and improves minimum detectable effect size estimates, eliminates many sources of bias from the study, and allows a broader, longer, and deeper evaluation of immunomodulatory treatment effects in COVID-19.

Secondary analyses of RCTs are, however, at risk of selection bias arising from loss to follow-up or analyses performed in sub-populations, that are not necessarily representative of the whole randomised comparison[443].

7.4.2 Routinely collected data sources

The linked RCD datasets have high levels of data completeness enabling robust follow-up for almost all patients randomised, particularly for major objective outcomes, such as death.

The breadth of data sources integrated is a strength of the analysis. There is coverage of event types from hospitalisation, death, primary care and microbiology datasets. Geographical coverage is broad with datasets from England, Scotland, and Wales. Unfortunately, linked RCD data was not available for patients randomised in Northern Ireland or at international sites. Northern Irish participants made up 2% of the overall RECOVERY population. International site participants were only relevant to the higher dose dexamethasone comparison – although in this comparison they made up over half of participants, limiting RCD-derived outcome evaluation in this treatment comparison. A 6-month trial follow-up CRF collected data on causes of re-hospitalisations as a substitute for RCD follow-up at international sites.

There were some gaps in the data collection of RCD events – while primary care data was available, the specific inclusion in the dataset of clusters of diagnostic codes determined if all events were detectable in that dataset or not. Date precision in the datasets also limited detection of events occurring close to randomisation. In the primary care prescription dataset, date precision was limited to the month of prescription meaning prescriptions occurring in the month of randomisation could not be distinguished between pre- or post-randomisation occurrences. Similarly, in the hospitalisation datasets diagnosis code-derived events occur in a hospital episode spanning several days duration (median 4 days [IQR 1-8 days] in the time from randomisation to 6-month follow-up in RECOVERY), limiting precision of event timing. Events occurring in the same hospital episode as randomisation could not be distinguished as pre- or post-randomisation events. In the main analysis peri-randomisation events were excluded - this creates a blind-spot in RCD assessment in the very early post-randomisation phase, particularly for acute safety evaluation events, meaning a higher proportion of very early occurrences could be missed. This was mitigated by the sensitivity analyses including peri-randomisation events, which showed similar results to the main analysis throughout. While no post-randomisation events should be intentionally excluded from the analysis, it is also possible that some events that occur very early post-randomisation are less likely to be modified by the treatment given.

7.4.3 Performance characteristics of assessments

An important limitation of the assessments using linked RCD remains data quality and the potential for misclassification bias. The derivation of events is only as good as the quality of diagnostic coding in the RCD record. The use of careful method development aimed to mitigate this by understanding the validity, limitations, and performance characteristics of each RCD-based assessment. RCD-derived assessment validity is outcome and dataset specific with significant variation in diagnostic performance[360]. The validation of VTE, GI bleeding, infections, and metabolic complications was more comprehensive than RCD-

coded fractures, psychiatric complications, and liver injury, based on data availability. In method development for this study, assessments generally displayed high specificity but modest sensitivity. Codelists were constructed with an emphasis on specificity. Randomisation increases the robustness to misclassification bias; in high specificity event derivation this should preserve unbiased point estimates from the randomised comparisons. For other study designs, a different balance of specificity and sensitivity may be desired. Sharing of codelists and validation data can help build knowledge regarding the optimal use of RCD-derived assessments for research studies.

There was some evidence of pre-existing disease appearing in post-randomisation diagnostic codes. This has been partially mitigated in the study design by screening out repeat diagnostic codes within 30 days, not using the peri-randomisation episode, and including sensitivity analyses to assess for differences in effects seen by varying data derivation parameters.

Diagnostic accuracy sensitivity was low across many assessments, although often improved greatly when peri-randomisation events were considered. In this study, sensitivity analyses evaluated peri-randomisation events to ensure they did not importantly alter the results from the main analysis. Absolute event rates should not be inferred from the data due to low sensitivity and uncertainty regarding whether more than one diagnosis could be derived from a single clinical event. For example, if different diagnostic codes were used to record the same clinical event in subsequent hospitalisation episodes. While this is unlikely to result in bias when assessing the proportional effects of treatment, the absolute risks should not be relied upon directly. An alternative analysis approach in this study could have employed statistical methods to consider multiple illness episodes per participant (rather than limiting to the first occurrence)[444], but this approach was not chosen due to the potential for duplicate coding for single events.

7.4.4 ISARIC4C data

The linkage at individual participant level with ISARIC4C data is a major strength, enabling characterisation of the effects of immunomodulatory treatments on biological measurements in a randomised comparison, assessment of further clinical outcomes, and delineation of subgroup effects more clearly. The linkage between RECOVERY and ISARIC4C was extensive - 52% of all RECOVERY participants, rising to 75% in the dexamethasone comparison. Nonetheless, the level of data completeness of the RECOVERY-ISARIC population precludes a true intention-to-treat population randomised comparison, with the potential for selection bias. For the baricitinib comparison, data completeness declined substantially in many assessments, limiting confidence in conclusions from this data. The comparability of baseline characteristic and outcomes in the randomised groups typically suggested that those included were representative of the whole randomised comparison, although less confidently so in the tocilizumab comparison, where heterogeneity between the trial primary outcome treatment effect estimates between those with linked ISARIC data and those without was close to nominal statistical significance. Many of the RECOVERY-ISARIC biological measurement assessments utilised multiple imputation methods to attempt to mitigate potential bias associated with missing data, however this can still be problematic if the employed imputation model does not account for all relevant factors relating to missingness, or if some data is 'not missing at random'[445].

Within the data collection of biological measurements in ISARIC4C, few participants had oxygenation or commonly-measured biomarkers recorded on a daily basis within the specified analysis time periods. This limited the methods of analysis and data comprehensiveness. All recorded biological measurements were mapped to individual participant RECOVERY randomisation dates to ensure follow-up measurements were truly taken at the correct time post-randomisation.

7.4.5 Competing risks

The potential for bias in this study arising from competing risks associated with differential mortality rates between randomised groups was carefully considered for all outcomes outside of all-cause mortality. Analysis methods were selected to aim to target the research question of interest. Here, the focus was on the question of underlying biological risk of an event associated with the immunomodulatory treatment in question, regardless of effect on other outcomes. Hence, cause-specific hazard estimates from Cox regression models using censoring at death were employed wherever possible as these were best suited to research questions concerning biological risk attributable to the immunomodulatory treatment, for example for major non-COVID infection[233].

Some binary outcome assessments used a logistic regression model due to a lack of granularity in date data precluding censoring at death. For these assessments, bias arising from competing risks was more likely. For example, in the higher dose dexamethasone comparison more participants randomised to higher dose dexamethasone died compared to usual care. Subsequently, the population at risk of experiencing an outcome such as psychiatric complications (analysed as a binary outcome using a logistic regression model) occurring after hospital discharge, was disproportionately large in the usual care group. In this assessment, it appeared that the risk of psychiatric complications was lower in those who were randomised to higher dose dexamethasone, but this observed effect could be entirely related to survivor bias.

7.4.6 Minimum detectable effect size

The sample size used in the randomised comparisons for possible treatment-related harms were fixed - based on the already completed RECOVERY treatment comparisons. Resultantly, the minimum detectable effect size for some outcomes was large – leaving the analysis underpowered to detect some effects to a magnitude that remains a clinically meaningful difference. For example, this is likely to be the case for GI complications and

incident diabetes. This limits definitive conclusions for some outcomes as a clinically-relevant effect could not be excluded, even if there was a null treatment effect estimate and no evidence of harm.

7.4.7 Other potential sources of error

RECOVERY is an open-label trial, and this can give rise to bias in outcome ascertainment by knowledge of treatment allocation. This should not affect the objective mortality estimates but could have a greater effect on other outcomes. The RCD and ISARIC4C data are collected and collated independently to RECOVERY, reducing potential biases of an open-label trial design. However, it remains possible that clinicians' documentation in the medical record could be influenced by knowledge of treatment assignment. For example, by recording complications that clinicians perceive to be associated with the treatments given with the potential for a subsequent effect on the RCD and ISARIC4C data extracted from a patient's medical records.

The data linkage itself between RECOVERY and RCD or ISARIC4C could be subject to errors – record linkage could have been missed or been linked incorrectly. Residual error in this area is not possible to eliminate entirely, but data linkage for this study was performed by experts at the University of Oxford, NHS Digital and eDRIS. Possible linkage errors detected by the RECOVERY trial team (including the thesis author) were investigated and reported back to NHS Digital during data checks performed for the main RECOVERY trial.

7.4.8 Generalisability

The generalisability of the methods and results of this study to all patient populations merits consideration. Nationally-available RCD with diagnostic codes and good data quality is not available throughout the world, limiting applicability of some methods.

The dynamic balance of clinical benefits and risks of immunomodulatory treatments could change in other settings – for example, in patient populations with high levels of frailty for

corticosteroids, or in geographical areas with higher burdens of TB, hepatitis B, and HIV which could be influenced by immunomodulatory treatment. Although there was no evidence of heterogeneity in higher dose dexamethasone treatment effect according to geographical region at short-term follow-up[44], differences in risks may require different monitoring and mitigation procedures specific to the local context. In the UK, the COVID-19 pandemic evolved rapidly across time with differing patient populations, disease severity, usual care treatment standards, and virus variants across the whole trial period. This meant that patients being included between (and sometimes within) RECOVERY treatment comparisons could differ over time. In earlier parts of the pandemic patients were typically slightly older, had more co-morbidities and had higher death rates. Later, standard dose corticosteroid treatment was widespread and COVID-19 mortality reduced with improved prevention and treatment. The underlying pathology of severe COVID-19 disease and the mechanism of efficacy of immunomodulatory treatment is likely to have remained stable over time but this contextual evolution limits any evidence using multiple treatment comparisons and may affect the dynamic benefit-risk balance of corticosteroids due to changes in the balance of these factors in different patient populations. A network meta-analysis across different dexamethasone doses in RECOVERY was not carried out given the changing nature of underlying factors between treatment comparisons that may bias findings.

The overall representativeness of RECOVERY participants of hospitalised patients with COVID-19 in the UK appears to be good[446]; RECOVERY patients were slightly younger and less co-morbid, compared with a reference population of all patients hospitalised with COVID-19 in England. While this could slightly impact the generalisability of the extended analysis relating to host vulnerability factors with corticosteroids to a real-world population, the bigger challenge for generalisability remains the changing nature of the disease.

7.5 Wider Applications and Future Directions of Research

The work in the extended analysis has broader applications and implications for future research.

The systematic review forms a comprehensive summary of the current evidence regarding important efficacy and safety outcomes for immunomodulatory treatments currently in use for COVID-19 and can be updated with the results of any future trials.

The method development work supports the responsible use of RCD-derived assessments in randomised trials, by adding to the body of evidence relating to their use for baseline characteristic or outcome derivation[354]. The method development work provides quantitative evidence of the performance characteristics of the assessments used to guide their utility, application and limitations when used in other research. The clinical codelists used for the extended analysis will be made available for replication or adaptation in other studies. The performance characteristics of different assessments should be considered carefully, depending on the research goals. In this analysis, assessments were typically of modest sensitivity, but this was substantially improved when peri-randomisation events were included. In other studies, where events of interest are not occurring in close proximity to randomisation, RCD-derived assessment utility will be even greater – with improved sensitivity and preserved specificity.

The comprehensive, systematic safety evaluation of the immunomodulatory treatments provides evidence that can support interventional studies in the future. The data can provide reassurance regarding the likelihood of some potential treatment-related harms with short-term treatment; for example, the reassuring data regarding baricitinib and VTE, and tocilizumab and infections. The findings also allow prioritisation of safety outcomes in future studies. For example, studies of short-term corticosteroids may wish to focus safety outcome data collection on metabolic complications and secondary infections; while baricitinib studies may wish to capture GI complications.

Identification of the importance of the dynamic balance of disease severity, drug dose and host vulnerability factors involved in short-term corticosteroid treatment could have applications to other conditions where corticosteroid treatment effects remain debated; such as community-acquired pneumonia, ARDS and influenza. Understanding these factors could help untangle contrasting findings from different trials and aid design and interpretation of future studies.

The totality of the extended analysis results can be used as a reference point for further COVID-19 immunomodulatory treatment research or used to guide future evaluations of treatment of other acute respiratory infections with immunomodulatory agents. The analysis provides a comprehensive set of results from the randomised comparisons for outcomes at clinical, biological and even genetic expression levels, which can give an indication of the type of treatment effects that might be observed with effective immunomodulatory treatments.

The linked RECOVERY and ISARIC4C data is a unique resource combining the two largest UK studies of hospitalised patients with COVID-19 into a rich set of data that can be used for future observational studies or further linkage with other studies. For example, it could be applied to develop clinical prediction models to try to optimise use and timing of combination immunomodulatory treatments or be linked with other COVID-19 studies, such as the Post-Hospitalisation COVID-19 Study (PHOSP-COVID) to better understand determinants of post-hospitalisation outcomes[70]. There may also be scope for future research to gain more comprehensive understanding of the detailed biological sample data within this linked data.

7.6 Conclusions

This study – the extended analysis of the RECOVERY immunomodulatory COVID-19 treatments - has expanded knowledge of the efficacy and safety of immunomodulatory treatments used for COVID-19 by utilising long-term follow-up data and systematic assessment for potential treatment-related harms from individual participant-level linked data sources. Explorations of factors contributing to the heterogeneity of corticosteroid treatment effect in COVID-19 and the randomised analysis of the effect of immunomodulatory treatments on biological measurements has deepened our understanding of corticosteroid treatment effects and provides data that can support the design and interpretation of future research.

The short-term mortality benefits of dexamethasone, tocilizumab and baricitinib treatment for patients hospitalised with COVID-19 are preserved at 6-month follow-up and beyond - these treatments can continue to be used in clinical practice with greater certainty in their benefit for clinicians and patients. There was no evidence that short-term immunomodulatory treatments given during the acute hospital admission altered functional recovery or long COVID risk at hospital discharge or long-term follow-up.

The immunomodulatory treatments safety evaluations were broadly reassuring, even with systematic evaluation in each treatment comparison. The benefits of immunomodulatory treatments for COVID-19 outweigh any risks. Corticosteroids meaningfully increase the risk of hyperglycaemia. Optimising management of metabolic complications has the potential to improve patient outcomes. At standard doses for COVID-19 (6mg/day dexamethasone), corticosteroids probably do not majorly increase the risk of non-COVID infection but a small magnitude treatment-related risk remains possible. Corticosteroids do not appear to impact the risk of GI complications, VTE, diabetes, fracture or psychiatric complications. There was no evidence that tocilizumab therapy for COVID-19 confers an increased risk of infection, GI complications, VTE or liver injury. There was no evidence that baricitinib therapy increases

non-COVID infection risk, VTE or liver injury. Combination immunomodulatory therapy with the addition of baricitinib, did not increase the risk of mortality or non-COVID infection compared to treatment with corticosteroids, tocilizumab, or both.

The overall treatment effect of corticosteroids in COVID-19 is likely determined by a balance of disease severity, drug dose, and host vulnerability to corticosteroid-related harms. Standard dose corticosteroids appear particularly effective in reducing mortality in patients requiring high levels of respiratory support and with low frailty. In those who require no oxygen, standard dose corticosteroids appear to be of no clinical benefit and could be associated with harm, particularly in patients with high levels of frailty. Higher dose corticosteroids (20mg/day dexamethasone) increase long-term mortality in patients not requiring ventilatory support, while their effect in patients on ventilation remains uncertain. Corticosteroid treatment-related hazard is likely to be multifactorial with no condition singly responsible for harm, although hyperglycaemia and non-COVID infection may be important. The understanding of the complexity of the potential contributors to the treatment effects of corticosteroids can help disentangle their effects in other acute respiratory infections and guide future trial design, implementation, and interpretation.

Randomised comparisons of the effect of immunomodulatory treatments on biological measurements provides reliable data that can aid the design and interpretation of further immunomodulatory therapy research.

The extended analysis results support current clinical practice in the treatment of COVID-19, contextualise the risk and benefits of treatments, and guide the most important monitoring and mitigation approaches. The RCD assessment methods developed for this study can be utilised in future research to improve our use and understanding of this data. The study provides a novel, linked dataset between RECOVERY and ISARIC4C of 25,000 patients that has rich data with the potential to be utilised in future research.

References

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/ (accessed 30 March 2024).
2. World Health Organization. WHO-convened Global Study of Origins of SARS-CoV-2: China Part. 2021. https://www.who.int/publications/i/item/who-convened-global-study-of-origins-of-sars-cov-2-china-part.
3. Sharma A, Ahmad Farouk I, Lal SK. COVID-19: A Review on the Novel Coronavirus Disease Evolution, Transmission, Detection, Control and Prevention. *Viruses* 2021; **13**(2).https://doi.org/10.3390/v13020202
4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**(10223): 497-506.https://doi.org/10.1016/s0140-6736(20)30183-5
5. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. 11 March 2020. https://tinyurl.com/hfb3t5ss.
6. Institute for Government. Timeline of UK government coronavirus lockdowns and measures, March 2020 to December 2021. 2021. https://www.instituteforgovernment.org.uk/sites/default/files/2022-12/timeline-coronavirus-lockdown-december-2021.pdf.
7. Office for National Statistics. Deaths registered in England and Wales: 2021. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregistrationsummarytables/2021.
8. World Health Organization 2023 data.who.int, WHO Coronavirus (COVID-19) dashboard > About [Dashboard]. https://data.who.int/dashboards/covid-19/about.
9. World Health Organization. Statement on the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 pandemic. 5 May 2023. https://tinyurl.com/3cja96c7.
10. Wang H, Paulson KR, Pease SA, et al. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality. *The Lancet* 2022; **399**(10334): 1513-36.https://doi.org/10.1016/S0140-6736(21)02796-3
11. Huang G, Guo F, Zimmermann KF, et al. The effect of the COVID-19 pandemic on life expectancy in 27 countries. *Scientific Reports* 2023; **13**(1): 8911.https://doi.org/10.1038/s41598-023-35592-9
12. Nishiura H, Kobayashi T, Miyama T, et al. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). *Int J Infect Dis* 2020; **94**: 154-5.https://doi.org/10.1016/j.ijid.2020.03.020
13. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**(18): 1708-20.https://doi.org/10.1056/NEJMoa2002032
14. Luo X, Lv M, Zhang X, et al. Clinical manifestations of COVID-19: An overview of 102 systematic reviews with evidence mapping. *J Evid Based Med* 2022; **15**(3): 201-15.https://doi.org/10.1111/jebm.12483
15. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet* 2020; **395**(10229): 1054-62.https://doi.org/10.1016/S0140-6736(20)30566-3
16. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020; **180**(7): 934-43.https://doi.org/10.1001/jamainternmed.2020.0994
17. Pijls BG, Jolani S, Atherley A, et al. Demographic risk factors for COVID-19 infection, severity, ICU admission and death: a meta-analysis of 59 studies. *BMJ Open* 2021; **11**(1): e044640.https://doi.org/10.1136/bmjopen-2020-044640

18. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; **584**(7821): 430-6.https://doi.org/10.1038/s41586-020-2521-4
19. Del Valle DM, Kim-Schulze S, Huang HH, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med* 2020; **26**(10): 1636-43.https://doi.org/10.1038/s41591-020-1051-9
20. Pairo-Castineira E, Clohisey S, Klaric L, et al. Genetic mechanisms of critical illness in COVID-19. *Nature* 2021; **591**(7848): 92-8.https://doi.org/10.1038/s41586-020-03065-y
21. Crook H, Raza S, Nowell J, Young M, Edison P. Long covid—mechanisms, risk factors, and management. *BMJ* 2021; **374**: n1648.https://doi.org/10.1136/bmj.n1648
22. Ni W, Yang X, Yang D, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Critical Care* 2020; **24**(1): 422.https://doi.org/10.1186/s13054-020-03120-0
23. Lamers MM, Haagmans BL. SARS-CoV-2 pathogenesis. *Nature Reviews Microbiology* 2022; **20**(5): 270-84.https://doi.org/10.1038/s41579-022-00713-0
24. Milross L, Majo J, Cooper N, et al. Post-mortem lung tissue: the fossil record of the pathophysiology and immunopathology of severe COVID-19. *The Lancet Respiratory Medicine* 2022; **10**(1): 95-106.https://doi.org/10.1016/S2213-2600(21)00408-2
25. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. https://www.covid19treatmentguidelines.nih.gov/ (accessed 1 February 2024).
26. Agarwal A, Rochwerg B, Lamontagne F, et al. A living WHO guideline on drugs for covid-19. *BMJ* 2020; **370**: m3379.https://doi.org/10.1136/bmj.m3379
27. University of Oxford. Randomised Evaluation of COVID-19 Therapy (RECOVERY) study website. https://www.recoverytrial.net/.
28. World Health Organization. WHO COVID-19 Solidarity Therapeutics Trial. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments (accessed 5 May 2024).
29. RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. *New England Journal of Medicine* 2021; **384**(8): 693-704.https://doi.org/10.1056/NEJMoa2021436
30. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; **397**(10285): 1637-45.https://doi.org/10.1016/s0140-6736(21)00676-0
31. RECOVERY Collaborative Group. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. *The Lancet* 2022; **400**(10349): 359-68.https://doi.org/10.1016/S0140-6736(22)01109-6
32. Matthay MA, Thompson BT. Dexamethasone in hospitalised patients with COVID-19: addressing uncertainties. *Lancet Respir Med* 2020; **8**(12): 1170-2.https://doi.org/10.1016/s2213-2600(20)30503-8
33. Prescott HC, Rice TW. Corticosteroids in COVID-19 ARDS: Evidence and Hope During the Pandemic. *JAMA* 2020; **324**(13): 1292-5.https://doi.org/10.1001/jama.2020.16747
34. Gupta S, Leaf DE. Tocilizumab in COVID-19: some clarity amid controversy. *The Lancet* 2021; **397**(10285): 1599-601.https://doi.org/10.1016/S0140-6736(21)00712-1
35. Barnett ML, Sax PE. Long-term Follow-up After Critical COVID-19: REMAP-CAP Revisited. *JAMA* 2023; **329**(1): 25-7.https://doi.org/10.1001/jama.2022.23700
36. Matthay MA, Luetkemeyer AF. IL-6 Receptor Antagonist Therapy for Patients Hospitalized for COVID-19: Who, When, and How? *JAMA* 2021; **326**(6): 483-5.https://doi.org/10.1001/jama.2021.11121
37. Ramzi ZS. Hospital readmissions and post-discharge all-cause mortality in COVID-19 recovered patients; A systematic review and meta-analysis. *The American Journal of Emergency Medicine* 2022; **51**: 267-79.https://doi.org/10.1016/j.ajem.2021.10.059

38. Bhaskaran K, Rentsch CT, Hickman G, et al. Overall and cause-specific hospitalisation and death after COVID-19 hospitalisation in England: A cohort study using linked primary care, secondary care, and death registration data in the OpenSAFELY platform. *PLOS Medicine* 2022; **19**(1): e1003871.https://doi.org/10.1371/journal.pmed.1003871
39. Electronic Medicines Compendium. Dexamethasone 2mg Tablets Summary of Product Characteristics: Undesirable effects. https://www.medicines.org.uk/emc/product/5411/smpc (accessed 1 Febuary 2022).
40. Johannesdottir SA, Horváth-Puhó E, Dekkers OM, et al. Use of glucocorticoids and risk of venous thromboembolism: a nationwide population-based case-control study. *JAMA Intern Med* 2013; **173**(9): 743-52.https://doi.org/10.1001/jamainternmed.2013.122
41. Fardet L, Petersen I, Nazareth I. Common Infections in Patients Prescribed Systemic Glucocorticoids in Primary Care: A Population-Based Cohort Study. *PLoS Med* 2016; **13**(5): e1002024.https://doi.org/10.1371/journal.pmed.1002024
42. Waljee AK, Rogers MA, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *Bmj* 2017; **357**: j1415.https://doi.org/10.1136/bmj.j1415
43. Yao T-C, Huang Y-W, Chang S-M, Tsai S-Y, Wu AC, Tsai H-J. Association Between Oral Corticosteroid Bursts and Severe Adverse Events. *Annals of Internal Medicine* 2020; **173**(5): 325-30.https://doi.org/10.7326/M20-0432
44. RECOVERY Collaborative Group. Higher dose corticosteroids in patients admitted to hospital with COVID-19 who are hypoxic but not requiring ventilatory support (RECOVERY): a randomised, controlled, open-label, platform trial. *The Lancet* 2023; **401**(10387): 1499-507.https://doi.org/10.1016/S0140-6736(23)00510-X
45. Electronic Medicines Compendium. RoActemra 20mg/ml Concetrate for Solution for Infusion Summary of Product Characeristics: Undesirable effects. https://www.medicines.org.uk/emc/product/6673/smpc (accessed 1 Feburary 2022).
46. Electronic Medicines Compendium. Olumiant 2mg Film-Coated Tablets Summary of Product Characteristics - Undesirable Effects. 2021. https://www.medicines.org.uk/emc/product/2434/smpc (accessed 5 April 2022).
47. UK Department of Health and Social Care. Baricitinib for Patients Hospitalised Due to COVID-19. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103203 (accessed 21 July 2022).
48. Musuuza JS, Watson L, Parmasad V, Putman-Buehler N, Christensen L, Safdar N. Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: A systematic review and meta-analysis. *PLoS ONE [Electronic Resource]* 2021; **16**(5): e0251170.https://doi.org/10.1371/journal.pone.0251170
49. Baghdadi JD, Coffey KC, Adediran T, et al. Antibiotic Use and Bacterial Infection among Inpatients in the First Wave of COVID-19: a Retrospective Cohort Study of 64,691 Patients. *Antimicrobial Agents & Chemotherapy* 2021; **65**(11): e0134121.https://doi.org/10.1128/aac.01341-21
50. Khatri A, Malhotra P, Izard S, et al. Hospital-Acquired Bloodstream Infections in Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 Infection (Coronavirus Disease 2019): association With Immunosuppressive Therapies. *Open forum infectious diseases* 2021; **8**(7): ofab339.https://doi.org/10.1093/ofid/ofab339
51. Massart N, Maxime V, Fillatre P, et al. Characteristics and prognosis of bloodstream infection in patients with COVID-19 admitted in the ICU: an ancillary study of the COVID-ICU study. *Ann Intensive Care* 2021; **11**(1): 183.https://doi.org/10.1186/s13613-021-00971-w
52. Yeo I, Baek S, Kim J, et al. Assessment of thirty-day readmission rate, timing, causes and predictors after hospitalization with COVID-19. *J Intern Med* 2021; **290**(1): 157-65.https://doi.org/10.1111/joim.13241

53. Donnelly JP, Wang XQ, Iwashyna TJ, Prescott HC. Readmission and Death After Initial Hospital Discharge Among Patients With COVID-19 in a Large Multihospital System. *JAMA* 2021; **325**(3): 304-6.https://doi.org/10.1001/jama.2020.21465
54. Rouzé A, Martin-Loeches I, Povoa P, et al. Relationship between SARS-CoV-2 infection and the incidence of ventilator-associated lower respiratory tract infections: a European multicenter cohort study. *Intensive Care Med* 2021; **47**(2): 188-98.https://doi.org/10.1007/s00134-020-06323-9
55. Gangneux JP, Dannaoui E, Fekkar A, et al. Fungal infections in mechanically ventilated patients with COVID-19 during the first wave: the French multicentre MYCOVID study. *Lancet respiratory medicine* 2021.https://doi.org/10.1016/S2213-2600(21)00442-2
56. Cona A, Tavelli A, Renzelli A, et al. Incidence, Risk Factors and Impact on Clinical Outcomes of Bloodstream Infections in Patients Hospitalised with COVID-19: a Prospective Cohort Study. *Antibiotics (Basel, Switzerland)* 2021; **10**(9).https://doi.org/10.3390/antibiotics10091031
57. Martinez Martinez M, Ramos Gomez F J, Nuvials Casals F X, Roca O, R FR. Epidemiology and risk factors of ventilator-associated pneumonia in COVID-19 patients: a propensity-score matched analysis. *Intensive care medicine experimental* 2020; **8**(SUPPL 2).https://doi.org/10.1186/s40635-020-00354-8
58. Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol* 2020; **2**(8): e474-e84.https://doi.org/10.1016/s2665-9913(20)30173-9
59. Lewis TC, Adhikari S, Tatapudi V, et al. A Propensity-Matched Cohort Study of Tocilizumab in Patients With Coronavirus Disease 2019. *Crit Care Explor* 2020; **2**(11): e0283.https://doi.org/10.1097/cce.0000000000000283
60. Falcone M, Tiseo G, Giordano C, et al. Predictors of hospital-acquired bacterial and fungal superinfections in COVID-19: a prospective observational study. *Journal of Antimicrobial Chemotherapy* 2021; **76**(4): 1078-84.https://doi.org/10.1093/jac/dkaa530
61. Katsoularis I, Fonseca-Rodríguez O, Farrington P, et al. Risks of deep vein thrombosis, pulmonary embolism, and bleeding after covid-19: nationwide self-controlled cases series and matched cohort study. *Bmj* 2022; **377**: e069590.https://doi.org/10.1136/bmj-2021-069590.
62. Knight R, Walker V, Ip S, et al. Association of COVID-19 With Major Arterial and Venous Thrombotic Diseases: A Population-Wide Cohort Study of 48 Million Adults in England and Wales. *Circulation* 2022; **146**(12): 892-906.https://doi.org/10.1161/circulationaha.122.060785
63. Pranata R, Huang I, Lim MA, Yonas E, Vania R, Kuswardhani RAT. Delirium and Mortality in Coronavirus Disease 2019 (COVID-19) – A Systematic Review and Meta-analysis. *Archives of Gerontology and Geriatrics* 2021; **95**: 104388.https://doi.org/10.1016/j.archger.2021.104388
64. Shao S-C, Lai C-C, Chen Y-H, Chen Y-C, Hung M-J, Liao S-C. Prevalence, incidence and mortality of delirium in patients with COVID-19: a systematic review and meta-analysis. *Age and Ageing* 2021; **50**(5): 1445-53.https://doi.org/10.1093/ageing/afab103
65. Chew M, Tang Z, Radcliffe C, et al. Significant Liver Injury During Hospitalization for COVID-19 Is Not Associated With Liver Insufficiency or Death. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2021; **19**(10): 2182-91.e7.https://doi.org/10.1016/j.cgh.2021.05.022
66. Xu Z, Wang Z, Wang S, et al. The impact of type 2 diabetes and its management on the prognosis of patients with severe COVID-19. *Journal Of Diabetes* 2020; **12**(12): 909-18.https://doi.org/10.1111/1753-0407.13084
67. Rathmann W, Kuss O, Kostev K. Incidence of newly diagnosed diabetes after Covid-19. *Diabetologia* 2022: 1-6.https://doi.org/10.1007/s00125-022-05670-0

68. Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. *The Lancet Diabetes & Endocrinology* 2022.https://doi.org/10.1016/s2213-8587(22)00044-4
69. Office for National Statistics. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 30 March 2023.
70. Evans RA, McAuley H, Harrison EM, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. *The Lancet Respiratory Medicine* 2021; **9**(11): 1275-87.https://doi.org/10.1016/S2213-2600(21)00383-0
71. Sigfrid L, Drake TM, Pauley E, et al. Long Covid in adults discharged from UK hospitals after Covid-19: A prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol. *The Lancet Regional Health – Europe* 2021; **8**.https://doi.org/10.1016/j.lanepe.2021.100186
72. Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. *Nature Medicine* 2021; **27**(4): 626-31.https://doi.org/10.1038/s41591-021-01292-y
73. Michelen M, Manoharan L, Elkheir N, et al. Characterising long COVID: a living systematic review. *BMJ Global Health* 2021; **6**(9): 09.https://doi.org/10.1136/bmjgh-2021-005427
74. Barnes PJ. How corticosteroids control inflammation: Quintiles Prize Lecture 2005. *British Journal of Pharmacology* 2006; **148**(3): 245-54.https://doi.org/10.1038/sj.bjp.0706736
75. Stahn C, Buttgereit F. Genomic and nongenomic effects of glucocorticoids. *Nat Clin Pract Rheumatol* 2008; **4**(10): 525-33.https://doi.org/10.1038/ncprheum0898
76. Collins R, Bowman L, Landray M, Peto R. The Magic of Randomization versus the Myth of Real-World Evidence. *New England Journal of Medicine* 2020; **382**(7): 674-8.https://doi.org/10.1056/NEJMsb1901642
77. Peto R, Collins R, Gray R. Large-scale randomized evidence: large, simple trials and overviews of trials. *J Clin Epidemiol* 1995; **48**(1): 23-40.https://doi.org/10.1016/0895-4356(94)00150-o
78. NHS Central Alerting System. Dexamethasone in the treatment of COVID-19: Implementation and management of supply for treatment in hospitals. 2020. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103054 (accessed 14th December 2022).
79. Cochrane. Cochrane COVID-19 Study Register. https://covid-19.cochrane.org/ (accessed 26 September 2022).
80. COVID-NMA COVID-19 Open Living Evidence Synthesis to Inform Decision. A living mapping and living systematic review of Covid-19 trials. https://covid-nma.com (accessed 26 September 2022).
81. Cochrane. Cochrane Handbook for Systematic Reviews of Interventions, Chapter 4: Searching for and selecting studies, Section 4.4.7 Search filters. 2023. https://training.cochrane.org/handbook/current/chapter-04#section-4-4-7 (accessed 21 January 2024).
82. Fraser N, Brierley L, Dey G, et al. The evolving role of preprints in the dissemination of COVID-19 research and their impact on the science communication landscape. *PLOS Biology* 2021; **19**(4): e3000959.https://doi.org/10.1371/journal.pbio.3000959
83. Glasziou PP, Sanders S, Hoffmann T. Waste in covid-19 research. *BMJ* 2020; **369**: m1847.https://doi.org/10.1136/bmj.m1847
84. Metzendorf M-I, Featherstone RM. Evaluation of the comprehensiveness, accuracy and currency of the Cochrane COVID-19 Study Register for supporting rapid evidence synthesis production. *Research Synthesis Methods* 2021; **12**(5): 607-17.https://doi.org/10.1002/jrsm.1501
85. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Original methods for RBCTCG meta-analysis. *Worldwide Evidence, Oxford University Press* 1990;

1.https://www.ctsu.ox.ac.uk/research/the-early-breast-cancer-trialists-collaborative-group-ebctcg/original-methods-for-ebctcg-meta-analyses
86. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023), Chapter 10: Analysing data and undertaking meta-analyses.: Cochrane; 2023.
87. Cochrane Methods. Risk of Bias 2 (RoB 2) tool. https://methods.cochrane.org/risk-bias-2 (accessed 11 October 2022).
88. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *Bmj* 2004; **328**(7454): 1490.https://doi.org/10.1136/bmj.328.7454.1490
89. Jeronimo CMP, Farias MEL, Val FFA, et al. Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With Coronavirus Disease 2019 (COVID-19; Metcovid): A Randomized, Double-blind, Phase IIb, Placebo-controlled Trial. *Clinical Infectious Diseases* 2021; **72**(9): e373-e81.https://doi.org/10.1093/cid/ciaa1177
90. Barros C, Freire RS, Frota E, et al. Short-Course of Methylprednisolone Improves Respiratory Functional Parameters After 120 Days in Hospitalized COVID-19 Patients (Metcovid Trial): A Randomized Clinical Trial. *Front Med (Lausanne)* 2021; **8**: 758405.https://doi.org/10.3389/fmed.2021.758405
91. Angus DC, Derde L, Al-Beidh F, et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. *JAMA* 2020; **324**(13): 1317-29.https://doi.org/10.1001/jama.2020.17022
92. Writing Committee for the Remap-Cap Investigators HAMBLRLEMSMZMPRA-BFA. Long-term (180-Day) Outcomes in Critically Ill Patients With COVID-19 in the REMAP-CAP Randomized Clinical Trial. *Jama* 2023; **329**(1): 39-51.https://doi.org/10.1001/jama.2022.23257
93. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. *JAMA* 2020; **324**(13): 1307-16.https://doi.org/10.1001/jama.2020.17021
94. Dequin PF, Heming N, Meziani F, et al. Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial. *JAMA* 2020; **324**(13): 1298-306.https://doi.org/10.1001/jama.2020.16761
95. Tang X, Feng YM, Ni JX, et al. Early Use of Corticosteroid May Prolong SARS-CoV-2 Shedding in Non-Intensive Care Unit Patients with COVID-19 Pneumonia: A Multicenter, Single-Blind, Randomized Control Trial. *Respiration* 2021; **100**(2): 116-26.https://doi.org/10.1159/000512063
96. Les I, Loureiro-Amigo J, Capdevila F, et al. Methylprednisolone Pulses in Hospitalized COVID-19 Patients Without Respiratory Failure: A Randomized Controlled Trial. *Frontiers in Medicine* 2022; **9**.https://doi.org/10.3389/fmed.2022.807981
97. Edalatifard M, Akhtari M, Salehi M, et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. *European Respiratory Journal* 2020; **56**(6): 12.https://doi.org/10.1183/13993003.02808-2020
98. Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, et al. Methylprednisolone in adults hospitalized with COVID-19 pneumonia : An open-label randomized trial (GLUCOCOVID). *Wiener Klinische Wochenschrift* 2021; **133**(7-8): 303-11.https://doi.org/10.1007/s00508-020-01805-8
99. Jamaati H, Hashemian SM, Farzanegan B, et al. No clinical benefit of high dose corticosteroid administration in patients with COVID-19: A preliminary report of a randomized clinical trial. *European Journal of Pharmacology* 2021; **897**: 173947.https://doi.org/10.1016/j.ejphar.2021.173947

100. Odeyemi YE, Chalmers SJ, Barreto EF, Jentzer JC, Gajic O, Yadav H. Early, biomarker-guided steroid dosing in COVID-19 Pneumonia: a pilot randomized controlled trial. *Crit Care* 2022; **26**(1): 9.https://doi.org/10.1186/s13054-021-03873-2.
101. Munch MW, Meyhoff TS, Helleberg M, et al. Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia: The COVID STEROID randomised, placebo-controlled trial. *Acta Anaesthesiologica Scandinavica* 2021; **65**(10): 1421-30.https://doi.org/10.1111/aas.13941
102. Munch MW, Granholm A, Kjær M-BN, et al. Long-term mortality and health-related quality of life in the COVID STEROID trial. *Acta Anaesthesiologica Scandinavica* 2022; **66**(4): 543-5.https://doi.org/10.1111/aas.14029
103. Farahani RH, Mosaed R, Nezami-Asl A, et al. Evaluation of the Efficacy of Methylprednisolone Pulse Therapy in Treatment of Covid-19 Adult Patients with Severe Respiratory Failure: Randomized, Clinical Trial. 2020.https://doi.org/10.21203/rs.3.rs-66909/v1
104. Sivapalasingam S, Lederer DJ, Bhore R, et al. Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2022.https://doi.org/10.1093/cid/ciac153
105. Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. *N Engl J Med* 2021; **384**(16): 1491-502.https://doi.org/10.1056/NEJMoa2100433
106. Rosas IO, Diaz G, Gottlieb RL, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. *Intensive Care Medicine* 2021; **47**(11): 1258-70.https://doi.org/10.1007/s00134-021-06507-x
107. Hermine O, Mariette X, Porcher R, et al. Tocilizumab plus dexamethasone versus dexamethasone in patients with moderate-to-severe COVID-19 pneumonia: A randomised clinical trial from the CORIMUNO-19 study group. *eClinicalMedicine* 2022; **46**: 101362.https://doi.org/10.1016/j.eclinm.2022.101362
108. Rosas IO, Bräu N, Waters M, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. *N Engl J Med* 2021; **384**(16): 1503-16.https://doi.org/10.1056/NEJMoa2028700
109. Lescure FX, Honda H, Fowler RA, et al. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2021; **9**(5): 522-32.https://doi.org/10.1016/s2213-2600(21)00099-0
110. Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. 2020; **384**(1): 20-30.https://doi.org/10.1056/NEJMoa2030340
111. Rutgers A, Westerweel PE, van der Holt B, et al. Timely administration of tocilizumab improves outcome of hospitalized COVID-19 patients. *PLoS One* 2022; **17**(8): e0271807.https://doi.org/10.1371/journal.pone.0271807
112. Declercq J, Van Damme KFA, De Leeuw E, et al. Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. *The Lancet Respiratory Medicine* 2021; **9**(12): 1427-38.https://doi.org/10.1016/S2213-2600(21)00377-5
113. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. *New England Journal of Medicine* 2020; **383**(24): 2333-44.https://doi.org/10.1056/NEJMoa2028836
114. Sancho-López A, Caballero-Bermejo AF, Ruiz-Antorán B, et al. Efficacy and Safety of Sarilumab in patients with COVID19 Pneumonia: A Randomized, Phase III Clinical Trial (SARTRE Study). *Infect Dis Ther* 2021; **10**(4): 2735-48.https://doi.org/10.1007/s40121-021-00543-2
115. Malik MI, Zafar SAF, Qayyum F, et al. Tocilizumab in severe COVID-19 – A randomized, double-blind, placebo-controlled trial. *Infectious Medicine* 2022; **1**(2): 88-94.https://doi.org/10.1016/j.imj.2022.05.001

116. Mastrorosa I, Gagliardini R, Segala FV, et al. Sarilumab plus standard of care vs standard of care for the treatment of severe COVID-19: a phase 3, randomized, open-labeled, multi-center study (ESCAPE study). *eClinicalMedicine* 2023; **57**.https://doi.org/10.1016/j.eclinm.2023.101895
117. Soin AS, Kumar K, Choudhary NS, et al. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. *Lancet Respir Med* 2021; **9**(5): 511-21.https://doi.org/10.1016/S2213-2600(21)00081-3
118. CORIMUNO-19 Collaborative group. Sarilumab in adults hospitalised with moderate-to-severe COVID-19 pneumonia (CORIMUNO-SARI-1): An open-label randomised controlled trial. *Lancet Rheumatol* 2022; **4**(1): e24-e32.https://doi.org/10.1016/S2665-9913(21)00315-5
119. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med* 2021; **181**(1): 32-40.https://doi.org/10.1001/jamainternmed.2020.6820
120. Veiga VC, Prats J, Farias DLC, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *Bmj* 2021; **372**: n84.https://doi.org/10.1136/bmj.n84
121. Salvarani C, Dolci G, Massari M, et al. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med* 2021; **181**(1): 24-31.https://doi.org/10.1001/jamainternmed.2020.6615
122. Merchante N, Cárcel S, Garrido-Gracia JC, et al. Early Use of Sarilumab in Patients Hospitalized with COVID-19 Pneumonia and Features of Systemic Inflammation: the SARICOR Randomized Clinical Trial. 2022; **66**(2): e02107-21.https://doi.org/10.1128/aac.02107-21
123. Swadi AA, Shlash RF, Dibby HJ, Kadhim SAA, Abas SM. Efficacy of Tocilizumab among Severe COVID-19 patients. *HIV Nursing* 2022; **22**(2).https://hivnursing.net/index.php/hiv/article/view/355
124. Rabie ASI, Salah H, Said ASA, et al. Clinical Consequences for Individuals Treated with Tocilizumab for Serious COVID-19 Infection. *Healthcare (Basel)* 2023; **11**(4).https://doi.org/10.3390/healthcare11040607
125. Hermine O, Mariette X, Porcher R, Resche-Rigon M, Tharaux PL, Ravaud P. Effect of Interleukin-6 Receptor Antagonists in Critically Ill Adult Patients with COVID-19 Pneumonia: two Randomised Controlled Trials of the CORIMUNO-19 Collaborative Group. *Eur Respir J* 2022.https://doi.org/10.1183/13993003.02523-2021
126. Broman N, Feuth T, Vuorinen T, et al. Early administration of tocilizumab in hospitalized COVID-19 patients with elevated inflammatory markers; COVIDSTORM-a prospective, randomized, single-centre, open-label study. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2022.https://doi.org/10.1016/j.cmi.2022.02.027
127. Wang D, Fu B, Peng Z, et al. Tocilizumab in patients with moderate or severe COVID-19: a randomized, controlled, open-label, multicenter trial. *Frontiers of medicine* 2021; **15**(3): 486-94.https://doi.org/10.1007/s11684-020-0824-3
128. Branch-Elliman W, Ferguson R, Doros G, et al. Subcutaneous sarilumab for the treatment of hospitalized patients with moderate to severe COVID19 disease: A pragmatic, embedded randomized clinical trial. *PLOS ONE* 2022; **17**(2): e0263591.https://doi.org/10.1371/journal.pone.0263591
129. Sunden-Cullberg J, Chen P, Habel H, et al. Anakinra or tocilizumab in patients admitted to hospital with severe covid-19 at high risk of deterioration (IMMCoVA): A randomized, controlled, open-label trial. *PLoS ONE* 2023; **18**(12): e0295838.https://dx.doi.org/10.1371/journal.pone.0295838

130. Talaschian M, Akhtari M, Mahmoudi M, et al. Tocilizumab Failed to Reduce Mortality in Severe COVID-19 Patients: Results from a Randomized Controlled Clinical Trial. *Iran J Allergy Asthma Immunol* 2024; **23**(1): 82-96.https://doi.org/10.18502/ijaai.v23i1.14956.
131. García-Vicuña R, Rodriguez-García SC, Abad-Santos F, et al. Subcutaneous IL-6 Inhibitor Sarilumab vs. Standard Care in Hospitalized Patients With Moderate-To-Severe COVID-19: An Open Label Randomized Clinical Trial. *Front Med (Lausanne)* 2022; **9**: 819621.https://doi.org/10.3389/fmed.2022.819621
132. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med* 2021; **9**(12): 1407-18.https://doi.org/10.1016/S2213-2600(21)00331-3
133. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med* 2021; **384**(9): 795-807.https://doi.org/10.1056/NEJMoa2031994
134. Han MK, Antila M, Ficker JH, et al. Ruxolitinib in addition to standard of care for the treatment of patients admitted to hospital with COVID-19 (RUXCOVID): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Rheumatol* 2022.https://doi.org/10.1016/S2665-9913(22)00044-3
135. Guimarães PO, Quirk D, Furtado RH, et al. Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. *New England Journal of Medicine* 2021; **385**(5): 406-15.https://doi.org/10.1056/NEJMoa2101643
136. Montejano R, de la Calle-Prieto F, Velasco M, et al. Tenofovir Disoproxil Fumarate/Emtricitabine and Baricitinib for Patients at High Risk of Severe Coronavirus Disease 2019: The PANCOVID Randomized Clinical Trial. *Clinical Infectious Diseases* 2022.https://doi.org/10.1093/cid/ciac628
137. Trøseid M, Arribas JR, Assoumou L, et al. Efficacy and safety of baricitinib in hospitalized adults with severe or critical COVID-19 (Bari-SolidAct): a randomised, double-blind, placebo-controlled phase 3 trial. *Crit Care* 2023; **27**(1): 9.https://doi.org/10.1186/s13054-022-04205-8.
138. Hall FC, Cheriyan J, Cope AP, et al. Efficacy and safety of baricitinib or ravulizumab in adult patients with severe COVID-19 (TACTIC-R): a randomised, parallel-arm, open-label, phase 4 trial. *Lancet Respir Med* 2023; **11**(12): 1064-74.https://dx.doi.org/10.1016/S2213-2600(23)00376-4
139. Rein L, Calero K, Shah R, et al. Randomized Phase 3 Trial of Ruxolitinib for COVID-19-Associated Acute Respiratory Distress Syndrome. *Crit Care Med* 2022; **50**(12): 1701-13.https://doi.org/10.1097/CCM.0000000000005682
140. Cafardi J, Miller C, Terebelo H, et al. Efficacy and Safety of Pacritinib vs Placebo for Patients With Severe COVID-19: A Phase 2 Randomized Clinical Trial. *JAMA Network Open* 2022; **5**(12): e2242918-e.https://doi.org/10.1001/jamanetworkopen.2022.42918
141. Ferrarini A, Vacca A, Solimando AG, et al. Early administration of tofacitinib in COVID-19 pneumonitis: An open randomised controlled trial. *European Journal of Clinical Investigation* 2023; **53**(2): e13898.https://doi.org/10.1111/eci.13898
142. Morales-Ortega A, Farfán-Sedano AI, San Martín-López JV, et al. Baricitinib or imatinib in hospitalized COVID-19 patients: Results from COVINIB, an exploratory randomized clinical trial. *Journal of Medical Virology* 2023; **95**(2): e28495.https://doi.org/10.1002/jmv.28495
143. Ely EW, Ramanan AV, Kartman CE, et al. Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial. *Lancet Respir Med* 2022; **10**(4): 327-36.https://doi.org/10.1016/S2213-2600(22)00006-6
144. Murugesan H, Cs G, Nasreen HS, et al. An Evaluation of Efficacy and Safety of Tofacitinib, A JAK Inhibitor in the Management of Hospitalized Patients with Mild to

Moderate COVID-19 - An Open-Label Randomized Controlled Study. *J Assoc Physicians India* 2022; **69**(12): 11-2.https://pubmed.ncbi.nlm.nih.gov/35057599/
145. Dastan F, Jamaati H, Barati S, et al. The effects of combination-therapy of tocilizumab and baricitinib on the management of severe COVID-19 cases: a randomized open-label clinical trial. *Front Pharmacol* 2023; **14**: 1265541.https://dx.doi.org/10.3389/fphar.2023.1265541
146. Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol* 2020; **146**(1): 137-46.e3.https://doi.org/10.1016/j.jaci.2020.05.019
147. Covid Steroid Trial Group, Munch MW, Myatra SN, et al. Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults With COVID-19 and Severe Hypoxemia: The COVID STEROID 2 Randomized Trial. *JAMA* 2021; **326**(18): 1807-17
148. Granholm A, Kjær MN, Munch MW, et al. Long-term outcomes of dexamethasone 12 mg versus 6 mg in patients with COVID-19 and severe hypoxaemia. *Intensive Care Med* 2022; **48**(5): 580-9.https://doi.org/10.1007/s00134-022-06677-2
149. Salton F, Confalonieri P, Centanni S, et al. Prolonged higher dose methylprednisolone vs. conventional dexamethasone in COVID-19 pneumonia: a randomised controlled trial (MEDEAS). *European Respiratory Journal* 2022: 2201514.https://doi.org/10.1183/13993003.01514-2022
150. Bouadma L, Mekontso-Dessap A, Burdet C, et al. High-Dose Dexamethasone and Oxygen Support Strategies in Intensive Care Unit Patients With Severe COVID-19 Acute Hypoxemic Respiratory Failure: The COVIDICUS Randomized Clinical Trial. *JAMA Internal Medicine* 2022.https://doi.org/10.1001/jamainternmed.2022.2168
151. Salvarani C, Massari M, Costantini M, et al. Intravenous methylprednisolone pulses in hospitalised patients with severe COVID-19 pneumonia, A double-blind, randomised, placebo-controlled trial. *Eur Respir J* 2022.https://doi.org/10.1183/13993003.00025-2022
152. Taboada M, Rodríguez N, Varela PM, et al. Effect of high versus low dose of dexamethasone on clinical worsening in patients hospitalised with moderate or severe COVID-19 Pneumonia: an open-label, randomised clinical trial. *Eur Respir J* 2021.https://doi.org/10.1183/13993003.02518-2021.
153. Toroghi N, Abbasian L, Nourian A, et al. Comparing efficacy and safety of different doses of dexamethasone in the treatment of COVID-19: a three-arm randomized clinical trial. *Pharmacol Rep* 2022; **74**(1): 229-40.https://doi.org/10.1007/s43440-021-00341-0
154. Dastenae ZH, Bahadori A, Dehghani M, Asadi-Samani M, Izadi I, Shahraki HR. Comparison of the effect of intravenous dexamethasone and methylprednisolone on the treatment of hospitalized patients with COVID-19: A randomized clinical trial. *Int J Infect Dis* 2022; **122**: 659-64.https://doi.org/10.1016/j.ijid.2022.07.019.
155. Rabascall CX, Lou BX, Dhar S, et al. Randomized Open Investigation Determining Steroid Dose in Severe COVID-19: The ROIDS-Dose Clinical Trial. *Cureus* 2022; **14**(11): e31086.https://doi.org/10.7759/cureus.31086
156. Gautam PB, Kumar A, Kannojia BL, Chaudhary R. A comparative study of the efficacy and outcome of methylprednisolone and dexamethasone in moderate to severe COVID-19 disease. *Asian Journal of Medical Sciences* 2021; **12**(12): 17-22.https://doi.org/10.3126/ajms.v12i12.39294
157. Corral-Gudino L, Cusacovich I, Martín-González JI, et al. Effect of intravenous pulses of methylprednisolone 250 mg versus dexamethasone 6 mg in hospitalised adults with severe COVID-19 pneumonia: An open-label randomised trial. *European Journal of Clinical Investigation*; **n/a**(n/a): e13881.https://doi.org/10.1111/eci.13881
158. Sadeghi S, Arezoomandi N, Ardestani MM, Ardestani ME, Ghiasi F, Farajzadegan Z. Efficacy and Safety Comparison of Two Different Doses of Dexamethasone in Hospitalized Patients with COVID-19: A Randomized Clinical Trial. *Journal of Research in Pharmacy Practice* 2022; **11**(4): 136-43.https://dx.doi.org/10.4103/jrpp.jrpp_42_22

159. Wu H, Daouk S, Kebbe J, Chaudry F, Harper J, Brown B. Low-dose versus high-dose dexamethasone for hospitalized patients with COVID-19 pneumonia: A randomized clinical trial. *PLOS ONE* 2022; **17**(10): e0275217.https://doi.org/10.1371/journal.pone.0275217
160. Maskin LP, Bonelli I, Olarte GL, et al. High- Versus Low-Dose Dexamethasone for the Treatment of COVID-19-Related Acute Respiratory Distress Syndrome: A Multicenter, Randomized Open-Label Clinical Trial. *J Intensive Care Med* 2022; **37**(4): 491-9.https://doi.org/10.1177/08850666211066799
161. Ranjbar K, Moghadami M, Mirahmadizadeh A, et al. Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: a triple-blinded randomized controlled trial. *BMC Infect Dis* 2021; **21**(1): 337.https://doi.org/10.1186/s12879-021-06045-3.
162. Montalvan E, Carcamo B, Palacion D, et al. High-dose vs low-dose dexamethasone in patients with COVID-19 in a tertiary hospital in western Honduras. *Chest* 2021; **160**(4): A1117-A8.https://doi.org/10.1016/j.chest.2021.07.1027
163. Soliman OM, Moeen SM, Abbas YA, Kamel EZ. The impact of dexamethasone versus methylprednisolone upon neutrophil/lymphocyte ratio in COVID-19 patients admitted to ICU and its implication upon mortality. *Egyptian Journal of Anaesthesia* 2022; **38**(1): 78-84.https://doi.org/10.1080/11101849.2021.2024985
164. Schroll JB, Maund E, Gøtzsche PC. Challenges in Coding Adverse Events in Clinical Trials: A Systematic Review. *PLOS ONE* 2012; **7**(7): e41174.https://doi.org/10.1371/journal.pone.0041174
165. Ioannidis JPA, Lau J. Completeness of Safety Reporting in Randomized TrialsAn Evaluation of 7 Medical Areas. *JAMA* 2001; **285**(4): 437-43.https://doi.org/10.1001/jama.285.4.437
166. Fitzpatrick T, Perrier L, Shakik S, et al. Assessment of Long-term Follow-up of Randomized Trial Participants by Linkage to Routinely Collected Data: A Scoping Review and Analysis. *JAMA Network Open* 2018; **1**(8): e186019.https://doi.org/10.1001/jamanetworkopen.2018.6019
167. Kumar G, Patel D, Odeh T, et al. Incidence of Venous Thromboembolism and Effect of Anticoagulant Dosing in Hospitalized COVID-19 Patients. *J Hematol* 2020; **10**(4): 162-70.https://doi.org/10.14740/jh836
168. Katzenschlager S, Zimmer AJ, Gottschalk C, et al. Can we predict the severe course of COVID-19 - a systematic review and meta-analysis of indicators of clinical outcome? *PLOS ONE* 2021; **16**(7): e0255154.https://doi.org/10.1371/journal.pone.0255154
169. Malik P, Patel U, Mehta D, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. *BMJ Evidence-Based Medicine* 2021; **26**(3): 107-8.https://doi.org/10.1136/bmjebm-2020-111536
170. Wong HS, Guo CL, Lin GH, Lee KY, Okada Y, Chang WC. Transcriptome network analyses in human coronavirus infections suggest a rational use of immunomodulatory drugs for COVID-19 therapy. *Genomics* 2021; **113**(2): 564-75.https://doi.org/10.1016/j.ygeno.2020.12.041
171. Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M. Corticosteroids for pneumonia. *Cochrane Database Syst Rev* 2017; **12**(12): Cd007720.https://doi.org//10.1002/14651858.CD007720.pub3
172. Saleem N, Kulkarni A, Snow TAC, Ambler G, Singer M, Arulkumaran N. Effect of Corticosteroids on Mortality and Clinical Cure in Community-Acquired Pneumonia: A Systematic Review, Meta-analysis, and Meta-regression of Randomized Control Trials. *CHEST* 2023; **163**(3): 484-97.https://doi.org/10.1016/j.chest.2022.08.2229
173. Wu J-Y, Tsai Y-W, Hsu W-H, et al. Efficacy and safety of adjunctive corticosteroids in the treatment of severe community-acquired pneumonia: a systematic review and meta-analysis of randomized controlled trials. *Critical Care* 2023; **27**(1): 274.https://doi.org/10.1186/s13054-023-04561-z

174. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015; **12**(10): e1001885.https://doi.org/10.1371/journal.pmed.1001885
175. University of Oxford. RECOVERY Trial Randomisation Case Report Form. https://www.recoverytrial.net/files/recovery-randomisation-form-v20-00-covid-19-adult-2024-01-08.pdf (accessed 25 May 2024).
176. University of Oxford. RECOVERY Trial Follow-up Case Report Form. https://www.recoverytrial.net/files/recovery-follow-up-crf-v20-0.pdf (accessed 31 October 2022).
177. University of Oxford. Randomised Evaluation of COVID-19 Therapy (RECOVERY) Definitions and Derivations of Baseline Characteristics and Outcomes version 4.0. https://www.recoverytrial.net/files/recovery-outcomes-definitions-v4-0.pdf (accessed 2 May 2022).
178. NHS Digital. Hospital Episode Statistics (HES). updated 6 June 2022. https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics (accessed 28 July 2022).
179. World Health Organization. International Statistical Classification of Diseases and Related Health Problems. https://www.who.int/standards/classifications/classification-of-diseases (accessed 20 September 2022).
180. NHS Digital. OPCS-4. https://digital.nhs.uk/services/terminology-and-classifications/clinical-classifications (accessed 25 May 2024).
181. Public Health Scotland. SMR Data Manual. https://publichealthscotland.scot/services/national-data-catalogue/smr-data-manual/ (accessed 25 May 2024).
182. Digital Health and Care Wales. PEDW Data Online. https://dhcw.nhs.wales/information-services/health-intelligence/pedw-data-online/ (accessed 28 July 2022).
183. NHS Digital. Linked HES-ONS mortality data. updated 15 January 2020. https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/linked-hes-ons-mortality-data#using-hes-data-alone-to-analyse-deaths (accessed 28 July 2022).
184. National Records of Scotland. NHS Central Register Vital Events and Medical Research FAQ. https://www.nrscotland.gov.uk/statistics-and-data/nhs-central-register/vital-events-and-medical-research-faq (accessed 28 July 2022).
185. NHS Digital. GPES data for pandemic planning and research (COVID-19). updated 26 April 2022. https://digital.nhs.uk/coronavirus/gpes-data-for-pandemic-planning-and-research (accessed 28 July 2022).
186. NHS Digital. General Practice Extraction Service (GPES) Data for pandemic planning and research: a guide for analysts and users of the data. updated 8 June 2022. https://digital.nhs.uk/coronavirus/gpes-data-for-pandemic-planning-and-research/guide-for-analysts-and-users-of-the-data#top (accessed 28 July 2022).
187. NHS Digital. SNOMED CT. https://digital.nhs.uk/services/terminology-and-classifications/snomed-ct (accessed 20 September 2022).
188. Health Data Research Innovation Gateway. Welsh Longitudinal General Practice Dataset (WLGP) - Welsh Primary Care. https://web.www.healthdatagateway.org/dataset/33fc3ffd-aa4c-4a16-a32f-0c900aaea3d2 (accessed 5 February 2024).
189. NHS Digital. Terminology and Classifications: Read Codes. https://digital.nhs.uk/services/terminology-and-classifications/read-codes (accessed 5 February 2024).
190. NHS Digital. Medicines dispensed in Primary Care NHS Business Service Authority Data. updated 20 January 2022. https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/medicines-dispensed-in-primary-care-nhsbsa-data (accessed 28 July 2022).

191. Bennett Institute for Applied Data Science. Prescribing Data: BNF Codes. https://tinyurl.com/5aydje8h (accessed 20 September 2022).
192. Public Health England. Laboratory reporting to Public Health England, A guide for diagnostic laboratories. updated October 2020. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/926838/PHE_Laboratory_reporting_guidelines_October-2020-v3.pdf (accessed 28 July 2022).
193. Public Health England. Mandatory Healthcare Associated Infection Surveillance: Data Quality Statement October 2020. https://tinyurl.com/4u499fdh (accessed 2 May 2022).
194. NHS Digital. COVID-19 UK Non-hospital Antigen Testing Results (pillar 2). https://digital.nhs.uk/services/data-services-for-commissioners/datasets/covid-19-uk-non-hospital-antigen-testing-results-pillar-2 (accessed 10 February 2024).
195. International Severe Acute Respiratory Disease Consortium. ISARIC/WHO COVID-19 Core Case Report Form. https://isaricdev.wpenginepowered.com/wp-content/uploads/2021/02/ISARIC-WHO-COVID-19-CORE-CRF_EN.pdf (accessed 31 October 2022).
196. International Severe Acute Respiratory Disease Consortium. ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections in the UK version 3.2. https://tinyurl.com/5n775bsb (accessed 31 October 2022).
197. RECOVERY Collaborative Group. Lopinavir and ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *The Lancet* 2020; **396**(10259): 1345-52.https://doi.org/10.1016/S0140-6736(20)32013-4
198. RECOVERY Collaborative Group. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med* 2020; **383**(21): 2030-40.https://doi.org/10.1056/NEJMoa2022926
199. RECOVERY Collaborative Group. Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *The Lancet* 2021; **397**(10274): 605-12.https://doi.org/10.1016/S0140-6736(21)00149-5
200. RECOVERY Collaborative Group. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *The Lancet Respiratory Medicine* 2021; **9**(12): 1419-26.https://doi.org/10.1016/S2213-2600(21)00435-5
201. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. *The Lancet* 2021; **397**(10289): 2049-59.https://doi.org/10.1016/S0140-6736(21)00897-7
202. RECOVERY Collaborative Group. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *The Lancet* 2022; **399**(10320): 143-51.https://doi.org/10.1016/S0140-6736(21)01825-0
203. RECOVERY Collaborative Group. Empagliflozin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *The Lancet Diabetes & Endocrinology* 2023; **11**(12): 905-14.https://doi.org/10.1016/S2213-8587(23)00253-X
204. RECOVERY Collaborative Group. Dimethyl fumarate in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Nature Communications* 2024; **15**(1): 924.https://doi.org/10.1038/s41467-023-43644-x
205. Horby PW, Staplin N, Peto L, et al. Molnupiravir or nirmatrelvir-ritonavir versus usual care in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *medRxiv* 2024: 2024.05.23.24307731.https://doi.org/10.1101/2024.05.23.24307731
206. RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *The Lancet* 2022; **399**(10325): 665-76.https://doi.org/10.1016/S0140-6736(22)00163-5

207. University of Oxford. Randomised Evaluation of COVID-19 Therapies (RECOVERY) trial Statistical Analysis Plan. https://www.recoverytrial.net/files/recovery-sap-v4-0_2022-09-20.pdf (accessed 22 September 2022).
208. NHS Digital. The processing cycle and HES data quality. updated 20 July 2022. https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics/the-processing-cycle-and-hes-data-quality#sus-and-hes-data-quality (accessed 28 July 2022).
209. NHS Digital. Hospital Admitted Patient Care Activity, 2021-22. https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 (accessed 12 January 2023).
210. NHS Digital. National Clinical Coding Standards ICD-10 5th Edition. 2021. https://classbrowser.nhs.uk/ICD-10-5TH-Edition/NCCS.pdf.
211. NHS Digital. NHS Technology Reference Update Distribution, NHS UK Read Codes https://isd.digital.nhs.uk/trud/users/guest/filters/2/categories/9 (accessed 6 July 2023).
212. Walker AJ, MacKenna B, Inglesby P, et al. Clinical coding of long COVID in English primary care: a federated analysis of 58 million patient records in situ using OpenSAFELY. *Br J Gen Pract* 2021; **71**(712): e806-e14.https://doi.org/10.3399/BJGP.2021.0301.
213. EASL Clinical Practice Guidelines: Drug-induced liver injury. *J Hepatol* 2019; **70**(6): 1222-61.https://doi.org/10.1016/j.jhep.2019.02.014
214. Office for National Statistics. Guidance for doctors completing Medical Certificates of Cause of Death in England and Wales. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1062236/Guidance_for_Doctors_completing_medical_certificates_Mar_22.pdf (accessed 25 May 2024).
215. Fioredda F, Skokowa J, Tamary H, et al. The European Guidelines on Diagnosis and Management of Neutropenia in Adults and Children: A Consensus Between the European Hematology Association and the EuNet-INNOCHRON COST Action. *Hemasphere* 2023; **7**(4): e872.https://doi.org/10.1097/hs9.0000000000000872
216. World Health Organization. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia. 2006. https://www.who.int/publications/i/item/definition-and-diagnosis-of-diabetes-mellitus-and-intermediate-hyperglycaemia (accessed 3 March 2023).
217. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012; **120**(4): c179-84.https://doi.org/10.1159/000339789
218. NHS Digital. COVID-19 - high risk shielded patient list identification methodology: Rule Logic; Clinical Inclusion criteria. https://digital.nhs.uk/coronavirus/shielded-patient-list/methodology/rule-logic (accessed 16 March 2022).
219. UK Health Security Agency. COVID-19: the green book, chapter 14a. https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a (accessed 16 March 2022).
220. Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. *Lancet* 2018; **391**(10132): 1775-82.https://doi.org/10.1016/S0140-6736(18)30668-8.
221. NHS Data Model and Dictionary. Severe Mental Illness codelist for COVID-19 Population Risk Assessment. https://www.datadictionary.nhs.uk/Covid19PRA/Severe_Mental_Illness.html (accessed 16 March 2022).
222. Clift AK, Coupland CAC, Keogh RH, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. *BMJ* 2020; **371**: m3731.https://doi.org/10.1136/bmj.m3731
223. Costa-Silva J, Domingues D, Lopes FM. RNA-Seq differential expression analysis: An extended review and a software tool. *PLOS ONE* 2017; **12**(12): e0190152.https://doi.org/10.1371/journal.pone.0190152

224. McDermaid A, Monier B, Zhao J, Liu B, Ma Q. Interpretation of differential gene expression results of RNA-seq data: review and integration. *Brief Bioinform* 2019; **20**(6): 2044-54.https://doi.org/10.1093/bib/bby067
225. Harris MA, Clark J, Ireland A, et al. The Gene Ontology (GO) database and informatics resource. *Nucleic Acids Res* 2004; **32**(Database issue): D258-61.https://doi.org/10.1093/nar/gkh036
226. Takiguchi H, Chen V, Obeidat M, et al. Effect of short-term oral prednisone therapy on blood gene expression: a randomised controlled clinical trial. *Respir Res* 2019; **20**(1): 176.https://doi.org/10.1186/s12931-019-1147-2
227. Kousathanas A, Pairo-Castineira E, Rawlik K, et al. Whole-genome sequencing reveals host factors underlying critical COVID-19. *Nature* 2022; **607**(7917): 97-103.https://doi.org/10.1038/s41586-022-04576-6
228. Pairo-Castineira E, Rawlik K, Bretherick AD, et al. GWAS and meta-analysis identifies 49 genetic variants underlying critical COVID-19. *Nature* 2023; **617**(7962): 764-8.https://doi.org/10.1038/s41586-023-06034-3
229. COVID-19 Multi-omics Blood ATlas (COMBAT) Consortium. A blood atlas of COVID-19 defines hallmarks of disease severity and specificity. *Cell* 2022; **185**(5): 916-38.e58.https://doi.org/10.1016/j.cell.2022.01.012
230. Jackson H, Rivero Calle I, Broderick C, et al. Characterisation of the blood RNA host response underpinning severity in COVID-19 patients. *Sci Rep* 2022; **12**(1): 12216.https://doi.org/10.1038/s41598-022-15547-2.
231. Cox DR. Regression Models and Life-Tables. *Journal of the Royal Statistical Society: Series B (Methodological)* 1972; **34**(2): 187-202.https://doi.org/10.1111/j.2517-6161.1972.tb00899.x
232. Betensky RA, Schoenfeld DA. Nonparametric estimation in a cure model with random cure times. *Biometrics* 2001; **57**(1): 282-6.https://doi.org/10.1111/j.0006-341x.2001.00282.x.
233. Varadhan R, Weiss CO, Segal JB, Wu AW, Scharfstein D, Boyd C. Evaluating health outcomes in the presence of competing risks: a review of statistical methods and clinical applications. *Med Care* 2010; **48**(6 Suppl): S96-105.https://doi.org/10.1097/MLR.0b013e3181d99107.
234. Freidlin B, Korn EL. Testing treatment effects in the presence of competing risks. *Stat Med* 2005; **24**(11): 1703-12.https://doi.org/10.1002/sim.2054.
235. Diggle P, Kenward MG. Informative Drop-Out in Longitudinal Data Analysis. *Journal of the Royal Statistical Society Series C (Applied Statistics)* 1994; **43**(1): 49-93.https://doi.org/10.2307/2986113
236. Levey AS, Inker LA, Matsushita K, et al. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. *Am J Kidney Dis* 2014; **64**(6): 821-35.https://doi.org/10.1053/j.ajkd.2014.07.030
237. McCullagh P. Regression Models for Ordinal Data. *Journal of the Royal Statistical Society: Series B (Methodological)* 1980; **42**(2): 109-27.https://doi.org/10.1111/j.2517-6161.1980.tb01109.x
238. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome Biology* 2014; **15**(12): 550.https://doi.org/10.1186/s13059-014-0550-8
239. Soneson C, Delorenzi M. A comparison of methods for differential expression analysis of RNA-seq data. *BMC Bioinformatics* 2013; **14**(1): 91.https://doi.org/10.1186/1471-2105-14-91
240. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. *BMJ* 1995; **310**(6973): 170.https://doi.org/10.1136/bmj.310.6973.170
241. Alexa A, Rahnenfuhrer J. topGO: Enrichment Analysis for Gene Ontology. 2023.https://doi.org/10.18129/B9.bioc.topGO

242. Agresti A. Categorical data analysis. 2nd ed. New York: Wiley; 2002.
243. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society Series B (Methodological)* 1995; **57**(1): 289-300.https://doi.org/10.1111/j.2517-6161.1995.tb02031.x
244. Massey FJ. The Kolmogorov-Smirnov Test for Goodness of Fit. *Journal of the American Statistical Association* 1951; **46**(253): 68-78.https://doi.org/10.2307/2280095
245. Varadhan R, Wang SJ. Standardization for subgroup analysis in randomized controlled trials. *J Biopharm Stat* 2014; **24**(1): 154-67.https://doi.org/10.1080/10543406.2013.856023.
246. Bain C, Page A, Webb P. Essential Epidemiology: An Introduction for Students and Health Professionals. 4 ed. Cambridge: Cambridge University Press; 2019.
247. van Buuren S, Oudshoorn K. Flexible multivariate imputation by MICE: Netherlands Organization for Applied Scientific Research (TNO). 1999. https://stefvanbuuren.name/publications/Flexible%20multivariate%20-%20TNO99054%201999.pdf.
248. Rubin DB. Multiple Imputation for Nonresponse in Surveys: John Wiley & Sons; 1987.
249. Savarese PT, Patetta MJ. An Overview of the CLASS, CONTRAST, and HAZARDRATIO Statements in the SAS ® 9.2 PHREG Procedure. 2010. https://support.sas.com/resources/papers/proceedings10/253-2010.pdf.
250. Rosen AK, Itani KMF, Cevasco M, et al. Validating the patient safety indicators in the veterans health administration: Do they accurately identify true safety events? *Med Care* 2012; **50(1)**: 74-85.https://dx.doi.org/10.1097/MLR.0b013e3182293edf
251. McIsaac DI, Hamilton GM, Abdulla K, et al. Validation of new ICD-10-based patient safety indicators for identification of in-hospital complications in surgical patients: A study of diagnostic accuracy. *BMJ Quality and Safety* 2020; **29(3)**: 209-16.https://dx.doi.org/10.1136/bmjqs-2018-008852
252. Taylor KS, Mahtani KR, Aronson JK. Extracting data from diagnostic test accuracy studies for meta-analysis. *BMJ Evidence-Based Medicine* 2021; **26**(1): 19-21.https://doi.org/10.1136/bmjebm-2020-111650
253. Fox MP, Lash TL, Bodnar LM. Common misconceptions about validation studies. *Int J Epidemiol* 2020; **49**(4): 1392-6.https://doi.org/10.1093/ije/dyaa090.
254. Brown LD, Cai TT, DasGupta A. Interval Estimation for a Binomial Proportion. *Statistical Science* 2001; **16**(2): 101-33, 33.https://doi.org/10.1214/ss/1009213286
255. Reitsma JB, Glas AS, Rutjes AWS, Scholten RJPM, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005; **58**(10): 982-90.https://doi.org/10.1016/j.jclinepi.2005.02.022
256. Curtis JR, Patkar N, Xie A, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. *Arthritis and rheumatism* 2007; **56**(4): 1125-33.https://doi.org/10.1002/art.22504
257. Drahos J, Vanwormer JJ, Greenlee RT, Landgren O, Koshiol J. Accuracy of ICD-9-CM codes in identifying infections of pneumonia and herpes simplex virus in administrative data. *Ann Epidemiol* 2013; **23**(5): 291-3.https://dx.doi.org/10.1016/j.annepidem.2013.02.005
258. Grijalva CG, Chung CP, Stein CM, et al. Computerized definitions showed high positive predictive values for identifying hospitalizations for congestive heart failure and selected infections in Medicaid enrollees with rheumatoid arthritis. *Pharmacoepidemiology and Drug Safety* 2008; **17(9)**: 890-5.https://dx.doi.org/10.1002/pds.1625
259. Holland-Bill L, Xu H, Sorensen HT, et al. Positive predictive value of primary inpatient discharge diagnoses of infection among cancer patients in the Danish National Registry of Patients. *Ann Epidemiol* 2014; **24**(8): 593-7, 7.e1-18.https://dx.doi.org/10.1016/j.annepidem.2014.05.011

260. Ingeman A, Andersen G, Hundborg HH, Johnsen SP. Medical complications in patients with stroke: Data validity in a stroke registry and a hospital discharge registry. *Clin Epidemiol* 2010; **2(1)**: 5-13.https://dx.doi.org/10.2147/clep.s8908
261. Jackson LA, Neuzil KM, Yu O, et al. Effectiveness of pneumococcal polysaccharide vaccine in older adults. *N Engl J Med* 2003; **348**(18): 1747-55.https://doi.org/10.1056/NEJMoa022678.
262. Kern DM, Davis J, Williams SA, et al. Validation of an administrative claims-based diagnostic code for pneumonia in a US-based commercially insured COPD population. *Int J Chron Obstruct Pulmon Dis* 2015; **10**: 1417-25.https://doi.org/10.2147/COPD.S83135
263. Levine PJ, Elman MR, Kullar R, et al. Use of electronic health record data to identify skin and soft tissue infections in primary care settings: A validation study. *BMC Infect Dis* 2013; **13(1)**.https://dx.doi.org/10.1186/1471-2334-13-171
264. Marrie TJ, Durant H, Sealy E. Pneumonia--the quality of medical records data. *Med Care* 1987; **25**(1): 20-4.https://doi.org/10.1097/00005650-198701000-00003.
265. Patkar NM, Curtis JR, Teng GG, et al. Administrative codes combined with medical records based criteria accurately identified bacterial infections among rheumatoid arthritis patients. *J Clin Epidemiol* 2009; **62**(3): 321-7, 7.e1-7.https://dx.doi.org/10.1016/j.jclinepi.2008.06.006
266. Sahli L, Lapeyre-Mestre M, Derumeaux H, Moulis G. Positive predictive values of selected hospital discharge diagnoses to identify infections responsible for hospitalization in the French national hospital database. *Pharmacoepidemiol Drug Saf* 2016; **25**(7): 785-9.https://dx.doi.org/10.1002/pds.4006
267. Schneeweiss S, Robicsek A, Scranton R, Zuckerman D, Solomon DH. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. *J Clin Epidemiol* 2007; **60(4)**: 397-409.https://dx.doi.org/10.1016/j.jclinepi.2006.07.011
268. Skull SA, Andrews RM, Byrnes GB, et al. ICD-10 codes are a valid tool for identification of pneumonia in hospitalized patients aged ⩾65 years. *Epidemiol Infect* 2008; **136**(2): 232-40.https://doi.org/10.1017/S0950268807008564
269. Smith JB, Li BH, Gonzales EG, Langer-Gould A. Validation of algorithms for identifying outpatient infections in MS patients using electronic medical records. *Mult Scler Relat Disord* 2022; **57**: 103449.https://dx.doi.org/10.1016/j.msard.2021.103449
270. Wiese AD, Griffin MR, Stein CM, et al. Validation of discharge diagnosis codes to identify serious infections among middle age and older adults. *BMJ Open* 2018; **8**(6): e020857.https://dx.doi.org/10.1136/bmjopen-2017-020857
271. Whittle J, Fine MJ, Joyce DZ, et al. Community-acquired pneumonia: can it be defined with claims data? *Am J Med Qual* 1997; **12**(4): 187-93.https://doi.org/10.1177/0885713X9701200404.
272. Yu O, Nelson JC, Bounds L, Jackson LA. Classification algorithms to improve the accuracy of identifying patients hospitalized with community-acquired pneumonia using administrative data. *Epidemiol Infect* 2011; **139**(9): 1296-306.https://doi.org/10.1017/S0950268810002529
273. Gedeborg R, Furebring M, Michaelsson K. Diagnosis-dependent misclassification of infections using administrative data variably affected incidence and mortality estimates in ICU patients. *J Clin Epidemiol* 2007; **60**(2): 155-62.https://doi.org/10.1016/j.jclinepi.2006.05.013
274. Glenn DA, Zee J, Hegde A, et al. Validation of Diagnosis Codes to Identify Infection-Related Acute Care Events in Patients With Glomerular Disease. *Kidney International Reports* 2021; **6(12)**: 3079-82.https://dx.doi.org/10.1016/j.ekir.2021.08.019
275. Henriksen DP, Nielsen SL, Laursen CB, Hallas J, Pedersen C, Lassen AT. How well do discharge diagnoses identify hospitalised patients with community-acquired infections? - A validation study. *PLoS ONE* 2014; **9(3)**.https://dx.doi.org/10.1371/journal.pone.0092891

276. Al-Ani F, Shariff S, Siqueira L, Seyam A, Lazo-Langner A. Identifying venous thromboembolism and major bleeding in emergency room discharges using administrative data. *Thromb Res* 2015; **136**(6): 1195-8.https://dx.doi.org/10.1016/j.thromres.2015.10.035
277. Ammann EM, Cuker A, Carnahan RM, et al. Chart validation of inpatient International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) administrative diagnosis codes for venous thromboembolism (VTE) among intravenous immune globulin (IGIV) users in the Sentinel Distributed Database. *Medicine (Baltimore)* 2018; **97**(8): e9960.https://dx.doi.org/10.1097/MD.0000000000009960
278. Arnason T, Wells PS, van Walraven C, Forster AJ. Accuracy of coding for possible warfarin complications in hospital discharge abstracts. *Thromb Res* 2006; **118**(2): 253-62.https://doi.org/10.1016/j.thromres.2005.06.015
279. Burles K, Innes G, Senior K, Lang E, McRae A. Limitations of pulmonary embolism ICD-10 codes in emergency department administrative data: let the buyer beware. *BMC Med Res Methodol* 2017; **17**(1): 89.https://dx.doi.org/10.1186/s12874-017-0361-1
280. Drljevic A, Borre M, Hoyer M, Ehrenstein V, Nguyen-Nielsen M. Quality of venous thromboembolism diagnoses among prostate cancer patients in the Danish National Registry of Patients. *Clin Epidemiol* 2014; **6**: 351-7.https://dx.doi.org/10.2147/CLEP.S65681
281. Fang MC, Fan D, Sung SH, et al. Validity of Using Inpatient and Outpatient Administrative Codes to Identify Acute Venous Thromboembolism: The CVRN VTE Study. *Med Care* 2017; **55**(12): e137-e43.https://dx.doi.org/10.1097/MLR.0000000000000524
282. Gerstman BB, Freiman JP, Hine LK. Use of subsequent anticoagulants to increase the predictive value of Medicaid deep venous thromboembolism diagnoses. *Epidemiology (Cambridge, Mass)* 1990; **1**(2): 122-7.https://doi.org/10.1097/00001648-199003000-00007
283. Molander V, Bower H, Askling J. Validation and characterization of venous thromboembolism diagnoses in the Swedish National Patient Register among patients with rheumatoid arthritis. *Scand J Rheumatol* 2022: 1-7.https://dx.doi.org/10.1080/03009742.2021.2001907
284. Ohman L, Johansson M, Jansson JH, Lind M, Johansson L. Positive predictive value and misclassification of diagnosis of pulmonary embolism and deep vein thrombosis in Swedish patient registries. *Clin Epidemiol* 2018; **10**: 1215-21.https://dx.doi.org/10.2147/CLEP.S177058
285. Prat M, Derumeaux H, Sailler L, Lapeyre-Mestre M, Moulis G. Positive predictive values of peripheral arterial and venous thrombosis codes in French hospital database. *Fundam Clin Pharmacol* 2018; **32**(1): 108-13.https://dx.doi.org/10.1111/fcp.12326
286. Sanfilippo KM, Wang TF, Gage BF, Liu W, Carson KR. Improving accuracy of International Classification of Diseases codes for venous thromboembolism in administrative data. *Thromb Res* 2015; **135**(4): 616-20.https://dx.doi.org/10.1016/j.thromres.2015.01.012
287. Scarvelis D, Anderson J, Davis L, et al. Hospital mortality due to pulmonary embolism and an evaluation of the usefulness of preventative interventions. *Thromb Res* 2010; **125**(2): 166-70.https://doi.org/10.1016/j.thromres.2009.06.025
288. Severinsen MT, Kristensen SR, Overvad K, Dethlefsen C, Tjonneland A, Johnsen SP. Venous thromboembolism discharge diagnoses in the Danish National Patient Registry should be used with caution. *J Clin Epidemiol* 2010; **63**(2): 223-8.https://dx.doi.org/10.1016/j.jclinepi.2009.03.018
289. Sundboll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open* 2016; **6**(11): e012832.https://dx.doi.org/10.1136/bmjopen-2016-012832
290. White RH, Garcia M, Sadeghi B, et al. Evaluation of the predictive value of ICD-9-CM coded administrative data for venous thromboembolism in the United States. *Thromb Res* 2010; **126**(1): 61-7.https://dx.doi.org/10.1016/j.thromres.2010.03.009
291. Birman-Deych E, Waterman AD, Yan Y, Nilasena DS, Radford MJ, Gage BF. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. *Med Care* 2005; **43**(5): 480-5.https://doi.org/10.1097/01.mlr.0000160417.39497.a9

292. Heckbert SR, Kooperberg C, Safford MM, et al. Comparison of self-report, hospital discharge codes, and adjudication of cardiovascular events in the Women's Health Initiative. *Am J Epidemiol* 2004; **160**(12): 1152-8.https://doi.org/10.1093/aje/kwh314.
293. Johnson SA, Signor EA, Lappe KL, et al. A comparison of natural language processing to ICD-10 codes for identification and characterization of pulmonary embolism. *Thromb Res* 2021; **203**: 190-5.https://dx.doi.org/10.1016/j.thromres.2021.04.020
294. Abraham NS, Cohen DC, Rivers B, Richardson P. Validation of administrative data used for the diagnosis of upper gastrointestinal events following nonsteroidal anti-inflammatory drug prescription. *Aliment Pharmacol Ther* 2006; **24**(2): 299-306.https://doi.org/10.1111/j.1365-2036.2006.02985.x
295. Andrade SE, Gurwitz JH, Chan KA, et al. Validation of diagnoses of peptic ulcers and bleeding from administrative databases: a multi-health maintenance organization study. *J Clin Epidemiol* 2002; **55**(3): 310-3.https://doi.org/10.1016/s0895-4356(01)00480-2
296. Cattaruzzi C, Troncon MG, Agostinis L, Garcia Rodriguez LA. Positive predictive value of ICD-9th codes for upper gastrointestinal bleeding and perforation in the Sistema Informativo Sanitario Regionale database. *J Clin Epidemiol* 1999; **52**(6): 499-502.https://doi.org/10.1016/s0895-4356(99)00004-9
297. Curtis JR, Chen SY, Werther W, John A, Johnson DA. Validation of ICD-9-CM codes to identify gastrointestinal perforation events in administrative claims data among hospitalized rheumatoid arthritis patients. *Pharmacoepidemiol Drug Saf* 2011; **20**(11): 1150-8.https://dx.doi.org/10.1002/pds.2215
298. Orso M, Abraha I, Mengoni A, et al. Accuracy of ICD-9 codes in identifying patients with peptic ulcer and gastrointestinal hemorrhage in the regional healthcare administrative database of Umbria. *PLoS ONE* 2020; **15**(7): e0235714.https://dx.doi.org/10.1371/journal.pone.0235714
299. Pisa F, Castellsague J, Drigo D, et al. Accuracy of International Classification of Diseases, 9th Revision, Clinical Modification codes for upper gastrointestinal complications varied by position and age: a validation study in a cohort of nonsteroidal anti-inflammatory drugs users in Friuli Venezia Giulia, Italy. *Pharmacoepidemiol Drug Saf* 2013; **22**(11): 1195-204.https://dx.doi.org/10.1002/pds.3504
300. Raiford DS, Gutthann SP, Garcia Rodriguez LA. Positive predictive value of ICD-9 codes in the identification of cases of complicated peptic ulcer disease in the Saskatchewan Hospital automated database. *Epidemiology* 1996; **7(1)**: 101-4.http://dx.doi.org/10.1097/00001648-199601000-00018
301. Shehab N, Ziemba R, Campbell KN, et al. Assessment of ICD-10-CM code assignment validity for case finding of outpatient anticoagulant-related bleeding among Medicare beneficiaries. *Pharmacoepidemiology and Drug Safety* 2019; **28(7)**: 951-64.https://dx.doi.org/10.1002/pds.4783
302. Tanigawa M, Kataoka Y, Kishino T, et al. Identification of gastrointestinal perforation based on ICD-10 code in a Japanese administrative medical information database and associated drug exposure risk factors. *Pharmacoepidemiol Drug Saf* 2019; **28**(7): 976-84.https://dx.doi.org/10.1002/pds.4837
303. Valkhoff VE, Coloma PM, Masclee GM, et al. Validation study in four health-care databases: upper gastrointestinal bleeding misclassification affects precision but not magnitude of drug-related upper gastrointestinal bleeding risk. *J Clin Epidemiol* 2014; **67**(8): 921-31.https://dx.doi.org/10.1016/j.jclinepi.2014.02.020
304. Wahl PM, Rodgers K, Schneeweiss S, et al. Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. *Pharmacoepidemiol Drug Saf* 2010; **19**(6): 596-603.https://dx.doi.org/10.1002/pds.1924
305. Joos C, Lawrence K, Jones AE, Johnson SA, Witt DM. Accuracy of ICD-10 codes for identifying hospitalizations for acute anticoagulation therapy-related bleeding events. *Thromb Res* 2019; **181**: 71-6.https://dx.doi.org/10.1016/j.thromres.2019.07.021

306. Crane MH, Kadane BJ, Crane KP, Kitahata MM. Diabetes Case Identification Methods Applied to Electronic Medical Record Systems: Their Use in HIV-Infected Patients. *Curr HIV Res* 2006; **4**(1): 97-106.http://dx.doi.org/10.2174/157016206775197637
307. Gini R, Schuemie MJ, Mazzaglia G, et al. Automatic identification of type 2 diabetes, hypertension, ischaemic heart disease, heart failure and their levels of severity from Italian General Practitioners' electronic medical records: a validation study. *BMJ Open* 2016; **6**(12): e012413.https://dx.doi.org/10.1136/bmjopen-2016-012413
308. Institute for Clinical Evaluative Sciences, Juurlink D, Preyra C, et al. Canadian Institute for Health Information Discharge Abstract Database: a Validation Study. 2006. https://www.ices.on.ca/wp-content/uploads/2023/06/Full-report-48.pdf.
309. Solberg LI, Engebretson KI, Sperl-Hillen JM, Hroscikoski MC, O'Connor PJ. Are Claims Data Accurate Enough to Identify Patients for Performance Measures or Quality Improvement? The Case of Diabetes, Heart Disease, and Depression. *Am J Med Qual* 2006; **21**(4): 238-45.https://doi.org/10.1177/1062860606288243
310. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol* 2011; **11**: 83.https://dx.doi.org/10.1186/1471-2288-11-83
311. Zgibor JC, Orchard TJ, Saul M, et al. Developing and validating a diabetes database in a large health system. *Diabetes Res Clin Pract* 2007; **75**(3): 313-9.https://doi.org/10.1016/j.diabres.2006.07.007
312. Ahmad FS, Chan C, Rosenman MB, et al. Validity of Cardiovascular Data From Electronic Sources: The Multi-Ethnic Study of Atherosclerosis and HealthLNK. *Circulation* 2017; **136**(13): 1207-16.https://dx.doi.org/10.1161/CIRCULATIONAHA.117.027436
313. Borzecki AM, Wong AT, Hickey EC, Ash AS, Berlowitz DR. Identifying Hypertension-Related Comorbidities From Administrative Data: What's the Optimal Approach? *Am J Med Qual* 2004; **19**(5): 201-6.https://doi.org/10.1177/106286060401900504
314. Chen G, Khan N, Walker R, Quan H. Validating ICD coding algorithms for diabetes mellitus from administrative data. *Diabetes Res Clin Pract* 2010; **89**(2): 189-95.https://dx.doi.org/10.1016/j.diabres.2010.03.007
315. Fleming ST, Sabatino SA, Kimmick G, et al. Developing a claim-based version of the ACE-27 comorbidity index: a comparison with medical record review. *Med Care* 2011; **49**(8): 752-60.https://dx.doi.org/10.1097/MLR.0b013e318215d7dd
316. Fuentes S, Cosson E, Mandereau-Bruno L, et al. Identifying diabetes cases in health administrative databases: a validation study based on a large French cohort. *Int J Public Health* 2019; **64**(3): 441-50.https://dx.doi.org/10.1007/s00038-018-1186-3
317. Hara K, Tomio J, Svensson T, Ohkuma R, Svensson AK, Yamazaki T. Association measures of claims-based algorithms for common chronic conditions were assessed using regularly collected data in Japan. *J Clin Epidemiol* 2018; **99**: 84-95.https://dx.doi.org/10.1016/j.jclinepi.2018.03.004
318. Harris SB, Glazier RH, Tompkins JW, et al. Investigating concordance in diabetes diagnosis between primary care charts (electronic medical records) and health administrative data: a retrospective cohort study. *BMC Health Serv Res* 2010; **10**: 347.https://dx.doi.org/10.1186/1472-6963-10-347
319. Humphries KH, Rankin JM, Carere RG, Buller CE, Kiely FM, Spinelli JJ. Co-morbidity data in outcomes research: are clinical data derived from administrative databases a reliable alternative to chart review? *J Clin Epidemiol* 2000; **53**(4): 343-9.https://doi.org/10.1016/s0895-4356(99)00188-2.
320. Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care* 2002; **25**(3): 512-6.https://doi.org/10.2337/diacare.25.3.512.
321. Jollis JG, Ancukiewicz M, DeLong ER, Pryor DB, Muhlbaier LH, Mark DB. Discordance of databases designed for claims payment versus clinical information systems.

Implications for outcomes research. *Ann Intern Med* 1993; **119**(8): 844-50.https://doi.org/10.7326/0003-4819-119-8-199310150-00011.
322. Kadhim-Saleh A, Green M, Williamson T, Hunter D, Birtwhistle R. Validation of the diagnostic algorithms for 5 chronic conditions in the Canadian Primary Care Sentinel Surveillance Network (CPCSSN): a Kingston Practice-based Research Network (PBRN) report. *J Am Board Fam Med* 2013; **26**(2): 159-67.https://dx.doi.org/10.3122/jabfm.2013.02.120183
323. Kashner TM. Agreement between administrative files and written medical records: a case of the Department of Veterans Affairs. *Med Care* 1998; **36**(9): 1324-36.https://doi.org/10.1097/00005650-199809000-00005
324. Lee S, Doktorchik C, Martin EA, et al. Electronic Medical Record-Based Case Phenotyping for the Charlson Conditions: Scoping Review. *JMIR Med Inform* 2021; **9**(2): e23934.https://dx.doi.org/10.2196/23934
325. Lipscombe LL, Hwee J, Webster L, Shah BR, Booth GL, Tu K. Identifying diabetes cases from administrative data: a population-based validation study. *BMC Health Serv Res* 2018; **18**(1): 316.https://dx.doi.org/10.1186/s12913-018-3148-0
326. Luthi JC, Troillet N, Eisenring MC, et al. Administrative data outperformed single-day chart review for comorbidity measure. *Int J Qual Health Care* 2007; **19**(4): 225-31.https://doi.org/10.1093/intqhc/mzm017
327. Marrie RA, Yu BN, Leung S, et al. Rising prevalence of vascular comorbidities in multiple sclerosis: Validation of administrative definitions for diabetes, hypertension, and hyperlipidemia. *Multiple Sclerosis Journal* 2012; **18(9)**: 1310-9.https://dx.doi.org/10.1177/1352458512437814
328. McGinnis KA, Justice AC, Bailin S, Wellons M, Freiberg M, Koethe JR. High concordance between chart review adjudication and electronic medical record data to identify prevalent and incident diabetes mellitus among persons with and without HIV. *Pharmacoepidemiol Drug Saf* 2020; **29**(11): 1432-9.https://dx.doi.org/10.1002/pds.5111
329. Morris AD, Boyle DI, MacAlpine R, et al. The diabetes audit and research in Tayside Scotland (DARTS) study: electronic record linkage to create a diabetes register. DARTS/MEMO Collaboration. *Bmj* 1997; **315**(7107): 524-8.https://doi.org/10.1136/bmj.315.7107.524
330. Nedkoff L, Knuiman M, Hung J, Sanfilippo FM, Katzenellenbogen JM, Briffa TG. Concordance between administrative health data and medical records for diabetes status in coronary heart disease patients: a retrospective linked data study. *BMC Med Res Methodol* 2013; **13**: 121.https://dx.doi.org/10.1186/1471-2288-13-121
331. Nimmo A, Steenkamp R, Ravanan R, Taylor D. Do routine hospital data accurately record comorbidity in advanced kidney disease populations? A record linkage cohort study. *BMC Nephrol* 2021; **22**(1): 95.https://dx.doi.org/10.1186/s12882-021-02301-5
332. Peng M, Southern DA, Williamson T, Quan H. Under-coding of secondary conditions in coded hospital health data: Impact of co-existing conditions, death status and number of codes in a record. *Health Inform J* 2017; **23**(4): 260-7.https://dx.doi.org/10.1177/1460458216647089
333. Powell H, Lim LL, Heller RF. Accuracy of administrative data to assess comorbidity in patients with heart disease. an Australian perspective. *J Clin Epidemiol* 2001; **54**(7): 687-93.https://doi.org/10.1016/s0895-4356(00)00364-4
334. Preen DB, Holman CD, Lawrence DM, Baynham NJ, Semmens JB. Hospital chart review provided more accurate comorbidity information than data from a general practitioner survey or an administrative database. *J Clin Epidemiol* 2004; **57**(12): 1295-304.https://doi.org/10.1016/j.jclinepi.2004.03.016.
335. Quan H, Parsons GA, Ghali WA. Validity of information on comorbidity derived rom ICD-9-CCM administrative data. *Med Care* 2002; **40**(8): 675-85.https://doi.org/10.1097/00005650-200208000-00007.

336. Quan H, Li B, Duncan Saunders L, et al. Assessing Validity of ICD-9-CM and ICD-10 Administrative Data in Recording Clinical Conditions in a Unique Dually Coded Database. *Health Serv Res* 2008; **43**(4): 1424-41.https://doi.org/10.1111/j.1475-6773.2007.00822.x
337. Tu K, Manuel D, Lam K, Kavanagh D, Mitiku TF, Guo H. Diabetics can be identified in an electronic medical record using laboratory tests and prescriptions. *J Clin Epidemiol* 2011; **64**(4): 431-5.https://dx.doi.org/10.1016/j.jclinepi.2010.04.007
338. van Doorn C, Bogardus ST, Williams CS, Concato J, Towle VR, Inouye SK. Risk adjustment for older hospitalized persons: a comparison of two methods of data collection for the Charlson index. *J Clin Epidemiol* 2001; **54**(7): 694-701.https://doi.org/10.1016/s0895-4356(00)00367-x
339. Weintraub WS, Deaton C, Shaw L, et al. Can cardiovascular clinical characteristics be identified and outcome models be developed from an in-patient claims database? *The American Journal of Cardiology* 1999; **84**(2): 166-9.https://doi.org/10.1016/S0002-9149(99)00228-3
340. Wilchesky M, Tamblyn RM, Huang A. Validation of diagnostic codes within medical services claims. *J Clin Epidemiol* 2004; **57**(2): 131-41.https://doi.org/10.1016/S0895-4356(03)00246-4
341. Williamson T, Green ME, Birtwhistle R, et al. Validating the 8 CPCSSN Case Definitions for Chronic Disease Surveillance in a Primary Care Database of Electronic Health Records. *The Annals of Family Medicine* 2014; **12**(4): 367-72.https://doi.org/10.1370/afm.1644
342. Wilson C, Susan L, Lynch A, Saria R, Peterson D. Patients with diagnosed diabetes mellitus can be accurately identified in an Indian Health Service patient registration database. *Public Health Rep* 2001; **116**(1): 45-50.https://pubmed.ncbi.nlm.nih.gov/11571407/
343. Youngson E, Welsh RC, McAlister F, Kaul P, Bakal J. Evaluating the use of administrative comorbidity definitions in a registry of STEMI patients. *Can J Cardiol* 2015; **1)**: S285.https://doi.org/10.1016/j.cjca.2015.07.593
344. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *Journal of Clinical Epidemiology* 2005; **58**(4): 323-37.https://doi.org/10.1016/j.jclinepi.2004.10.012
345. Barber C, Lacaille D, Fortin PR. Systematic review of validation studies of the use of administrative data to identify serious infections. *Arthritis Care Res (Hoboken)* 2013; **65**(8): 1343-57.https://dx.doi.org/10.1002/acr.21959
346. Harper C, Mafham M, Herrington W, et al. Reliability of major bleeding events in UK routine data versus clinical trial adjudicated follow-up data. *Heart* 2023; **109**(19): 1467-72.https://doi.org/10.1136/heartjnl-2023-322616
347. Saine ME, Gizaw M, Carbonari DM, et al. Validity of diagnostic codes to identify hospitalizations for infections among patients treated with oral anti-diabetic drugs. *Pharmacoepidemiol Drug Saf* 2018; **27**(10): 1147-50.https://dx.doi.org/10.1002/pds.4368
348. Wei WQ, Teixeira PL, Mo H, Cronin RM, Warner JL, Denny JC. Combining billing codes, clinical notes, and medications from electronic health records provides superior phenotyping performance. *J Am Med Inform Assoc* 2016; **23**(e1): e20-7.https://dx.doi.org/10.1093/jamia/ocv130
349. Kim DH, Lee J, Kim CA, et al. Evaluation of algorithms to identify delirium in administrative claims and drug utilization database. *Pharmacoepidemiol Drug Saf* 2017; **26**(8): 945-53.https://dx.doi.org/10.1002/pds.4226
350. Caillet P, Oberlin P, Monnet E, et al. [Algorithms for the identification of hospital stays due to osteoporotic femoral neck fractures in European medical administrative databases using ICD-10 codes: A non-systematic review of the literature]. *Rev Epidemiol Sante Publique* 2017; **65 Suppl 4**: S198-S208.https://dx.doi.org/10.1016/j.respe.2017.04.058
351. Udo R, Maitland-van der Zee AH, Egberts TC, et al. Validity of diagnostic codes and laboratory measurements to identify patients with idiopathic acute liver injury in a hospital

database. *Pharmacoepidemiol Drug Saf* 2016; **25 Suppl 1**: 21-8.https://dx.doi.org/10.1002/pds.3824
352. Vinker S, Fogelman Y, Elhayany A, Nakar S, Kahan E. Usefulness of electronic databases for the detection of unrecognized diabetic patients. *Cardiovasc* 2003; **2**.https://dx.doi.org/10.1186/1475-2840-2-13
353. Thornley S, Wright C, Marshall R, et al. Can the prevalence of diagnosed diabetes be estimated from linked national health records? The validity of a method applied in New Zealand. *J Prim Health Care* 2011; **3**(4): 262-8.https://pubmed.ncbi.nlm.nih.gov/22132378/
354. Mc Cord KA, Al-Shahi Salman R, Treweek S, et al. Routinely collected data for randomized trials: promises, barriers, and implications. *Trials [Electronic Resource]* 2018; **19**(1): 29.https://doi.org/10.1186/s13063-017-2394-5
355. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *The Lancet* 2016; **388**(10059): 2532-61.https://doi.org/10.1016/S0140-6736(16)31357-5
356. Hemkens LG, Contopoulos-Ioannidis DG, Ioannidis JPA. Routinely collected data and comparative effectiveness evidence: promises and limitations. *Cmaj* 2016; **188**(8): E158-e64.https://doi.org/10.1503/cmaj.150653
357. Brennan JM, Wruck L, Pencina MJ, et al. Claims-based cardiovascular outcome identification for clinical research: Results from 7 large randomized cardiovascular clinical trials. *American Heart Journal* 2019; **218**: 110-22.https://doi.org/10.1016/j.ahj.2019.09.002
358. Hlatky MA, Ray RM, Burwen DR, et al. Use of Medicare data to identify coronary heart disease outcomes in the Women's Health Initiative. *Circ Cardiovasc Qual Outcomes* 2014; **7**(1): 157-62.https://doi.org/10.1161/CIRCOUTCOMES.113.000373
359. Mathes T, Klaßen P, Pieper D. No differences were found between effect estimates from conventional and registry-based randomized controlled trials. *Journal of Clinical Epidemiology* 2019; **105**: 80-91.https://doi.org/10.1016/j.jclinepi.2018.09.011
360. Harper C, Mafham M, Herrington W, et al. Comparison of the Accuracy and Completeness of Records of Serious Vascular Events in Routinely Collected Data vs Clinical Trial–Adjudicated Direct Follow-up Data in the UK: Secondary Analysis of the ASCEND Randomized Clinical Trial. *JAMA Network Open* 2021; **4**(12): e2139748-e.https://doi.org/10.1001/jamanetworkopen.2021.39748
361. Kjøller E, Hilden J, Winkel P, et al. Agreement between public register and adjudication committee outcome in a cardiovascular randomized clinical trial. *Am Heart J* 2014; **168**(2): 197-204.e1-4.https://doi.org/10.1016/j.ahj.2013.12.032
362. Barry SJ, Dinnett E, Kean S, Gaw A, Ford I. Are routinely collected NHS administrative records suitable for endpoint identification in clinical trials? Evidence from the West of Scotland Coronary Prevention Study. *PLoS One* 2013; **8**(9): e75379.https://doi.org/10.1371/journal.pone.0075379
363. Mc Cord KA, Ewald H, Agarwal A, et al. Treatment effects in randomised trials using routinely collected data for outcome assessment versus traditional trials: meta-research study. *BMJ* 2021; **372**: n450.https://doi.org/10.1136/bmj.n450
364. Watson J, Nicholson BD, Hamilton W, Price S. Identifying clinical features in primary care electronic health record studies: methods for codelist development. *BMJ Open* 2017; **7**(11): e019637.https://doi.org/10.1136/bmjopen-2017-019637
365. Bennett Institute for Applied Data Science. OpenCodeslists. https://www.opencodelists.org/ (accessed 23 March 2023).
366. University of Manchester. ClinicalCodes repository. https://clinicalcodes.rss.mhs.man.ac.uk/ (accessed 23 March 2023).
367. London School of Hygiene and Tropical Medicine. LSHTM Data Compass. https://datacompass.lshtm.ac.uk/ (accessed 23 March 2023).
368. NHS Digital. Reference data for clinical clusters for GPES Data for Pandemic Planning and Research (GDPPR). https://tinyurl.com/4js4h9e5 (accessed 23 March 2023).

369. NHS Digital. Electronic Prescribing and Administration (EPMA) Data in Secondary Care under the COVID-19 Direction. https://digital.nhs.uk/data-and-information/data-collections-and-data-sets/data-collections/electronic-prescribing-and-administration-epma-data-in-secondary-care (accessed 26 September 2022).
370. Lansbury LN, Roberts HC, Clift E, Herklots A, Robinson N, Sayer AA. Use of the electronic Frailty Index to identify vulnerable patients: a pilot study in primary care. *British Journal of General Practice* 2017; **67**(664): e751-e6.https://doi.org/10.3399/bjgp17X693089
371. NHS England. Electronic Frailty Index. https://www.england.nhs.uk/ourwork/clinical-policy/older-people/frailty/efi/ (accessed 24 February 2024).
372. Healthcare Improvement Scotland. Frailty and the electronic frailty index. 2019. https://ihub.scot/media/6106/frailty-and-the-electronic-frailty-index.pdf.
373. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *Canadian Medical Association Journal* 2005; **173**(5): 489-95.https://doi.org/10.1503/cmaj.050051
374. Spearman C. The Proof and Measurement of Association between Two Things. *The American Journal of Psychology* 1904; **15**(1): 72-101.https://doi.org/10.2307/1412159
375. Kruskal WH, Wallis WA. Use of Ranks in One-Criterion Variance Analysis. *Journal of the American Statistical Association* 1952; **47**(260): 583-621.https://doi.org/10.1080/01621459.1952.10483441
376. Cohen J. A Coefficient of Agreement for Nominal Scales. *Educational and Psychological Measurement* 1960; **20**(1): 37-46.https://doi.org/10.1177/001316446002000104
377. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; **33**(1): 159-74.https://doi.org/10.2307/2529310
378. Chen G, Faris P, Hemmelgarn B, Walker RL, Quan H. Measuring agreement of administrative data with chart data using prevalence unadjusted and adjusted kappa. *BMC Med Res Methodol* 2009; **9**: 5.https://doi.org/10.1186/1471-2288-9-5
379. Feinstein AR, Cicchetti DV. High agreement but low kappa: I. The problems of two paradoxes. *J Clin Epidemiol* 1990; **43**(6): 543-9.https://doi.org/10.1016/0895-4356(90)90158-l.
380. Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. *J Clin Epidemiol* 1993; **46**(5): 423-9.https://doi.org/10.1016/0895-4356(93)90018-v.
381. Centers for Disease Control and Prevention. ICD-10-CM Official Coding Guidelines. 2020. https://www.cdc.gov/nchs/data/icd/ICD-10-CM-Official-Coding-Gudance-Interim-Advice-coronavirus-feb-20-2020.pdf (accessed 14 March 2023).
382. Schultze A, Nightingale E, Evans D, et al. Mortality among Care Home Residents in England during the first and second waves of the COVID-19 pandemic: an observational study of 4.3 million adults over the age of 65. *The Lancet Regional Health – Europe* 2022; **14**.https://doi.org/10.1016/j.lanepe.2021.100295
383. Peto R. Current misconception 3: that subgroup-specific trial mortality results often provide a good basis for individualising patient care. *Br J Cancer* 2011; **104**(7): 1057-8.https://doi.org/10.1038/bjc.2011.79.
384. Yusuf S, Wittes J, Probstfield J, Tyroler HA. Analysis and Interpretation of Treatment Effects in Subgroups of Patients in Randomized Clinical Trials. *JAMA* 1991; **266**(1): 93-8.https://doi.org/10.1001/jama.1991.03470010097038
385. Siempos II, Kalil AC, Belhadi D, et al. Immunomodulators for immunocompromised patients hospitalized for COVID-19: a meta-analysis of randomized controlled trials. *eClinicalMedicine* 2024; **69**.https://doi.org/10.1016/j.eclinm.2024.102472
386. Dickersin K, Chan S, Chalmersx TC, Sacks HS, Smith H. Publication bias and clinical trials. *Controlled Clinical Trials* 1987; **8**(4): 343-53.https://doi.org/10.1016/0197-2456(87)90155-3

387. Bassler D, Briel M, Montori VM, et al. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. *Jama* 2010; **303**(12): 1180-7.https://doi.org/10.1001/jama.2010.310.
388. Rubin S, Orieux A, Prezelin-Reydit M, et al. Impact of dexamethasone in severe COVID-19-induced acute kidney injury: a multicenter cohort study. *Ann Intensive Care* 2024; **14**(1): 26.https://dx.doi.org/10.1186/s13613-024-01258-6
389. Wang F, Sun L, Wang S, et al. Efficacy and Safety of Tofacitinib, Baricitinib, and Upadacitinib for Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *Mayo Clinic Proceedings* 2020; **95**(7): 1404-19.https://doi.org/10.1016/j.mayocp.2020.01.039
390. Singh JA, Beg S, Lopez-Olivo MA. Tocilizumab for rheumatoid arthritis. *Cochrane Database Syst Rev* 2010; (7): Cd008331.https://doi.org/10.1002/14651858.CD008331.pub2
391. Freeman J, McGowan JE, Jr. Risk Factors for Nosocomial Infection. *The Journal of infectious diseases* 1978; **138**(6): 811-9.https://doi.org/10.1093/infdis/138.6.811
392. Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. *Clinical Microbiology & Infection* 2020; **26**(12): 1622-9.https://doi.org/10.1016/j.cmi.2020.07.016
393. Qiu D, He J, Zhang C, et al. Associations between frailty, depression and risk of hospitalisation for infection: A large prospective cohort study. *Journal of Affective Disorders* 2024; **361**: 104-12.https://www.sciencedirect.com/science/article/pii/S0165032724009431
394. Xu M, Gong Y, Yin X. Association of frailty with risk of incident hospital-treated infections in middle-aged and older adults: A large-scale prospective cohort study. *The Journals of Gerontology: Series A* 2024.https://doi.org/10.1093/gerona/glae146
395. Yoshikawa TT. Epidemiology and Unique Aspects of Aging and Infectious Diseases. *Clinical Infectious Diseases* 2000; **30**(6): 931-3.https://doi.org/10.1086/313792
396. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. *Nature Reviews Immunology* 2017; **17**(4): 233-47.https://doi.org/10.1038/nri.2017.1
397. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis* 1989; **11**(6): 954-63.https://doi.org/10.1093/clinids/11.6.954
398. Alderson P, Roberts I. Corticosteroids for acute traumatic brain injury. *Cochrane Database of Systematic Reviews* 2005; (1).https://doi.org//10.1002/14651858.CD000196.pub2
399. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis in children and adults. *Cochrane Database of Systematic Reviews* 2019; (12).https://doi.org//10.1002/14651858.CD002243.pub4
400. Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M. Corticosteroids for pneumonia. *Cochrane Database of Systematic Reviews* 2017; (12).https://doi.org//10.1002/14651858.CD007720.pub3
401. Leung E, Crass RL, Jorgensen SCJ, et al. Pharmacokinetic/Pharmacodynamic Considerations of Alternate Dosing Strategies of Tocilizumab in COVID-19. *Clin Pharmacokinet* 2022; **61**(2): 155-65.https://doi.org/10.1007/s40262-021-01092-0
402. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008; **67**(11): 1516-23.https://doi.org/10.1136/ard.2008.092932
403. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum* 2008; **58**(10): 2968-80.https://doi.org/10.1002/art.23940.
404. Agarwal A, Rochwerg B, Lamontagne F, et al. A living WHO guideline on drugs for covid-19. *BMJ* 2020; **370**: m3379.https://www.ncbi.nlm.nih.gov/pubmed/32887691

405. Bieber T, Reich K, Paul C, et al. Efficacy and safety of baricitinib in combination with topical corticosteroids in patients with moderate-to-severe atopic dermatitis with inadequate response, intolerance or contraindication to ciclosporin: results from a randomized, placebo-controlled, phase III clinical trial (BREEZE-AD4). *Br J Dermatol* 2022; **187**(3): 338-52.https://doi.org/10.1111/bjd.21630
406. Genovese MC, Kremer J, Zamani O, et al. Baricitinib in Patients with Refractory Rheumatoid Arthritis. *New England Journal of Medicine* 2016; **374**(13): 1243-52.https://doi.org/10.1056/NEJMoa1507247
407. Hwang JL, Weiss RE. Steroid-induced diabetes: a clinical and molecular approach to understanding and treatment. *Diabetes/Metabolism Research and Reviews* 2014; **30**(2): 96-102.https://doi.org/10.1002/dmrr.2486
408. Rayman G, Lumb AN, Kennon B, et al. Dexamethasone therapy in COVID-19 patients: implications and guidance for the management of blood glucose in people with and without diabetes. *Diabet Med* 2021; **38**(1): e14378.https://doi.org/10.1111/dme.14378
409. Krinsley JS, Egi M, Kiss A, et al. Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. *Crit Care* 2013; **17**(2): R37.https://doi.org/10.1186/cc12547.
410. Kosiborod M, Rathore SS, Inzucchi SE, et al. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. *Circulation* 2005; **111**(23): 3078-86.https://doi.org/10.1161/CIRCULATIONAHA.104.517839.
411. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; **345**(19): 1359-67.https://doi.org/10.1056/NEJMoa011300.
412. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; **354**(5): 449-61.https://doi.org/10.1056/NEJMoa052521.
413. Fu Y, Sun Y, Zhang J, Cheng Y. Intensive glucose control for critically ill patients: an updated meta-analysis. *Endocr Connect* 2018; **7**(12): 1288-98.https://doi.org/10.1530/EC-18-0393.
414. Aberer F, Hochfellner DA, Sourij H, Mader JK. A Practical Guide for the Management of Steroid Induced Hyperglycaemia in the Hospital. *J Clin Med* 2021; **10**(10).https://doi.org/10.3390/jcm10102154.
415. Tamez-Pérez HE, Quintanilla-Flores DL, Rodríguez-Gutiérrez R, González-González JG, Tamez-Peña AL. Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. *World J Diabetes* 2015; **6**(8): 1073-81.https://doi.org/10.4239/wjd.v6.i8.1073.
416. The National Diabetes Inpatient COVID Response Team. COncise adVice on Inpatient Diabetes - Dexamethasone therapy in covid-19 patients: implications and guidance for the management of blood glucose in people with and without diabetes. 2020. https://tinyurl.com/4myjjz7r (accessed 30 March 2024).
417. Gulliford MC, Charlton J, Latinovic R. Risk of Diabetes Associated With Prescribed Glucocorticoids in a Large Population. *Diabetes Care* 2006; **29**(12): 2728-9.https://doi.org/10.2337/dc06-1499
418. Taylor PC, Weinblatt ME, Burmester GR, et al. Cardiovascular Safety During Treatment With Baricitinib in Rheumatoid Arthritis. *Arthritis Rheumatol* 2019; **71**(7): 1042-55.https://doi.org/10.1002/art.40841
419. Medicines and Healthcare products Regulatory Agency. Baricitinib (Olumiant): risk of venous thromboembolism. 2020. https://www.gov.uk/drug-safety-update/baricitinib-olumiant-risk-of-venous-thromboembolism.
420. Roberts LN, Navaratnam AV, Arya R, Briggs TWR, Gray WK. Venous thromboembolism in patients hospitalised with COVID-19 in England. *Thromb Res* 2022; **213**: 138-44.https://doi.org/10.1016/j.thromres.2022.03.017
421. Ayodele OA, Cabral HJ, McManus DD, Jick SS. Glucocorticoids and Risk of Venous Thromboembolism in Asthma Patients Aged 20–59 Years in the United Kingdom's CPRD

1995–2015. *Clinical Epidemiology* 2022; **14**(null): 83-93.https://doi.org/10.2147/CLEP.S341048
422. Bieber T, Feist E, Irvine AD, et al. A Review of Safety Outcomes from Clinical Trials of Baricitinib in Rheumatology, Dermatology and COVID-19. *Advances in Therapy* 2022; **39**(11): 4910-60.https://doi.org/10.1007/s12325-022-02281-4
423. Medicines and Healthcare products Regulatory Agency. Baricitinib (Olumiant): increased risk of diverticulitis, particularly in patients with risk factors. 2020. https://www.gov.uk/drug-safety-update/baricitinib-olumiant-increased-risk-of-diverticulitis-particularly-in-patients-with-risk-factors.
424. Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. *BMJ Open* 2014; **4**(5): e004587.https://doi.org/10.1136/bmjopen-2013-004587
425. Strangfeld A, Richter A, Siegmund B, et al. Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs. *Annals of the Rheumatic Diseases* 2017; **76**(3): 504-10.https://doi.org/10.1136/annrheumdis-2016-209773
426. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. *Mayo Clin Proc* 2006; **81**(10): 1361-7.https://doi.org/10.4065/81.10.1361.
427. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *The Lancet* 2008; **371**(9617): 987-97.https://doi.org/10.1016/S0140-6736(08)60453-5
428. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 2000; **15**(6): 993-1000.https://doi.org/10.1359/jbmr.2000.15.6.993.
429. Chalitsios CV, Shaw DE, McKeever TM. Risk of osteoporosis and fragility fractures in asthma due to oral and inhaled corticosteroids: two population-based nested case-control studies. *Thorax*; **76**(1): 21-8.https://doi.org/10.1136/thoraxjnl-2020-215664
430. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV, Condition WHOCCDWGoP-C-. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *The Lancet Infectious Diseases* 2021; **21**: 21.https://doi.org/10.1016/S1473-3099(21)00703-9
431. Tikkinen K. NCT05220280 SOLIDARITY Finland Plus Long-COVID Trial Registration Record. https://clinicaltrials.gov/study/NCT05220280 (accessed 6 April 2024).
432. Akgun M. NCT04988282 Systemic Corticosteroids in Treatment of Post-COVID-19 Interstitial Lung Disease (STERCOV-ILD) Trial Registration Record. https://clinicaltrials.gov/study/NCT04988282 (accessed 6 April 2024).
433. Xue Q-L. The Frailty Syndrome: Definition and Natural History. *Clinics in Geriatric Medicine* 2011; **27**(1): 1-15.https://doi.org/10.1016/j.cger.2010.08.009
434. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *The journals of gerontology Series A, Biological sciences and medical sciences* 2001; **56**(3): M146-56.https://doi.org/10.1093/gerona/56.3.m146
435. Graham JE, Snih SA, Berges IM, Ray LA, Markides KS, Ottenbacher KJ. Frailty and 10-year mortality in community-living Mexican American older adults. *Gerontology* 2009; **55**(6): 644-51.https://doi.org/10.1159/000235653
436. Cui Z, Merritt Z, Assa A, et al. Early and Significant Reduction in C-Reactive Protein Levels After Corticosteroid Therapy Is Associated With Reduced Mortality in Patients With COVID-19. *Journal of Hospital Medicine (Online)* 2021; **16**(3): 142-8.https://doi.org/10.12788/jhm.3560
437. Blum CA, Nigro N, Briel M, et al. Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. *The Lancet* 2015; **385**(9977): 1511-8.https://doi.org/10.1016/S0140-6736(14)62447-8
438. Meijvis SC, Hardeman H, Remmelts HH, et al. Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind,

placebo-controlled trial. *Lancet* 2011; **377**(9782): 2023-30.https://doi.org/10.1016/S0140-6736(11)60607-7
439. Mammen JJ, Kumar S, Thomas L, et al. Factors associated with mortality among moderate and severe patients with COVID-19 in India: a secondary analysis of a randomised controlled trial. *BMJ Open* 2021; **11**(10): e050571.https://doi.org/10.1136/bmjopen-2021-050571.
440. Claman HN. 6 - Anti-inflammatory Effects of Corticosteroids. *Clinics in Immunology and Allergy* 1984; **4**(2): 317-29.https://doi.org/10.1016/S0260-4639(22)00182-7
441. Gelzo M, Cacciapuoti S , Pinchera B, et al. Prognostic Role of Neutrophil to Lymphocyte Ratio in COVID-19 Patients: still Valid in Patients That Had Started Therapy? *Frontiers in public health* 2021; **9**: 664108.https://doi.org/10.3389/fpubh.2021.664108
442. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ* 2018; **362**: k601. https://doi.org/10.1136/bmj.k601
443. Ananth CV, Lavery JA. Biases in secondary analyses of randomised trials: recognition, correction, and implications. *Bjog* 2016; **123**(7): 1056-9.https://doi.org/10.1111/1471-0528.13732
444. Rogers JK, Yaroshinsky A, Pocock SJ, Stokar D, Pogoda J. Analysis of recurrent events with an associated informative dropout time: Application of the joint frailty model. *Stat Med* 2016; **35**(13): 2195-205.https://doi.org/10.1002/sim.6853
445. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009; **338**: b2393.https://doi.org/10.1136/bmj.b2393
446. Pessoa-Amorim G, Goldacre R, Crichton C, et al. Clinical trial results in context: comparison of baseline characteristics and outcomes of 38,510 RECOVERY trial participants versus a reference population of 346,271 people hospitalised with COVID-19 in England. *Trials* 2024; **25**(1): 429.https://doi.org/10.1186/s13063-024-08273-9
447. Ginde AA, Blanc PG, Lieberman RM, Camargo CA, Jr. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. *BMC Endocr Disord* 2008; **8**: 4.https://dx.doi.org/10.1186/1472-6823-8-4
448. Hodge MC, Dixon S, Garg AX, Clemens KK. Validation of an International Statistical Classification of Diseases and Related Health Problems 10th Revision Coding Algorithm for Hospital Encounters with Hypoglycemia. *Can* 2017; **41**(3): 322-8.https://dx.doi.org/10.1016/j.jcjd.2016.11.003
449. Yang TH, Ziemba R, Shehab N, et al. Assessment of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Code Assignment Validity for Case Finding of Medication-related Hypoglycemia Acute Care Visits Among Medicare Beneficiaries. *Med Care* 2022; **60**(3): 219-26.https://dx.doi.org/10.1097/MLR.0000000000001682
450. Min JY, Presley CA, Wharton J, et al. Accuracy of a composite event definition for hypoglycemia. *Pharmacoepidemiol Drug Saf* 2019; **28**(5): 625-31.https://doi.org/10.1002/pds.4712
451. Tam JWK, Thomson GA, Fernando DJS. How accurate are diagnostic coding data? *European Journal of Internal Medicine* 2008; **19(3)**: 225.https://dx.doi.org/10.1016/j.ejim.2007.08.001
452. VanderWeele J, Pollack T, Oakes DJ, et al. Validation of data from electronic data warehouse in diabetic ketoacidosis: Caution is needed. *J Diabetes Complications* 2018; **32**(7): 650-4.https://dx.doi.org/10.1016/j.jdiacomp.2018.05.004
453. Bergdahl C, Nilsson F, Wennergren D, Ekholm C, Moller M. Completeness in the Swedish Fracture Register and the Swedish National Patient Register: An Assessment of Humeral Fracture Registrations. *Clin Epidemiol* 2021; **13**: 325-33.https://dx.doi.org/10.2147/CLEP.S307762

454. Curtis JR, Mudano AS, Solomon DH, Xi J, Melton ME, Saag KG. Identification and validation of vertebral compression fractures using administrative claims data. *Med Care* 2009; **47**(1): 69-72.https://dx.doi.org/10.1097/MLR.0b013e3181808c05
455. Helgeland J, Kristoffersen DT, Skyrud KD, Lindman AS. Variation between Hospitals with Regard to Diagnostic Practice, Coding Accuracy, and Case-Mix. A Retrospective Validation Study of Administrative Data versus Medical Records for Estimating 30-Day Mortality after Hip Fracture. *PLoS ONE* 2016; **11**(5): e0156075.https://dx.doi.org/10.1371/journal.pone.0156075
456. Hjelholt TJ, Edwards NM, Vesterager JD, Kristensen PK, Pedersen AB. The Positive Predictive Value of Hip Fracture Diagnoses and Surgical Procedure Codes in the Danish Multidisciplinary Hip Fracture Registry and the Danish National Patient Registry. *Clin Epidemiol* 2020; **12**: 123-31.https://dx.doi.org/10.2147/CLEP.S238722
457. Hoiberg MP, Gram J, Hermann P, Brixen K, Haugeberg G. The incidence of hip fractures in Norway -accuracy of the national Norwegian patient registry. *BMC Musculoskelet Disord* 2014; **15**: 372.https://dx.doi.org/10.1186/1471-2474-15-372
458. Huttunen TT, Kannus P, Pihlajamaki H, Mattila VM. Pertrochanteric fracture of the femur in the Finnish National Hospital Discharge Register: validity of procedural coding, external cause for injury and diagnosis. *BMC Musculoskelet Disord* 2014; **15**: 98.https://dx.doi.org/10.1186/1471-2474-15-98
459. Lofthus CM, Cappelen I, Osnes EK, et al. Local and national electronic databases in Norway demonstrate a varying degree of validity. *J Clin Epidemiol* 2005; **58**(3): 280-5.https://doi.org/10.1016/j.jclinepi.2004.07.003
460. Ray WA, Griffin MR, Fought RL, Adams ML. Identification of fractures from computerized Medicare files. *J Clin Epidemiol* 1992; **45**(7): 703-14.https://doi.org/10.1016/0895-4356(92)90047-q
461. Sing CW, Woo YC, Lee ACH, et al. Validity of major osteoporotic fracture diagnosis codes in the Clinical Data Analysis and Reporting System in Hong Kong. *Pharmacoepidemiol Drug Saf* 2017; **26**(8): 973-6.https://dx.doi.org/10.1002/pds.4208
462. Thuy Trinh LT, Achat H, Loh SM, et al. Validity of routinely collected data in identifying hip fractures at a major tertiary hospital in Australia. *Health Inf Manag* 2018; **47**(1): 38-45.https://dx.doi.org/10.1177/1833358317721305
463. Lee YK, Yoo JI, Kim TY, et al. Validation of Operational Definition to Identify Patients with Osteoporotic Hip Fractures in Administrative Claims Data. *Healthcare (Basel)* 2022; **10**(9): 08.https://dx.doi.org/10.3390/healthcare10091724
464. Inouye SK, Leo-Summers L, Zhang Y, Bogardus Jr ST, Leslie DL, Agostini JV. A chart-based method for identification of delirium: Validation compared with interviewer ratings using the confusion assessment method. *J Am Geriatr Soc* 2005; **53(2)**: 312-8.https://dx.doi.org/10.1111/j.1532-5415.2005.53120.x
465. Pendlebury ST, Lovett NG, Thomson RJ, Smith SC. Impact of a system-wide multicomponent intervention on administrative diagnostic coding for delirium and other cognitive frailty syndromes: observational prospective study. *Clin Med* 2020; **20**(5): 454-64.https://dx.doi.org/10.7861/clinmed.2019-0470
466. Bui CL, Kaye JA, Castellsague J, et al. Validation of acute liver injury cases in a population-based cohort study of oral antimicrobial users. *Curr Drug Saf* 2014; **9**(1): 23-8.https://doi.org/10.2174/15748863113086660051
467. Forns J, Cainzos-Achirica M, Hellfritzsch M, et al. Validity of ICD-9 and ICD-10 codes used to identify acute liver injury: A study in three European data sources. *Pharmacoepidemiol Drug Saf* 2019; **28**(7): 965-75.https://dx.doi.org/10.1002/pds.4803
468. Lo Re V, 3rd, Haynes K, Goldberg D, et al. Validity of diagnostic codes to identify cases of severe acute liver injury in the US Food and Drug Administration's Mini-Sentinel Distributed Database. *Pharmacoepidemiol Drug Saf* 2013; **22**(8): 861-72.https://dx.doi.org/10.1002/pds.3470

469. Timmer A, de Sordi D, Kappen S, et al. Validity of hospital ICD-10-GM codes to identify acute liver injury in Germany. *Pharmacoepidemiol Drug Saf* 2019; **28**(10): 1344-52.https://dx.doi.org/10.1002/pds.4855

Supplementary Figures and Tables

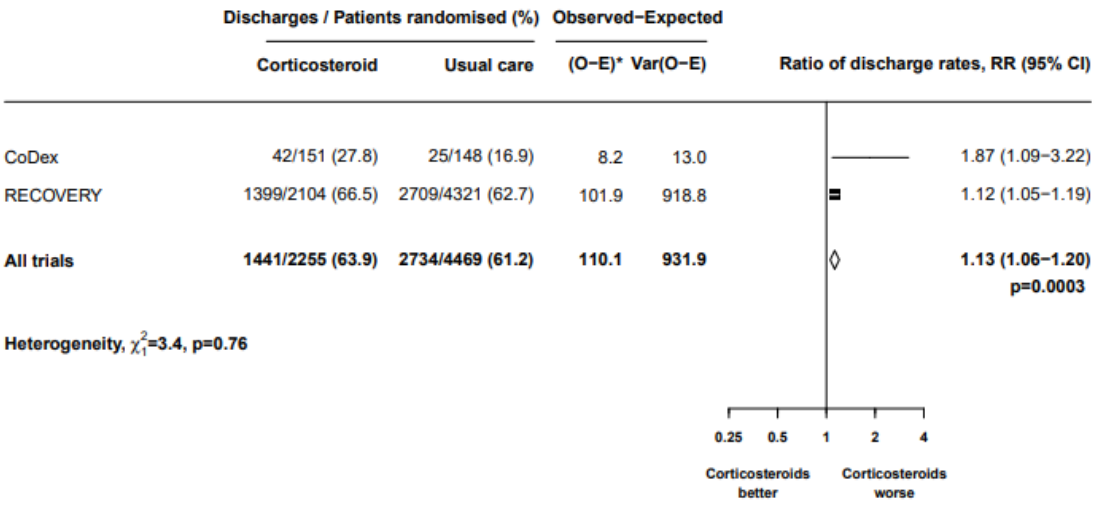
Supplementary Figures

List of Supplementary Figures

Supplementary Figure 1: Meta-analysis of discharge alive from hospital within 28 days in randomised controlled trials of systemic corticosteroids in patients hospitalised with COVID-19..... 384
Supplementary Figure 2: Meta-analysis of abnormal liver function test results within 28 days in randomised controlled trials of interleukin-6 receptor antagonists compared with usual care/placebo in hospitalised patients with COVID-19. 385
Supplementary Figure 3: Meta-analysis of neutropenia events within 28 days in randomised controlled trials of interleukin-6 receptor antagonists compared with usual care/placebo in hospitalised patients with COVID-19. 386
Supplementary Figure 4: Meta-analysis of discharge alive from hospital within 28 days in randomised controlled trials of interleukin-6 receptor antagonists in patients hospitalised with COVID-19. 387
Supplementary Figure 5: Meta-analysis of discharge alive from hospital within 90 days in randomised controlled trials of interleukin-6 receptor antagonists in patients hospitalised with COVID-19. 388
Supplementary Figure 6: Meta-analysis of venous thromboembolism within 28 days in randomised controlled trials of Janus kinase inhibitors compared with usual care/placebo in hospitalised patients with COVID-19. 389
Supplementary Figure 7: Meta-analysis of gastrointestinal complications within 28 days in randomised controlled trials of Janus kinase inhibitors in patients hospitalised with COVID-19..... 390

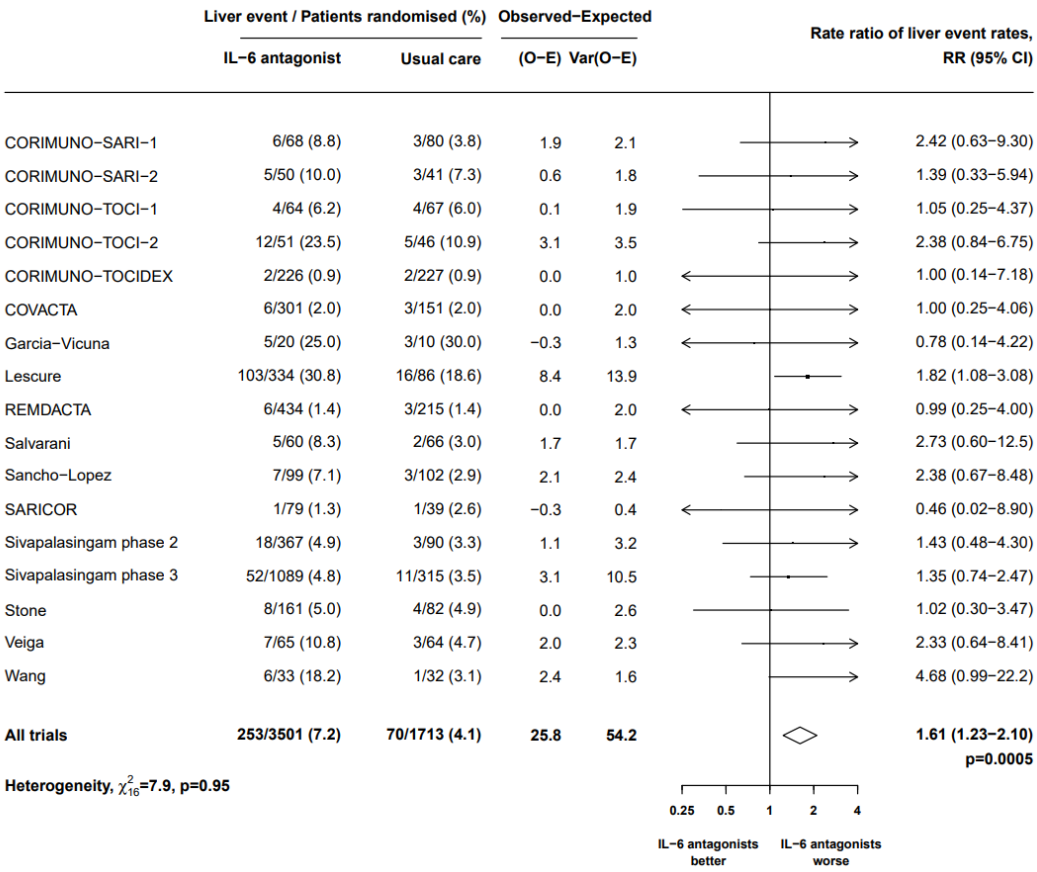
Supplementary Figure 8: Meta-analysis of abnormal liver function events within 28 days in randomised controlled trials of Janus kinase inhibitors in patients hospitalised with COVID-19..... 390
Supplementary Figure 9: Meta-analysis of discharge alive from hospital within 28 days in randomised controlled trials of Janus kinase inhibitors in patients hospitalised with COVID-19..... 391
Supplementary Figure 10: Meta-analysis of discharge alive from hospital within 90 days in randomised controlled trials of Janus kinase inhibitors in patients hospitalised with COVID-19..... 392
Supplementary Figure 11: Meta-analysis of venous thromboembolism within 28 days in randomised controlled trials of higher dose corticosteroids compared with lower dose corticosteroids in patients hospitalised with COVID-19..... 393
Supplementary Figure 12: Meta-analysis of psychiatric complications within 28 days in randomised controlled trials of higher dose corticosteroids compared with lower dose corticosteroids in patients hospitalised with COVID-19..... 394
Supplementary Figure 13: Meta-analysis of gastrointestinal complications within 28 days in randomised controlled trials of higher dose corticosteroids compared with lower dose corticosteroids in patients hospitalised with COVID-19..... 395
Supplementary Figure 14: Meta-analysis of discharge alive from hospital within 28 days in randomised controlled trials of higher-dose corticosteroids compared with lower dose corticosteroids in hospitalised patients with COVID-19..... 396
Supplementary Figure 15: Subgroup analysis of effect of allocation to dexamethasone on all-cause mortality within 28 days. 397
Supplementary Figure 16: Subgroup analysis of effect of allocation to tocilizumab on all-cause mortality within 28 days. 398
Supplementary Figure 17: Subgroup analysis of effect of allocation to baricitinib on all-cause mortality within 28 days..... 399

Supplementary Figure 18: Subgroup analysis of effect of allocation to higher dose dexamethasone on all-cause mortality within 28 days. 400
Supplementary Figure 19: Subgroup analysis of 28-day mortality by Charlson Co-morbidity Index score group in the RECOVERY dexamethasone comparison population. 401
Supplementary Figure 20: Effect of allocation to dexamethasone on relative odds of a bad outcome on the ordinal scale score at day 5, for each alternative definition of bad outcome. 401
Supplementary Figure 21: Subgroup analysis of daily rate of change in glucose within the first 7 days after randomisation in the RECOVERY-ISARIC dexamethasone comparison population by respiratory support group. 402
Supplementary Figure 22: Subgroup analysis of daily rate of change in glucose within the first 7 days after randomisation in the RECOVERY-ISARIC dexamethasone comparison population by Hospital Frailty Risk Score group. 403
Supplementary Figure 23: Distribution of ordinal scale score at 5 days by randomised allocation in the RECOVERY-ISARIC tocilizumab comparison. 404
Supplementary Figure 24: Effect of allocation to tocilizumab on relative odds of a bad outcome on the ordinal scale score at day 5, for each alternative definition of bad outcome. 404
Supplementary Figure 25: Subgroup analyses by treatment allocation in the RECOVERY-ISARIC tocilizumab comparison population. 405
Supplementary Figure 26: Distribution of ordinal scale score at 5 days by randomised allocation in the RECOVERY-ISARIC baricitinib comparison. 406
Supplementary Figure 27: Effect of allocation to baricitinib on relative odds of a bad outcome on the ordinal scale score at day 5, for each alternative definition of bad outcome. 406
Supplementary Figure 28: Heat map with clustering of differentially expressed genes in the dexamethasone comparison, by randomised treatment allocation and vital status at 28 days. 407



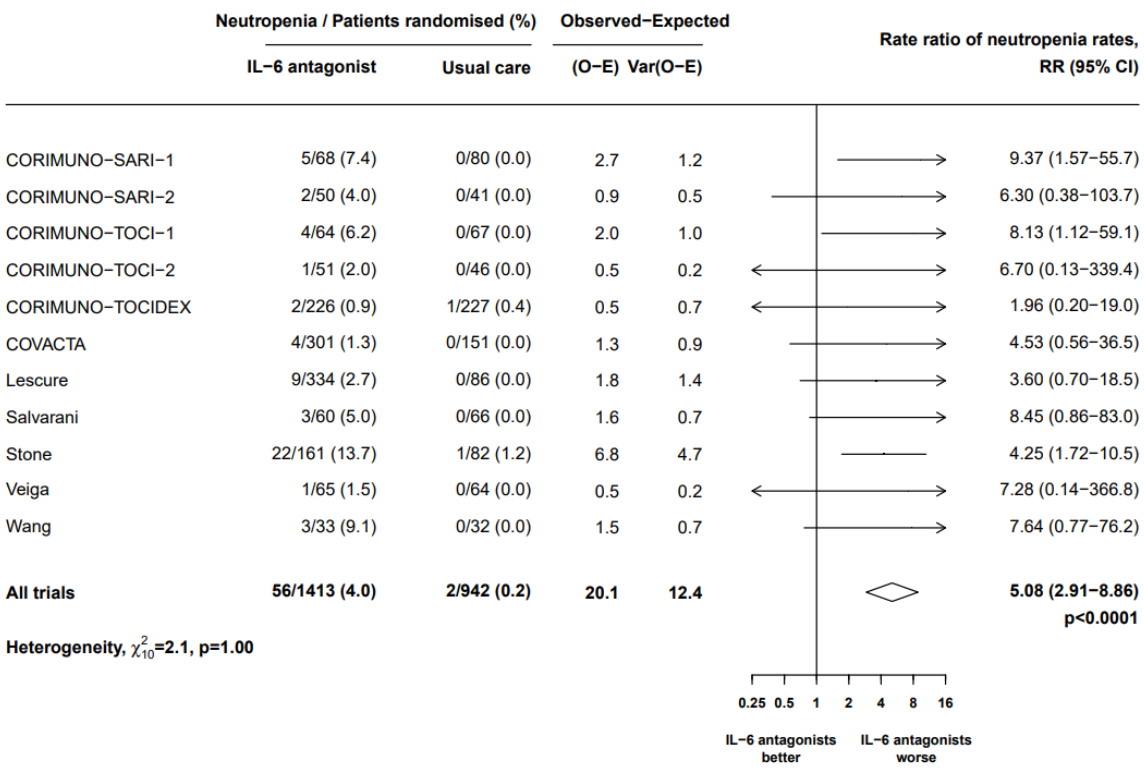
Supplementary Figure 1: Meta-analysis of discharge alive from hospital within 28 days in randomised controlled trials of systemic corticosteroids in patients hospitalised with COVID-19.
This outcome has been assessed in the RECOVERY dexamethasone comparison.

[back to main text]



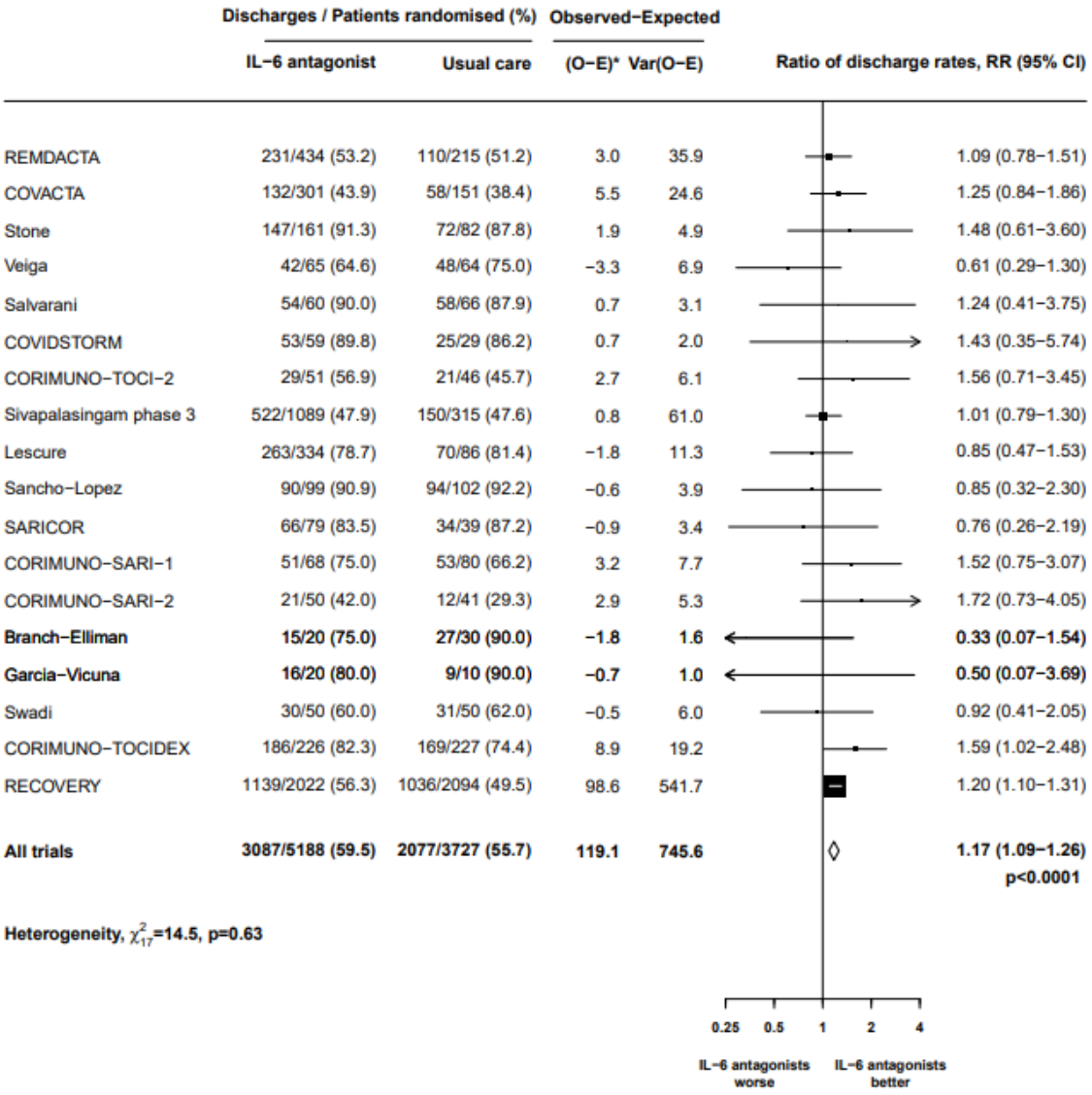
Supplementary Figure 2: Meta-analysis of abnormal liver function test results within 28 days in randomised controlled trials of interleukin-6 receptor antagonists compared with usual care/placebo in hospitalised patients with COVID-19.
This outcome has not been assessed in the RECOVERY tocilizumab comparison.

[back to main text]



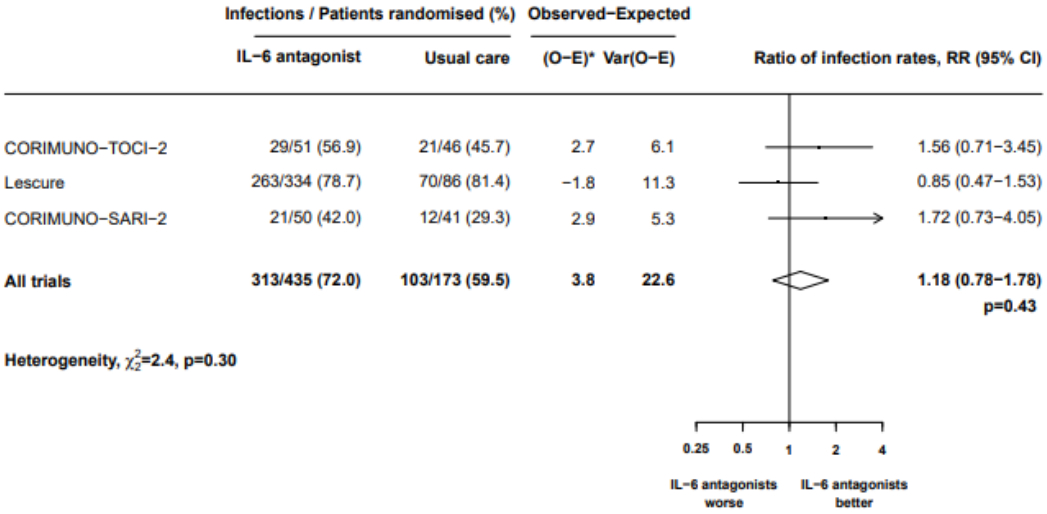
Supplementary Figure 3: Meta-analysis of neutropenia events within 28 days in randomised controlled trials of interleukin-6 receptor antagonists compared with usual care/placebo in hospitalised patients with COVID-19.
This outcome has not been assessed in the RECOVERY tocilizumab comparison.

[back to main text]



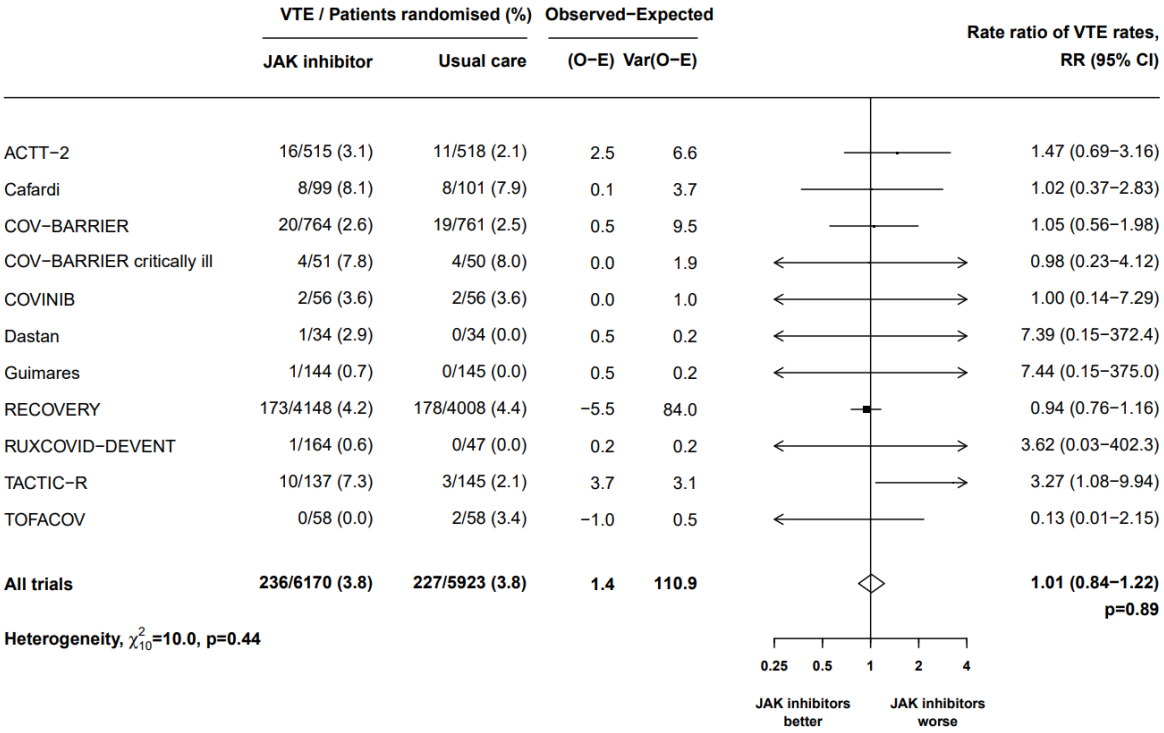
Supplementary Figure 4: Meta-analysis of discharge alive from hospital within 28 days in randomised controlled trials of interleukin-6 receptor antagonists in patients hospitalised with COVID-19. This outcome has been assessed in the RECOVERY tocilizumab comparison.

[back to main text]



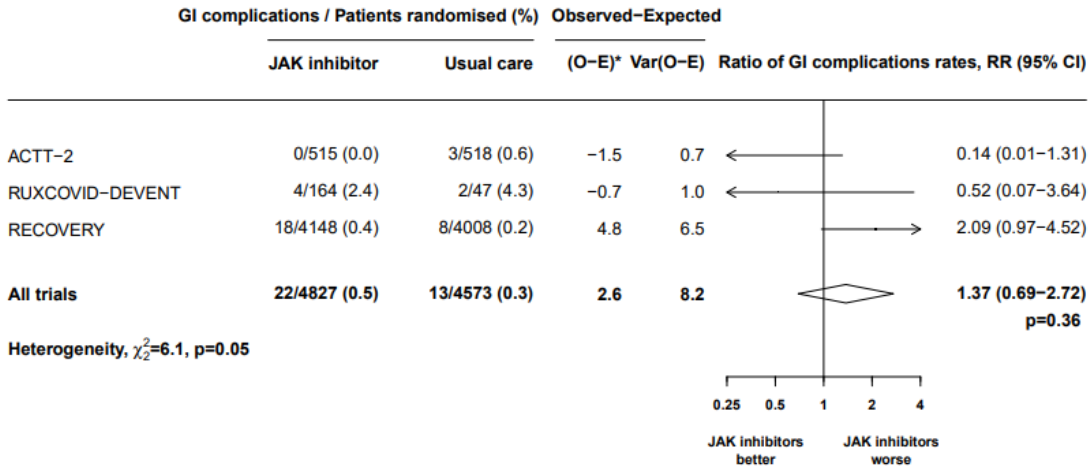
Supplementary Figure 5: Meta-analysis of discharge alive from hospital within 90 days in randomised controlled trials of interleukin-6 receptor antagonists in patients hospitalised with COVID-19.
This outcome has not been assessed in the RECOVERY tocilizumab comparison.

[back to main text]



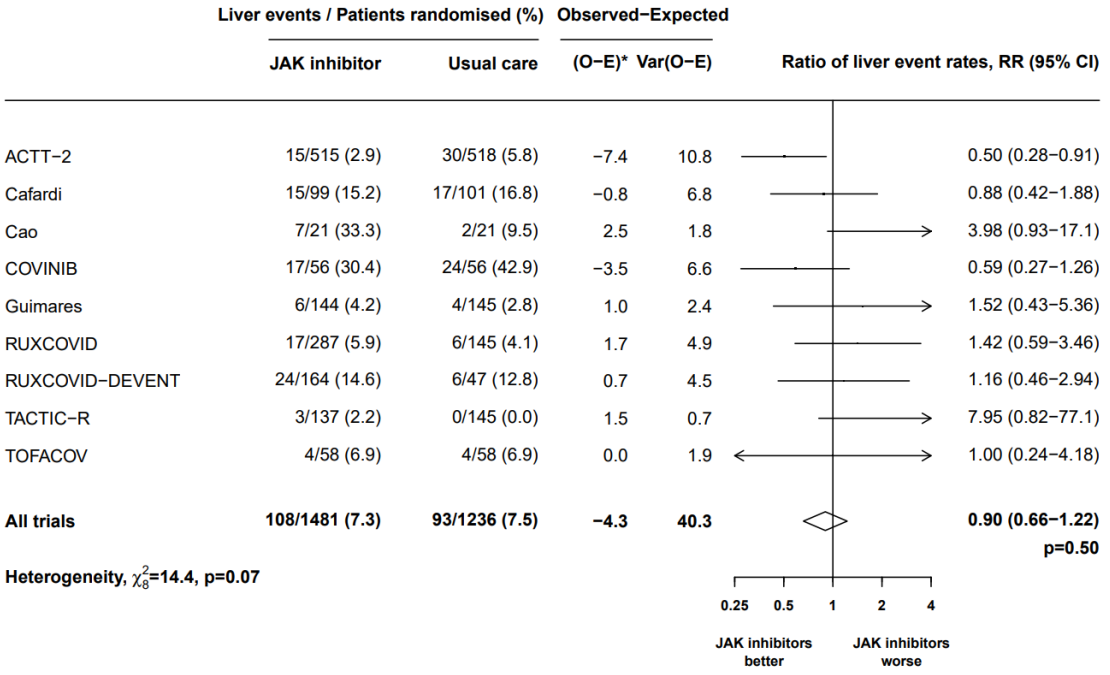
Supplementary Figure 6: Meta-analysis of venous thromboembolism within 28 days in randomised controlled trials of Janus kinase inhibitors compared with usual care/placebo in hospitalised patients with COVID-19.
This outcome has been assessed in the RECOVERY baricitinib comparison.

[back to main text]



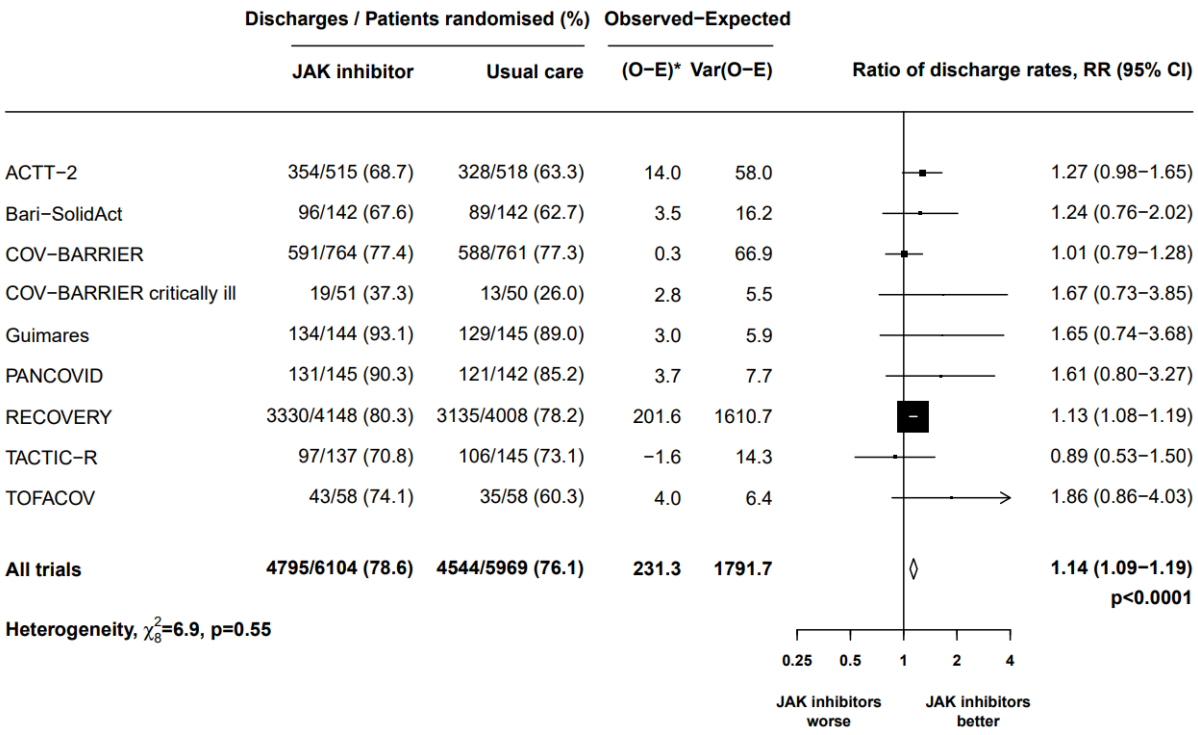
Supplementary Figure 7: Meta-analysis of gastrointestinal complications within 28 days in randomised controlled trials of Janus kinase inhibitors in patients hospitalised with COVID-19.
This outcome has been assessed in the RECOVERY baricitinib comparison.

[back to main text]



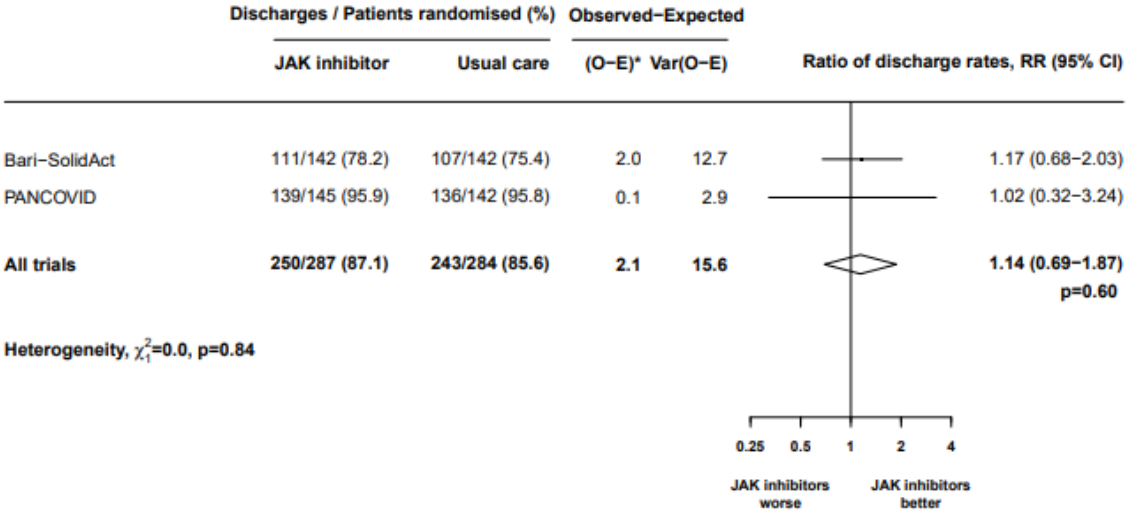
Supplementary Figure 8: Meta-analysis of abnormal liver function events within 28 days in randomised controlled trials of Janus kinase inhibitors in patients hospitalised with COVID-19.
This outcome has not been assessed in the RECOVERY baricitinib comparison.

[back to main text]



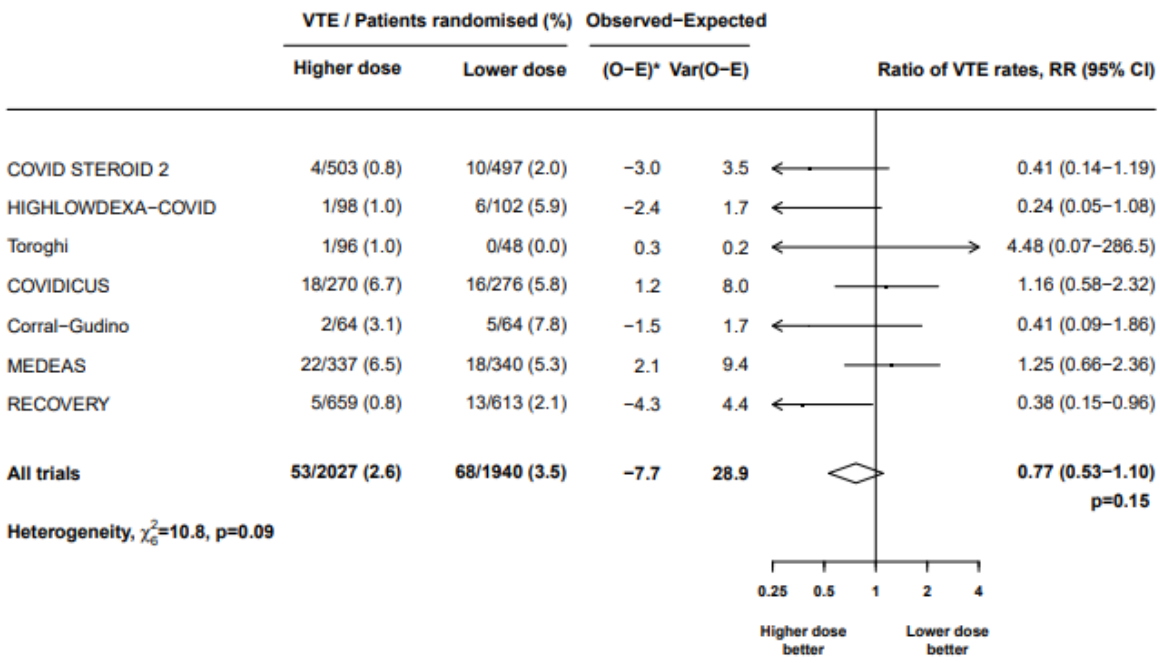
Supplementary Figure 9: Meta-analysis of discharge alive from hospital within 28 days in randomised controlled trials of Janus kinase inhibitors in patients hospitalised with COVID-19.
This outcome has been assessed in the RECOVERY baricitinib comparison.

[back to main text]



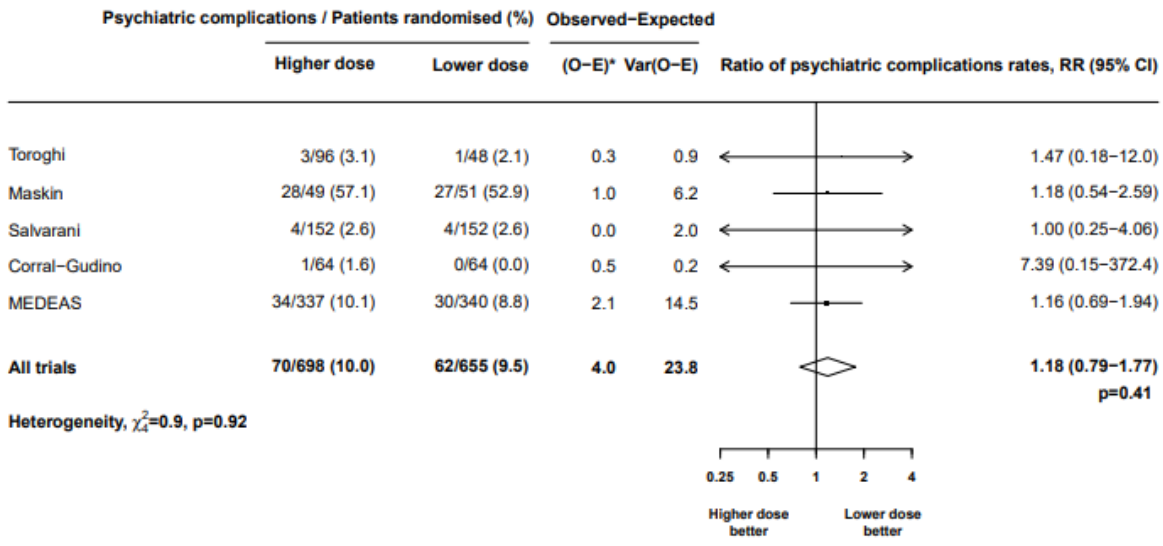
Supplementary Figure 10: Meta-analysis of discharge alive from hospital within 90 days in randomised controlled trials of Janus kinase inhibitors in patients hospitalised with COVID-19. This outcome has not been assessed in the RECOVERY baricitinib comparison.

[back to main text]



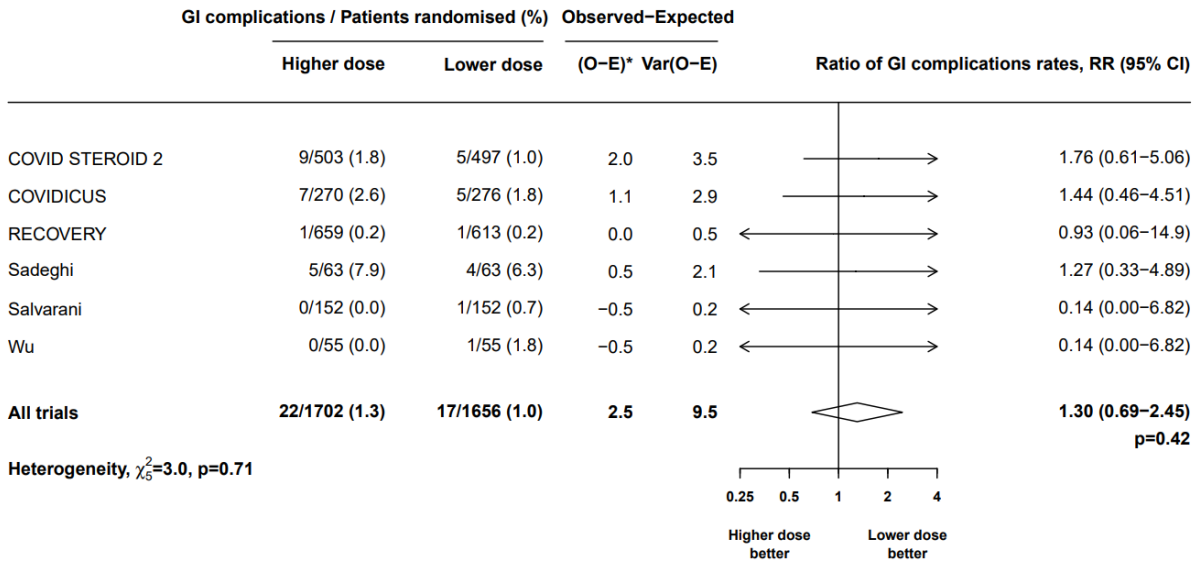
Supplementary Figure 11: Meta-analysis of venous thromboembolism within 28 days in randomised controlled trials of higher dose corticosteroids compared with lower dose corticosteroids in patients hospitalised with COVID-19.
This outcome has been assessed in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

[back to main text]



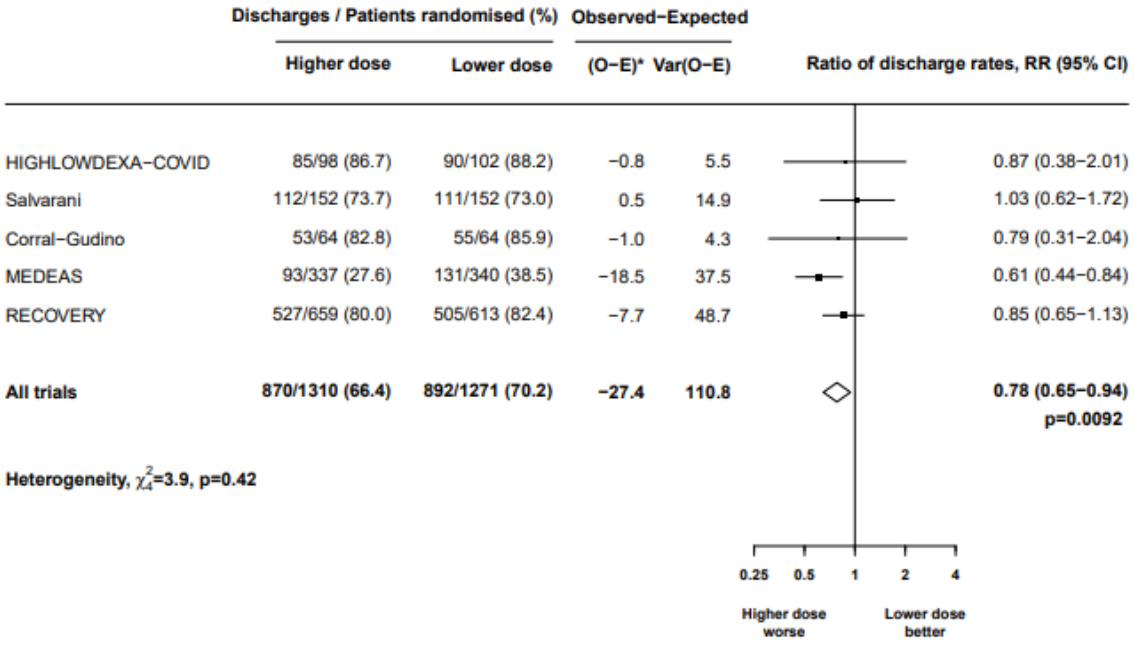
Supplementary Figure 12: Meta-analysis of psychiatric complications within 28 days in randomised controlled trials of higher dose corticosteroids compared with lower dose corticosteroids in patients hospitalised with COVID-19.
This outcome has not been assessed in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

[back to main text]



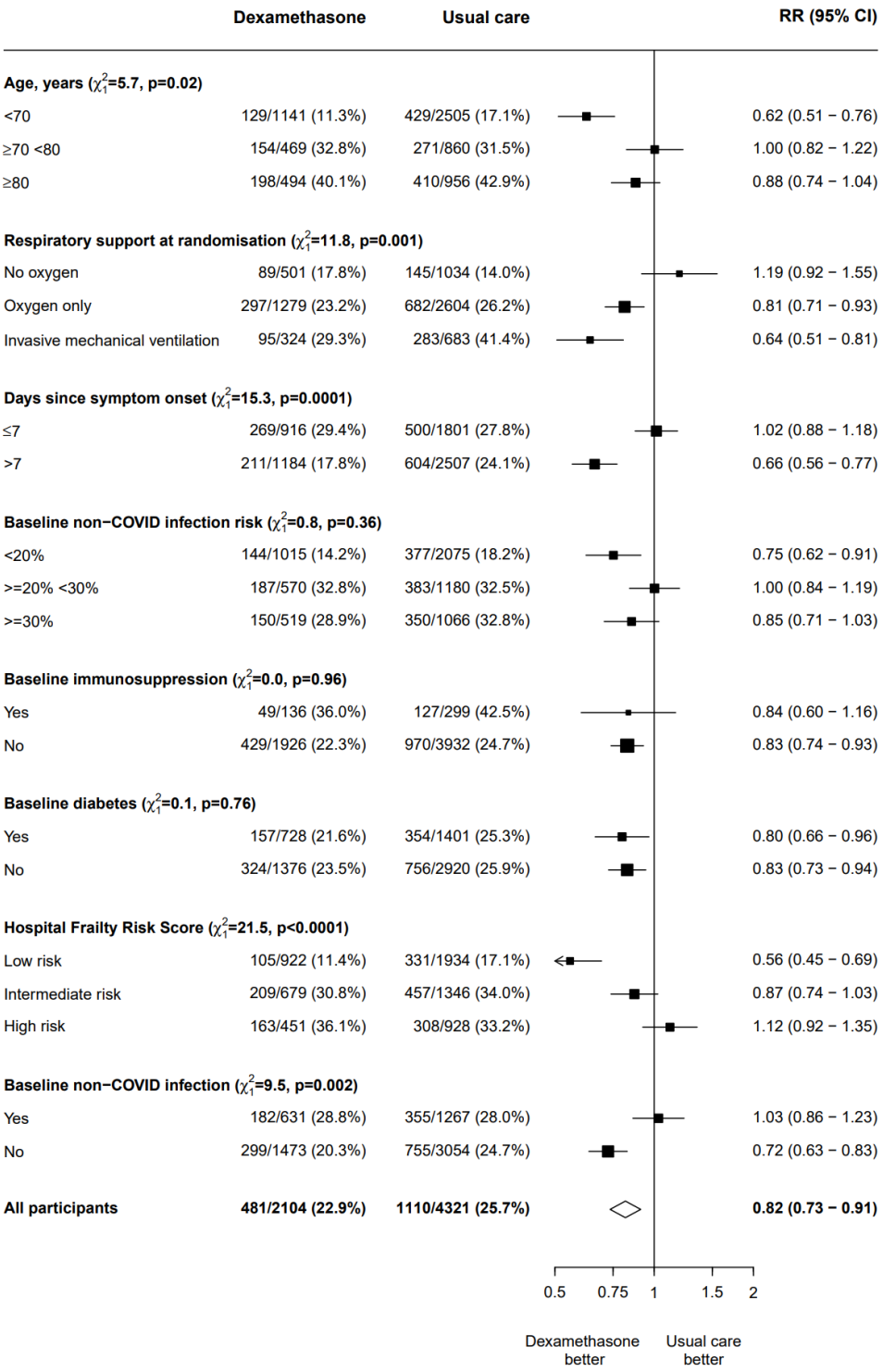
Supplementary Figure 13: Meta-analysis of gastrointestinal complications within 28 days in randomised controlled trials of higher dose corticosteroids compared with lower dose corticosteroids in patients hospitalised with COVID-19.
This outcome has been assessed in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

[back to main text]



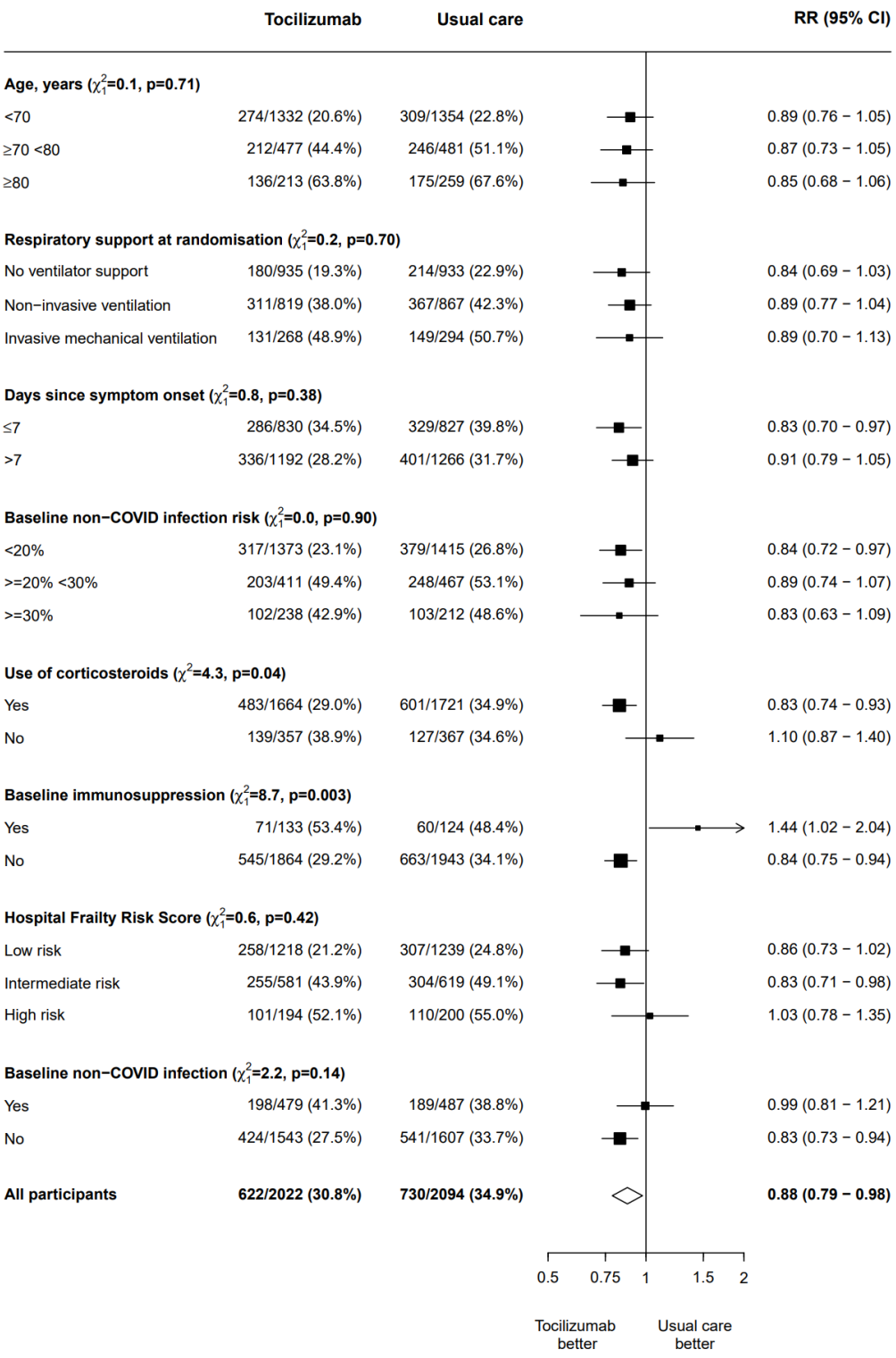
Supplementary Figure 14: Meta-analysis of discharge alive from hospital within 28 days in randomised controlled trials of higher-dose corticosteroids compared with lower dose corticosteroids in hospitalised patients with COVID-19.
This outcome has been assessed in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

[back to main text]



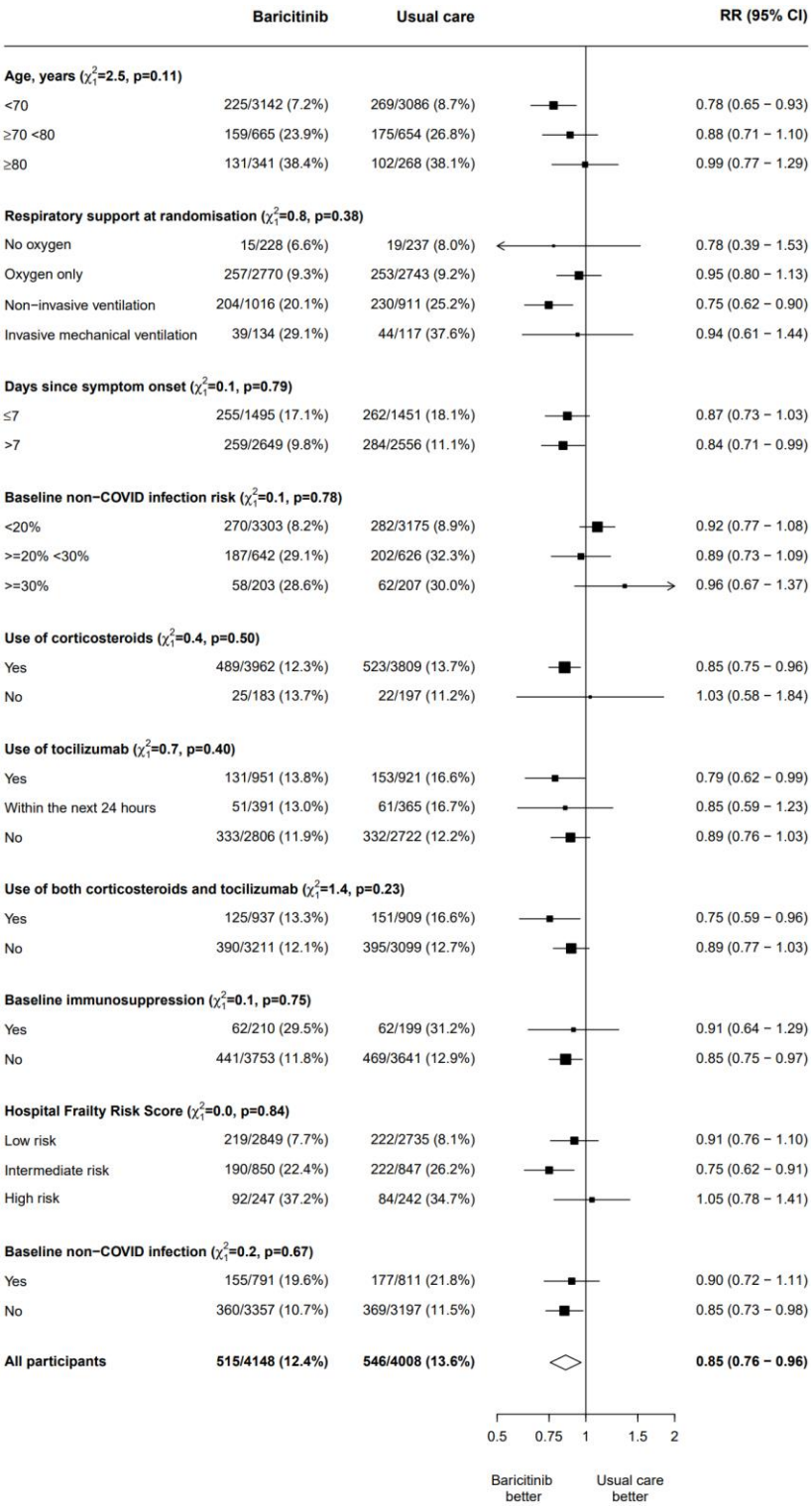
Supplementary Figure 15: Subgroup analysis of effect of allocation to dexamethasone on all-cause mortality within 28 days.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.

[back to main text]



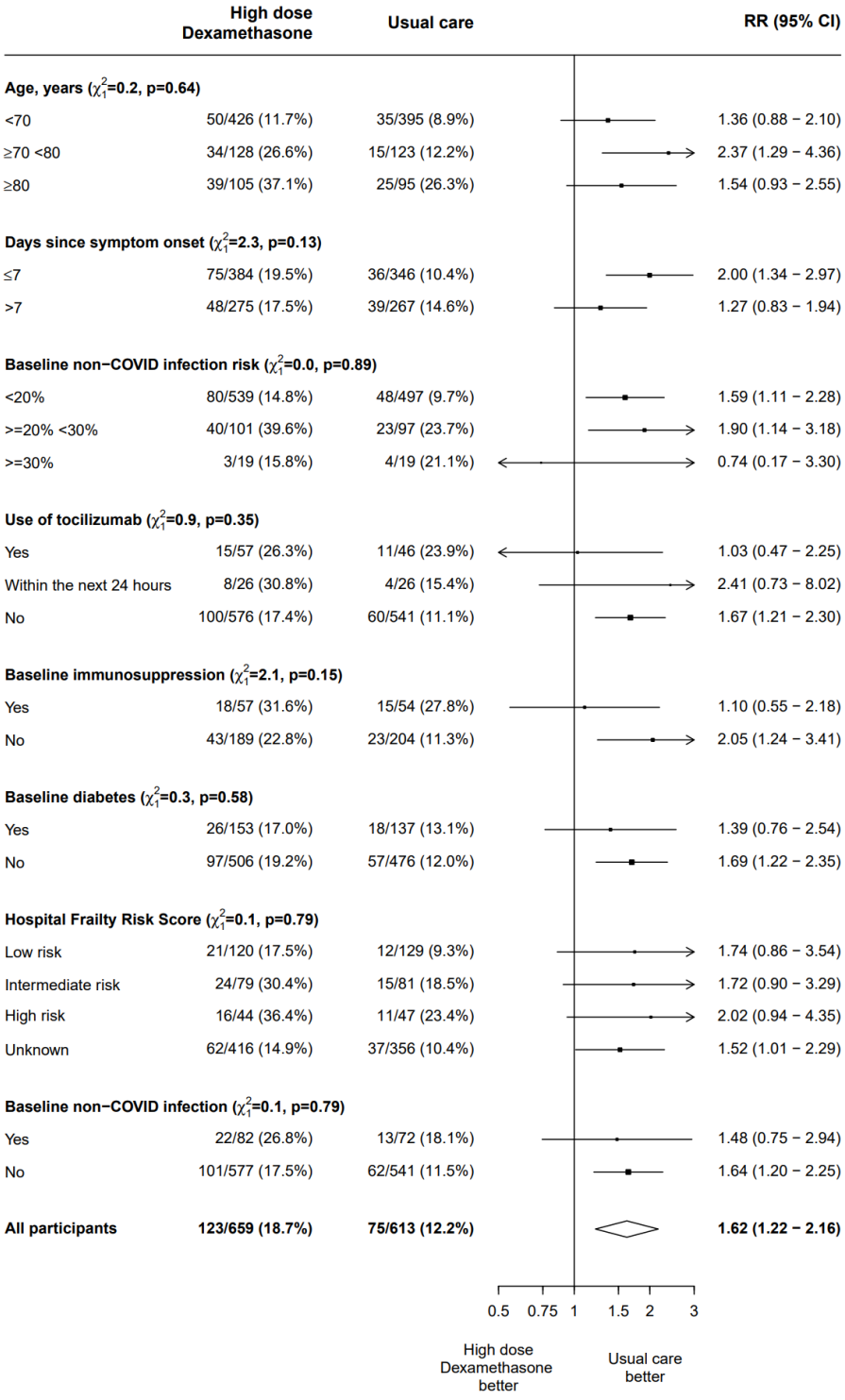
Supplementary Figure 16: Subgroup analysis of effect of allocation to tocilizumab on all-cause mortality within 28 days.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.

[back to main text]



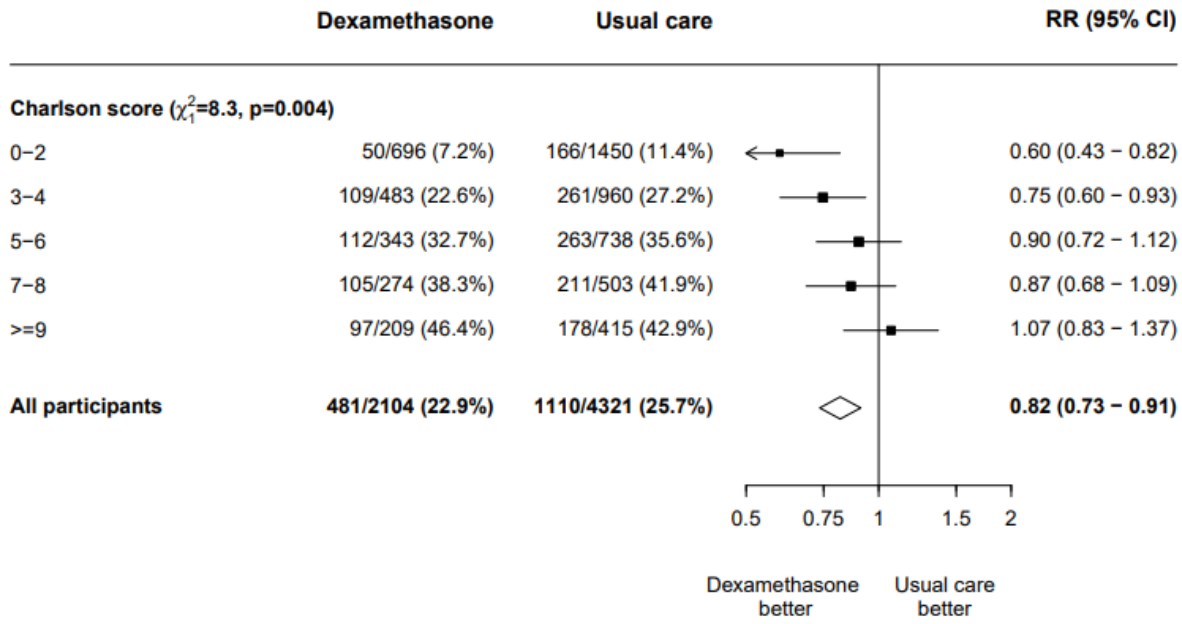
Supplementary Figure 17: Subgroup analysis of effect of allocation to baricitinib on all-cause mortality within 28 days.
RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age and respiratory support group at randomisation.

[back to main text]



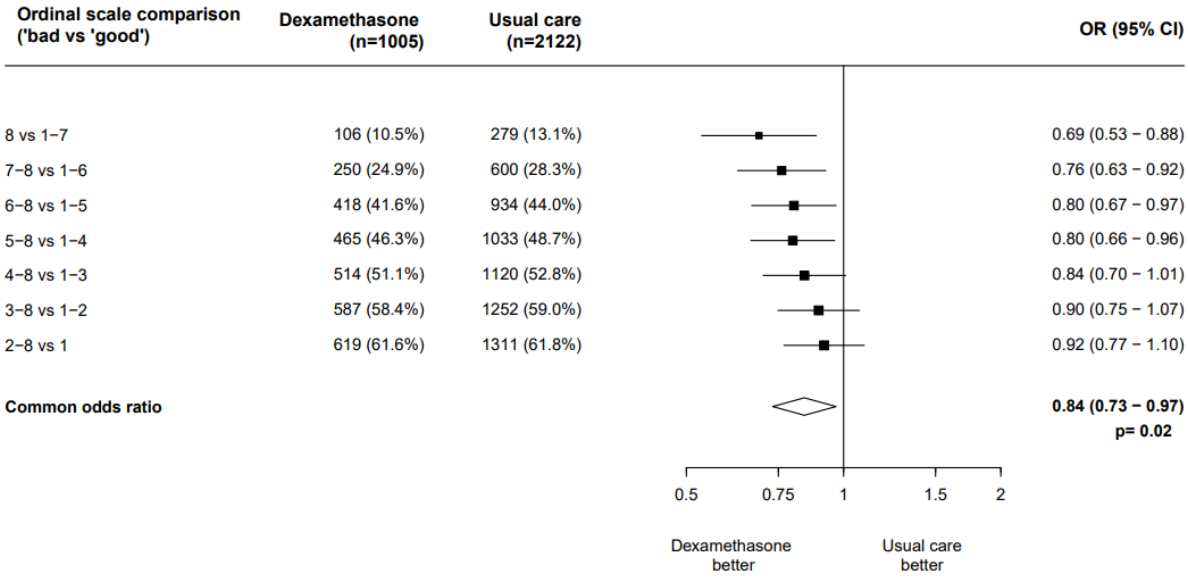
Supplementary Figure 18: Subgroup analysis of effect of allocation to higher dose dexamethasone on all-cause mortality within 28 days.
RR (95% Confidence Interval) = Rate Ratio (95% Confidence Interval), adjusted for age group at randomisation.

[back to main text]



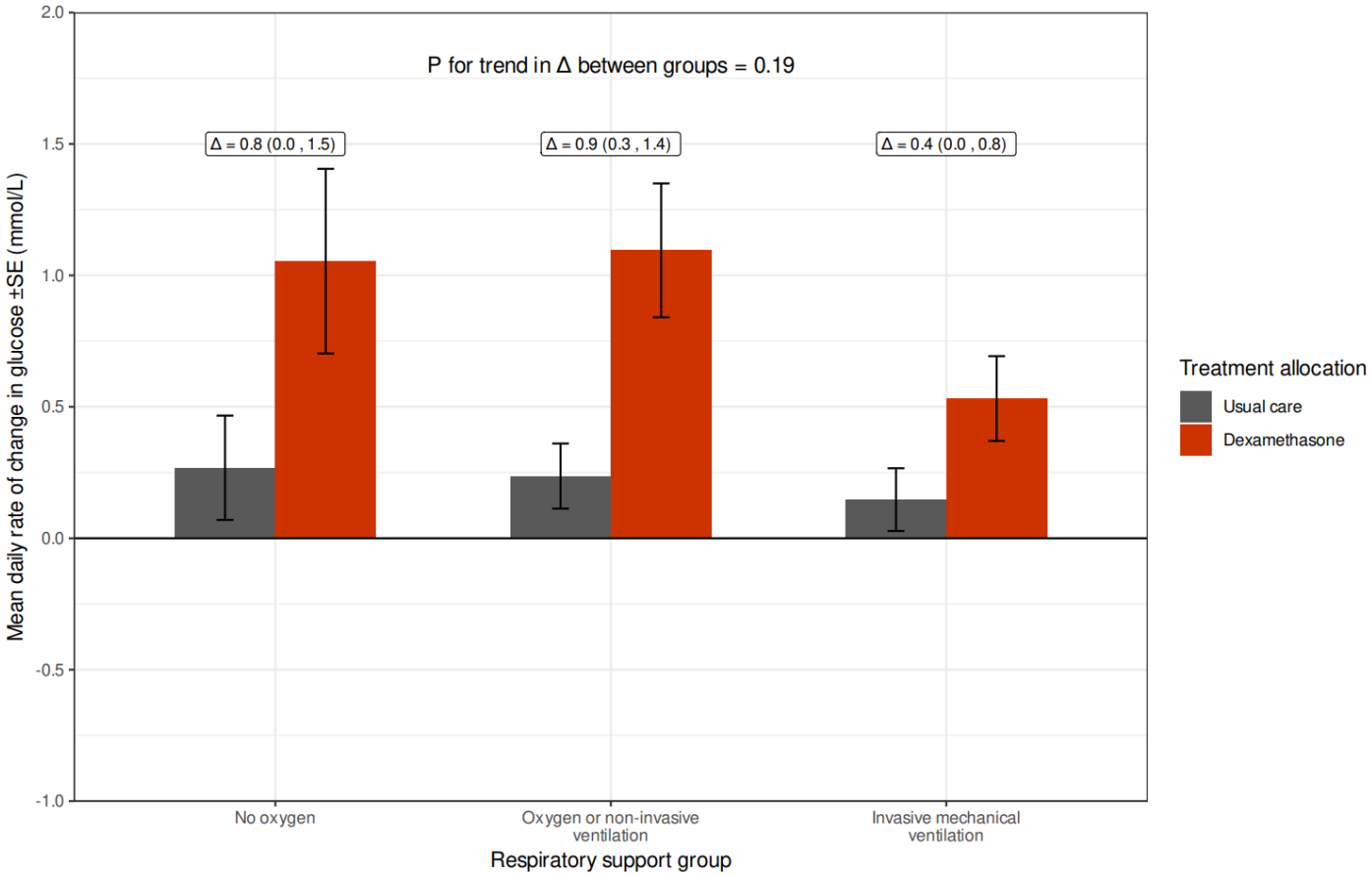
Supplementary Figure 19: Subgroup analysis of 28-day mortality by Charlson Co-morbidity Index score group in the RECOVERY dexamethasone comparison population.
RR (95% CI) = Rate Ratio (95% Confidence Interval).

[back to main text]



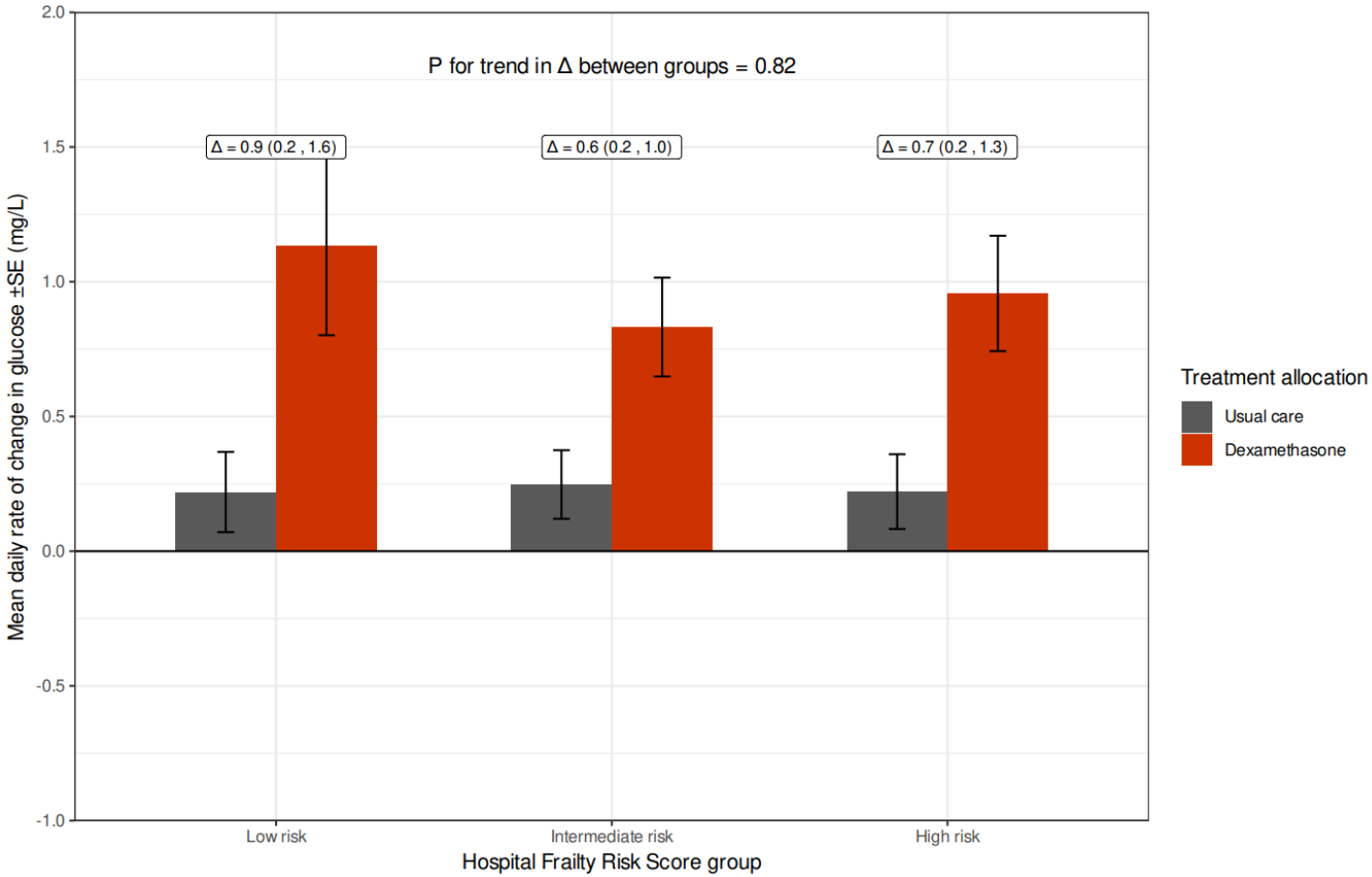
Supplementary Figure 20: Effect of allocation to dexamethasone on relative odds of a bad outcome on the ordinal scale score at day 5, for each alternative definition of bad outcome.
Assessed in the RECOVERY-ISARIC dexamethasone comparison population.
OR (95% CI) = Odds Ratio (95% Confidence Interval)

[back to main text]



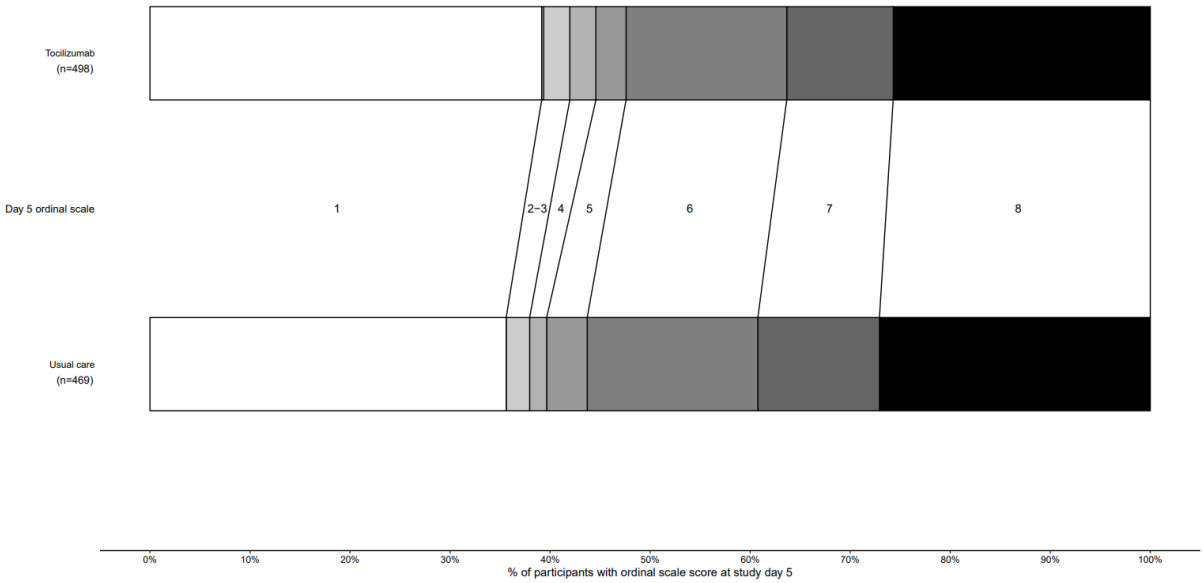
Supplementary Figure 21: Subgroup analysis of daily rate of change in glucose within the first 7 days after randomisation in the RECOVERY-ISARIC dexamethasone comparison population by respiratory support group.

[back to main text]



Supplementary Figure 22: Subgroup analysis of daily rate of change in glucose within the first 7 days after randomisation in the RECOVERY-ISARIC dexamethasone comparison population by Hospital Frailty Risk Score group.

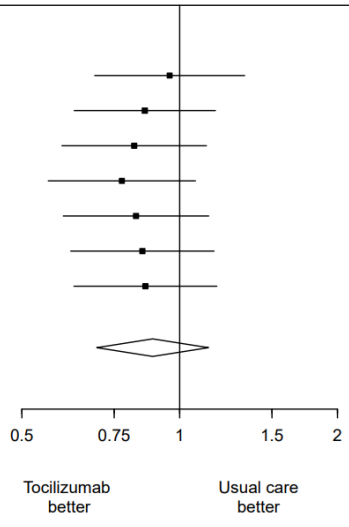
[back to main text]



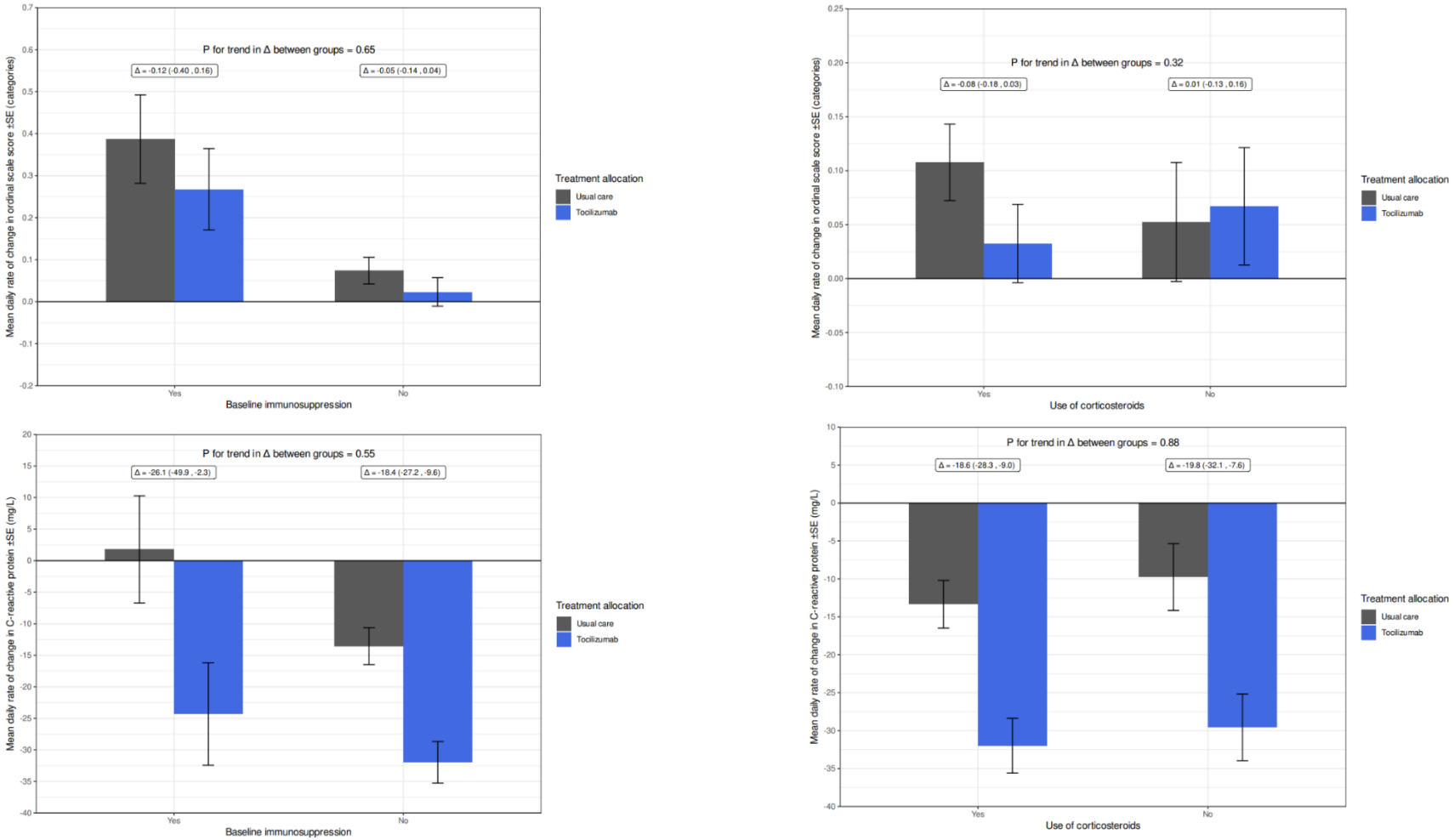
Supplementary Figure 23: Distribution of ordinal scale score at 5 days by randomised allocation in the RECOVERY-ISARIC tocilizumab comparison.

[back to main text]

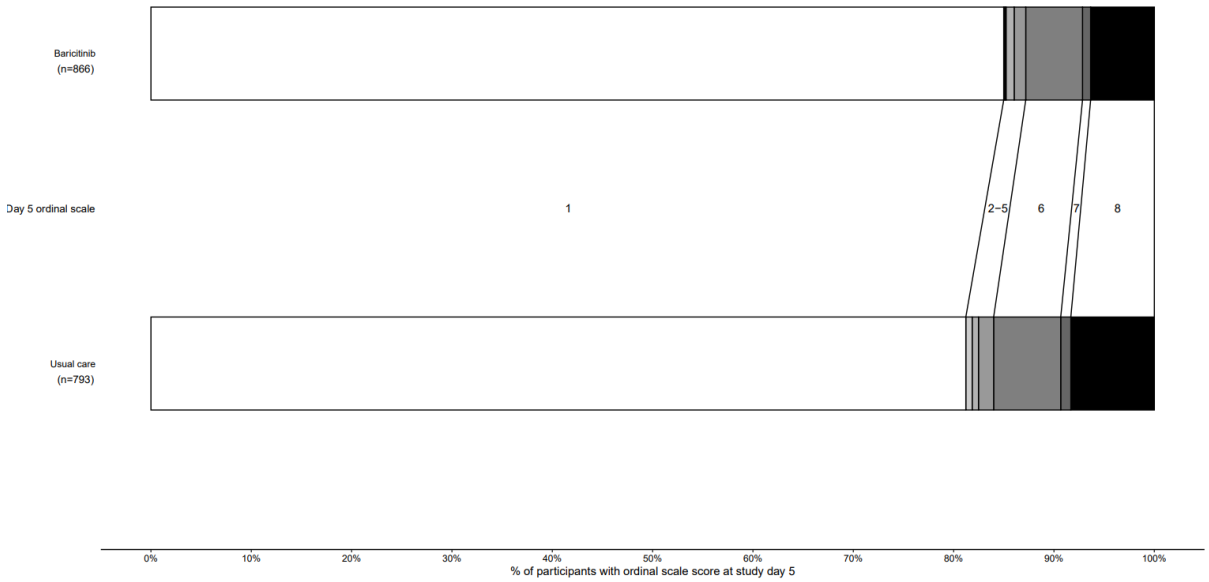
Ordinal scale comparison ('bad vs 'good')	Tocilizumab (n=498)	Usual care (n=469)	OR (95% CI)
8 vs 1–7	128 (25.7%)	127 (27.1%)	0.96 (0.69 – 1.33)
7–8 vs 1–6	181 (36.3%)	184 (39.2%)	0.86 (0.63 – 1.17)
6–8 vs 1–5	261 (52.4%)	264 (56.3%)	0.82 (0.60 – 1.12)
5–8 vs 1–4	276 (55.4%)	283 (60.3%)	0.78 (0.56 – 1.07)
4–8 vs 1–3	289 (58.0%)	291 (62.0%)	0.83 (0.60 – 1.14)
3–8 vs 1–2	302 (60.6%)	302 (64.4%)	0.85 (0.62 – 1.16)
2–8 vs 1	303 (60.8%)	302 (64.4%)	0.86 (0.63 – 1.18)
Common odds ratio			**0.89 (0.69 – 1.14)** **p= 0.34**



Supplementary Figure 24: Effect of allocation to tocilizumab on relative odds of a bad outcome on the ordinal scale score at day 5, for each alternative definition of bad outcome.
Assessed in the RECOVERY-ISARIC tocilizumab comparison population.
OR (95% CI) = Odds Ratio (95% Confidence Interval)

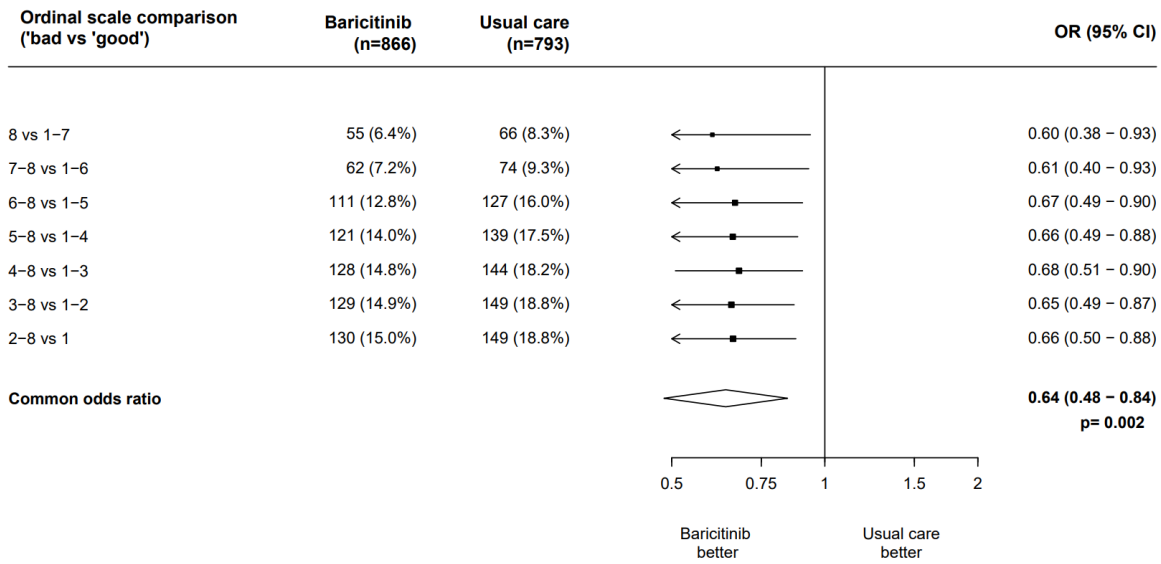


Supplementary Figure 25: Subgroup analyses by treatment allocation in the RECOVERY-ISARIC tocilizumab comparison population.
Top left: Daily rate of change in ordinal scale score by immunosuppression status. Top right: Daily rate of change in ordinal scale score by use of corticosteroids. Bottom left: Daily rate of change in C-reactive protein by immunosuppression status. Bottom right: Daily rate of change in C-reactive protein by use of corticosteroids. *[back to main text]*

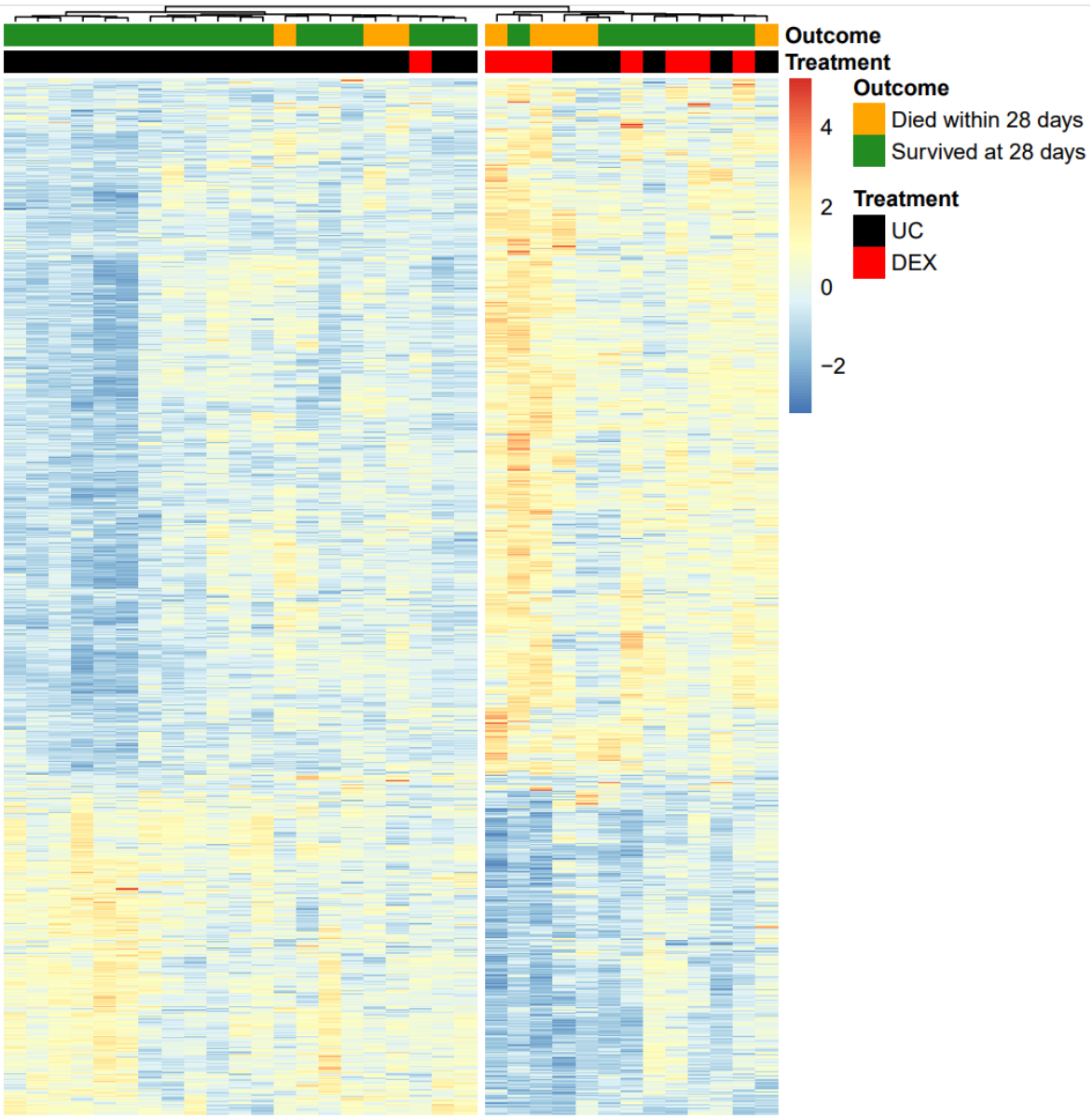


Supplementary Figure 26: Distribution of ordinal scale score at 5 days by randomised allocation in the RECOVERY-ISARIC baricitinib comparison.

[back to main text]



Supplementary Figure 27: Effect of allocation to baricitinib on relative odds of a bad outcome on the ordinal scale score at day 5, for each alternative definition of bad outcome.
Assessed in the RECOVERY-ISARIC baricitinib comparison population.
OR (95% CI) = Odds Ratio (95% Confidence Interval)



Supplementary Figure 28: Heat map with clustering of differentially expressed genes in the dexamethasone comparison, by randomised treatment allocation and vital status at 28 days.

[back to main text]

Supplementary Tables

List of Supplementary Tables

Supplementary Table 1: Risk of bias assessments for each corticosteroid trial and outcome. 416

Supplementary Table 2: Risk of bias assessments for each interleukin-6 receptor antagonist trial and outcome. 418

Supplementary Table 3: Risk of bias assessments for each Janus kinase inhibitor trial and outcome. 424

Supplementary Table 4: Risk of bias assessments for each higher dose corticosteroids compared with lower dose corticosteroids trial and outcome. 427

Supplementary Table 5: Classification of clinically important microbiological test results, according to specimen type and organism. 431

Supplementary Table 6: Summary of case validation studies evaluating routinely collected data-derived metabolic complication events. 432

Supplementary Table 7: Summary of case validation studies evaluating routinely collected data-derived long bone or vertebral fracture events. 433

Supplementary Table 8: Summary of diagnostic accuracy studies evaluating routinely collected data-derived long bone or vertebral fracture events. 434

Supplementary Table 9: Summary of diagnostic accuracy studies evaluating routinely collected data-derived psychiatric complication events. 434

Supplementary Table 10: Summary of case validation studies evaluating routinely collected data-derived acute liver injury events. 435

Supplementary Table 11: Effect of allocation to dexamethasone on diagnoses leading to death within 6 months of randomisation. 436

Supplementary Table 12: Organism classification of bloodstream infection events in the RECOVERY dexamethasone comparison. 438

Supplementary Table 13: Results of sensitivity analyses of non-COVID infection outcomes in the RECOVERY dexamethasone comparison. 439
Supplementary Table 14: Details of any non-COVID infection events in the RECOVERY dexamethasone comparison. 440
Supplementary Table 15: Details of microbiologically confirmed non-COVID infection events in the RECOVERY dexamethasone comparison. 441
Supplementary Table 16: Details of bloodstream infection events in the RECOVERY dexamethasone comparison. 442
Supplementary Table 17: Details of bacterial infection events in the RECOVERY dexamethasone comparison. 443
Supplementary Table 18: Details of fungal infection events in the RECOVERY dexamethasone comparison. 444
Supplementary Table 19: Details of metabolic complication events in the RECOVERY dexamethasone comparison. 445
Supplementary Table 20: Details of gastrointestinal complication events in the RECOVERY dexamethasone comparison. 446
Supplementary Table 21: Details of venous thromboembolism events in the RECOVERY dexamethasone comparison. 447
Supplementary Table 22: Details of long COVID events in the RECOVERY dexamethasone comparison. 447
Supplementary Table 23: Details of incident diabetes events in the RECOVERY dexamethasone comparison. 448
Supplementary Table 24: Details of long bone or vertebral fracture events in the RECOVERY dexamethasone comparison. 449
Supplementary Table 25: Details of psychiatric complication events in the RECOVERY dexamethasone comparison. 450

Supplementary Table 26: Details of clinically-defined liver injury events in the RECOVERY dexamethasone comparison. 451
Supplementary Table 27: Results of sensitivity analyses of other secondary outcomes in the RECOVERY dexamethasone comparison. 452
Supplementary Table 28: Effect of allocation to dexamethasone on hospital-recorded diagnoses* within 6 months of randomisation. 453
Supplementary Table 29: Effect of allocation to tocilizumab on diagnoses leading to death. 455
Supplementary Table 30: Results of sensitivity analyses of non-COVID infection outcomes in the RECOVERY tocilizumab comparison. 457
Supplementary Table 31: Details of any non-COVID infection events in the RECOVERY tocilizumab comparison. 458
Supplementary Table 32: Details of microbiologically confirmed non-COVID infection events in the RECOVERY tocilizumab comparison. 459
Supplementary Table 33: Details of bloodstream infection events in the RECOVERY tocilizumab comparison. 460
Supplementary Table 34: Organism classification of bloodstream infection events in the RECOVERY tocilizumab comparison. 461
Supplementary Table 35: Details of bacterial infection events in the RECOVERY tocilizumab comparison. 462
Supplementary Table 36: Details of fungal infection events in the RECOVERY tocilizumab comparison. 463
Supplementary Table 37: Details of gastrointestinal complication events in the RECOVERY tocilizumab comparison. 464
Supplementary Table 38: Details of venous thromboembolism events in the RECOVERY tocilizumab comparison. 465

Supplementary Table 39: Details of long COVID events in the RECOVERY tocilizumab comparison. 466
Supplementary Table 40: Details of metabolic complication events in the RECOVERY tocilizumab comparison. 467
Supplementary Table 41: Details of incident diabetes events in the RECOVERY tocilizumab comparison. 468
Supplementary Table 42: Details of long bone or vertebral fracture events in the RECOVERY tocilizumab comparison. 469
Supplementary Table 43: Details of psychiatric complication events in the RECOVERY tocilizumab comparison. 470
Supplementary Table 44: Details of clinically-defined liver injury events in the RECOVERY tocilizumab comparison. 471
Supplementary Table 45: Results of sensitivity analyses of other secondary outcomes in the RECOVERY tocilizumab comparison. 472
Supplementary Table 46: Effect of allocation to tocilizumab on primary hospital recorded diagnoses* within 6 months of randomisation. 473
Supplementary Table 47: Effect of allocation to baricitinib on diagnoses leading to death within 6 months of randomisation. 475
Supplementary Table 48: Details of any non-COVID infection events in the RECOVERY baricitinib comparison. 477
Supplementary Table 49: Details of microbiologically confirmed non-COVID infection events in the RECOVERY baricitinib comparison. 478
Supplementary Table 50: Details of bloodstream infection events in the RECOVERY baricitinib comparison. 479
Supplementary Table 51: Organism classification of bloodstream infection events in the RECOVERY baricitinib comparison. 480

Supplementary Table 52: Details of bacterial infection events in the RECOVERY baricitinib comparison. 481
Supplementary Table 53: Details of fungal infection events in the RECOVERY baricitinib comparison. 482
Supplementary Table 54: Results of sensitivity analyses of non-COVID infection outcomes in the RECOVERY baricitinib comparison. 483
Supplementary Table 55: Details of gastrointestinal complication events in the RECOVERY baricitinib comparison. 484
Supplementary Table 56: Details of venous thromboembolism events in the RECOVERY baricitinib comparison. 485
Supplementary Table 57: Details of long COVID events in the RECOVERY baricitinib comparison. 486
Supplementary Table 58: Details of metabolic complication events in the RECOVERY baricitinib comparison. 486
Supplementary Table 59: Details of incident diabetes events in the RECOVERY baricitinib comparison. 487
Supplementary Table 60: Details of long bone or vertebral fracture events in the RECOVERY baricitinib comparison. 488
Supplementary Table 61: Details of psychiatric complication events in the RECOVERY baricitinib comparison. 489
Supplementary Table 62: Details of clinically-defined liver injury events in the RECOVERY baricitinib comparison. 490
Supplementary Table 63: Results of sensitivity analyses of other secondary outcomes in the RECOVERY baricitinib comparison. 491
Supplementary Table 64: Effect of allocation to baricitinib on primary hospital recorded diagnoses* within 6 months of randomisation. 492

Supplementary Table 65: Effect of allocation to higher dose dexamethasone on diagnoses leading to death within 6 months of randomisation in the subgroup of participants who were hypoxic but not requiring ventilatory support at randomisation. .. 494
Supplementary Table 66: Details of any non-COVID infection events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison. 496
Supplementary Table 67: Details of microbiologically confirmed non-COVID infection events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison. 497
Supplementary Table 68: Details of bloodstream infection events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison. 498
Supplementary Table 69: Organism classification of bloodstream infection events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison. 499
Supplementary Table 70: Details of bacterial infection events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison. 500
Supplementary Table 71: Details of fungal infection events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison. 501
Supplementary Table 72: Details of metabolic complication events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison. 502
Supplementary Table 73: Details of gastrointestinal complication events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison. 503
Supplementary Table 74: Details of venous thromboembolism events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison. 504
Supplementary Table 75: Details of long COVID events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison. 505
Supplementary Table 76: Details of incident diabetes events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison. 506

Supplementary Table 77: Details of long bone or vertebral fracture events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison. 507
Supplementary Table 78: Details of psychiatric complication events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison. 508
Supplementary Table 79: Details of clinically-defined liver injury events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison. 509
Supplementary Table 80: Effect of allocation to higher dose dexamethasone on primary hospital-recorded diagnoses* within 6 months of randomisation..... 510
Supplementary Table 81: Contrast matrix of model of subgroup analysis of 28-day mortality in the RECOVERY dexamethasone comparison after including interaction with other key baseline subgroup. 512
Supplementary Table 82: 28-day mortality rates according to both respiratory support and Hospital Frailty Risk Score group in the RECOVERY dexamethasone comparison. 513
Supplementary Table 83: Results of sensitivity analyses of biological measurement outcomes in the RECOVERY-ISARIC dexamethasone comparison population. 514
Supplementary Table 84: Exploratory outcomes of daily rate of change in biological measurements in the first 7 days after randomisation in the RECOVERY-ISARIC tocilizumab comparison population. 515
Supplementary Table 85: Results of sensitivity analyses of biological measurement outcomes in the RECOVERY-ISARIC tocilizumab comparison population..... 516
Supplementary Table 86: Exploratory outcomes of daily rate of change in biological measurements in the first 7 days after randomisation in the RECOVERY-ISARIC baricitinib comparison population. 517
Supplementary Table 87: Results of sensitivity analyses of biological measurement outcomes in the RECOVERY-ISARIC baricitinib comparison population. 518
Supplementary Table 88: Differentially expressed genes between dexamethasone and usual care treatment groups. 519

Supplementary Table 89: Over-represented Gene Ontology Biological Processes in differentially expressed genes between dexamethasone and usual care treatment groups in the dexamethasone comparison. 531

Supplementary Table 1: Risk of bias assessments for each corticosteroid trial and outcome.

Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of outcome	Selection of reported result	Overall
Tang	For the outcome of short-term all-cause mortality					
	Some concerns	Low	Low	Low	Low	Some concerns
	Details: Unclear allocation concealment.					
	For the outcomes of secondary infections, hyperglycaemia					
	Some concerns	Low	Low	High	Some concerns	High
	Details: Unclear allocation concealment. Adverse event reporting in open-label trial					
Glucocovid	For the outcome of short-term all-cause mortality					
	Some concerns	Low	Low	Low	Some concerns	Some concerns
	Details: Unclear allocation concealment. No information on whether analysed as pre-specified					
	For the outcomes of secondary infections, hyperglycaemia					
	Some concerns	Low	Low	Some concerns	Low	Some concerns
	Details: Unclear allocation concealment. Open-label trial with clinical judgement in safety outcome definitions					
CORTIVID	For the outcomes of short-term all-cause mortality, secondary infections					
	Low	Low	Low	Low	Low	Low
	For the outcome of hyperglycaemia					
	Low	Low	Low	Low	Some concerns	Some concerns
	Details: No information on whether analysed as pre-specified					
CODEX	For the outcome of short-term all-cause mortality and discharged alive from hospital					
	Low	Some concerns	Low	Low	Low	Some concerns
	Details: 35% of usual care group received steroids					
	For the outcome of secondary infections					
	Low	Some concerns	Low	Some concerns	Some concerns	High
	Details: 35% of usual care group received steroids. Open-label trial with clinical judgement in safety outcome definitions. No information on whether analysed as pre-specified					
	For the outcome of hyperglycaemia					
	Low	Some concerns	Low	Low	Some concerns	Some concerns
	Details: 35% of usual care group received steroids. No information on whether analysed as pre-specified					
Metcovid	For the outcome of short-term all-cause mortality					
	Low	Low	Low	Low	Low	Low
	For the outcome of long-term all-cause mortality					
	Low	Low	High	Low	Some concerns	High
	Details: High proportion of missing outcome data. No information on whether analysed as pre-specified					

	For the outcome of secondary infections					
	Low	Low	High	Some concerns	Some concerns	High
	Details: High proportion of missing outcome data. No information on whether analysed as pre-specified. Adverse event reporting rather than systematic outcome collection					
	For the outcome of hyperglycaemia					
	Low	Low	Some concerns	Low	Some concerns	Some concerns
	Details: Moderate proportion of missing outcome data. No information on whether analysed as pre-specified					
Jamaati	For the outcome of short-term all-cause mortality					
	Some concerns	Some concerns	Low	Low	Some concerns	High
	Details: Unclear allocation concealment. No information on whether analysed as pre-specified. No information on co-interventions or cross-over.					
Edalatifard	For the outcome of short-term all-cause mortality					
	Some concerns	Some concerns	Low	Low	Low	Some concerns
	Details: Unclear allocation concealment. 17% in control group received steroids.					
	For the outcome of secondary infections					
	Some concerns	Some concerns	Low	High	Some concerns	High
	Details: Unclear allocation concealment. No information on whether analysed as pre-specified. 17% in control group received steroids. Adverse event reporting in open-label trial.					
REMAP-CAP	For the outcome of all-cause mortality					
	Low	Some concerns	Low	Low	Low	Some concerns
	Details: 15% on control group received steroids.					
RECOVERY	For the outcomes of short-term all-cause mortality and discharged alive from hospital					
	Low	Low	Low	Low	Low	Low
COVID-STEROID	For the outcome of all-cause mortality					
	Low	Low	Low	Low	Low	Low
SMART	For the outcomes of all-cause mortality and hyperglycaemia					
	Some concerns	Low	Low	Low	Low	Some concerns
	Details: Unclear allocation concealment					
CAPE COVID	For the outcomes of short-term all-cause mortality and secondary infections					
	Low	Low	Low	Low	Low	Low

[return to main text]

Supplementary Table 2: Risk of bias assessments for each interleukin-6 receptor antagonist trial and outcome.

Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of outcome	Selection of reported result	Overall
REMDACTA	For the outcomes of short-term mortality, short-term discharged alive from hospital, liver abnormalities					
	Low	Low	Low	Low	Low	Low
	For the outcome of short-term secondary infections					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection, COVID-19 included in secondary infections					
COVACTA	For the outcomes of short-term mortality, short-term discharged alive from hospital, liver abnormalities, neutropenia					
	Low	Low	Low	Low	Low	Low
	For the outcome of short-term secondary infections					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection, COVID-19 included in secondary infections					
EMPACTA	For the outcome of all-cause mortality					
	Low	Low	Low	Low	Low	Low
	For the outcome of secondary infections					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection.					
Rutgers	For the outcome of short-term all-cause mortality					
	Low	Low	Low	Low	Low	Low
	For the outcome of short-term secondary infections					
	Low	Low	Low	Some concerns	Some concerns	Some concerns
	Details: No information on whether analysed as pre-specified. Open-label trial with clinical judgement in safety outcome definitions					
Stone	For the outcomes of short-term all-cause mortality, short-term discharged alive from hospital, liver abnormalities, neutropenia					
	Low	Low	Low	Low	Low	Low
	For the outcome of short-term secondary infections					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection.					
COV-AID	For the outcome of all-cause mortality					
	Low	Low	Low	Low	Low	Low
	For the outcome of short-term secondary infections					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Open-label trial with clinical judgement in safety outcome definitions					
REMAP-CAP	For the outcome of all-cause mortality					
	Low	Low	Low	Low	Low	Low

Soin	For the outcome of short-term all-cause mortality					
	Low	Low	Low	Low	Low	Low
	For the outcome of short-term secondary infections					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Open-label trial with clinical judgement in safety outcome definitions					
Veiga	For the outcomes of short-term all-cause mortality, short-term discharged alive from hospital					
	Low	Low	Low	Low	Low	Low
	For the outcome of short-term secondary infections					
	Low	Low	Low	High	Low	High
	Details: Adverse event reporting in open-label trial					
	For the outcomes of liver abnormalities, neutropenia					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection.					
CORIMUNO-TOCI-1	For the outcome of all-cause mortality					
	Low	Some concerns	Low	Low	Low	Some concerns
	Details: Baseline imbalance in steroid use					
	For the outcome of short-term secondary infections					
	Low	Some concerns	Low	High	Low	High
	Details: Baseline imbalance in steroid use. Adverse event reporting in open-label trial					
	Or the outcomes of liver abnormalities, neutropenia					
	Low	Some concerns	Low	Some concerns	Low	Some concerns
	Details: Baseline imbalance in steroid use. Adverse event reporting rather than systematic outcome collection.					
Salvarani	For the outcome of short-term all-cause mortality					
	Low	Some concerns	Low	Low	Low	Some concerns
	Details: 23% in control arm received interleukin-6 receptor antagonist					
	For the outcome of short-term secondary infections					
	Low	Some concerns	Low	High	Low	High
	Details: 23% in control arm received interleukin-6 receptor antagonist. Adverse event reporting in open-label trial					
	For the outcome of short-term discharged alive from hospital					
	Low	Some concerns	Low	Low	Some concerns	Some concerns
	Details: 23% in control arm received interleukin-6 receptor antagonist. No information on whether analysed as pre-specified.					
	For the outcome of liver abnormalities, neutropenia					
	Low	Some concerns	Low	Some concerns	Low	Some concerns
	Details: 23% in control arm received interleukin-6 receptor antagonist. Adverse event reporting rather than systematic outcome collection.					
COVIDSTORM	For the outcomes of short-term all-cause mortality, short-term discharged alive from hospital					
	Low	Low	Low	Low	Low	Low
	For the outcome of short-term secondary infections					

	Low	Low	Low	High	Some concerns	High
	Details: Adverse event reporting in open-label trial. No information on whether analysed as pre-specified					
CORIMUNO-TOCI-2	For the outcomes of all-cause mortality, discharged alive from hospital					
	Low	Low	Low	Low	Low	Low
	For the outcome of secondary infections					
	Low	Low	Low	High	Low	High
	Details: Adverse event reporting in open-label trial					
	For the outcomes of liver abnormalities, neutropenia					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection.					
Wang	For the outcome of short-term all-cause mortality					
	Some concerns	Low	Low	Low	Low	Some concerns
	Details: Unclear allocation concealment					
	For the outcomes of liver abnormalities, neutropenia					
	Some concerns	Low	Low	Some concerns	Low	Some concerns
	Details: Unclear allocation concealment. Adverse event reporting rather than systematic outcome collection.					
Talaschian	For the outcome of short-term all-cause mortality					
	Some concerns	Low	Some concerns	Low	Low	Some concerns
	Details: Unclear allocation concealment. 10% missing outcome data.					
	For the outcome of short-term secondary infections					
	Some concerns	Low	Some concerns	Some concerns	Some concerns	High
	Details: Unclear allocation concealment. 10% missing outcome data. Adverse event reporting rather than systematic outcome collection. No information on whether analysed as pre-specified					
Sivapalasingam phase 2	For the outcome of short-term all-cause mortality, liver abnormalities					
	Some concerns	Low	Low	Low	Low	Some concerns
	Details: Unclear allocation concealment.					
	For the outcome of short-term secondary infections					
	Some concerns	Low	Low	Some concerns	Low	Some concerns
	Details: Unclear allocation concealment. Adverse event reporting rather than systematic outcome collection.					
Sivapalasingam phase 3	For the outcomes of all-cause mortality, short-term discharged alive from hospital, liver abnormalities					
	Some concerns	Low	Low	Low	Low	Some concerns
	Details: Unclear allocation concealment.					
	For the outcome of short-term secondary infections					
	Some concerns	Low	Low	Some concerns	Low	Some concerns
	Details: Unclear allocation concealment. Adverse event reporting rather than systematic outcome collection.					
Lescure	For the outcomes of all-cause mortality, discharged alive from hospital, liver abnormalities, neutropenia					
	Low	Low	Low	Low	Low	Low

	For the outcome of short-term secondary infections					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection.					
Sancho-Lopez	For the outcomes of short-term all-cause mortality, short-term discharged alive from hospital					
	Low	Low	Low	Low	Low	Low
	For the outcome of short-term secondary infections					
	Low	Low	Low	High	Low	High
	Details: Adverse event reporting in open label trial					
	For the outcome of liver abnormalities					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection.					
SARICOR	For the outcome of short-term all-cause mortality					
	Low	Low	Low	Low	Low	Low
	For the outcome of short-term secondary infections					
	Low	Low	Low	High	Some concerns	High
	Details: Adverse event reporting in open-label trial. No information on whether analysed as pre-specified					
	For the outcome short-term discharged alive from hospital					
	Low	Low	Low	Low	Some concerns	Some concerns
	Details: No information on whether analysed as pre-specified					
	For the outcome of liver abnormalities					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection.					
CORIMUNO-SARI-1	For the outcomes of all-cause mortality, short-term discharged alive from hospital					
	Low	Low	Low	Low	Low	Low
	For the outcome of short-term secondary infections					
	Low	Low	Low	High	Low	High
	Details: Adverse event reporting in open-label trial					
	For the outcomes of liver abnormalities, neutropenia					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection.					
CORIMUNO-SARI-2	For the outcomes of all-cause mortality, discharged alive from hospital					
	Low	Low	Some concerns	Low	Low	Some concerns
	Details: 10% missing outcome data					
	For the outcome of secondary infections					
	Low	Low	Some concerns	High	Low	High
	Details: 10% missing outcome data, Adverse event reporting in open-label trial					
	For the outcomes of liver abnormalities, neutropenia					

	Low	Low	Some concerns	Some concerns	Low	Some concerns
	Details: 10% missing outcome data. Adverse event reporting rather than systematic outcome collection.					
Branch-Elliman	For the outcome of short-term all-cause mortality					
	Low	Low	Low	Low	Low	Low
	For the outcome of short-term secondary infections					
	Low	Low	Low	High	Some concerns	High
	Details: Adverse event reporting in open-label trial. No information on whether analysed as pre-specified.					
	For the outcome of short-term discharged alive from hospital					
	Low	Low	Low	Low	Some concerns	Some concerns
	Details: No information on whether analysed as pre-specified.					
Garcia-Vicuna	For the outcome of all-cause mortality, short-term discharged alive from hospital					
	Low	High	Low	Low	Low	High
	Details: Large imbalance in steroid treatment between arms					
	For the outcome of secondary infections					
	Low	High	Low	High	Low	High
	Details: Large imbalance in steroid treatment between arms. Adverse event reporting in open-label trial					
	For the outcome of liver abnormalities					
	Low	High	Low	Some concerns	Low	High
	Details: Large imbalance in steroid treatment between arms. Adverse event reporting rather than systematic outcome collection.					
Swadi	For the outcomes of short-term all-cause mortality, short-term discharged alive from hospital					
	Some concerns	Some concerns	Low	Low	Low	Some concerns
	Details: Unclear allocation concealment. No information on co-interventions					
Malik	For the outcome of short-term all-cause mortality					
	High	Some concerns	Low	Low	Low	High
	Details: Risk of bias in allocation concealment. Baseline imbalances in other treatments.					
CORIMUNO-TOCI-DEX	For the outcome of all-cause mortality					
	Low	Low	Low	Low	Low	Low
	For the outcome of short-term secondary infections					
	Low	Low	Low	High	Low	High
	Details: Adverse event reporting in open-label trial					
	For the outcomes of liver abnormalities, neutropenia					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection.					
RECOVERY	For the outcomes of short-term all-cause mortality, short-term discharged alive from hospital					
	Low	Low	Low	Low	Low	Low
Mastarosa	For the outcome of short-term all-cause mortality:					
	Low	Low	Low	Low	Low	Low

	For the outcome of short-term secondary infections					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Open-label trial with clinical judgement in safety outcome definitions					
Rabie	For the outcome of short-term all-cause mortality					
	Some concerns	Some concerns	Low	Low	Low	Some concerns
	Details: Unclear allocation concealment. No information on co-interventions					
	For the outcome of short-term discharged alive from hospital					
	Some concerns	Some concerns	Low	Low	Some concerns	High
	Details: Unclear allocation concealment. No information on co-interventions. No information on whether analysed as pre-specified.					
IMMCoVA	For the outcome of all-cause mortality					
	Low	Low	Low	Low	Low	Low
	For the outcome of short-term secondary infections					
	Low	High	Low	High	Some concerns	High
	Details: Intervention arm received antibiotic prophylaxis. Adverse event reporting in open-label trial. Unclear if pre-specified.					

[return to main text]

Supplementary Table 3: Risk of bias assessments for each Janus kinase inhibitor trial and outcome.

Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of outcome	Selection of reported result	Overall
COV-BARRIER	For the outcomes of all-cause mortality, short-term discharged alive from hospital, venous thromboembolism					
	Low	Low	Low	Low	Low	Low
	For the outcome of secondary infections					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection.					
ACTT-2	For the outcomes of short-term all-cause mortality, short-term discharged alive from hospital, venous thromboembolism, liver abnormalities					
	Low	Low	Low	Low	Low	Low
	For the outcomes of secondary infections, gastrointestinal complications					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection.					
Bari-SolidAct	For the outcomes of all-cause mortality, discharged alive from hospital					
	Low	Low	Low	Low	Low	Low
	For the outcome of secondary infections					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection.					
RUXCOVID	For the outcomes of short-term all-cause mortality, liver abnormalities					
	Low	Low	Low	Low	Low	Low
	For the outcome of secondary infections					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection.					
Guimarães	For the outcomes of short-term all-cause mortality, short-term discharged alive from hospital, venous thromboembolism, liver abnormalities					
	Low	Low	Low	Low	Low	Low
	For the outcome of secondary infections					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection.					
RUXCOVID-DEVENT	For the outcomes of short-term all-cause mortality, venous thromboembolism, liver abnormalities					
	Low	Low	Low	Low	Low	Low
	For the outcomes of secondary infections, gastrointestinal abnormalities					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection.					
PANCOVID	For the outcomes of short-term all-cause mortality, discharged alive from hospital					
	Low	Low	Low	Low	Low	Low

Cao	For the outcomes of short-term all-cause mortality, liver abnormalities					
	Low	Low	Low	Low	Some concerns	Some concerns
	Details: No information on whether analysed as pre-specified					
	For the outcome of secondary infections					
	Low	Low	Low	Some concerns	Some concerns	Some concerns
	Details: No information on whether analysed as pre-specified. Adverse event reporting rather than systematic outcome collection.					
COV-BARRIER critically ill	For the outcome of short-term all-cause mortality					
	Low	Low	Low	Low	Low	Low
	For the outcomes of long-term all-cause mortality, short-term discharged alive from hospital, venous thromboembolism					
	Low	Low	Low	Low	Some concerns	Some concerns
	Details: No information on whether analysed as pre-specified					
	For the outcome of secondary infections					
	Low	Low	Low	Some concerns	Some concerns	Some concerns
	Details: No information on whether analysed as pre-specified. Adverse event reporting rather than systematic outcome collection.					
TOFACOV	For the outcomes of short-term all-cause mortality, short-term discharged alive from hospital, venous thromboembolism, liver abnormalities					
	Low	Some concerns	Low	Low	Low	Some concerns
	Details: 15% of intervention group discontinued treatment.					
RECOVERY	For the outcomes of short-term all-cause mortality, short-term discharged alive from hospital					
	Low	Low	Low	Low	Low	Low
	For the outcomes of secondary infections, venous thromboembolism, gastrointestinal complications					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Open-label trial with clinical judgement in safety outcome definitions					
Murugesan	For the outcome of short-term all-cause mortality					
	Some concerns	Low	Low	Low	Some concerns	Some concerns
	Details: Unclear allocation concealment. No information on whether analysed as pre-specified					
COVINIB	For the outcome of short-term all-cause mortality					
	Low	Low	Low	Low	Low	Low
	For the outcome of secondary infections					
	Low	Low	Low	High	Low	High
	Details: Adverse event reporting in open-label trial					
	For the outcomes of venous thromboembolism, liver abnormalities					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection.					
TACTIC-R	For the outcomes of all-cause mortality, short-term discharged alive from hospital					
	Low	Some concerns	Low	Low	Low	Some concerns
	Details: 48% of participants received less than 5 doses of treatment.					
	For the outcomes of secondary infections, venous thromboembolism,					

	Low	Some concerns	Low	Some concerns	Low	Some concerns
	Details: Open-label trial. 48% of participants received less than 5 doses of treatment.					
	For the outcome of liver injury					
	Low	Some concerns	Low	Some concerns	Some concerns	High
	Details: Adverse event reporting in open-label trial. 48% of participants received less than 5 doses of treatment. Unclear if pre-specified.					
Cafardi	For the outcome of short-term all-cause mortality					
	Low	Some concerns	Low	Low	Low	Some concerns
	Details: 33% discontinued intervention.					
	For the outcomes of secondary infections, venous thromboembolism, gastrointestinal complications, liver injury					
	Low	Some concerns	Low	Some concerns	Low	Some concerns
	Details: 33% discontinued intervention. Adverse event reporting.					
Dastan	For the outcome of short-term all-cause mortality					
	Some concerns	Low	Low	Low	Low	Some concerns
	Details: Unclear allocation concealment.					
	For the outcome of venous thromboembolism					
	Some concerns	Low	Low	Low	Some concerns	Some concerns
	Details: Unclear allocation concealment. Unclear if pre-specified.					

[return to main text]

Supplementary Table 4: Risk of bias assessments for each higher dose corticosteroids compared with lower dose corticosteroids trial and outcome.

Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of outcome	Selection of reported result	Overall
RECOVERY	For the outcomes of short-term all-cause mortality, discharged alive from hospital, hyperglycaemia					
	Low	Low	Low	Low	Low	Low
	For the outcomes of secondary infections, gastrointestinal complications, venous thromboembolism					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Open-label trial with clinical judgement in safety outcome definitions					
COVID STEROID 2	For the outcomes of all-cause mortality, secondary infections, gastrointestinal complications					
	Low	Low	Low	Low	Low	Low
	For the outcome of venous thromboembolism					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection					
Salvarani	For the outcomes of short-term all-cause mortality, discharged alive from hospital					
	Low	Low	Low	Low	Low	Low
	For the outcomes of secondary infections, gastrointestinal complications, psychiatric complications					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Adverse event reporting rather than systematic outcome collection					
COVIDICUS	For the outcome of all-cause mortality					
	Low	Low	Low	Low	Low	Low
	For the outcomes of secondary infections, hyperglycaemia					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Infections – open-label with clinical judgement in safety outcome definition. Hyperglycaemia – adverse event reporting rather than systematic outcome collection					
	For the outcomes of gastrointestinal complications, venous thromboembolism					
	Low	Low	Low	High	Low	High
	Details: Adverse event reporting in open-label trial					
HIGHLOWDEXA-COVID	For the outcomes of short-term all-cause mortality, discharged alive from hospital					
	Low	Some concerns	Low	Low	Low	Some concerns
	Details: 31% of the patients in the low dexamethasone group received high dose after clinical worsening as a rescue therapy					
	For the outcome of long-term all-cause mortality					
	Low	Some concerns	Some concerns	Low	Some concerns	High
	Details: 31% of the patients in the low dexamethasone group received high dose after clinical worsening as a rescue therapy. 9% missing outcome data. No information on whether analysed as pre-specified.					
	For the outcome of hyperglycaemia					

	Low	Some concerns	Low	Some concerns	Low	Some concerns
	Details: 31% of the patients in the low dexamethasone group received high dose after clinical worsening as a rescue therapy. Adverse event reporting rather than systematic outcome collection					
	For the outcomes of secondary infections, venous thromboembolism					
	Low	Some concerns	Low	High	Low	High
	Details: 31% of the patients in the low dexamethasone group received high dose after clinical worsening as a rescue therapy. Adverse event reporting in open-label trial					
Toroghi	For the outcome of all-cause mortality					
	Low	Low	Some concerns	Low	Low	Some concerns
	Details: 8% missing outcome data					
	For the outcome of hyperglycaemia					
	Low	Low	Some concerns	Some concerns	Low	Some concerns
	Details: 8% missing outcome data. Adverse event reporting rather than systematic outcome collection					
	For the outcomes of secondary infections, venous thromboembolism, psychiatric complications					
	Low	Low	Some concerns	High	Low	High
	Details: 8% missing outcome data. Adverse event reporting in open-label trial					
Ranjbar	For the outcome of short-term all-cause mortality					
	Low	Low	Low	Low	Some concerns	Some concerns
	Details: No information on whether analysed as pre-specified					
Gautam	For the outcome of short-term all-cause mortality					
	Some concerns	Low	Low	Low	Some concerns	Some concerns
	Details: No information on randomisation process. No information on whether analysed as pre-specified					
	For the outcome of hyperglycaemia					
	Some concerns	Low	Low	Some concerns	Some concerns	High
	Details: No information on randomisation process. No information on whether analysed as pre-specified. Adverse event reporting rather than systematic outcome collection					
Dastenae	For the outcomes of short-term all-cause mortality and hyperglycaemia					
	Low	Some concerns	Low	Low	Low	Some concerns
	Details: Participants excluded post-randomisation if discharge from hospital before recovery or death within the first 24 hours					
Corral-Gudino	For the outcomes of all-cause mortality, discharged alive from hospital, hyperglycaemia					
	Low	Low	Low	Low	Low	Low
	For the outcomes of secondary infections and psychiatric complications					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Open-label with clinical judgement in safety outcome definition.					
	For the outcome of venous thromboembolism					
	Low	Low	Low	High	Low	High
	Details: Adverse event reporting in open-label trial					

Wu	For the outcome of short-term all-cause mortality					
	Low	Low	Low	Low	Low	Low
	For the outcomes of secondary infections and gastrointestinal complications					
	Low	Low	Low	High	Some concerns	High
	Details: No information on whether analysed as pre-specified. Adverse event reporting in open-label trial.					
	For the outcome of hyperglycaemia					
	Low	Low	Low	Some concerns	Some concerns	Some concerns
	Details: No information on whether analysed as pre-specified. Adverse event reporting rather than systematic outcome collection					
MEDEAS	For the outcomes of all-cause mortality and discharged alive from hospital					
	Low	Some concerns	Low	Low	Low	Some concerns
	Details: 10% of participants in low dose group had dose increased or switched to other treatment arm after randomisation					
	For the outcomes of secondary infections, venous thromboembolism, psychiatric complications					
	Low	Some concerns	Low	High	Some concerns	High
	Details: 10% of participants in low dose group had dose increased or switched to other treatment arm after randomisation. No information on whether analysed as pre-specified. Adverse event reporting in open-label trial.					
	For the outcome of hyperglycaemia					
	Low	Some concerns	Low	Some concerns	Some concerns	High
	Details: 10% of participants in low dose group had dose increased or switched to other treatment arm after randomisation. No information on whether analysed as pre-specified. Adverse event reporting rather than systematic outcome collection					
ROIDS-Dose	For the outcomes of short-term all-cause mortality and hyperglycaemia					
	Low	Low	Low	Low	Low	Low
	For the outcome of secondary infections					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Open-label with clinical judgement in safety outcome definition.					
Maskin	For the outcome of all-cause mortality					
	Low	Low	Low	Low	Low	Low
	For the outcome of psychiatric complications					
	Low	Low	Low	Some concerns	Low	Some concerns
	Details: Open-label with clinical judgement in safety outcome definition.					
Soliman	For the outcome of short-term all-cause mortality					
	Some concerns	Low	Low	Low	Some concerns	Some concerns
	Details: Risk of bias in allocation concealment. No information on whether analysed as pre-specified					
Sadeghi	For the outcome of short-term all-cause mortality					
	Low	Low	Some concerns	Low	Low	Some concerns
	Details: Small numbers of participants excluded post-randomisation.					
	For the outcomes of hyperglycaemia and gastrointestinal complications.					
	Low	Low	Some concerns	Some concerns	Some concerns	High

	Details: Small numbers of participants excluded post-randomisation. Adverse event reporting. Unclear if pre-specified.
Montalvan	Abstract only

[return to main text]

Supplementary Table 5: Classification of clinically important microbiological test results, according to specimen type and organism.

Specimen Type	Clinically important	Not clinically important
Blood culture	*Staphylococcus aureus* *Streptococcus sp.* (except Oral *Streptococcus sp.)* *Enterococcus sp.* Any Gram negative bacterial isolate Any fungal isolate	Coagulase-negative *Staphylococcus* sp. Oral *Streptococcus sp.* E.g. *Streptococcus gordonii, Streptococcus mitis, Streptoccocus oralis* *Corynebacterium* sp.
Respiratory tract culture	*Staphylococcus aureus* Beta-haemolytic *Streptococci* *Streptococcus pneumoniae* Any Gram negative bacterial isolate *Aspergillus sp.*	Coagulase-negative *Staphylococcus* sp. Viridans-group *Streptococci* *Corynebacterium* sp. *Enterococcus sp.* *Candida sp.*

[back to main text]

Supplementary Table 6: Summary of case validation studies evaluating routinely collected data-derived metabolic complication events.

Study	Coding system	Population	Target condition	Diagnostic positions	Total number of index cases	Reference standard	Positive Predictive Value (95% CI)
Ginde (2008)[447]	ICD-9	Inpatients in USA	Hypoglycaemia	All	679	Medical chart review by 1 reviewer based on predetermined definition	0.64 (0.61 - 0.68)
Hodge (2017)[448]	ICD-10	Inpatients age ≥65 in Canada	Hypoglycaemia	All	201	Medical chart review by 2 study clinical reviewers based on predetermined definition, with discrepancies resolved by consensus	0.93 (0.90 - 0.97)
Yang (2022)[449]	ICD-10	Inpatients receiving medication for diabetes in USA	Hypoglycaemia	All	496	Medical chart review by clinical reviewer based on predetermined definition	0.69 (0.65 - 0.73)
Min (2019)[450]	ICD-9	Inpatients in USA	Hypoglycaemia	Primary only	15	Medical chart review by 2 reviewers based on predetermined definition	0.74 (0.54 - 0.94)
Tam (2007)[451]	ICD-10	Inpatients in UK	Diabetic ketoacidosis	Not stated	75	Medical chart review based on predetermined definition	0.34 (0.24 - 0.45)
Van der Weele (2018)[452]	ICD-9	Inpatients in USA	Diabetic ketoacidosis	Primary only	32	Medical chart review by 2 study clinical reviewers based on predetermined definition, with discrepancies resolved by 3rd study clinical reviewer	0.61 (0.45 - 0.77)

[back to main text]

Supplementary Table 7: Summary of case validation studies evaluating routinely collected data-derived long bone or vertebral fracture events.

Study	Coding system	Population	Target condition	Diagnostic positions	Total number of index cases	Reference standard	Positive Predictive Value (95% CI)
Bergdahl (2021)[453]	ICD-10	Inpatients in Sweden	Humeral fractures	Not stated	2,173	Medical chart review	0.70 (0.68 - 0.72)
Curtis (2009)[454]	ICD-9	Inpatients in USA	Vertebral fractures	All	63	Medical chart review by 2 reviewers based on predetermined definition, with discrepancies resolved by study clinical reviewers	0.46 (0.34 - 0.58)
Helgeland (2016)[455]	ICD-10	Inpatients age ≥65 in Norway	Hip fractures	All	1,043	Medical chart review by clinical reviewer based on predetermined definition	0.96 (0.94 - 0.97)
Hjelholt (2020)[456]	ICD-10	Inpatients age ≥65 in Denmark	Hip fractures	Not stated	750	Medical record review by clinical reviewer based on predetermined definition	0.94 (0.93 - 0.96)
Hoiberg (2014)[457]	ICD-10	Inpatients in Norway	Hip fractures	Not stated	307	Medical record review by study clinical reviewer based on predetermined definition	0.76 (0.71 - 0.80)
Huttunen (2014)[458]	ICD-10	Inpatients in Finland	Hip fractures	Not stated	741	Medical record review by 2 study clinical reviewers based on predetermined definition, with discrepancies resolved by consensus	1.00 (0.99 - 1.00)
Lofthus (2005)[459]	ICD-9	Inpatients in Norway	Hip fractures	All	1,407	Medical record review and theatre record search by 2 study reviewers based on clinical judgement	0.84 (0.82 - 0.86)
Ray (1992)[460]	ICD-9	Inpatients age ≥ 65 in USA	Fractures	Not stated	1,440	Medical record review by clinical reviewer based on predetermined definition	0.86 (0.84 - 0.88)
Sing (2017)[461]	ICD-9	Inpatients in Hong Kong	Long bone and vertebral fractures	Not stated	380	Medical record review by 3 study clinical reviewers based on predetermined definition with discrepancies resolved by consensus	0.96 (0.95 - 0.98)
Thuy Trinh (2018)[462]	ICD-10	Inpatients in Australia	Hip fractures	All	827	Prospective clinical database of hip fractures maintained by independent local clinicians	0.72 (0.69 - 0.75)

[back to main text]

Supplementary Table 8: Summary of diagnostic accuracy studies evaluating routinely collected data-derived long bone or vertebral fracture events.

Study	Coding system	Population	Target condition	Diagnostic positions	Number of participants	Reference standard	Blinding to index result	Sensitivity (95% CI)	Specificity (95% CI)
Lee (2022)[463]	ICD-10	Inpatients age ≥ 50 undergoing hip surgery in South Korea	Hip fractures	Primary only	522	Medical chart review by 2 independent clinical reviewers based on predetermined definition	Yes	0.96 (0.93 - 1.00)	0.921 (0.894 - 0.948)

Supplementary Table 9: Summary of diagnostic accuracy studies evaluating routinely collected data-derived psychiatric complication events.

Study	Coding system	Population	Target condition	Diagnostic positions	Number of participants	Reference standard	Blinding to index result	Sensitivity (95% CI)	Specificity (95% CI)
Inouye (2005)[464]	ICD-9	Inpatients age ≥70 in USA	Delirium	All	919	Prospective interviews and cognitive testing by clinical researchers	Yes	0.04 (0.01 - 0.08)	0.991 (0.985 - 0.998)
Pendlebury (2020)[465]	ICD-10	Inpatients age ≥70 in UK	Delirium	All	1,211	Prospective clinical assessment and cognitive testing by study clinicians	Yes	0.35 (0.29 - 0.40)	0.996 (0.991 - 1.000)

[back to main text]

Supplementary Table 10: Summary of case validation studies evaluating routinely collected data-derived acute liver injury events.

Study	Coding system	Population	Target condition	Diagnostic positions	Total number of index cases	Reference standard	Positive Predictive Value (95% CI)
Bui (2014)[466]	ICD-9	Inpatients in USA	Acute liver injury	All	420	Medical record review by 2 study clinical reviewers based on predetermined criteria	0.74 (0.70 - 0.78)
Forns (2019)[467]	ICD-9 and ICD-10	Inpatients and outpatients taking antidepressant medication in Spain and Denmark	Acute liver injury	Primary only	115	Review of adjudicated data by clinical reviewer, based on predetermined criteria	0.60 (0.51 - 0.68)
Lo Re (2013)[468]	ICD-9	Inpatients in USA	Severe acute liver injury	Primary only	105	Review of adjudicated data by 2 study clinical reviewers, based on predetermined criteria, with discrepancies resolved by 3rd clinical study reviewer	0.26 (0.17 - 0.34)
Timmer (2019)[469]	ICD-10	Inpatients taking anti-depressant medication in Germany	Acute liver injury	Primary only	143	Medical record review by 2 study clinical reviewers, based on predetermined criteria with discrepancies resolved by consensus	0.50 (0.42 - 0.58)

[back to main text]

Supplementary Table 11: Effect of allocation to dexamethasone on diagnoses leading to death within 6 months of randomisation.

	Dexamethasone (n=2104)[1]	Usual Care (n=4321)[1]	Rate Ratio (95% CI)
Event timing			
Study day of death[2]	11 (6, 22)	9 (5, 18)	
Death during index hospital admission	454 (22)	1,060 (25)	
COVID-19			
COVID-19	469 (22)	1,069 (25)	0.83 (0.74 - 0.92)
Non-COVID infection			
Pneumonia/Lower Respiratory Tract	39 (1.9)	73 (1.7)	
Urinary tract	5 (0.2)	5 (0.1)	
Intra-abdominal	2 (<0.1)	6 (0.1)	
Skin and soft tissue	1 (<0.1)	1 (<0.1)	
Bone and joint	0 (0)	0 (0)	
Upper Respiratory Tract	1 (<0.1)	0 (0)	
Other site	0 (0)	2 (<0.1)	
Unspecified site	20 (1.0)	11 (0.3)	
Bacterial	20 (1.0)	17 (0.4)	
Fungal	1 (<0.1)	0 (0)	
Other viral	0 (0)	0 (0)	
TB	0 (0)	0 (0)	
Other organism	0 (0)	0 (0)	
Unspecified organism	43 (2.0)	79 (1.8)	
Subtotal: Any non-COVID infection	59 (2.8)	90 (2.1)	1.24 (0.89 - 1.73)
Cardiac			
Myocardial infarction	8 (0.4)	14 (0.3)	
Other coronary heart disease	6 (0.3)	11 (0.3)	
Heart failure	9 (0.4)	21 (0.5)	
Other	8 (0.4)	17 (0.4)	
Subtotal: Any cardiac	25 (1.2)	49 (1.1)	0.97 (0.60 - 1.57)
Stroke			
Haemorrhagic stroke	4 (0.2)	4 (<0.1)	
Non-haemorrhagic stroke	12 (0.6)	14 (0.3)	
Subtotal: Any stroke	16 (0.8)	18 (0.4)	1.71 (0.87 - 3.35)
Other vascular			
Arterial thromboembolism	0 (0)	0 (0)	

Venous thromboembolism	8 (0.4)	16 (0.4)	
Other	5 (0.2)	14 (0.3)	
Subtotal: Any other vascular	13 (0.6)	30 (0.7)	0.83 (0.43 - 1.59)
Medical			
Cancer	32 (1.5)	47 (1.1)	
Diabetes	2 (<0.1)	6 (0.1)	
Gastrointestinal bleed or perforation	5 (0.2)	5 (0.1)	
Other extra-cranial bleed or perforation	6 (0.3)	7 (0.2)	
Liver	2 (<0.1)	5 (0.1)	
Renal	5 (0.2)	8 (0.2)	
Respiratory (non-infection)	58 (2.8)	104 (2.4)	
Other	22 (1.0)	51 (1.2)	
Subtotal: Any medical	87 (4.1)	164 (3.8)	1.01 (0.78 - 1.31)
External			
External with bleed	3 (0.1)	0 (0)	
External without bleed	11 (0.5)	9 (0.2)	
Subtotal: Any external	11 (0.5)	9 (0.2)	
Unknown			
No formal diagnosis recorded	70 (3.3)	146 (3.4)	
Total			
Total: All deaths	596 (28)	1,297 (30)	0.87 (0.79 - 0.96)

Diagnoses leading to death represented any diagnosis recorded in any row of part 1 of the death certificate
[1]n (%)
[2]Median (Lower quartile, Upper quartile)

[back to main text]

Supplementary Table 12: Organism classification of bloodstream infection events in the RECOVERY dexamethasone comparison.

	Bloodstream infection within 28 days		Bloodstream infection within 6 months	
	Dexamethasone (n=72)	**Usual Care (n=109)**	**Dexamethasone (n=99)**	**Usual Care (n=151)**
Bacterial				
Gram Positive	33 (46%)	35 (32%)	46 (46%)	52 (34%)
Enterococcus species	28 (39%)	29 (27%)	39 (39%)	42 (28%)
Staphylococcus aureus	4 (5.6%)	5 (4.6%)	5 (5.1%)	9 (6.0%)
Other Gram Positive	5 (6.9%)	1 (0.9%)	7 (7.1%)	3 (2.0%)
Gram Negative	35 (49%)	65 (60%)	54 (55%)	96 (64%)
E.coli	11 (15%)	14 (13%)	24 (24%)	32 (21%)
Enterobacter species	1 (1.4%)	6 (5.5%)	1 (1.0%)	7 (4.6%)
Klebsiella species	14 (19%)	37 (34%)	19 (19%)	43 (28%)
Pseudomonas aeruginosa	4 (5.6%)	10 (9.2%)	6 (6.1%)	11 (7.3%)
Other Gram Negative	10 (14%)	15 (14%)	14 (14%)	23 (15%)
Any bacterial	65 (90%)	99 (91%)	94 (95%)	141 (93%)
Fungal				
Candida species	11 (15%)	14 (13%)	13 (13%)	17 (11%)
Any fungal	11 (15%)	14 (13%)	13 (13%)	17 (11%)
Total				
Any bloodstream infection	72 (100%)	109 (100%)	99 (100%)	151 (100%)

[back to main text p.207]

Supplementary Table 13: Results of sensitivity analyses of non-COVID infection outcomes in the RECOVERY dexamethasone comparison.

	Dexamethasone (n=2104)	Usual Care (n=4321)	Rate or Risk Ratio (95% CI)	p-value
Primary outcome				
Major non-COVID infection within 28 days, 1st diagnostic position only	156 (7.4%)	278 (6.4%)	1.10 (0.90 - 1.34)	0.34
Major non-COVID infection within 6 months, 1st diagnostic position only	301 (14%)	536 (12%)	1.10 (0.95 - 1.26)	0.20
Major non-COVID infection within 28 days, including peri-randomisation episode diagnoses	773 (37%)	1,553 (36%)	1.02 (0.96 - 1.09)	0.48
Major non-COVID infection within 6 months, including peri-randomisation episode diagnoses	888 (42%)	1,768 (41%)	1.05 (0.94 - 1.17)	0.41
Major non-COVID infection within 28 days, excluding respiratory tract infections	187 (8.9%)	324 (7.5%)	1.16 (0.96 - 1.38)	0.12
Major non-COVID infection within 6 months, excluding respiratory tract infections	344 (16%)	595 (14%)	1.15 (1.01 - 1.31)	0.04
Secondary outcome				
Any non-COVID infection within 28 days, 1st diagnostic position only	289 (14%)	565 (13%)	1.06 (0.92 - 1.20)	0.42
Any non-COVID infection within 6 months, 1st diagnostic position only	604 (29%)	1,196 (28%)	1.03 (0.95 - 1.12)	0.47
Any non-COVID infection within 28 days, including peri-randomisation episode diagnoses	1,047 (50%)	2,147 (50%)	1.00 (0.95 - 1.05)	0.94
Any non-COVID infection within 6 months, including peri-randomisation episode diagnoses	1,214 (58%)	2,464 (57%)	1.01 (0.96 - 1.05)	0.81
Any non-COVID infection within 28 days, excluding respiratory tract infections	305 (14%)	580 (13%)	1.09 (0.96 - 1.24)	0.19
Any non-COVID infection within 6 months, excluding respiratory tract infections	633 (30%)	1,217 (28%)	1.06 (0.98 - 1.15)	0.14

[back to main text]

Supplementary Table 14: Details of any non-COVID infection events in the RECOVERY dexamethasone comparison.

	Any non-COVID infection within 28 days		Any non-COVID infection within 6 months	
	Dexamethasone (n=2104)	Usual Care (n=4321)	Dexamethasone (n=2104)	Usual Care (n=4321)
Organism				
Bacterial	277 (13)	557 (13)	581 (28)	1,142 (26)
Fungal	50 (2.4)	82 (1.9)	78 (3.7)	147 (3.4)
Viral (not SARS-CoV-2)	8 (0.4)	17 (0.4)	23 (1.1)	47 (1.1)
Tuberculosis	0 (0)	0 (0)	3 (0.1)	3 (<0.1)
Other organism	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Unspecified organism	94 (4.5)	170 (3.9)	109 (5.2)	203 (4.7)
Anatomical site				
Pneumonia/Lower respiratory tract	170 (8.1)	320 (7.4)	284 (13)	556 (13)
Bloodstream	72 (3.4)	109 (2.5)	99 (4.7)	151 (3.5)
Urinary tract	39 (1.9)	57 (1.3)	116 (5.5)	178 (4.1)
Intra-abdominal	9 (0.4)	24 (0.6)	38 (1.8)	76 (1.8)
Skin and soft tissue	10 (0.5)	30 (0.7)	43 (2.0)	89 (2.1)
Bone and joint	5 (0.2)	3 (<0.1)	9 (0.4)	13 (0.3)
Upper respiratory tract	5 (0.2)	5 (0.1)	11 (0.5)	23 (0.5)
Other anatomical site	29 (1.4)	52 (1.2)	52 (2.5)	102 (2.4)
Unspecified anatomical site	124 (5.9)	277 (6.4)	259 (12)	544 (13)
Event details				
Median event study day (IQR)	10 (5, 15)	8 (4, 16)	15 (8, 39)	13 (6, 36)
Occurred during index hospitalisation	236 (11)	461 (11)	273 (13)	525 (12)
Data source				
Hospitalisation datasets	181 (8.6)	325 (7.5)	372 (18)	658 (15)
Microbiology dataset	96 (4.6)	189 (4.4)	135 (6.4)	253 (5.9)
Primary care medication dispensing dataset	124 (5.9)	264 (6.1)	376 (18)	811 (19)
Primary care GP dataset	33 (1.6)	55 (1.3)	60 (2.9)	123 (2.8)
Death datasets	33 (1.6)	50 (1.2)	61 (2.9)	91 (2.1)
Total				
Any non-COVID infection	402 (19)	784 (18)	732 (35)	1,420 (33)

[back to main text]

Supplementary Table 15: Details of microbiologically confirmed non-COVID infection events in the RECOVERY dexamethasone comparison.

	Microbiologically confirmed non-COVID infection within 28 days		Microbiologically confirmed non-COVID infection within 6 months	
	Dexamethasone (n=2104)	Usual Care (n=4321)	Dexamethasone (n=2104)	Usual Care (n=4321)
Organism				
Bacterial	83 (3.9)	172 (4.0)	123 (5.8)	235 (5.4)
Fungal	18 (0.9)	25 (0.6)	22 (1.0)	30 (0.7)
Viral (not SARS-CoV-2)	1 (<0.1)	0 (0)	1 (<0.1)	0 (0)
Tuberculosis	0 (0)	0 (0)	0 (0)	0 (0)
Other organism	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified organism	0 (0)	0 (0)	0 (0)	0 (0)
Anatomical site				
Pneumonia/Lower respiratory tract	34 (1.6)	86 (2.0)	47 (2.2)	105 (2.4)
Bloodstream	72 (3.4)	109 (2.5)	99 (4.7)	151 (3.5)
Urinary tract	0 (0)	0 (0)	0 (0)	0 (0)
Intra-abdominal	1 (<0.1)	5 (0.1)	7 (0.3)	20 (0.5)
Skin and soft tissue	0 (0)	0 (0)	0 (0)	0 (0)
Bone and joint	0 (0)	0 (0)	0 (0)	0 (0)
Upper respiratory tract	1 (<0.1)	0 (0)	1 (<0.1)	0 (0)
Other anatomical site	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified anatomical site	4 (0.2)	6 (0.1)	4 (0.2)	7 (0.2)
Event details				
Median event study day (IQR)	10 (7, 15)	11 (6, 17)	14 (8, 34)	14 (8, 30)
Occurred during index hospitalisation	85 (4.0)	177 (4.1)	99 (4.7)	197 (4.6)
Data source				
Hospitalisation datasets	0 (0)	0 (0)	0 (0)	0 (0)
Microbiology dataset	96 (4.6)	189 (4.4)	135 (6.4)	253 (5.9)
Primary care medication dispensing dataset	0 (0)	0 (0)	0 (0)	0 (0)
Primary care GP dataset	0 (0)	0 (0)	0 (0)	0 (0)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Total				
Microbiologically confirmed non-COVID infection	96 (4.6)	189 (4.4)	135 (6.4)	253 (5.9)

[back to main text]

Supplementary Table 16: Details of bloodstream infection events in the RECOVERY dexamethasone comparison.

	Bloodstream infection within 28 days		Bloodstream infection within 6 months	
	Dexamethasone (n=2104)	Usual Care (n=4321)	Dexamethasone (n=2104)	Usual Care (n=4321)
Organism				
Bacterial	65 (3.1)	99 (2.3)	94 (4.5)	141 (3.3)
Fungal	11 (0.5)	14 (0.3)	13 (0.6)	17 (0.4)
Viral (not SARS-CoV-2)	0 (0)	0 (0)	0 (0)	0 (0)
Tuberculosis	0 (0)	0 (0)	0 (0)	0 (0)
Other organism	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified organism	0 (0)	0 (0)	0 (0)	0 (0)
Anatomical site				
Pneumonia/Lower respiratory tract	0 (0)	0 (0)	0 (0)	0 (0)
Bloodstream	72 (3.4)	109 (2.5)	99 (4.7)	151 (3.5)
Urinary tract	0 (0)	0 (0)	0 (0)	0 (0)
Intra-abdominal	0 (0)	0 (0)	0 (0)	0 (0)
Skin and soft tissue	0 (0)	0 (0)	0 (0)	0 (0)
Bone and joint	0 (0)	0 (0)	0 (0)	0 (0)
Upper respiratory tract	0 (0)	0 (0)	0 (0)	0 (0)
Other anatomical site	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified anatomical site	0 (0)	0 (0)	0 (0)	0 (0)
Event details				
Median event study day (IQR)	11 (8, 15)	11 (8, 17)	14 (9, 30)	16 (9, 36)
Occurred during index hospitalisation	65 (3.1)	104 (2.4)	74 (3.5)	118 (2.7)
Data source				
Hospitalisation datasets	0 (0)	0 (0)	0 (0)	0 (0)
Microbiology dataset	72 (3.4)	109 (2.5)	99 (4.7)	151 (3.5)
Primary care medication dispensing dataset	0 (0)	0 (0)	0 (0)	0 (0)
Primary care GP dataset	0 (0)	0 (0)	0 (0)	0 (0)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Total				
Bloodstream infection	72 (3.4)	109 (2.5)	99 (4.7)	151 (3.5)

[back to main text]

Supplementary Table 17: Details of bacterial infection events in the RECOVERY dexamethasone comparison.

	Bacterial infection within 28 days		Bacterial infection within 6 months	
	Dexamethasone (n=2104)	Usual Care (n=4321)	Dexamethasone (n=2104)	Usual Care (n=4321)
Organism				
Bacterial	277 (13)	557 (13)	581 (28)	1,142 (26)
Fungal	0 (0)	0 (0)	0 (0)	0 (0)
Viral (not SARS-CoV-2)	0 (0)	0 (0)	0 (0)	0 (0)
Tuberculosis	0 (0)	0 (0)	0 (0)	0 (0)
Other organism	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified organism	0 (0)	0 (0)	0 (0)	0 (0)
Anatomical site				
Pneumonia/Lower respiratory tract	50 (2.4)	115 (2.7)	68 (3.2)	142 (3.3)
Bloodstream	65 (3.1)	99 (2.3)	94 (4.5)	141 (3.3)
Urinary tract	0 (0)	0 (0)	0 (0)	0 (0)
Intra-abdominal	1 (<0.1)	6 (0.1)	12 (0.6)	29 (0.7)
Skin and soft tissue	6 (0.3)	22 (0.5)	33 (1.6)	63 (1.5)
Bone and joint	2 (<0.1)	0 (0)	2 (<0.1)	0 (0)
Upper respiratory tract	0 (0)	0 (0)	0 (0)	0 (0)
Other anatomical site	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified anatomical site	172 (8.2)	337 (7.8)	409 (19)	812 (19)
Event details				
Median event study day (IQR)	10 (5, 14)	9 (5, 17)	16 (8, 40)	15 (6, 35)
Occurred during index hospitalisation	138 (6.6)	283 (6.5)	165 (7.8)	325 (7.5)
Data source				
Hospitalisation datasets	87 (4.1)	166 (3.8)	197 (9.4)	344 (8.0)
Microbiology dataset	83 (3.9)	172 (4.0)	123 (5.8)	235 (5.4)
Primary care medication dispensing dataset	121 (5.8)	255 (5.9)	368 (17)	789 (18)
Primary care GP dataset	1 (<0.1)	1 (<0.1)	2 (<0.1)	2 (<0.1)
Death datasets	11 (0.5)	11 (0.3)	20 (1.0)	17 (0.4)
Total				
Bacterial infection	277 (13)	557 (13)	581 (28)	1,142 (26)

[back to main text]

Supplementary Table 18: Details of fungal infection events in the RECOVERY dexamethasone comparison.

	Fungal infection within 28 days		Fungal infection within 6 months	
	Dexamethasone (n=2104)	Usual Care (n=4321)	Dexamethasone (n=2104)	Usual Care (n=4321)
Organism				
Bacterial	0 (0)	0 (0)	0 (0)	0 (0)
Fungal	50 (2.4)	82 (1.9)	78 (3.7)	147 (3.4)
Viral (not SARS-CoV-2)	0 (0)	0 (0)	0 (0)	0 (0)
Tuberculosis	0 (0)	0 (0)	0 (0)	0 (0)
Other organism	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified organism	0 (0)	0 (0)	0 (0)	0 (0)
Anatomical site				
Pneumonia/Lower respiratory tract	6 (0.3)	13 (0.3)	6 (0.3)	18 (0.4)
Bloodstream	11 (0.5)	14 (0.3)	13 (0.6)	17 (0.4)
Urinary tract	0 (0)	0 (0)	0 (0)	0 (0)
Intra-abdominal	0 (0)	0 (0)	0 (0)	0 (0)
Skin and soft tissue	2 (<0.1)	6 (0.1)	5 (0.2)	12 (0.3)
Bone and joint	0 (0)	0 (0)	0 (0)	0 (0)
Upper respiratory tract	0 (0)	0 (0)	0 (0)	0 (0)
Other anatomical site	21 (1.0)	26 (0.6)	34 (1.6)	56 (1.3)
Unspecified anatomical site	11 (0.5)	26 (0.6)	21 (1.0)	49 (1.1)
Event details				
Median event study day (IQR)	10 (7, 16)	9 (5, 15)	15 (8, 32)	17 (8, 42)
Occurred during index hospitalisation	41 (1.9)	62 (1.4)	53 (2.5)	80 (1.9)
Data source				
Hospitalisation datasets	32 (1.5)	50 (1.2)	49 (2.3)	94 (2.2)
Microbiology dataset	18 (0.9)	25 (0.6)	22 (1.0)	30 (0.7)
Primary care medication dispensing dataset	3 (0.1)	10 (0.2)	11 (0.5)	30 (0.7)
Primary care GP dataset	0 (0)	0 (0)	0 (0)	0 (0)
Death datasets	0 (0)	0 (0)	1 (<0.1)	0 (0)
Total				
Fungal infection	50 (2.4)	82 (1.9)	78 (3.7)	147 (3.4)

[back to main text]

Supplementary Table 19: Details of metabolic complication events in the RECOVERY dexamethasone comparison.

	Metabolic complications at 28 days		Metabolic complications at 6 months	
	Dexamethasone (n=2104)	**Usual Care (n=4321)**	**Dexamethasone (n=2104)**	**Usual Care (n=4321)**
Metabolic complication type				
Ketoacidosis	0 (0)	2 (<0.1)	3 (0.1)	9 (0.2)
Hyperglycaemia	6 (0.3)	4 (<0.1)	10 (0.5)	8 (0.2)
Hypoglycaemia	12 (0.6)	14 (0.3)	27 (1.3)	35 (0.8)
Other metabolic complication	1 (<0.1)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Unspecified metabolic complication	2 (<0.1)	1 (<0.1)	4 (0.2)	12 (0.3)
Event occurred in participant with baseline diabetes	14 (0.7)	17 (0.4)	33 (1.6)	53 (1.2)
Event details				
Median event study day (IQR)	10 (8, 18)	7 (3, 16)	30 (11, 70)	50 (15, 96)
Occurred during index hospitalisation	13 (0.6)	16 (0.4)	19 (0.9)	19 (0.4)
Data source				
Hospitalisation diagnosis code	17 (0.8)	18 (0.4)	37 (1.8)	44 (1.0)
Primary care GP dataset	3 (0.1)	2 (<0.1)	7 (0.3)	19 (0.4)
Death datasets	0 (0)	1 (<0.1)	0 (0)	1 (<0.1)
Total				
Any metabolic complication	20 (1.0)	21 (0.5)	43 (2.0)	60 (1.4)

[back to main text]

Supplementary Table 20: Details of gastrointestinal complication events in the RECOVERY dexamethasone comparison.

	Gastrointestinal complications within 28 days		Gastrointestinal complications within 6 months	
	Dexamethasone (n=2104)	**Usual Care (n=4321)**	**Dexamethasone (n=2104)**	**Usual Care (n=4321)**
GI complication type				
Gastrointestinal bleed	17 (0.8)	20 (0.5)	37 (1.8)	57 (1.3)
Gastrointestinal perforation	2 (<0.1)	2 (<0.1)	3 (0.1)	4 (<0.1)
Gastrointestinal ulcer	1 (<0.1)	5 (0.1)	6 (0.3)	15 (0.3)
Event details				
Median event study day (IQR)	8.0 (5.0, 12.0)	7.0 (4.0, 9.0)	34 (10, 98)	69 (9, 106)
Occurred during index hospitalisation	13 (0.6)	21 (0.5)	17 (0.8)	25 (0.6)
Data source				
Hospitalisation diagnosis code	19 (0.9)	23 (0.5)	42 (2.0)	66 (1.5)
Hospitalisation operation code	0 (0)	2 (<0.1)	0 (0)	2 (<0.1)
Death datasets	1 (<0.1)	1 (<0.1)	3 (0.1)	5 (0.1)
Total				
Any gastrointestinal complication	19 (0.9)	25 (0.6)	44 (2.1)	71 (1.6)

[back to main text]

Supplementary Table 21: Details of venous thromboembolism events in the RECOVERY dexamethasone comparison.

	Venous thromboembolism within 28 days		Venous thromboembolism within 6 months	
	Dexamethasone (n=2104)	**Usual Care (n=4321)**	**Dexamethasone (n=2104)**	**Usual Care (n=4321)**
Venous thromboembolism type				
Pulmonary Embolism	35 (1.7)	55 (1.3)	49 (2.3)	81 (1.9)
Deep Vein Thrombosis	8 (0.4)	13 (0.3)	18 (0.9)	26 (0.6)
Other venous thromboembolism	2 (<0.1)	6 (0.1)	3 (0.1)	12 (0.3)
Unspecified venous thromboembolism	4 (0.2)	7 (0.2)	5 (0.2)	9 (0.2)
Event details				
Median event study day (IQR)	12 (7, 20)	6 (3, 13)	20 (11, 36)	16 (4, 54)
Occurred during index hospitalisation	27 (1.3)	63 (1.5)	32 (1.5)	69 (1.6)
Data source				
Hospitalisation diagnosis code	42 (2.0)	65 (1.5)	65 (3.1)	106 (2.5)
Death datasets	6 (0.3)	13 (0.3)	8 (0.4)	16 (0.4)
Total				
Any venous thromboembolism	48 (2.3)	76 (1.8)	72 (3.4)	119 (2.8)

[back to main text]

Supplementary Table 22: Details of long COVID events in the RECOVERY dexamethasone comparison.

	Long COVID within 18 months	
	Dexamethasone (n=2104)	**Usual Care (n=4321)**
Event details		
Median event study day (IQR)	395 (345, 481)	401 (322, 468)
Data source		
Primary care GP dataset	64 (3.0)	120 (2.8)
Total		
Long COVID	64 (3.0)	120 (2.8)

Supplementary Table 23: Details of incident diabetes events in the RECOVERY dexamethasone comparison.

	Incident diabetes within 12 months	
	Dexamethasone (n=1376)	**Usual care (n=2920)**
Event timing		
Median event study day (IQR)	30 (8, 101)	188 (40, 299)
Occurred during index hospitalisation	5 (0.4)	7 (0.2)
Data source		
Hospitalisation diagnosis code	12 (0.9)	16 (0.5)
Primary care medication dispensing dataset	2 (0.1)	1 (<0.1)
Primary care GP dataset	4 (0.3)	14 (0.5)
Death datasets	0 (0)	0 (0)
Total		
Incident diabetes	15/1,376 (1.1%)	26/2,920 (0.9%)

[back to main text]

Supplementary Table 24: Details of long bone or vertebral fracture events in the RECOVERY dexamethasone comparison.

	Long bone or vertebral fracture within 28 days		Long bone or vertebral fracture within 6 months	
	Dexamethasone (n=2104)	**Usual Care (n=4321)**	**Dexamethasone (n=2104)**	**Usual Care (n=4321)**
Fracture type				
Hip fracture	3 (0.1)	6 (0.1)	7 (0.3)	20 (0.5)
Long bone fracture	4 (0.2)	6 (0.1)	13 (0.6)	14 (0.3)
Vertebral fracture	1 (<0.1)	1 (<0.1)	2 (<0.1)	7 (0.2)
Unspecified long bone or vertebral fracture	4 (0.2)	4 (<0.1)	16 (0.8)	14 (0.3)
Event details				
Median event study day (IQR)	12 (6, 24)	11 (6, 17)	65 (25, 108)	45 (22, 114)
Occurred during index hospitalisation	5 (0.2)	8 (0.2)	5 (0.2)	11 (0.3)
Data source				
Hospitalisation diagnosis code	5 (0.2)	12 (0.3)	22 (1.0)	41 (0.9)
Hospitalisation operation code	2 (<0.1)	6 (0.1)	7 (0.3)	11 (0.3)
Primary care GP dataset	4 (0.2)	0 (0)	10 (0.5)	5 (0.1)
Death datasets	1 (<0.1)	1 (<0.1)	2 (<0.1)	2 (<0.1)
Total				
Any long bone or vertebral fracture	10 (0.5)	16 (0.4)	33 (1.6)	49 (1.1)

[back to main text]

Supplementary Table 25: Details of psychiatric complication events in the RECOVERY dexamethasone comparison.

	Psychiatric complications within 28 days		Psychiatric complications within 6 months	
	Dexamethasone (n=2104)	**Usual Care (n=4321)**	**Dexamethasone (n=2104)**	**Usual Care (n=4321)**
Psychiatric complication type				
Psychosis	0 (0)	2 (<0.1)	2 (<0.1)	10 (0.2)
Mania	0 (0)	1 (<0.1)	3 (0.1)	3 (<0.1)
Delirium	51 (2.4)	79 (1.8)	81 (3.8)	144 (3.3)
Other psychiatric complication	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified psychiatric complication	6 (0.3)	20 (0.5)	14 (0.7)	42 (1.0)
Event details				
Median event study day (IQR)	10 (4, 15)	8 (4, 15)	22 (8, 53)	25 (7, 69)
Occurred during index hospitalisation	36 (1.7)	63 (1.5)	46 (2.2)	72 (1.7)
Data source				
Hospitalisation diagnosis code	49 (2.3)	78 (1.8)	79 (3.8)	144 (3.3)
Primary care medication dispensing dataset	6 (0.3)	21 (0.5)	15 (0.7)	52 (1.2)
Primary care GP dataset	0 (0)	3 (<0.1)	5 (0.2)	12 (0.3)
Death datasets	2 (<0.1)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Total				
Any psychiatric complication	57 (2.7)	102 (2.4)	100 (4.8)	198 (4.6)

[back to main text]

Supplementary Table 26: Details of clinically-defined liver injury events in the RECOVERY dexamethasone comparison.

	Clinically-defined liver injury within 28 days		Clinically-defined liver injury within 6 months	
	Dexamethasone (n=2104)	**Usual Care (n=4321)**	**Dexamethasone (n=2104)**	**Usual Care (n=4321)**
Event details				
Median event study day (IQR)	11 (5, 19)	6 (3, 13)	18 (7, 35)	17 (5, 54)
Occurred during index hospitalisation	10 (0.5)	31 (0.7)	12 (0.6)	33 (0.8)
Data source				
Hospitalisation diagnosis code	14 (0.7)	34 (0.8)	21 (1.0)	56 (1.3)
Primary care GP dataset	3 (0.1)	2 (<0.1)	4 (0.2)	6 (0.1)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Total				
Any clinically-defined liver injury	16 (0.8)	36 (0.8)	23 (1.1)	61 (1.4)

[back to main text]

Supplementary Table 27: Results of sensitivity analyses of other secondary outcomes in the RECOVERY dexamethasone comparison.

	Dexamethasone (n=2104)	Usual Care (n=4321)	Rate or Risk Ratio (95% CI)	p-value
Gastrointestinal complications				
Gastrointestinal complication within 28 days, 1st diagnostic position only	3 (0.1%)	6 (0.1%)	0.94 (0.24 - 3.77)	0.93
Gastrointestinal complication within 6 months, 1st diagnostic position only	16 (0.8%)	27 (0.6%)	1.16 (0.63 - 2.16)	0.63
Gastrointestinal complication within 28 days, including peri-randomisation episode diagnoses	51 (2.4%)	93 (2.2%)	1.10 (0.78 - 1.53)	0.58
Gastrointestinal complication within 6 months, including peri-randomisation episode diagnoses	76 (3.6%)	135 (3.1%)	1.13 (0.86 - 1.49)	0.38
Venous thromboembolism				
Venous thromboembolism within 28 days, 1st diagnostic position only	22 (1.0%)	23 (0.5%)	1.91 (1.06 - 3.43)	0.03
Venous thromboembolism within 6 months, 1st diagnostic position only	37 (1.8%)	44 (1.0%)	1.67 (1.08 - 2.59)	0.02
Venous thromboembolism within 28 days, including peri-randomisation episode diagnoses	124 (5.9%)	232 (5.4%)	1.11 (0.89 - 1.36)	0.35
Venous thromboembolism within 6 months, including peri-randomisation episode diagnoses	146 (6.9%)	267 (6.2%)	1.13 (0.93 - 1.37)	0.22

[back to main text]

Supplementary Table 28: Effect of allocation to dexamethasone on hospital-recorded diagnoses[*] within 6 months of randomisation.

	Dexamethasone (n=2104)[1]	Usual Care (n=4321)[1]	Rate Ratio (95% CI)
Event timing			
Number of hospital admission days			
Median (Lower quartile, Upper quartile)	9 (4, 17)	8 (4, 17)	
Mean (Standard Deviation)	17 (26)	16 (25)	
Study day of diagnosis start			
Median (Lower quartile, Upper quartile)	26 (10, 66)	28 (10, 75)	
Diagnosis start during index hospital admission	263 (13)	490 (11)	
Admission type			
Emergency admission (including transfers)	618 (29)	1,100 (25)	
Elective admission	151 (7.2)	313 (7.2)	
COVID-19			
Readmission due to COVID-19	84 (4.0)	127 (2.9)	1.30 (0.99 - 1.71)
Non-COVID infection			
Pneumonia/Lower Respiratory Tract	81 (3.8)	152 (3.5)	
Urinary tract	32 (1.5)	52 (1.2)	
Intra-abdominal	13 (0.6)	25 (0.6)	
Skin and soft tissue	17 (0.8)	19 (0.4)	
Bone and joint	4 (0.2)	7 (0.2)	
Upper Respiratory Tract	0 (0)	3 (<0.1)	
Other site	8 (0.4)	10 (0.2)	
Unspecified site	42 (2.0)	75 (1.7)	
Bacterial	66 (3.1)	90 (2.1)	
Fungal	0 (0)	0 (0)	
Other viral	6 (0.3)	3 (<0.1)	
TB	1 (<0.1)	2 (<0.1)	
Other organism	0 (0)	0 (0)	
Unspecified organism	115 (5.5)	232 (5.4)	
Subtotal: Any non-COVID infection	166 (7.9)	288 (6.7)	1.15 (0.95 - 1.39)
Cardiac			
Myocardial infarction	7 (0.3)	9 (0.2)	
Other coronary heart disease	10 (0.5)	21 (0.5)	
Heart failure	20 (1.0)	54 (1.2)	
Other	17 (0.8)	45 (1.0)	

Subtotal: Any cardiac	50 (2.4)	114 (2.6)	0.84 (0.60 - 1.17)
Stroke			
Haemorrhagic stroke	4 (0.2)	5 (0.1)	
Non-haemorrhagic stroke	9 (0.4)	20 (0.5)	
Subtotal: Any stroke	13 (0.6)	25 (0.6)	1.00 (0.51 - 1.95)
Other vascular			
Arterial thromboembolism	2 (<0.1)	9 (0.2)	
Venous thromboembolism	22 (1.0)	24 (0.6)	
Other	24 (1.1)	44 (1.0)	
Subtotal: Any other vascular	48 (2.3)	76 (1.8)	1.25 (0.87 - 1.80)
Medical			
Cancer	23 (1.1)	60 (1.4)	
Diabetes	4 (0.2)	11 (0.3)	
Gastrointestinal bleed or perforation	13 (0.6)	22 (0.5)	
Other extra-cranial bleed or perforation	21 (1.0)	39 (0.9)	
Liver	3 (0.1)	8 (0.2)	
Renal	37 (1.8)	63 (1.5)	
Respiratory (non-infection)	45 (2.1)	99 (2.3)	
Other	178 (8.5)	323 (7.5)	
Subtotal: Any medical	252 (12)	472 (11)	1.07 (0.92 - 1.24)
External			
External with bleed	2 (<0.1)	7 (0.2)	
External without bleed	57 (2.7)	108 (2.5)	
Subtotal: Any external	58 (2.8)	115 (2.7)	
Unknown			
No formal diagnosis recorded	147 (7.0)	265 (6.1)	
Total			
Total: Any hospital recorded diagnosis	682 (32)	1,259 (29)	1.08 (0.98 - 1.19)

[*]Hospital-recorded diagnoses reflected the categorisation of any ICD-10 codes in the primary diagnostic position recorded in a hospital admission dataset from episodes of care with a start date within 6 months after randomisation.
[1]n (%)

[back to main text]

Supplementary Table 29: Effect of allocation to tocilizumab on diagnoses leading to death.

	Tocilizumab (n=2022)[1]	Usual Care (n=2094)[1]	Rate Ratio (95% CI)
Event timing			
Study day of death[2]	9 (5, 17)	9 (5, 16)	
Death during index hospital admission	627 (31)	765 (37)	
COVID-19			
COVID-19	644 (32)	764 (36)	0.86 (0.78 - 0.96)
Non-COVID infection			
Pneumonia/Lower Respiratory Tract	27 (1.3)	26 (1.2)	
Urinary tract	1 (<0.1)	3 (0.1)	
Intra-abdominal	2 (<0.1)	1 (<0.1)	
Skin and soft tissue	0 (0)	0 (0)	
Bone and joint	0 (0)	0 (0)	
Upper Respiratory Tract	0 (0)	0 (0)	
Other site	0 (0)	1 (<0.1)	
Unspecified site	15 (0.7)	13 (0.6)	
Bacterial	12 (0.6)	17 (0.8)	
Fungal	1 (<0.1)	0 (0)	
Other viral	1 (<0.1)	0 (0)	
TB	0 (0)	0 (0)	
Other organism	1 (<0.1)	0 (0)	
Unspecified organism	29 (1.4)	26 (1.2)	
Subtotal: Any non-COVID infection	42 (2.1)	41 (2.0)	1.03 (0.67 - 1.59)
Cardiac			
Myocardial infarction	2 (<0.1)	6 (0.3)	
Other coronary heart disease	4 (0.2)	6 (0.3)	
Heart failure	4 (0.2)	7 (0.3)	
Other	1 (<0.1)	8 (0.4)	
Subtotal: Any cardiac	9 (0.4)	20 (1.0)	0.46 (0.21 - 1.00)
Stroke			
Haemorrhagic stroke	2 (<0.1)	2 (<0.1)	
Non-haemorrhagic stroke	4 (0.2)	11 (0.5)	
Subtotal: Any stroke	6 (0.3)	13 (0.6)	0.46 (0.17 - 1.21)
Other vascular			
Arterial thrombo-embolism	1 (<0.1)	0 (0)	

Venous thrombo-embolism	21 (1.0)	22 (1.1)	
Other	9 (0.4)	6 (0.3)	
Subtotal: Any other vascular	29 (1.4)	27 (1.3)	1.08 (0.64 - 1.82)
Medical			
Cancer	15 (0.7)	11 (0.5)	
Diabetes	4 (0.2)	2 (<0.1)	
Gastrointestinal bleed or perforation	4 (0.2)	1 (<0.1)	
Other extra-cranial bleed or perforation	7 (0.3)	1 (<0.1)	
Liver	1 (<0.1)	1 (<0.1)	
Renal	5 (0.2)	0 (0)	
Respiratory (non-infection)	61 (3.0)	48 (2.3)	
Other	3 (0.1)	9 (0.4)	
Subtotal: Any medical	72 (3.6)	60 (2.9)	1.21 (0.86 - 1.70)
External			
External with bleed	0 (0)	1 (<0.1)	
External without bleed	6 (0.3)	1 (<0.1)	
Subtotal: Any external	6 (0.3)	1 (<0.1)	
Unknown			
No formal diagnosis recorded	75 (3.7)	85 (4.1)	
Total			
Total: All deaths	694 (34)	816 (39)	0.87 (0.79 - 0.96)
Diagnoses leading to death represented any diagnosis written in any row of part 1 of the death certificate *[1]n (%)* *[2]Median (Lower quartile, Upper quartile)*			

[back to main text]

Supplementary Table 30: Results of sensitivity analyses of non-COVID infection outcomes in the RECOVERY tocilizumab comparison.

	Tocilizumab (n=2022)	Usual Care (n=2094)	Rate or Risk Ratio (95% CI)	p-value
Primary outcome				
Major non-COVID infection within 28 days, 1st diagnostic position only	170 (8.4%)	172 (8.2%)	1.02 (0.83 - 1.27)	0.83
Major non-COVID infection within 6 months, 1st diagnostic position only	256 (13%)	263 (13%)	0.99 (0.83 - 1.18)	0.91
Major non-COVID infection within 28 days, including peri-randomisation episode diagnoses	657 (32%)	731 (35%)	0.91 (0.80 - 1.04)	0.18
Major non-COVID infection within 6 months, including peri-randomisation episode diagnoses	727 (36%)	797 (38%)	0.93 (0.81 - 1.06)	0.26
Major non-COVID infection within 28 days, excluding respiratory tract infections	187 (9.2%)	202 (9.6%)	0.94 (0.77 - 1.15)	0.58
Major non-COVID infection within 6 months, excluding respiratory tract infections	269 (13%)	274 (13%)	0.99 (0.84 - 1.17)	0.91
Secondary outcome				
Any non-COVID infection within 28 days, 1st diagnostic position only	276 (14%)	261 (12%)	1.11 (0.95 - 1.30)	0.18
Any non-COVID infection within 6 months, 1st diagnostic position only	511 (25%)	494 (24%)	1.08 (0.97 - 1.20)	0.18
Any non-COVID infection within 28 days, including peri-randomisation episode diagnoses	395 (20%)	429 (20%)	0.97 (0.86 - 1.10)	0.65
Any non-COVID infection within 6 months, including peri-randomisation episode diagnoses	1,044 (52%)	1,115 (53%)	0.98 (0.92 - 1.04)	0.45
Any non-COVID infection within 28 days, excluding respiratory tract infections	284 (14%)	279 (13%)	1.07 (0.92 - 1.24)	0.39
Any non-COVID infection within 6 months, excluding respiratory tract infections	508 (25%)	491 (23%)	1.08 (0.97 - 1.20)	0.17

[back to main text]

Supplementary Table 31: Details of any non-COVID infection events in the RECOVERY tocilizumab comparison.

	Any non-COVID infection within 28 days		Any non-COVID infection within 6 months	
	Tocilizumab (n=2022)	Usual Care (n=2094)	Tocilizumab (n=2022)	Usual Care (n=2094)
Organism				
Bacterial	286 (14)	287 (14)	498 (25)	486 (23)
Fungal	42 (2.1)	44 (2.1)	61 (3.0)	70 (3.3)
Viral (not SARS-CoV-2)	5 (0.2)	9 (0.4)	10 (0.5)	21 (1.0)
Tuberculosis	0 (0)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Other organism	1 (<0.1)	1 (<0.1)	2 (<0.1)	2 (<0.1)
Unspecified organism	60 (3.0)	79 (3.8)	78 (3.9)	90 (4.3)
Anatomical site				
Pneumonia/Lower respiratory tract	159 (7.9)	191 (9.1)	235 (12)	274 (13)
Bloodstream	85 (4.2)	82 (3.9)	100 (4.9)	108 (5.2)
Urinary tract	24 (1.2)	33 (1.6)	51 (2.5)	62 (3.0)
Intra-abdominal	9 (0.4)	6 (0.3)	20 (1.0)	20 (1.0)
Skin and soft tissue	5 (0.2)	8 (0.4)	27 (1.3)	20 (1.0)
Bone and joint	2 (<0.1)	0 (0)	7 (0.3)	7 (0.3)
Upper respiratory tract	4 (0.2)	4 (0.2)	13 (0.6)	11 (0.5)
Other anatomical site	24 (1.2)	29 (1.4)	32 (1.6)	45 (2.1)
Unspecified anatomical site	120 (5.9)	94 (4.5)	230 (11)	204 (9.7)
Event details				
Median event study day (IQR)	10 (5, 15)	9 (5, 15)	12 (6, 28)	11 (5, 24)
Occurred during index hospitalisation	250 (12)	297 (14)	271 (13)	325 (16)
Data source				
Hospitalisation datasets	159 (7.9)	186 (8.9)	272 (13)	286 (14)
Microbiology dataset	129 (6.4)	134 (6.4)	148 (7.3)	167 (8.0)
Primary care medication dispensing dataset	102 (5.0)	83 (4.0)	305 (15)	274 (13)
Primary care GP dataset	14 (0.7)	22 (1.1)	36 (1.8)	41 (2.0)
Death datasets	29 (1.4)	34 (1.6)	42 (2.1)	41 (2.0)
Total				
Any non-COVID infection	372 (18)	394 (19)	606 (30)	612 (29)

[back to main text]

Supplementary Table 32: Details of microbiologically confirmed non-COVID infection events in the RECOVERY tocilizumab comparison.

	Microbiologically confirmed non-COVID infection within 28 days		Microbiologically confirmed non-COVID infection within 6 months	
	Tocilizumab (n=2022)	Usual Care (n=2094)	Tocilizumab (n=2022)	Usual Care (n=2094)
Organism				
Bacterial	124 (6.1)	123 (5.9)	144 (7.1)	157 (7.5)
Fungal	11 (0.5)	12 (0.6)	12 (0.6)	14 (0.7)
Viral (not SARS-CoV-2)	0 (0)	2 (<0.1)	0 (0)	2 (<0.1)
Tuberculosis	0 (0)	0 (0)	0 (0)	0 (0)
Other organism	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified organism	0 (0)	0 (0)	0 (0)	0 (0)
Anatomical site				
Pneumonia/Lower respiratory tract	61 (3.0)	66 (3.2)	68 (3.4)	82 (3.9)
Bloodstream	85 (4.2)	82 (3.9)	100 (4.9)	108 (5.2)
Urinary tract	0 (0)	0 (0)	0 (0)	0 (0)
Intra-abdominal	2 (<0.1)	0 (0)	4 (0.2)	3 (0.1)
Skin and soft tissue	0 (0)	0 (0)	0 (0)	0 (0)
Bone and joint	0 (0)	0 (0)	0 (0)	0 (0)
Upper respiratory tract	0 (0)	2 (<0.1)	0 (0)	2 (<0.1)
Other anatomical site	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified anatomical site	2 (<0.1)	0 (0)	2 (<0.1)	0 (0)
Event details				
Median event study day (IQR)	11 (8, 16)	10 (6, 17)	12 (8, 21)	13 (7, 24)
Occurred during index hospitalisation	120 (5.9)	131 (6.3)	131 (6.5)	148 (7.1)
Data source				
Hospitalisation datasets	0 (0)	0 (0)	0 (0)	0 (0)
Microbiology dataset	129 (6.4)	134 (6.4)	148 (7.3)	167 (8.0)
Primary care medication administration dataset	0 (0)	0 (0)	0 (0)	0 (0)
Primary care GP dataset	0 (0)	0 (0)	0 (0)	0 (0)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Total				
Microbiologically confirmed non-COVID infection	129 (6.4)	134 (6.4)	148 (7.3)	167 (8.0)

[back to main text]

Supplementary Table 33: Details of bloodstream infection events in the RECOVERY tocilizumab comparison.

	Bloodstream infection within 28 days		Bloodstream infection within 6 months	
	Tocilizumab (n=2022)	Usual Care (n=2094)	Tocilizumab (n=2022)	Usual Care (n=2094)
Organism				
Bacterial	82 (4.1)	75 (3.6)	97 (4.8)	102 (4.9)
Fungal	4 (0.2)	8 (0.4)	5 (0.2)	9 (0.4)
Viral (not SARS-CoV-2)	0 (0)	0 (0)	0 (0)	0 (0)
Tuberculosis	0 (0)	0 (0)	0 (0)	0 (0)
Other organism	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified organism	0 (0)	0 (0)	0 (0)	0 (0)
Anatomical site				
Pneumonia/Lower respiratory tract	0 (0)	0 (0)	0 (0)	0 (0)
Bloodstream	85 (4.2)	82 (3.9)	100 (4.9)	108 (5.2)
Urinary tract	0 (0)	0 (0)	0 (0)	0 (0)
Intra-abdominal	0 (0)	0 (0)	0 (0)	0 (0)
Skin and soft tissue	0 (0)	0 (0)	0 (0)	0 (0)
Bone and joint	0 (0)	0 (0)	0 (0)	0 (0)
Upper respiratory tract	0 (0)	0 (0)	0 (0)	0 (0)
Other anatomical site	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified anatomical site	0 (0)	0 (0)	0 (0)	0 (0)
Event details				
Median event study day (IQR)	12 (9, 16)	13 (8, 18)	14 (10, 23)	17 (10, 27)
Occurred during index hospitalisation	80 (4.0)	80 (3.8)	90 (4.5)	95 (4.5)
Data source				
Hospitalisation datasets	0 (0)	0 (0)	0 (0)	0 (0)
Microbiology dataset	85 (4.2)	82 (3.9)	100 (4.9)	108 (5.2)
Primary care medication administration dataset	0 (0)	0 (0)	0 (0)	0 (0)
Primary care GP dataset	0 (0)	0 (0)	0 (0)	0 (0)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Total				
Bloodstream infection	85 (4.2)	82 (3.9)	100 (4.9)	108 (5.2)

[back to main text]

Supplementary Table 34: Organism classification of bloodstream infection events in the RECOVERY tocilizumab comparison.

	Bloodstream infection within 28 days		Bloodstream infection within 6 months	
	Tocilizumab (n=85)	**Usual Care (n=82)**	**Tocilizumab (n=85)**	**Usual Care (n=82)**
Bacterial				
Gram Positive	31 (36%)	36 (44%)	39 (39%)	46 (43%)
Enterococcus species	23 (27%)	27 (33%)	28 (28%)	34 (31%)
Staphylococcus aureus	5 (5.9%)	8 (9.8%)	9 (9.0%)	12 (11%)
Other Gram Positive	3 (3.5%)	3 (3.7%)	3 (3.0%)	3 (2.8%)
Gram Negative	55 (65%)	37 (45%)	66 (66%)	54 (50%)
E.coli	9 (11%)	5 (6.1%)	10 (10%)	14 (13%)
Enterobacter species	7 (8.2%)	4 (4.9%)	8 (8.0%)	5 (4.6%)
Klebsiella species	25 (29%)	19 (23%)	29 (29%)	24 (22%)
Pseudomonas aeruginosa	7 (8.2%)	9 (11%)	9 (9.0%)	14 (13%)
Other Gram Negative	17 (20%)	10 (12%)	24 (24%)	14 (13%)
Any bacterial	82 (96%)	75 (91%)	97 (97%)	102 (94%)
Fungal				
Candida species	4 (4.7%)	8 (9.8%)	5 (5.0%)	9 (8.3%)
Any fungal	4 (4.7%)	8 (9.8%)	5 (5.0%)	9 (8.3%)
Total				
Any bloodstream infection	85 (100%)	82 (100%)	100 (100%)	108 (100%)

[back to main text]

Supplementary Table 35: Details of bacterial infection events in the RECOVERY tocilizumab comparison.

	Bacterial infection within 28 days		Bacterial infection within 6 months	
	Tocilizumab (n=2022)	Usual Care (n=2094)	Tocilizumab (n=2022)	Usual Care (n=2094)
Organism				
Bacterial	286 (14)	287 (14)	498 (25)	486 (23)
Fungal	0 (0)	0 (0)	0 (0)	0 (0)
Viral (not SARS-CoV-2)	0 (0)	0 (0)	0 (0)	0 (0)
Tuberculosis	0 (0)	0 (0)	0 (0)	0 (0)
Other organism	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified organism	0 (0)	0 (0)	0 (0)	0 (0)
Anatomical site				
Pneumonia/Lower respiratory tract	79 (3.9)	86 (4.1)	95 (4.7)	108 (5.2)
Bloodstream	82 (4.1)	75 (3.6)	97 (4.8)	102 (4.9)
Urinary tract	0 (0)	0 (0)	0 (0)	0 (0)
Intra-abdominal	2 (<0.1)	2 (<0.1)	4 (0.2)	4 (0.2)
Skin and soft tissue	2 (<0.1)	6 (0.3)	19 (0.9)	13 (0.6)
Bone and joint	0 (0)	0 (0)	0 (0)	1 (<0.1)
Upper respiratory tract	0 (0)	0 (0)	0 (0)	0 (0)
Other anatomical site	0 (0)	1 (<0.1)	0 (0)	1 (<0.1)
Unspecified anatomical site	146 (7.2)	138 (6.6)	318 (16)	296 (14)
Event details				
Median event study day (IQR)	10 (5, 15)	8 (4, 16)	12 (6, 22)	10 (5, 22)
Occurred during index hospitalisation	181 (9.0)	204 (9.7)	194 (9.6)	225 (11)
Data source				
Hospitalisation datasets	96 (4.7)	106 (5.1)	153 (7.6)	152 (7.3)
Microbiology dataset	124 (6.1)	123 (5.9)	144 (7.1)	157 (7.5)
Primary care medication administration dataset	97 (4.8)	80 (3.8)	294 (15)	263 (13)
Primary care GP dataset	0 (0)	0 (0)	0 (0)	0 (0)
Death datasets	9 (0.4)	14 (0.7)	12 (0.6)	17 (0.8)
Total				
Bacterial infection	286 (14)	287 (14)	498 (25)	486 (23)

[back to main text]

Supplementary Table 36: Details of fungal infection events in the RECOVERY tocilizumab comparison.

	Fungal infection within 28 days		Fungal infection within 6 months	
	Tocilizumab (n=2022)	Usual Care (n=2094)	Tocilizumab (n=2022)	Usual Care (n=2094)
Organism				
Bacterial	0 (0)	0 (0)	0 (0)	0 (0)
Fungal	42 (2.1)	44 (2.1)	61 (3.0)	70 (3.3)
Viral (not SARS-CoV-2)	0 (0)	0 (0)	0 (0)	0 (0)
Tuberculosis	0 (0)	0 (0)	0 (0)	0 (0)
Other organism	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified organism	0 (0)	0 (0)	0 (0)	0 (0)
Anatomical site				
Pneumonia/Lower respiratory tract	11 (0.5)	5 (0.2)	14 (0.7)	8 (0.4)
Bloodstream	4 (0.2)	8 (0.4)	5 (0.2)	9 (0.4)
Urinary tract	0 (0)	0 (0)	0 (0)	0 (0)
Intra-abdominal	0 (0)	0 (0)	0 (0)	0 (0)
Skin and soft tissue	0 (0)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Bone and joint	0 (0)	0 (0)	0 (0)	0 (0)
Upper respiratory tract	0 (0)	0 (0)	0 (0)	0 (0)
Other anatomical site	15 (0.7)	18 (0.9)	21 (1.0)	26 (1.2)
Unspecified anatomical site	12 (0.6)	13 (0.6)	21 (1.0)	26 (1.2)
Event details				
Median event study day (IQR)	9 (4, 14)	9 (6, 13)	11 (6, 22)	13 (6, 39)
Occurred during index hospitalisation	34 (1.7)	34 (1.6)	40 (2.0)	42 (2.0)
Data source				
Hospitalisation datasets	26 (1.3)	24 (1.1)	38 (1.9)	36 (1.7)
Microbiology dataset	11 (0.5)	12 (0.6)	12 (0.6)	14 (0.7)
Primary care medication administration dataset	4 (0.2)	8 (0.4)	13 (0.6)	20 (1.0)
Primary care GP dataset	0 (0)	1 (<0.1)	0 (0)	1 (<0.1)
Death datasets	1 (<0.1)	0 (0)	1 (<0.1)	0 (0)
Total				
Fungal infection	42 (2.1)	44 (2.1)	61 (3.0)	70 (3.3)

[back to main text]

Supplementary Table 37: Details of gastrointestinal complication events in the RECOVERY tocilizumab comparison.

	Gastrointestinal complications at 28 days		Gastrointestinal complications at 6 months	
	Tocilizumab (n=2022)	**Usual Care (n=2094)**	**Tocilizumab (n=2022)**	**Usual Care (n=2094)**
GI complication type				
Gastrointestinal bleed	19 (0.9)	14 (0.7)	22 (1.1)	24 (1.1)
Gastrointestinal perforation	1 (<0.1)	0 (0)	1 (<0.1)	0 (0)
Gastrointestinal ulcer	4 (0.2)	5 (0.2)	6 (0.3)	9 (0.4)
Event details				
Median event study day (IQR)	7 (6, 13)	10 (4, 18)	10 (6, 22)	23 (9, 70)
Occurred during index hospitalisation	18 (0.9)	13 (0.6)	18 (0.9)	15 (0.7)
Data source				
Hospitalisation diagnosis code	23 (1.1)	15 (0.7)	28 (1.4)	26 (1.2)
Hospitalisation operation code	0 (0)	1 (<0.1)	0 (0)	1 (<0.1)
Death datasets	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Total				
Any gastrointestinal complication	23 (1.1)	16 (0.8)	28 (1.4)	28 (1.3)

[back to main text]

Supplementary Table 38: Details of venous thromboembolism events in the RECOVERY tocilizumab comparison.

	Venous thromboembolism within 28 days		Venous thromboembolism within 6 months	
	Tocilizumab (n=2022)	**Usual Care (n=2094)**	**Tocilizumab (n=2022)**	**Usual Care (n=2094)**
Venous thromboembolism type				
Pulmonary Embolism	63 (3.1)	75 (3.6)	83 (4.1)	99 (4.7)
Deep Vein Thrombosis	8 (0.4)	5 (0.2)	17 (0.8)	9 (0.4)
Other venous thromboembolism	2 (<0.1)	0 (0)	5 (0.2)	2 (<0.1)
Unspecified venous thromboembolism	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Event details				
Median event study day (IQR)	9 (5, 13)	8 (4, 13)	12 (7, 32)	12 (5, 29)
Occurred during index hospitalisation	58 (2.9)	67 (3.2)	64 (3.2)	72 (3.4)
Data source				
Hospitalisation diagnosis code	53 (2.6)	61 (2.9)	76 (3.8)	86 (4.1)
Death datasets	18 (0.9)	20 (1.0)	21 (1.0)	22 (1.1)
Total				
Any venous thromboembolism	70 (3.5)	80 (3.8)	95 (4.7)	107 (5.1)

[back to main text]

Supplementary Table 39: Details of long COVID events in the RECOVERY tocilizumab comparison.

	Tocilizumab (n=2022)	Usual Care (n=2094)
Event details		
Median event study day (IQR)	184 (102, 314)	211 (119, 340)
Data source		
GP diagnosis code	146 (7.2)	165 (7.9)
Total		
Long COVID	146 (7.2)	165 (7.9)

[back to main text]

Supplementary Table 40: Details of metabolic complication events in the RECOVERY tocilizumab comparison.

	Metabolic complications within 28 days		Metabolic complications within 6 months	
	Tocilizumab (n=2022)	**Usual Care (n=2094)**	**Tocilizumab (n=2022)**	**Usual Care (n=2094)**
Metabolic complication type				
Ketoacidosis	1 (<0.1)	4 (0.2)	6 (0.3)	6 (0.3)
Hyperglycaemia	7 (0.3)	14 (0.7)	8 (0.4)	15 (0.7)
Hypoglycaemia	9 (0.4)	14 (0.7)	21 (1.0)	22 (1.1)
Other metabolic complication	1 (<0.1)	2 (<0.1)	3 (0.1)	3 (0.1)
Unspecified metabolic complication	0 (0)	1 (<0.1)	4 (0.2)	5 (0.2)
Event occurred in participant with baseline diabetes	16 (0.8)	24 (1.1)	35 (1.7)	36 (1.7)
Event details				
Median event study day (IQR)	7 (5, 10)	6 (3, 11)	32 (7, 68)	10 (4, 36)
Occurred during index hospitalisation	15 (0.7)	34 (1.6)	22 (1.1)	41 (2.0)
Data source				
Hospitalisation diagnosis code	17 (0.8)	30 (1.4)	33 (1.6)	40 (1.9)
Primary care GP dataset	1 (<0.1)	5 (0.2)	8 (0.4)	12 (0.6)
Death datasets	1 (<0.1)	0 (0)	1 (<0.1)	0 (0)
Total				
Any metabolic complication	18 (0.9)	35 (1.7)	39 (1.9)	50 (2.4)

[back to main text]

Supplementary Table 41: Details of incident diabetes events in the RECOVERY tocilizumab comparison.

	Tocilizumab (n=1262)	Usual care (n=1321)
Event details		
Median event study day (IQR)	85 (18, 213)	108 (20, 228)
Occurred during index hospitalisation	10 (0.8)	7 (0.5)
Data source		
Hospitalisation diagnosis code	13 (1.0)	12 (0.9)
Primary care medication dispensing dataset	2 (0.2)	4 (0.3)
Primary care GP dataset	9 (0.7)	10 (0.8)
Death datasets	0 (0)	0 (0)
Total		
Incident diabetes	22/1,262 (1.7%)	22/1,321 (1.7%)

[back to main text]

Supplementary Table 42: Details of long bone or vertebral fracture events in the RECOVERY tocilizumab comparison.

	Long bone or vertebral fracture within 28 days		Long bone or vertebral fracture within 6 months	
	Tocilizumab (n=2022)	**Usual Care (n=2094)**	**Tocilizumab (n=2022)**	**Usual Care (n=2094)**
Fracture type				
Hip fracture	0 (0)	0 (0)	2 (<0.1)	0 (0)
Other long bone fracture	1 (<0.1)	3 (0.1)	3 (0.1)	3 (0.1)
Vertebral fracture	0 (0)	0 (0)	1 (<0.1)	2 (<0.1)
Unspecified long bone or vertebral fracture	1 (<0.1)	0 (0)	5 (0.2)	2 (<0.1)
Event details				
Occurred during index hospitalisation	1 (<0.1)	3 (0.1)	1 (<0.1)	4 (0.2)
Median event study day (IQR)	-	-	62 (29, 117)	33 (16, 145)
Data source				
Hospitalisation diagnosis code	2 (<0.1)	3 (0.1)	6 (0.3)	6 (0.3)
Hospitalisation operation code	0 (0)	0 (0)	0 (0)	0 (0)
Primary care GP dataset	0 (0)	0 (0)	3 (0.1)	2 (<0.1)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Total				
Any long bone or vertebral fracture	2 (<0.1)	3 (0.1)	8 (0.4)	7 (0.3)

[back to main text]

Supplementary Table 43: Details of psychiatric complication events in the RECOVERY tocilizumab comparison.

	Psychiatric complications within 28 days		Psychiatric complications within 6 months	
	Tocilizumab (n=2022)	**Usual Care (n=2094)**	**Tocilizumab (n=2022)**	**Usual Care (n=2094)**
Psychiatric complication type				
Psychosis	3 (0.1)	0 (0)	6 (0.3)	0 (0)
Mania	1 (<0.1)	0 (0)	2 (<0.1)	2 (<0.1)
Delirium	27 (1.3)	51 (2.4)	43 (2.1)	65 (3.1)
Other psychiatric complication	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified psychiatric complication	2 (<0.1)	1 (<0.1)	7 (0.3)	8 (0.4)
Event details				
Median event study day (IQR)	10 (3, 16)	9 (5, 20)	17 (7, 54)	12 (5, 27)
Occurred during index hospitalisation	26 (1.3)	48 (2.3)	37 (1.8)	52 (2.5)
Data source				
Hospitalisation diagnosis code	27 (1.3)	51 (2.4)	45 (2.2)	65 (3.1)
Primary care medication dispensing dataset	3 (0.1)	1 (<0.1)	11 (0.5)	9 (0.4)
Primary care GP dataset	4 (0.2)	0 (0)	7 (0.3)	1 (<0.1)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Total				
Any psychiatric complication	33 (1.6)	52 (2.5)	58 (2.9)	74 (3.5)

[back to main text]

Supplementary Table 44: Details of clinically-defined liver injury events in the RECOVERY tocilizumab comparison.

	Clinically defined liver injury within 28 days		Clinically defined liver injury within 6 months	
	Tocilizumab (n=2022)	**Usual Care (n=2094)**	**Tocilizumab (n=2022)**	**Usual Care (n=2094)**
Event details				
Occurred during index hospitalisation	24 (1.2)	27 (1.3)	27 (1.3)	29 (1.4)
Data source				
Hospitalisation diagnosis code	24 (1.2)	27 (1.3)	32 (1.6)	34 (1.6)
Primary care GP dataset	4 (0.2)	3 (0.1)	6 (0.3)	4 (0.2)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Total				
Any clinically defined liver injury	27 (1.3)	30 (1.4)	36 (1.8)	38 (1.8)

[back to main text]

Supplementary Table 45: Results of sensitivity analyses of other secondary outcomes in the RECOVERY tocilizumab comparison.

	Tocilizumab (n=2022)	Usual Care (n=2094)	Rate or Risk Ratio (95% CI)	p-value
Gastrointestinal complications				
Gastrointestinal complication within 28 days, 1st diagnostic position only	6 (0.3%)	4 (0.2%)	1.47 (0.41 - 5.22)	0.55
Gastrointestinal complication within 6 months, 1st diagnostic position only	8 (0.4%)	11 (0.5%)	0.72 (0.29 - 1.79)	0.48
Gastrointestinal complication within 28 days, including peri-randomisation episode diagnoses	55 (2.7%)	53 (2.5%)	1.10 (0.75 - 1.59)	0.63
Gastrointestinal complication within 6 months, including peri-randomisation episode diagnoses	60 (3.0%)	64 (3.1%)	0.99 (0.70 - 1.40)	0.94
Venous thromboembolism				
Venous thromboembolism within 28 days, 1st diagnostic position only	22 (1.1%)	28 (1.3%)	0.79 (0.45 - 1.39)	0.42
Venous thromboembolism within 6 months, 1st diagnostic position only	36 (1.8%)	42 (2.0%)	0.85 (0.55 - 1.33)	0.48
Venous thromboembolism within 28 days, including peri-randomisation episode diagnoses	193 (9.5%)	197 (9.4%)	1.02 (0.85 - 1.23)	0.83
Venous thromboembolism within 6 months, including peri-randomisation episode diagnoses	213 (11%)	221 (11%)	1.00 (0.84 - 1.19)	1.00

[back to main text]

Supplementary Table 46: Effect of allocation to tocilizumab on primary hospital recorded diagnoses within 6 months of randomisation.*

	Tocilizumab (n=2022)[1]	Usual Care (n=2094)[1]	Rate Ratio (95% CI)
Event timing			
Number of hospital admission days			
Median (Lower quartile, Upper quartile)	9 (5, 17)	9 (5, 18)	
Mean (Standard Deviation)	16 (23)	17 (25)	
Study day of diagnosis start			
Median (Lower quartile, Upper quartile)	29 (11, 71)	30 (10, 77)	
Diagnosis start during index hospital admission	199 (9.8)	202 (9.6)	
Admission type			
Emergency admission (including transfers)	413 (20)	398 (19)	
Elective admission	132 (6.5)	143 (6.8)	
COVID-19			
Readmission due to COVID-19	50 (2.5)	37 (1.8)	1.31 (0.86 - 2.00)
Non-COVID infection			
Pneumonia/Lower Respiratory Tract	60 (3.0)	51 (2.4)	
Urinary tract	10 (0.5)	9 (0.4)	
Intra-abdominal	9 (0.4)	8 (0.4)	
Skin and soft tissue	11 (0.5)	6 (0.3)	
Bone and joint	5 (0.2)	2 (<0.1)	
Upper Respiratory Tract	0 (0)	1 (<0.1)	
Other site	3 (0.1)	5 (0.2)	
Unspecified site	14 (0.7)	22 (1.1)	
Bacterial	24 (1.2)	28 (1.3)	
Fungal	1 (<0.1)	1 (<0.1)	
Other viral	0 (0)	0 (0)	
TB	0 (0)	0 (0)	
Other organism	0 (0)	1 (<0.1)	
Unspecified organism	85 (4.2)	69 (3.3)	
Subtotal: Any non-COVID infection	105 (5.2)	88 (4.2)	1.18 (0.89 - 1.56)
Cardiac			
Myocardial infarction	4 (0.2)	6 (0.3)	
Other coronary heart disease	8 (0.4)	6 (0.3)	
Heart failure	9 (0.4)	11 (0.5)	
Other	8 (0.4)	19 (0.9)	

Subtotal: Any cardiac	28 (1.4)	40 (1.9)	0.70 (0.43 - 1.13)
Stroke			
Haemorrhagic stroke	0 (0)	2 (<0.1)	
Non-haemorrhagic stroke	3 (0.1)	6 (0.3)	
Subtotal: Any stroke	3 (0.1)	8 (0.4)	0.37 (0.10 - 1.41)
Other vascular			
Arterial thromboembolism	5 (0.2)	2 (<0.1)	
Venous thromboembolism	17 (0.8)	20 (1.0)	
Other	15 (0.7)	18 (0.9)	
Subtotal: Any other vascular	35 (1.7)	37 (1.8)	0.92 (0.58 - 1.47)
Medical			
Cancer	12 (0.6)	25 (1.2)	
Diabetes	8 (0.4)	3 (0.1)	
Gastrointestinal bleed or perforation	9 (0.4)	8 (0.4)	
Other extra-cranial bleed or perforation	12 (0.6)	13 (0.6)	
Liver	2 (<0.1)	0 (0)	
Renal	14 (0.7)	14 (0.7)	
Respiratory (non-infection)	42 (2.1)	37 (1.8)	
Other	141 (7.0)	113 (5.4)	
Subtotal: Any medical	199 (9.8)	170 (8.1)	1.16 (0.95 - 1.42)
External			
External with bleed	1 (<0.1)	0 (0)	
External without bleed	24 (1.2)	11 (0.5)	
Subtotal: Any external	25 (1.2)	11 (0.5)	
Unknown			
No formal diagnosis recorded	90 (4.5)	92 (4.4)	
Total			
Total: Any hospital recorded diagnosis	486 (24)	482 (23)	0.99 (0.87 - 1.12)

[*] *Hospital-recorded diagnoses reflected the categorisation of any ICD-10 codes in the primary diagnostic position recorded in a hospital admission dataset from episodes of care with a start date within 6 months after randomisation.*
[1] *n (%)*

[back to main text]

Supplementary Table 47: Effect of allocation to baricitinib on diagnoses leading to death within 6 months of randomisation.

	Baricitinib (n=4148)[1]	Usual Care (n=4008)[1]	Rate Ratio (95% CI)
Event timing			
Study day of death[2]	13 (7, 25)	13 (6, 23)	
Death during index hospital admission	536 (13)	569 (14)	
COVID-19			
COVID-19	546 (13)	571 (14)	0.86 (0.77 - 0.97)
Non-COVID infection			
Pneumonia/Lower Respiratory Tract	37 (0.9)	28 (0.7)	
Urinary tract	2 (<0.1)	1 (<0.1)	
Intra-abdominal	2 (<0.1)	2 (<0.1)	
Skin and soft tissue	1 (<0.1)	1 (<0.1)	
Bone and joint	1 (<0.1)	0 (0)	
Upper Respiratory Tract	0 (0)	0 (0)	
Other site	2 (<0.1)	0 (0)	
Unspecified site	24 (0.6)	14 (0.3)	
Bacterial	26 (0.6)	20 (0.5)	
Fungal	1 (<0.1)	0 (0)	
Other viral	0 (0)	0 (0)	
TB	0 (0)	1 (<0.1)	
Other organism	0 (0)	0 (0)	
Unspecified organism	37 (0.9)	24 (0.6)	
Subtotal: Any non-COVID infection	58 (1.4)	42 (1.0)	1.24 (0.83 - 1.84)
Cardiac			
Myocardial infarction	9 (0.2)	9 (0.2)	
Other coronary heart disease	9 (0.2)	5 (0.1)	
Heart failure	15 (0.4)	11 (0.3)	
Other	4 (<0.1)	6 (0.1)	
Subtotal: Any cardiac	28 (0.7)	27 (0.7)	0.94 (0.55 - 1.59)
Stroke			
Haemorrhagic stroke	1 (<0.1)	1 (<0.1)	
Non-haemorrhagic stroke	0 (0)	0 (0)	
Subtotal: Any stroke	1 (<0.1)	1 (<0.1)	0.88 (0.06 - 14.09)
Other vascular			
Arterial thrombo-embolism	0 (0)	1 (<0.1)	

Venous thrombo-embolism	13 (0.3)	16 (0.4)	
Other	10 (0.2)	8 (0.2)	
Subtotal: Any other vascular	20 (0.5)	24 (0.6)	0.76 (0.42 - 1.37)
Medical			
Cancer	21 (0.5)	17 (0.4)	
Diabetes	3 (<0.1)	4 (<0.1)	
Gastrointestinal bleed or perforation	3 (<0.1)	3 (<0.1)	
Other extra-cranial bleed or perforation	4 (<0.1)	5 (0.1)	
Liver	2 (<0.1)	2 (<0.1)	
Renal	2 (<0.1)	5 (0.1)	
Respiratory (non-infection)	58 (1.4)	58 (1.4)	
Other	17 (0.4)	13 (0.3)	
Subtotal: Any medical	81 (2.0)	81 (2.0)	0.90 (0.66 - 1.22)
External			
External with bleed	0 (0)	2 (<0.1)	
External without bleed	7 (0.2)	13 (0.3)	
Subtotal: Any external	7 (0.2)	13 (0.3)	
Unknown			
No formal diagnosis recorded	72 (1.7)	75 (1.9)	
Total			
Total: All deaths	651 (16)	664 (17)	0.88 (0.79 - 0.98)
Diagnoses leading to death represented any diagnosis recorded on any row in part 1 of the death certificate *[1]n (%)* *[2]Median (Lower quartile, Upper quartile)*			

[back to main text]

Supplementary Table 48: Details of any non-COVID infection events in the RECOVERY baricitinib comparison.

	Any non-COVID infection within 28 days		Any non-COVID infection within 6 months	
	Baricitinib (n=4148)	**Usual Care (n=4008)**	**Baricitinib (n=4148)**	**Usual Care (n=4008)**
Organism				
Bacterial	467 (11)	469 (12)	973 (23)	950 (24)
Fungal	99 (2.4)	109 (2.7)	141 (3.4)	134 (3.3)
Viral (not SARS-CoV-2)	21 (0.5)	18 (0.4)	51 (1.2)	38 (0.9)
Tuberculosis	0 (0)	1 (<0.1)	0 (0)	1 (<0.1)
Other organism	18 (0.4)	13 (0.3)	19 (0.5)	15 (0.4)
Unspecified organism	361 (8.7)	314 (7.8)	375 (9.0)	313 (7.8)
Anatomical site				
Pneumonia/Lower respiratory tract	463 (11)	411 (10)	641 (15)	563 (14)
Bloodstream	117 (2.8)	121 (3.0)	134 (3.2)	144 (3.6)
Urinary tract	100 (2.4)	101 (2.5)	147 (3.5)	138 (3.4)
Intra-abdominal	14 (0.3)	14 (0.3)	33 (0.8)	36 (0.9)
Skin and soft tissue	41 (1.0)	39 (1.0)	66 (1.6)	73 (1.8)
Bone and joint	3 (<0.1)	4 (<0.1)	11 (0.3)	12 (0.3)
Upper respiratory tract	10 (0.2)	10 (0.2)	41 (1.0)	45 (1.1)
Other anatomical site	107 (2.6)	131 (3.3)	131 (3.2)	146 (3.6)
Unspecified anatomical site	231 (5.6)	249 (6.2)	548 (13)	530 (13)
Event details				
Median event study day (IQR)	9 (5, 16)	10 (4, 16)	15 (7, 36)	14 (7, 31)
Occurred during index hospitalisation	596 (14)	580 (14)	622 (15)	599 (15)
Data source				
Hospitalisation datasets	269 (6.5)	267 (6.7)	485 (12)	455 (11)
Microbiology dataset	186 (4.5)	190 (4.7)	222 (5.4)	222 (5.5)
Primary care medication dispensing dataset	246 (5.9)	248 (6.2)	732 (18)	712 (18)
Primary care GP dataset	40 (1.0)	30 (0.7)	118 (2.8)	103 (2.6)
Death datasets	30 (0.7)	21 (0.5)	58 (1.4)	42 (1.0)
Follow-up case report form	412 (9.9)	399 (10.0)	412 (9.9)	399 (10.0)
Total				
Any non-COVID infection	886 (21)	852 (21)	1,404 (34)	1,321 (33)

[back to main text]

Supplementary Table 49: Details of microbiologically confirmed non-COVID infection events in the RECOVERY baricitinib comparison.

	Microbiologically confirmed non-COVID infection within 28 days		Microbiologically confirmed non-COVID infection within 6 months	
	Baricitinib (n=4148)	Usual Care (n=4008)	Baricitinib (n=4148)	Usual Care (n=4008)
Organism				
Bacterial	132 (3.2)	148 (3.7)	165 (4.0)	180 (4.5)
Fungal	25 (0.6)	25 (0.6)	31 (0.7)	27 (0.7)
Viral (not SARS-CoV-2)	4 (<0.1)	5 (0.1)	6 (0.1)	6 (0.1)
Tuberculosis	0 (0)	0 (0)	0 (0)	0 (0)
Other organism	2 (<0.1)	3 (<0.1)	2 (<0.1)	3 (<0.1)
Unspecified organism	57 (1.4)	61 (1.5)	57 (1.4)	61 (1.5)
Anatomical site				
Pneumonia/Lower respiratory tract	112 (2.7)	113 (2.8)	128 (3.1)	127 (3.2)
Bloodstream	117 (2.8)	121 (3.0)	134 (3.2)	144 (3.6)
Urinary tract	6 (0.1)	8 (0.2)	6 (0.1)	8 (0.2)
Intra-abdominal	0 (0)	5 (0.1)	3 (<0.1)	8 (0.2)
Skin and soft tissue	4 (<0.1)	5 (0.1)	4 (<0.1)	5 (0.1)
Bone and joint	0 (0)	0 (0)	0 (0)	0 (0)
Upper respiratory tract	3 (<0.1)	2 (<0.1)	5 (0.1)	3 (<0.1)
Other anatomical site	13 (0.3)	14 (0.3)	13 (0.3)	14 (0.3)
Unspecified anatomical site	4 (<0.1)	1 (<0.1)	5 (0.1)	1 (<0.1)
Event details				
Median event study day (IQR)	9 (5, 15)	10 (6, 16)	11 (6, 21)	12 (7, 21)
Occurred during index hospitalisation	176 (4.2)	182 (4.5)	192 (4.6)	200 (5.0)
Data source				
Hospitalisation datasets	0 (0)	0 (0)	0 (0)	0 (0)
Microbiology dataset	143 (3.4)	153 (3.8)	180 (4.3)	186 (4.6)
Primary care medication dispensing dataset	0 (0)	0 (0)	0 (0)	0 (0)
Primary care GP dataset	0 (0)	0 (0)	0 (0)	0 (0)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Follow-up case report form	70 (1.7)	80 (2.0)	70 (1.7)	80 (2.0)
Total				
Any microbiologically confirmed infection	186 (4.5)	190 (4.7)	222 (5.4)	222 (5.5)

[back to main text]

Supplementary Table 50: Details of bloodstream infection events in the RECOVERY baricitinib comparison.

	Bloodstream infection within 28 days		Bloodstream infection within 6 months	
	Baricitinib (n=4148)	Usual Care (n=4008)	Baricitinib (n=4148)	Usual Care (n=4008)
Organism				
Bacterial	67 (1.6)	77 (1.9)	85 (2.0)	100 (2.5)
Fungal	12 (0.3)	18 (0.4)	14 (0.3)	19 (0.5)
Viral (not SARS-CoV-2)	2 (<0.1)	3 (<0.1)	2 (<0.1)	3 (<0.1)
Tuberculosis	0 (0)	0 (0)	0 (0)	0 (0)
Other organism	2 (<0.1)	3 (<0.1)	2 (<0.1)	3 (<0.1)
Unspecified organism	57 (1.4)	61 (1.5)	57 (1.4)	61 (1.5)
Anatomical site				
Pneumonia/Lower respiratory tract	30 (0.7)	30 (0.7)	30 (0.7)	30 (0.7)
Bloodstream	117 (2.8)	121 (3.0)	134 (3.2)	144 (3.6)
Urinary tract	6 (0.1)	8 (0.2)	6 (0.1)	8 (0.2)
Intra-abdominal	0 (0)	1 (<0.1)	0 (0)	1 (<0.1)
Skin and soft tissue	4 (<0.1)	5 (0.1)	4 (<0.1)	5 (0.1)
Bone and joint	0 (0)	0 (0)	0 (0)	0 (0)
Upper respiratory tract	0 (0)	0 (0)	0 (0)	0 (0)
Other anatomical site	13 (0.3)	14 (0.3)	13 (0.3)	14 (0.3)
Unspecified anatomical site	0 (0)	0 (0)	0 (0)	0 (0)
Event details				
Median event study day (IQR)	12 (7, 18)	12 (8, 18)	15 (9, 24)	16 (9, 27)
Occurred during index hospitalisation	109 (2.6)	118 (2.9)	118 (2.8)	132 (3.3)
Data source				
Hospitalisation datasets	0 (0)	0 (0)	0 (0)	0 (0)
Microbiology dataset	69 (1.7)	79 (2.0)	88 (2.1)	103 (2.6)
Primary care medication dispensing dataset	0 (0)	0 (0)	0 (0)	0 (0)
Primary care GP dataset	0 (0)	0 (0)	0 (0)	0 (0)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Follow-up case report form	70 (1.7)	80 (2.0)	70 (1.7)	80 (2.0)
Total				
Any bloodstream infection	117 (2.8)	121 (3.0)	134 (3.2)	144 (3.6)

[back to main text]

Supplementary Table 51: Organism classification of bloodstream infection events in the RECOVERY baricitinib comparison.

	Bloodstream infection within 28 days		Bloodstream infection within 6 months	
	Baricitinib (n=69)*	**Usual Care (n=79)***	**Baricitinib (n=69)***	**Usual Care (n=79)***
Bacterial				
Gram Positive	29 (42%)	31 (39%)	37 (42%)	40 (39%)
Enterococcus species	13 (19%)	10 (13%)	19 (22%)	15 (15%)
Staphylococcus aureus	14 (20%)	17 (22%)	16 (18%)	19 (18%)
Other Gram Positive	4 (5.8%)	6 (7.6%)	6 (6.8%)	8 (7.8%)
Gram Negative	40 (58%)	48 (61%)	53 (60%)	61 (59%)
E.coli	13 (19%)	14 (18%)	19 (22%)	18 (17%)
Enterobacter species	8 (12%)	6 (7.6%)	10 (11%)	6 (5.8%)
Klebsiella species	14 (20%)	15 (19%)	17 (19%)	22 (21%)
Pseudomonas aeruginosa	6 (8.7%)	4 (5.1%)	6 (6.8%)	7 (6.8%)
Other Gram Negative	9 (13%)	17 (22%)	12 (14%)	19 (18%)
Any bacterial	67 (97%)	77 (97%)	85 (97%)	100 (97%)
Fungal				
Candida species	3 (4.3%)	5 (6.3%)	5 (5.7%)	6 (5.8%)
Any fungal	3 (4.3%)	5 (6.3%)	5 (5.7%)	6 (5.8%)
Total				
Any bloodstream infection	69 (100%)	79 (100%)	88 (100%)	103 (100%)

**Includes only participants from the microbiology dataset which contained organism information. Does not contain participants from the follow-up case report form data which did not contain organism information.*

[back to main text]

Supplementary Table 52: Details of bacterial infection events in the RECOVERY baricitinib comparison.

	Bacterial infection within 28 days		Bacterial infection within 6 months	
	Baricitinib (n=4148)	Usual Care (n=4008)	Baricitinib (n=4148)	Usual Care (n=4008)
Organism				
Bacterial	467 (11)	469 (12)	973 (23)	950 (24)
Fungal	0 (0)	0 (0)	0 (0)	0 (0)
Viral (not SARS-CoV-2)	0 (0)	0 (0)	0 (0)	0 (0)
Tuberculosis	0 (0)	0 (0)	0 (0)	0 (0)
Other organism	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified organism	0 (0)	0 (0)	0 (0)	0 (0)
Anatomical site				
Pneumonia/Lower respiratory tract	120 (2.9)	118 (2.9)	147 (3.5)	140 (3.5)
Bloodstream	67 (1.6)	77 (1.9)	85 (2.0)	100 (2.5)
Urinary tract	0 (0)	0 (0)	0 (0)	0 (0)
Intra-abdominal	1 (<0.1)	5 (0.1)	7 (0.2)	9 (0.2)
Skin and soft tissue	11 (0.3)	5 (0.1)	33 (0.8)	34 (0.8)
Bone and joint	1 (<0.1)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Upper respiratory tract	0 (0)	0 (0)	0 (0)	0 (0)
Other anatomical site	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Unspecified anatomical site	291 (7.0)	291 (7.3)	737 (18)	709 (18)
Event details				
Median event study day (IQR)	9 (5, 15)	8 (4, 14)	12 (6, 25)	12 (5, 26)
Occurred during index hospitalisation	208 (5.0)	227 (5.7)	237 (5.7)	253 (6.3)
Data source				
Hospitalisation datasets	124 (3.0)	136 (3.4)	217 (5.2)	221 (5.5)
Microbiology dataset	132 (3.2)	148 (3.7)	165 (4.0)	180 (4.5)
Primary care medication dispensing dataset	234 (5.6)	236 (5.9)	712 (17)	690 (17)
Primary care GP dataset	0 (0)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Death datasets	17 (0.4)	12 (0.3)	26 (0.6)	20 (0.5)
Follow-up case report form	0 (0)	0 (0)	0 (0)	0 (0)
Total				
Any bacterial infection	467 (11)	469 (12)	973 (23)	950 (24)

[back to main text]

Supplementary Table 53: Details of fungal infection events in the RECOVERY baricitinib comparison.

	Fungal infection within 28 days		Fungal infection within 6 months	
	Baricitinib (n=4148)	Usual Care (n=4008)	Baricitinib (n=4148)	Usual Care (n=4008)
Organism				
Bacterial	0 (0)	0 (0)	0 (0)	0 (0)
Fungal	99 (2.4)	109 (2.7)	141 (3.4)	134 (3.3)
Viral (not SARS-CoV-2)	0 (0)	0 (0)	0 (0)	0 (0)
Tuberculosis	0 (0)	0 (0)	0 (0)	0 (0)
Other organism	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified organism	0 (0)	0 (0)	0 (0)	0 (0)
Anatomical site				
Pneumonia/Lower respiratory tract	41 (1.0)	33 (0.8)	46 (1.1)	36 (0.9)
Bloodstream	12 (0.3)	18 (0.4)	14 (0.3)	19 (0.5)
Urinary tract	8 (0.2)	9 (0.2)	8 (0.2)	9 (0.2)
Intra-abdominal	0 (0)	0 (0)	0 (0)	0 (0)
Skin and soft tissue	12 (0.3)	10 (0.2)	13 (0.3)	10 (0.2)
Bone and joint	0 (0)	0 (0)	0 (0)	0 (0)
Upper respiratory tract	0 (0)	0 (0)	0 (0)	0 (0)
Other anatomical site	37 (0.9)	63 (1.6)	50 (1.2)	68 (1.7)
Unspecified anatomical site	22 (0.5)	23 (0.6)	45 (1.1)	42 (1.0)
Event details				
Median event study day (IQR)	9 (6, 13)	11 (4, 17)	15 (8, 40)	14 (5, 21)
Occurred during index hospitalisation	82 (2.0)	92 (2.3)	94 (2.3)	94 (2.3)
Data source				
Hospitalisation datasets	34 (0.8)	48 (1.2)	56 (1.4)	56 (1.4)
Microbiology dataset	17 (0.4)	13 (0.3)	23 (0.6)	15 (0.4)
Primary care medication dispensing dataset	10 (0.2)	11 (0.3)	29 (0.7)	32 (0.8)
Primary care GP dataset	0 (0)	0 (0)	0 (0)	0 (0)
Death datasets	1 (<0.1)	0 (0)	1 (<0.1)	0 (0)
Follow-up case report form	52 (1.3)	49 (1.2)	52 (1.3)	49 (1.2)
Total				
Any fungal infection	99 (2.4)	109 (2.7)	141 (3.4)	134 (3.3)

[back to main text]

Supplementary Table 54: Results of sensitivity analyses of non-COVID infection outcomes in the RECOVERY baricitinib comparison.

	Baricitinib (n=4148)	Usual Care (n=4008)	Rate or Risk Ratio (95% CI)	p-value
Primary outcome				
Major non-COVID infection within 28 days, 1st diagnostic position only	538 (13%)	502 (13%)	1.00 (0.87 - 1.15)	0.98
Major non-COVID infection within 6 months, 1st diagnostic position only	684 (16%)	630 (16%)	1.02 (0.90 - 1.16)	0.72
Major non-COVID infection within 28 days, including peri-randomisation episode diagnoses	1,235 (30%)	1,188 (30%)	0.98 (0.89 - 1.08)	0.65
Major non-COVID infection within 6 months, including peri-randomisation episode diagnoses	1,356 (33%)	1,286 (32%)	1.00 (0.91 - 1.10)	>0.99
Major non-COVID infection within 28 days, excluding respiratory tract infections	338 (8.1%)	351 (8.8%)	0.89 (0.76 - 1.04)	0.16
Major non-COVID infection within 6 months, excluding respiratory tract infections	469 (11%)	455 (11%)	0.96 (0.84 - 1.11)	0.60
Secondary outcome				
Any non-COVID infection within 28 days, 1st diagnostic position only	769 (19%)	733 (18%)	0.99 (0.88 - 1.11)	0.87
Any non-COVID infection within 6 months, 1st diagnostic position only	1,288 (31%)	1,217 (30%)	1.01 (0.92 - 1.12)	0.76
Any non-COVID infection within 28 days, including peri-randomisation episode diagnoses	1,731 (42%)	1,694 (42%)	0.96 (0.87 - 1.05)	0.34
Any non-COVID infection within 6 months, including peri-randomisation episode diagnoses	2,074 (50%)	1,983 (49%)	1.00 (0.92 - 1.10)	0.93
Any non-COVID infection within 28 days, excluding respiratory tract infections	566 (14%)	575 (14%)	0.94 (0.84 - 1.05)	0.25
Any non-COVID infection within 6 months, excluding respiratory tract infections	1,083 (26%)	1,038 (26%)	1.00 (0.93 - 1.08)	0.93

[back to main text]

Supplementary Table 55: Details of gastrointestinal complication events in the RECOVERY baricitinib comparison.

	Gastrointestinal complications at 28 days		Gastrointestinal complications at 6 months	
	Baricitinib (n=4148)	**Usual Care (n=4008)**	**Baricitinib (n=4148)**	**Usual Care (n=4008)**
GI complication type				
Gastrointestinal bleed	36 (0.9)	24 (0.6)	61 (1.5)	31 (0.8)
Gastrointestinal perforation	5 (0.1)	0 (0)	5 (0.1)	1 (<0.1)
Gastrointestinal ulcer	3 (<0.1)	4 (<0.1)	10 (0.2)	10 (0.2)
Event details				
Median event study day (IQR)	10.0 (6.5, 17.0)	10.0 (4.0, 15.0)	25 (10, 74)	17 (7, 44)
Occurred during index hospitalisation	39 (0.9)	23 (0.6)	43 (1.0)	25 (0.6)
Data source				
Hospitalisation diagnosis code	30 (0.7)	22 (0.5)	59 (1.4)	35 (0.9)
Hospitalisation operation code	0 (0)	1 (<0.1)	0 (0)	1 (<0.1)
Death datasets	2 (<0.1)	0 (0)	2 (<0.1)	1 (<0.1)
Follow-up case report form	19 (0.5)	8 (0.2)	19 (0.5)	8 (0.2)
Total				
Any gastrointestinal complication	43 (1.0)	27 (0.7)	71 (1.7)	40 (1.0)

[back to main text]

Supplementary Table 56: Details of venous thromboembolism events in the RECOVERY baricitinib comparison.

	Venous thromboembolism at 28 days		Venous thromboembolism at 6 months	
	Baricitinib (n=4148)	**Usual Care (n=4008)**	**Baricitinib (n=4148)**	**Usual Care (n=4008)**
Venous thromboembolism type				
Pulmonary Embolism	202 (4.9)	209 (5.2)	221 (5.3)	237 (5.9)
Deep Vein Thrombosis	18 (0.4)	22 (0.5)	26 (0.6)	34 (0.8)
Other venous thromboembolism	4 (<0.1)	3 (<0.1)	4 (<0.1)	7 (0.2)
Unspecified venous thromboembolism	2 (<0.1)	3 (<0.1)	5 (0.1)	5 (0.1)
Event details				
Median event study day (IQR)	14 (7, 19)	10 (6, 16)	19 (10, 36)	17 (8, 37)
Occurred during index hospitalisation	191 (4.6)	197 (4.9)	198 (4.8)	203 (5.1)
Data source				
Hospitalisation diagnosis code	59 (1.4)	78 (1.9)	88 (2.1)	119 (3.0)
Death datasets	10 (0.2)	11 (0.3)	13 (0.3)	16 (0.4)
Follow-up case report form	173 (4.2)	178 (4.4)	173 (4.2)	178 (4.4)
Total				
Any venous thromboembolism	220 (5.3)	227 (5.7)	247 (6.0)	266 (6.6)

[back to main text]

Supplementary Table 57: Details of long COVID events in the RECOVERY baricitinib comparison.

	Baricitinib (n=4148)	Usual Care (n=4008)
Event details		
Median event study day (IQR)	108 (52, 209)	110 (50, 197)
Data source		
Primary care GP dataset	373 (9.0)	325 (8.1)
Total		
Long COVID	373 (9.0)	325 (8.1)

[back to main text]

Supplementary Table 58: Details of metabolic complication events in the RECOVERY baricitinib comparison.

	Metabolic complications at 28 days		Metabolic complications at 6 months	
	Baricitinib (n=4148)	Usual Care (n=4008)	Baricitinib (n=4148)	Usual Care (n=4008)
Event type				
Ketoacidosis	5 (0.1%)	7 (0.2%)	8 (0.2%)	8 (0.2%)
Hyperglycaemia	20 (0.5%)	20 (0.5%)	26 (0.6%)	23 (0.6%)
Hypoglycaemia	26 (0.6%)	18 (0.4%)	45 (1.1%)	31 (0.8%)
Other metabolic complication	2 (<0.1%)	1 (<0.1%)	5 (0.1%)	3 (<0.1%)
Unspecified metabolic complication	5 (0.1%)	7 (0.2%)	29 (0.7%)	28 (0.7%)
Event details				
Median event study day (IQR)	5 (3, 11)	8 (3, 10)	20 (5, 80)	21 (5, 75)
Occurred during index hospitalisation	45 (1.1%)	44 (1.1%)	53 (1.3%)	45 (1.1%)
Data source				
Hospitalisation diagnosis code	46 (1.1%)	42 (1.0%)	71 (1.7%)	59 (1.5%)
GP diagnosis code	12 (0.3%)	11 (0.3%)	41 (1.0%)	33 (0.8%)
Death datasets	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total				
Any metabolic complication	57 (1.4%)	52 (1.3%)	108 (2.6%)	88 (2.2%)

Supplementary Table 59: Details of incident diabetes events in the RECOVERY baricitinib comparison.

	Baricitinib (n=2879)	Usual Care (n=2766)
Event details		
Median event study day (IQR)	35 (8, 122)	50 (11, 194)
Occurred during index hospitalisation	18 (0.4)	14 (0.3)
Data source		
Hospitalisation diagnosis code	28 (0.7)	20 (0.5)
Dispensing data	14 (0.3)	9 (0.2)
GP diagnosis code	26 (0.6)	26 (0.6)
Death datasets	0 (0)	0 (0)
Total		
Incident diabetes	52/2,879 (1.8%)	45/2,766 (1.6%)

[back to main text]

Supplementary Table 60: Details of long bone or vertebral fracture events in the RECOVERY baricitinib comparison.

	Long bone or vertebral fracture at 28 days		Long bone or vertebral fracture at 6 months	
	Baricitinib (n=4148)	**Usual Care (n=4008)**	**Baricitinib (n=4148)**	**Usual Care (n=4008)**
Fracture type				
Hip fracture	1 (<0.1)	1 (<0.1)	5 (0.1)	5 (0.1)
Long bone fracture	1 (<0.1)	1 (<0.1)	9 (0.2)	10 (0.2)
Vertebral fracture	0 (0)	1 (<0.1)	2 (<0.1)	2 (<0.1)
Unspecified long bone or vertebral fracture	4 (<0.1)	3 (<0.1)	8 (0.2)	8 (0.2)
Event details				
Median event study day (IQR)	11 (8, 18)	14 (6, 22)	59 (29, 120)	55 (31, 92)
Occurred during index hospitalisation	5 (0.1)	4 (<0.1)	8 (0.2)	6 (0.1)
Data source				
Hospitalisation diagnosis code	4 (<0.1)	3 (<0.1)	16 (0.4)	17 (0.4)
Hospitalisation operation code	1 (<0.1)	0 (0)	7 (0.2)	4 (<0.1)
Primary care GP dataset	1 (<0.1)	1 (<0.1)	5 (0.1)	3 (<0.1)
Death datasets	0 (0)	2 (<0.1)	0 (0)	2 (<0.1)
Total				
Any long bone or vertebral fracture	6 (0.1)	6 (0.1)	22 (0.5)	23 (0.6)

[back to main text]

Supplementary Table 61: Details of psychiatric complication events in the RECOVERY baricitinib comparison.

	Psychiatric complications within 28 days		Psychiatric complications within 6 months	
	Baricitinib (n=4148)	**Usual Care (n=4008)**	**Baricitinib (n=4148)**	**Usual Care (n=4008)**
Psychiatric complication type				
Psychosis	7 (0.2)	1 (<0.1)	10 (0.2)	5 (0.1)
Mania	0 (0)	3 (<0.1)	2 (<0.1)	10 (0.2)
Delirium	46 (1.1)	40 (1.0)	73 (1.8)	69 (1.7)
Other psychiatric complication	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified psychiatric complication	3 (<0.1)	3 (<0.1)	8 (0.2)	9 (0.2)
Event details				
Median event study day (IQR)	10 (6, 15)	7 (4, 14)	19 (8, 56)	20 (7, 55)
Occurred during index hospitalisation	39 (0.9)	36 (0.9)	47 (1.1)	47 (1.2)
Data source				
Hospitalisation diagnosis code	49 (1.2)	43 (1.1)	75 (1.8)	74 (1.8)
Primary care medication dispensing dataset	5 (0.1)	4 (<0.1)	12 (0.3)	16 (0.4)
Primary care GP dataset	2 (<0.1)	1 (<0.1)	8 (0.2)	10 (0.2)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Total				
Any psychiatric complication	54 (1.3)	47 (1.2)	90 (2.2)	91 (2.3)

[back to main text]

Supplementary Table 62: Details of clinically-defined liver injury events in the RECOVERY baricitinib comparison.

	Clinically defined liver injury at 28 days		Clinically defined liver injury at 6 months	
	Baricitinib (n=4148)	**Usual Care (n=4008)**	**Baricitinib (n=4148)**	**Usual Care (n=4008)**
Event details				
Median event study day (IQR)	6 (3, 11)	6 (4, 12)	8 (4, 18)	10 (4, 25)
Occurred during index hospitalisation	44 (1.1)	59 (1.5)	47 (1.1)	62 (1.5)
Data source				
Hospitalisation diagnosis code	55 (1.3)	67 (1.7)	69 (1.7)	88 (2.2)
Primary care GP dataset	5 (0.1)	10 (0.2)	6 (0.1)	13 (0.3)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Total				
Any clinically defined liver injury	59 (1.4)	77 (1.9)	73 (1.8)	101 (2.5)

[back to main text]

Supplementary Table 63: Results of sensitivity analyses of other secondary outcomes in the RECOVERY baricitinib comparison.

	Baricitinib (n=4148)	Usual Care (n=4008)	Rate or Risk Ratio (95% CI)	p-value
Gastrointestinal complications				
Gastrointestinal complication within 28 days, 1st diagnostic position only	25 (0.6%)	9 (0.2%)	2.60 (1.26 - 5.88)	0.01
Gastrointestinal complication within 6 months, 1st diagnostic position only	34 (0.8%)	14 (0.3%)	2.27 (1.25 - 4.36)	0.01
Gastrointestinal complication within 28 days, including peri-randomisation episode diagnoses	68 (1.6%)	59 (1.5%)	1.08 (0.76 - 1.53)	0.67
Gastrointestinal complication within 6 months, including peri-randomisation episode diagnoses	95 (2.3%)	70 (1.7%)	1.27 (0.94 - 1.73)	0.13
Venous thromboembolism				
Venous thromboembolism within 28 days, 1st diagnostic position only	200 (4.8%)	197 (4.9%)	0.97 (0.80 - 1.17)	0.75
Venous thromboembolism within 6 months, 1st diagnostic position only	212 (5.1%)	223 (5.6%)	0.91 (0.76 - 1.09)	0.30
Venous thromboembolism within 28 days, including peri-randomisation episode diagnoses	286 (6.9%)	288 (7.2%)	0.95 (0.81 - 1.11)	0.49
Venous thromboembolism within 6 months, including peri-randomisation episode diagnoses	312 (7.5%)	324 (8.1%)	0.92 (0.79 - 1.07)	0.26

[back to main text]

Supplementary Table 64: Effect of allocation to baricitinib on primary hospital recorded diagnoses within 6 months of randomisation.*

	Baricitinib (n=4148)[1]	Usual Care (n=4008)[1]	Rate Ratio (95% CI)
Event timing			
Number of hospital admission days			
Median (Lower quartile, Upper quartile)	7 (4, 12)	7 (4, 13)	
Mean (Standard Deviation)	12 (21)	13 (20)	
Study day of diagnosis start			
Median (Lower quartile, Upper quartile)	29 (13, 78)	33 (13, 80)	
Diagnosis start during index hospital admission	256 (6.2)	264 (6.6)	
Admission type			
Emergency admission (including transfers)	822 (20)	763 (19)	
Elective admission	309 (7.4)	325 (8.1)	
COVID-19			
Readmission due to COVID-19	134 (3.2)	118 (2.9)	1.07 (0.84 - 1.38)
Non-COVID infection			
Pneumonia/Lower Respiratory Tract	158 (3.8)	113 (2.8)	
Urinary tract	18 (0.4)	13 (0.3)	
Intra-abdominal	10 (0.2)	15 (0.4)	
Skin and soft tissue	13 (0.3)	15 (0.4)	
Bone and joint	7 (0.2)	5 (0.1)	
Upper Respiratory Tract	1 (<0.1)	1 (<0.1)	
Other site	6 (0.1)	5 (0.1)	
Unspecified site	36 (0.9)	34 (0.8)	
Bacterial	50 (1.2)	43 (1.1)	
Fungal	3 (<0.1)	1 (<0.1)	
Other viral	4 (<0.1)	0 (0)	
TB	0 (0)	0 (0)	
Other organism	1 (<0.1)	2 (<0.1)	
Unspecified organism	187 (4.5)	148 (3.7)	
Subtotal: Any non-COVID infection	231 (5.6)	184 (4.6)	1.17 (0.96 - 1.42)
Cardiac			
Myocardial infarction	10 (0.2)	12 (0.3)	
Other coronary heart disease	12 (0.3)	20 (0.5)	
Heart failure	28 (0.7)	25 (0.6)	
Other	21 (0.5)	27 (0.7)	

Subtotal: Any cardiac	64 (1.5)	72 (1.8)	0.82 (0.58 - 1.14)
Stroke			
Haemorrhagic stroke	2 (<0.1)	4 (<0.1)	
Non-haemorrhagic stroke	9 (0.2)	7 (0.2)	
Subtotal: Any stroke	11 (0.3)	10 (0.2)	1.02 (0.43 - 2.40)
Other vascular			
Arterial thrombo-embolism	3 (<0.1)	4 (<0.1)	
Venous thrombo-embolism	37 (0.9)	37 (0.9)	
Other	22 (0.5)	36 (0.9)	
Subtotal: Any other vascular	62 (1.5)	73 (1.8)	0.80 (0.57 - 1.12)
Medical			
Cancer	48 (1.2)	54 (1.3)	
Diabetes	9 (0.2)	15 (0.4)	
Gastrointestinal bleed or perforation	18 (0.4)	5 (0.1)	
Other extra-cranial bleed or perforation	28 (0.7)	14 (0.3)	
Liver	4 (<0.1)	2 (<0.1)	
Renal	24 (0.6)	17 (0.4)	
Respiratory (non-infection)	80 (1.9)	75 (1.9)	
Other	299 (7.2)	284 (7.1)	
Subtotal: Any medical	412 (9.9)	384 (9.6)	1.02 (0.89 - 1.17)
External			
External with bleed	2 (<0.1)	3 (<0.1)	
External without bleed	37 (0.9)	45 (1.1)	
Subtotal: Any external	39 (0.9)	47 (1.2)	
Unknown			
No formal diagnosis recorded	198 (4.8)	174 (4.3)	
Total			
Total: Any hospital recorded diagnosis	1,009 (24)	969 (24)	0.98 (0.90 - 1.07)

[*] *Hospital-recorded diagnoses reflected the categorisation of any ICD-10 codes in the primary diagnostic position recorded in a hospital admission dataset from episodes of care with a start date within 6 months after randomisation.*
[1] *n (%)*

[back to main text]

Supplementary Table 65: Effect of allocation to higher dose dexamethasone on diagnoses leading to death within 6 months of randomisation in the subgroup of participants who were hypoxic but not requiring ventilatory support at randomisation.

	Higher dose Dexamethasone (n=659)[1]	Usual Care (n=613)[1]	Rate Ratio (95% CI)
Event timing			
Study day of death[2]	13 (8, 22)	24 (10, 54)	
COVID-19			
COVID-19	95 (14)	68 (11)	1.31 (0.98 - 1.75)
Non-COVID infection			
Pneumonia/Lower Respiratory Tract	9 (1.4)	15 (2.4)	
Urinary tract	2 (0.3)	1 (0.2)	
Intra-abdominal	0 (0)	0 (0)	
Skin and soft tissue	0 (0)	0 (0)	
Bone and joint	0 (0)	0 (0)	
Upper Respiratory Tract	0 (0)	0 (0)	
Other site	0 (0)	0 (0)	
Unspecified site	5 (0.8)	4 (0.7)	
Bacterial	5 (0.8)	4 (0.7)	
Fungal	0 (0)	0 (0)	
Other viral	0 (0)	0 (0)	
TB	0 (0)	0 (0)	
Other organism	0 (0)	0 (0)	
Unspecified organism	11 (1.7)	15 (2.4)	
Subtotal: Any non-COVID infection	19 (2.9)	17 (2.8)	1.03 (0.54 - 1.96)
Cardiac			
Myocardial infarction	1 (0.2)	1 (0.2)	
Other coronary heart disease	1 (0.2)	1 (0.2)	
Heart failure	3 (0.5)	2 (0.3)	
Other	4 (0.6)	0 (0)	
Subtotal: Any cardiac	9 (1.4)	2 (0.3)	4.14 (1.08 - 27.03)
Stroke			
Haemorrhagic stroke	0 (0)	0 (0)	
Non-haemorrhagic stroke	2 (0.3)	1 (0.2)	
Subtotal: Any stroke	3 (0.5)	1 (0.2)	2.87 (0.36 - 58.27)
Other vascular			

Arterial thrombo-embolism	0 (0)	0 (0)	
Venous thrombo-embolism	3 (0.5)	4 (0.7)	
Other	2 (0.3)	2 (0.3)	
Subtotal: Any other vascular	8 (1.2)	6 (1.0)	1.25 (0.44 - 3.76)
Medical			
Cancer	7 (1.1)	10 (1.6)	
Diabetes	0 (0)	0 (0)	
Gastrointestinal bleed or perforation	1 (0.2)	0 (0)	
Other extra-cranial bleed or perforation	1 (0.2)	1 (0.2)	
Liver	0 (0)	0 (0)	
Renal	0 (0)	3 (0.5)	
Respiratory (non-infection)	21 (3.2)	11 (1.8)	
Other	5 (0.8)	6 (1.0)	
Subtotal: Any medical	40 (6.1)	28 (4.6)	1.32 (0.83 - 2.11)
External			
External with bleed	0 (0)	0 (0)	
External without bleed	2 (0.3)	1 (0.2)	
Subtotal: Any external	2 (0.3)	1 (0.2)	
Unknown			
No formal diagnosis recorded	6 (0.9)	5 (0.8)	
Total			
Total: All deaths	146 (22)	108 (18)	1.35 (1.05 - 1.73)

Diagnoses leading to death represented any diagnosis recorded on any row in part 1 of the death certificate
[1]n (%)
[2]Median (Lower quartile, Upper quartile)

[back to main text]

Supplementary Table 66: Details of any non-COVID infection events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

	Any non-COVID infection within 28 days		Any non-COVID infection within 6 months	
	High dose Dexamethasone (n=659)	Usual Care (n=613)	High dose Dexamethasone (n=659)	Usual Care (n=613)
Organism				
Bacterial	95 (14)	81 (13)	137 (21)	129 (21)
Fungal	11 (1.7)	9 (1.5)	15 (2.3)	19 (3.1)
Viral (not SARS-CoV-2)	3 (0.5)	1 (0.2)	11 (1.7)	4 (0.7)
Tuberculosis	0 (0)	0 (0)	0 (0)	2 (0.3)
Other organism	1 (0.2)	3 (0.5)	1 (0.2)	5 (0.8)
Unspecified organism	34 (5.2)	27 (4.4)	43 (6.5)	30 (4.9)
Anatomical site				
Pneumonia/Lower respiratory tract	91 (14)	56 (9.1)	112 (17)	87 (14)
Bloodstream	9 (1.4)	4 (0.7)	11 (1.7)	6 (1.0)
Urinary tract	14 (2.1)	16 (2.6)	19 (2.9)	26 (4.2)
Intra-abdominal	1 (0.2)	2 (0.3)	3 (0.5)	5 (0.8)
Skin and soft tissue	3 (0.5)	7 (1.1)	10 (1.5)	16 (2.6)
Bone and joint	0 (0)	2 (0.3)	1 (0.2)	2 (0.3)
Upper respiratory tract	0 (0)	1 (0.2)	3 (0.5)	5 (0.8)
Other anatomical site	11 (1.7)	14 (2.3)	13 (2.0)	20 (3.3)
Unspecified anatomical site	38 (5.8)	33 (5.4)	54 (8.2)	53 (8.6)
Event details				
Median event study day (IQR)	10 (7, 15)	9 (5, 16)	21 (9, 58)	18 (7, 38)
Occurred during index hospitalisation	100 (15)	74 (12)	103 (16)	78 (13)
Data source				
Hospitalisation datasets	30 (4.6)	39 (6.4)	64 (9.7)	74 (12)
Microbiology dataset	4 (0.6)	5 (0.8)	8 (1.2)	8 (1.3)
Primary care medication dispensing dataset	25 (3.8)	26 (4.2)	61 (9.3)	69 (11)
Primary care GP dataset	7 (1.1)	4 (0.7)	16 (2.4)	9 (1.5)
Death datasets	9 (1.4)	5 (0.8)	15 (2.3)	17 (2.8)
Follow-up case report form	81 (12)	58 (9.5)	83 (13)	58 (9.5)
Total				
Any non-COVID infection	138 (21)	109 (18)	183 (28)	158 (26)

[back to main text]

Supplementary Table 67: Details of microbiologically confirmed non-COVID infection events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

	Microbiologically confirmed non-COVID infection within 28 days		Microbiologically confirmed non-COVID infection within 6 months	
	High dose Dexamethasone (n=659)	Usual Care (n=613)	High dose Dexamethasone (n=659)	Usual Care (n=613)
Organism				
Bacterial	8 (1.2)	7 (1.1)	11 (1.7)	10 (1.6)
Fungal	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Viral (not SARS-CoV-2)	0 (0)	1 (0.2)	1 (0.2)	1 (0.2)
Tuberculosis	0 (0)	0 (0)	0 (0)	0 (0)
Other organism	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified organism	2 (0.3)	0 (0)	2 (0.3)	0 (0)
Anatomical site				
Pneumonia/Lower respiratory tract	1 (0.2)	3 (0.5)	2 (0.3)	4 (0.7)
Bloodstream	9 (1.4)	4 (0.7)	11 (1.7)	6 (1.0)
Urinary tract	0 (0)	0 (0)	0 (0)	0 (0)
Intra-abdominal	1 (0.2)	0 (0)	2 (0.3)	0 (0)
Skin and soft tissue	0 (0)	0 (0)	0 (0)	0 (0)
Bone and joint	0 (0)	0 (0)	0 (0)	0 (0)
Upper respiratory tract	0 (0)	1 (0.2)	1 (0.2)	1 (0.2)
Other anatomical site	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified anatomical site	0 (0)	0 (0)	0 (0)	0 (0)
Event details				
Median event study day (IQR)	-	-	35 (22, 48)	22 (10, 77)
Occurred during index hospitalisation	9 (1.4)	8 (1.3)	9 (1.4)	9 (1.5)
Data source				
Hospitalisation datasets	0 (0)	0 (0)	0 (0)	0 (0)
Microbiology dataset	4 (0.6)	5 (0.8)	8 (1.2)	8 (1.3)
Primary care medication dispensing dataset	0 (0)	0 (0)	0 (0)	0 (0)
Primary care GP dataset	0 (0)	0 (0)	0 (0)	0 (0)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Follow-up case report form	7 (1.1)	3 (0.5)	7 (1.1)	3 (0.5)
Total				
Any microbiologically confirmed non-COVID infection	10 (1.5)	8 (1.3)	14 (2.1)	11 (1.8)

[back to main text]

Supplementary Table 68: Details of bloodstream infection events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

	Bloodstream infection within 28 days		Bloodstream infection within 6 months	
	High dose Dexamethasone (n=659)	Usual Care (n=613)	High dose Dexamethasone (n=659)	Usual Care (n=613)
Organism				
Bacterial	7 (1.1)	4 (0.7)	9 (1.4)	6 (1.0)
Fungal	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Viral (not SARS-CoV-2)	0 (0)	0 (0)	0 (0)	0 (0)
Tuberculosis	0 (0)	0 (0)	0 (0)	0 (0)
Other organism	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified organism	2 (0.3)	0 (0)	2 (0.3)	0 (0)
Anatomical site				
Pneumonia/Lower respiratory tract	0 (0)	0 (0)	0 (0)	0 (0)
Bloodstream	9 (1.4)	4 (0.7)	11 (1.7)	6 (1.0)
Urinary tract	0 (0)	0 (0)	0 (0)	0 (0)
Intra-abdominal	0 (0)	0 (0)	0 (0)	0 (0)
Skin and soft tissue	0 (0)	0 (0)	0 (0)	0 (0)
Bone and joint	0 (0)	0 (0)	0 (0)	0 (0)
Upper respiratory tract	0 (0)	0 (0)	0 (0)	0 (0)
Other anatomical site	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified anatomical site	0 (0)	0 (0)	0 (0)	0 (0)
Event details				
Median event study day (IQR)	-	-	-	-
Occurred during index hospitalisation	8 (1.2)	4 (0.7)	9 (1.4)	4 (0.7)
Data source				
Hospitalisation datasets	0 (0)	0 (0)	0 (0)	0 (0)
Microbiology dataset	3 (0.5)	1 (0.2)	5 (0.8)	3 (0.5)
Primary care medication dispensing dataset	0 (0)	0 (0)	0 (0)	0 (0)
Primary care GP dataset	0 (0)	0 (0)	0 (0)	0 (0)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Follow-up case report form	7 (1.1)	3 (0.5)	7 (1.1)	3 (0.5)
Total				
Any bloodstream infection	9 (1.4)	4 (0.7)	11 (1.7)	6 (1.0)

[back to main text]

Supplementary Table 69: Organism classification of bloodstream infection events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

	Bloodstream infection within 28 days		Bloodstream infection within 6 months	
	High dose dexamethasone (n=3)*	**Usual Care (n=1)***	**High dose dexamethasone (n=5)***	**Usual Care (n=3)***
Bacterial				
Gram Positive	0 (0%)	0 (0%)	1 (20%)	0 (0%)
Enterococcus species	0 (0%)	0 (0%)	1 (20%)	0 (0%)
Gram Negative	2 (67%)	1 (100%)	4 (80%)	2 (67%)
E.coli	1 (33%)	1 (100%)	2 (40%)	1 (33%)
Enterobacter species	1 (33%)	0 (0%)	1 (20%)	0 (0%)
Pseudomonas aeruginosa	1 (33%)	0 (0%)	1 (20%)	1 (33%)
Other Gram Negative	0 (0%)	0 (0%)	1 (20%)	1 (33%)
Any bacterial	3 (100%)	1 (100%)	5 (100%)	3 (100%)
Fungal				
Any fungal	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total				
Any bloodstream infection	3 (100%)	1 (100%)	5 (100%)	3 (100%)

**Includes only participants from the microbiology dataset which contained organism information. Does not contain participants from the follow-up case report form data which did not contain organism information.*

[back to main text]

Supplementary Table 70: Details of bacterial infection events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

	Bacterial infection within 28 days		Bacterial infection within 6 months	
	High dose Dexamethasone (n=659)	Usual Care (n=613)	High dose Dexamethasone (n=659)	Usual Care (n=613)
Organism				
Bacterial	95 (14)	81 (13)	137 (21)	129 (21)
Fungal	0 (0)	0 (0)	0 (0)	0 (0)
Viral (not SARS-CoV-2)	0 (0)	0 (0)	0 (0)	0 (0)
Tuberculosis	0 (0)	0 (0)	0 (0)	0 (0)
Other organism	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified organism	0 (0)	0 (0)	0 (0)	0 (0)
Anatomical site				
Pneumonia/Lower respiratory tract	56 (8.5)	34 (5.5)	60 (9.1)	38 (6.2)
Bloodstream	7 (1.1)	4 (0.7)	9 (1.4)	6 (1.0)
Urinary tract	6 (0.9)	9 (1.5)	6 (0.9)	9 (1.5)
Intra-abdominal	1 (0.2)	1 (0.2)	2 (0.3)	2 (0.3)
Skin and soft tissue	3 (0.5)	5 (0.8)	7 (1.1)	11 (1.8)
Bone and joint	0 (0)	1 (0.2)	0 (0)	1 (0.2)
Upper respiratory tract	0 (0)	0 (0)	0 (0)	0 (0)
Other anatomical site	6 (0.9)	9 (1.5)	7 (1.1)	9 (1.5)
Unspecified anatomical site	30 (4.6)	33 (5.4)	64 (9.7)	72 (12)
Event details				
Median event study day (IQR)	13 (9, 18)	7 (5, 16)	30 (11, 64)	20 (7, 80)
Occurred during index hospitalisation	68 (10)	55 (9.0)	71 (11)	56 (9.1)
Data source				
Hospitalisation datasets	15 (2.3)	17 (2.8)	32 (4.9)	40 (6.5)
Microbiology dataset	4 (0.6)	4 (0.7)	7 (1.1)	7 (1.1)
Primary care medication dispensing dataset	22 (3.3)	24 (3.9)	57 (8.6)	65 (11)
Primary care GP dataset	1 (0.2)	0 (0)	1 (0.2)	0 (0)
Death datasets	2 (0.3)	1 (0.2)	5 (0.8)	4 (0.7)
Follow-up case report form	63 (9.6)	46 (7.5)	65 (9.9)	46 (7.5)
Total				
Any bacterial infection	95 (14)	81 (13)	137 (21)	129 (21)

[back to main text]

Supplementary Table 71: Details of fungal infection events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

	Fungal infection within 28 days		Fungal infection within 6 months	
	High dose Dexamethasone (n=659)	Usual Care (n=613)	High dose Dexamethasone (n=659)	Usual Care (n=613)
Organism				
Bacterial	0 (0)	0 (0)	0 (0)	0 (0)
Fungal	11 (1.7)	9 (1.5)	15 (2.3)	19 (3.1)
Viral (not SARS-CoV-2)	0 (0)	0 (0)	0 (0)	0 (0)
Tuberculosis	0 (0)	0 (0)	0 (0)	0 (0)
Other organism	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified organism	0 (0)	0 (0)	0 (0)	0 (0)
Anatomical site				
Pneumonia/Lower respiratory tract	3 (0.5)	3 (0.5)	3 (0.5)	4 (0.7)
Bloodstream	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Urinary tract	2 (0.3)	0 (0)	2 (0.3)	0 (0)
Intra-abdominal	0 (0)	0 (0)	0 (0)	0 (0)
Skin and soft tissue	0 (0)	2 (0.3)	1 (0.2)	3 (0.5)
Bone and joint	0 (0)	0 (0)	0 (0)	0 (0)
Upper respiratory tract	0 (0)	0 (0)	0 (0)	0 (0)
Other anatomical site	6 (0.9)	4 (0.7)	6 (0.9)	9 (1.5)
Unspecified anatomical site	3 (0.5)	2 (0.3)	6 (0.9)	5 (0.8)
Event details				
Median event study day (IQR)	-	-	23 (18, 57)	50 (30, 84)
Occurred during index hospitalisation	6 (0.9)	7 (1.1)	6 (0.9)	7 (1.1)
Data source				
Hospitalisation datasets	4 (0.6)	2 (0.3)	6 (0.9)	11 (1.8)
Microbiology dataset	0 (0)	0 (0)	0 (0)	0 (0)
Primary care medication dispensing dataset	2 (0.3)	2 (0.3)	6 (0.9)	4 (0.7)
Primary care GP dataset	0 (0)	0 (0)	0 (0)	0 (0)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Follow-up case report form	5 (0.8)	6 (1.0)	5 (0.8)	6 (1.0)
Total				
Any fungal infection	11 (1.7)	9 (1.5)	15 (2.3)	19 (3.1)

[back to main text]

Supplementary Table 72: Details of metabolic complication events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

	Metabolic complication within 28 days		Metabolic complication within 6 months	
	High dose dexamethasone (n=659)	Usual Care (n=613)	High dose dexamethasone (n=659)	Usual Care (n=613)
Metabolic complication type				
Ketoacidosis	0 (0)	0 (0)	0 (0)	0 (0)
Hyperglycaemia	144 (22)	86 (14)	144 (22)	87 (14)
Hypoglycaemia	5 (0.8)	5 (0.8)	5 (0.8)	7 (1.1)
Other metabolic complication	0 (0)	0 (0)	0 (0)	2 (0.3)
Unspecified metabolic complication	0 (0)	0 (0)	3 (0.5)	2 (0.3)
Event timing				
Median event study day (IQR)	-	-	13 (5, 36)	62 (18, 107)
Occurred during index hospitalisation	146 (22)	90 (15)	146 (22)	90 (15)
Data source				
Hospitalisation diagnosis code	6 (0.9)	3 (0.5)	6 (0.9)	6 (1.0)
Primary care GP dataset	0 (0)	0 (0)	3 (0.5)	3 (0.5)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Follow-up case report form	144 (22)	87 (14)	144 (22)	88 (14)
Total				
Any metabolic complication	148 (22)	90 (15)	150 (23)	96 (16)

[back to main text p.255]

Supplementary Table 73: Details of gastrointestinal complication events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

	Gastrointestinal complications at 28 days		Gastrointestinal complications at 6 months	
	High dose dexamethasone (n=659)	Usual Care (n=613)	High dose dexamethasone (n=659)	Usual Care (n=613)
GI complication type				
Gastrointestinal bleed	3 (0.5)	6 (1.0)	4 (0.6)	9 (1.5)
Gastrointestinal perforation	0 (0)	0 (0)	1 (0.2)	0 (0)
Gastrointestinal ulcer	0 (0)	0 (0)	0 (0)	1 (0.2)
Event details				
Median event study day (IQR)	-	-	27 (20, 34)	13 (4, 48)
Occurred during index hospitalisation	3 (0.5)	6 (1.0)	4 (0.6)	7 (1.1)
Data source				
Hospitalisation diagnosis code	2 (0.3)	5 (0.8)	4 (0.6)	9 (1.5)
Hospitalisation operation code	0 (0)	0 (0)	0 (0)	0 (0)
Death datasets	0 (0)	0 (0)	1 (0.2)	0 (0)
Follow-up case report form	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Total				
Any gastrointestinal complication	3 (0.5)	6 (1.0)	5 (0.8)	10 (1.6)

[back to main text p.255]

Supplementary Table 74: Details of venous thromboembolism events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

	Venous thromboembolism within 28 days		Venous thromboembolism within 6 months	
	High dose dexamethasone (n=659)	Usual Care (n=613)	High dose dexamethasone (n=659)	Usual Care (n=613)
Venous thromboembolism type				
Pulmonary Embolism	12 (1.8)	17 (2.8)	14 (2.1)	21 (3.4)
Deep Vein Thrombosis	1 (0.2)	2 (0.3)	1 (0.2)	2 (0.3)
Other venous thromboembolism	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified venous thromboembolism	0 (0)	0 (0)	0 (0)	0 (0)
Event details				
Median event study day (IQR)	11.0 (7.0, 18.0)	11.0 (7.0, 13.0)	17 (9, 19)	15 (10, 31)
Occurred during index hospitalisation	8 (1.2)	14 (2.3)	8 (1.2)	15 (2.4)
Data source				
Hospitalisation diagnosis code	7 (1.1)	7 (1.1)	9 (1.4)	10 (1.6)
Death datasets	3 (0.5)	2 (0.3)	3 (0.5)	4 (0.7)
Follow-up case report form	5 (0.8)	12 (2.0)	5 (0.8)	12 (2.0)
Total				
Any venous thromboembolism	13 (2.0)	18 (2.9)	15 (2.3)	22 (3.6)

[back to main text p.255]

Supplementary Table 75: Details of long COVID events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

	Long COVID within 18 months	
	High dose dexamethasone (n=659)	**Usual Care (n=613)**
Event details		
Median event study day (IQR)	128 (93, 150)	145 (58, 173)
Data source		
Primary care GP dataset	4 (0.6)	13 (2.1)
Total		
Long COVID	4 (0.6)	13 (2.1)

[back to main text p.255]

Supplementary Table 76: Details of incident diabetes events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

	Incident diabetes within 12 months	
	High dose dexamethasone (n=506)	**Usual Care (n=476)**
Event details		
Median event study day (IQR)	-	-
Occurred during index hospitalisation	1 (0.2)	0 (0)
Data source		
Hospitalisation diagnosis code	1 (0.2)	0 (0)
Primary care medication dispensing dataset	0 (0)	1 (0.2)
Primary care GP dataset	1 (0.2)	1 (0.2)
Death datasets	0 (0)	0 (0)
Total		
Incident diabetes	2/506 (0.4%)	1/476 (0.2%)

[back to main text p.255]

Supplementary Table 77: Details of long bone or vertebral fracture events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

	Long bone or vertebral fracture within 28 days		Long bone or vertebral fracture within 6 months	
	High dose dexamethasone (n=659)	Usual Care (n=613)	High dose dexamethasone (n=659)	Usual Care (n=613)
Fracture type				
Hip fracture	1 (0.2)	0 (0)	2 (0.3)	0 (0)
Other long bone fracture	0 (0)	0 (0)	2 (0.3)	0 (0)
Vertebral fracture	1 (0.2)	0 (0)	1 (0.2)	0 (0)
Other long bone or vertebral fracture	0 (0)	1 (0.2)	0 (0)	2 (0.3)
Unspecified long bone or vertebral fracture	0 (0)	0 (0)	1 (0.2)	0 (0)
Event details				
Median event study day (IQR)	-	-	-	-
Occurred during index hospitalisation	2 (0.3)	1 (0.2)	2 (0.3)	2 (0.3)
Data source				
Hospitalisation diagnosis code	2 (0.3)	1 (0.2)	5 (0.8)	2 (0.3)
Hospitalisation operation code	0 (0)	0 (0)	2 (0.3)	0 (0)
Primary care GP dataset	0 (0)	0 (0)	0 (0)	0 (0)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Total				
Any long bone or vertebral fracture	2 (0.3)	1 (0.2)	5 (0.8)	2 (0.3)

[back to main text p.255]

Supplementary Table 78: Details of psychiatric complication events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

	Psychiatric complication within 28 days		Psychiatric complication within 6 months	
	High dose dexamethasone (n=659)	Usual Care (n=613)	High dose dexamethasone (n=659)	Usual Care (n=613)
Psychiatric complication type				
Psychosis	0 (0)	0 (0)	1 (0.2)	3 (0.5)
Mania	0 (0)	0 (0)	0 (0)	0 (0)
Delirium	2 (0.3)	3 (0.5)	6 (0.9)	12 (2.0)
Other psychiatric complication	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified psychiatric complication	0 (0)	1 (0.2)	0 (0)	3 (0.5)
Event details				
Median event study day (IQR)	-	-	38 (22, 50)	51 (35, 96)
Occurred during index hospitalisation	0 (0)	2 (0.3)	0 (0)	3 (0.5)
Data source				
Hospitalisation diagnosis code	2 (0.3)	3 (0.5)	6 (0.9)	13 (2.1)
Primary care medication dispensing dataset	0 (0)	1 (0.2)	1 (0.2)	5 (0.8)
Primary care GP dataset	0 (0)	0 (0)	1 (0.2)	2 (0.3)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Total				
Any psychiatric complication	2 (0.3)	4 (0.7)	7 (1.1)	18 (2.9)

[back to main text p.255]

Supplementary Table 79: Details of clinically-defined liver injury events in the completed subgroup of the RECOVERY higher dose dexamethasone comparison.

	Clinically defined liver injury within 28 days		Clinically defined liver injury within 6 months	
	High dose dexamethasone (n=659)	Usual Care (n=613)	High dose dexamethasone (n=659)	Usual Care (n=613)
Event timing				
Median event study day (IQR)	-	-	11 (10, 15)	37 (22, 100)
Occurred during index hospitalisation	5 (0.8)	2 (0.3)	5 (0.8)	2 (0.3)
Data source				
Hospitalisation diagnosis code	6 (0.9)	3 (0.5)	7 (1.1)	8 (1.3)
Primary care GP dataset	0 (0)	1 (0.2)	0 (0)	1 (0.2)
Death datasets	0 (0)	0 (0)	0 (0)	0 (0)
Total				
Any liver injury	6 (0.9)	4 (0.7)	7 (1.1)	8 (1.3)

[back to main text p.255]

Supplementary Table 80: Effect of allocation to higher dose dexamethasone on primary hospital-recorded diagnoses[*] within 6 months of randomisation.

	Higher dose Dexamethasone (n=659)[1]	Usual Care (n=613)[1]	Rate Ratio (95% CI)
Event timing			
Number of hospital admission days			
Median (Lower quartile, Upper quartile)	9 (5, 13)	8 (5, 15)	
Mean (Standard Deviation)	13 (19)	14 (20)	
Study day of diagnosis start			
Median (Lower quartile, Upper quartile)	25 (10, 65)	23 (11, 56)	
Admission type			
Emergency admission (including transfers)	108 (16)	125 (20)	
Elective admission	27 (4.1)	33 (5.4)	
COVID-19			
Readmission due to COVID-19	12 (1.8)	21 (3.4)	0.53 (0.26 - 1.05)
Non-COVID infection			
Pneumonia/Lower Respiratory Tract	26 (3.9)	26 (4.2)	
Urinary tract	3 (0.5)	6 (1.0)	
Intra-abdominal	0 (0)	0 (0)	
Skin and soft tissue	4 (0.6)	4 (0.7)	
Bone and joint	0 (0)	2 (0.3)	
Upper Respiratory Tract	0 (0)	0 (0)	
Other site	1 (0.2)	0 (0)	
Unspecified site	5 (0.8)	10 (1.6)	
Bacterial	14 (2.1)	15 (2.4)	
Fungal	0 (0)	1 (0.2)	
Other viral	1 (0.2)	0 (0)	
TB	0 (0)	0 (0)	
Other organism	0 (0)	1 (0.2)	
Unspecified organism	26 (3.9)	29 (4.7)	
Subtotal: Any non-COVID infection	37 (5.6)	42 (6.9)	0.81 (0.53 - 1.25)
Cardiac			
Myocardial infarction	2 (0.3)	2 (0.3)	
Other coronary heart disease	1 (0.2)	1 (0.2)	
Heart failure	5 (0.8)	8 (1.3)	
Other	0 (0)	4 (0.7)	

Subtotal: Any cardiac	8 (1.2)	13 (2.1)	0.58 (0.23 - 1.36)
Stroke			
Haemorrhagic stroke	2 (0.3)	2 (0.3)	
Non-haemorrhagic stroke	1 (0.2)	2 (0.3)	
Subtotal: Any stroke	1 (0.2)	4 (0.7)	0.23 (0.01 - 1.56)
Other vascular			
Arterial thrombo-embolism	1 (0.2)	1 (0.2)	
Venous thrombo-embolism	4 (0.6)	5 (0.8)	
Other	1 (0.2)	1 (0.2)	
Subtotal: Any other vascular	5 (0.8)	7 (1.1)	0.66 (0.20 - 2.06)
Medical			
Cancer	3 (0.5)	18 (2.9)	
Diabetes	2 (0.3)	2 (0.3)	
Gastrointestinal bleed or perforation	2 (0.3)	2 (0.3)	
Other extra-cranial bleed or perforation	3 (0.5)	3 (0.5)	
Liver	0 (0)	1 (0.2)	
Renal	2 (0.3)	3 (0.5)	
Respiratory (non-infection)	12 (1.8)	13 (2.1)	
Other	30 (4.6)	28 (4.6)	
Subtotal: Any medical	49 (7.4)	47 (7.7)	0.96 (0.66 - 1.42)
External			
External with bleed	0 (0)	0 (0)	
External without bleed	6 (0.9)	7 (1.1)	
Subtotal: Any external	6 (0.9)	7 (1.1)	
Unknown			
No formal diagnosis recorded	35 (5.3)	43 (7.0)	
Total			
Total: Any hospital recorded diagnosis	122 (19)	144 (23)	0.78 (0.63 - 0.96)

[*] *Hospital-recorded diagnoses reflected the categorisation of any ICD-10 codes in the primary diagnostic position recorded in a hospital admission dataset from episodes of care with a start date within 6 months after randomisation.*
[1] *n (%)*

[back to main text]

Supplementary Table 81: Contrast matrix of model of subgroup analysis of 28-day mortality in the RECOVERY dexamethasone comparison after including interaction with other key baseline subgroup.

Respiratory support group	Hospital Frailty Risk Score group		
	Low risk	Intermediate risk	High risk
	RR (95% CI)	RR (95% CI)	RR (95% CI)
No oxygen	0.76 (0.54 - 1.08)	1.20 (0.88 - 1.64)	1.39 (1.04 - 1.85)
Oxygen or non-invasive ventilation	0.59 (0.47 - 0.74)	0.92 (0.76 - 1.12)	1.06 (0.86 - 1.31)
Invasive mechanical ventilation	0.45 (0.33 - 0.62)	0.71 (0.55 - 0.90)	0.82 (0.59 - 1.12)

RR (95% CI) = Rate Ratio (95% Confidence Interval), adjusted for age group at randomisation.

[back to main text]

Supplementary Table 82: 28-day mortality rates according to both respiratory support and Hospital Frailty Risk Score group in the RECOVERY dexamethasone comparison.

Respiratory support group	Hospital Frailty Risk Score group*					
	Low risk (<5)		Intermediate risk (5-15)		High risk (>15)	
	Dexamethasone	Usual care	Dexamethasone	Usual care	Dexamethasone	Usual care
No oxygen	9/159 (5.7%)	17/359 (4.7%)	27/139 (19%)	40/258 (16%)	51/185 (28%)	84/382 (22%)
Oxygen or non-invasive ventilation	67/658 (10%)	217/1347 (16%)	122/355 (34%)	249/714 (35%)	106/239 (44%)	208/482 (43%)
Invasive mechanical ventilation	29/105 (28%)	97/228 (43%)	60/185 (32%)	168/374 (45%)	6/27 (22%)	16/64 (25%)

** Does not include 52 participants (4 deaths) in the dexamethasone group and 113 participants (14 deaths) in the usual care group with Hospital Frailty Risk Score group 'Unknown'.*

[back to main text]

Supplementary Table 83: Results of sensitivity analyses of biological measurement outcomes in the RECOVERY-ISARIC dexamethasone comparison population.

Daily rate of change in biological measurement	Analysis method	Follow-up time period	Dexamethasone mean (SE)	Usual Care mean (SE)	Difference in adjusted means[1] (95% CI)	p-value
Ordinal scale score (categories)	Complete case analysis	7 days	-0.21 (0.03)	-0.14 (0.02)	-0.07 (-0.14, -0.01)	0.03
	Multiple imputation	14 days	-0.09 (0.04)	0.02 (0.02)	-0.10 (-0.18, -0.02)	0.01
	Multiple imputation	28 days	-0.08 (0.03)	0.01 (0.03)	-0.09 (-0.16, -0.02)	0.006
C-reactive protein (mg/L)	Complete case analysis	7 days	-24.4 (1.9)	-5.5 (1.3)	-19.0 (-23.5, -14.4)	<0.0001
	Multiple imputation	14 days	-21.6 (1.9)	-3.3 (1.2)	-18.3 (-22.7, -13.9)	<0.0001
	Multiple imputation	28 days	-17.8 (1.5)	-5.8 (1.1)	-12.0 (-15.5, -8.5)	<0.0001
Neutrophil:lymphocyte ratio	Complete case analysis	7 days	0.71 (0.17)	-0.32 (0.11)	1.03 (0.63, 1.43)	<0.0001
	Multiple imputation	14 days	0.82 (0.15)	-0.40 (0.12)	1.22 (0.84, 1.61)	<0.0001
	Multiple imputation	28 days	0.72 (0.16)	-0.40 (0.11)	1.12 (0.76, 1.48)	<0.0001
Glucose (mmol/L)	Complete case analysis	7 days	0.66 (0.11)	0.11 (0.08)	0.55 (0.29, 0.81)	<0.0001
	Multiple imputation	14 days	0.97 (0.22)	0.24 (0.11)	0.73 (0.20, 1.26)	0.007
	Multiple imputation	28 days	0.83 (0.22)	0.16 (0.09)	0.67 (0.19, 1.15)	0.007
Creatinine (µmol/L)	Complete case analysis	7 days	-1.9 (1.3)	-1.7 (0.9)	-0.2 (-3.4, 2.9)	0.89
	Multiple imputation	14 days	-2.0 (1.4)	-2.5 (1.0)	0.5 (-3.0, 4.0)	0.77
	Multiple imputation	28 days	-1.5 (1.1)	-2.2 (0.9)	0.7 (-2.1, 3.6)	0.61
Alanine aminotransferase (IU/L)	Complete case analysis	7 days	6.0 (2.5)	7.7 (1.7)	-1.7 (-7.5, 4.2)	0.58
	Multiple imputation	14 days	6.3 (1.3)	6.6 (1.2)	-0.3 (-3.9, 3.3)	0.86
	Multiple imputation	28 days	5.2 (1.2)	5.9 (1.0)	-0.7 (-3.8, 2.3)	0.64

SE = Standard Error
95% CI = 95% Confidence Interval
[1]Adjusted for age and respiratory support group at randomisation

[back to main text p.284]

Supplementary Table 84: Exploratory outcomes of daily rate of change in biological measurements in the first 7 days after randomisation in the RECOVERY-ISARIC tocilizumab comparison population.

Daily rate of change in biological measurement	Tocilizumab mean (SE)	Usual Care mean (SE)	Difference in adjusted means[1] (95% CI)	p-value
Ordinal scale score (categories)	0.04 (0.03)	0.09 (0.03)	-0.05 (-0.14 , 0.04)	0.24
C-reactive protein (mg/L)	-31.5 (3.2)	-12.6 (2.8)	-18.9 (-27.4 , -10.3)	<0.0001
Neutrophil:lymphocyte ratio	0.28 (0.44)	1.87 (0.54)	-1.59 (-2.91 , -0.27)	0.02
Glucose (mmol/L)	0.74 (0.23)	0.34 (0.23)	0.40 (-0.25 , 1.04)	0.22
Creatinine (µmol/L)	-0.8 (3.4)	-5.0 (1.3)	4.2 (-3.4 , 11.7)	0.28
Alanine aminotransferase (IU/L)	11.0 (4.3)	5.8 (2.3)	5.3 (-4.0 , 14.5)	0.26

SE = Standard Error
95% CI = 95% Confidence Interval
[1]Adjusted for age and respiratory support group at randomisation

[back to main text]

Supplementary Table 85: Results of sensitivity analyses of biological measurement outcomes in the RECOVERY-ISARIC tocilizumab comparison population.

Daily rate of change in biological measurement	Analysis method	Follow-up time period	Tocilizumab mean (SE)	Usual care mean (SE)	Difference in adjusted means[1] (95% CI)	p-value
Ordinal scale score (categories)	Complete case analysis	7 days	-0.12 (0.03)	-0.04 (0.04)	-0.08 (-0.18, 0.01)	0.10
	Multiple imputation	14 days	-0.09 (0.02)	-0.03 (0.02)	-0.07 (-0.13, 0.00)	0.04
	Multiple imputation	28 days	-0.13 (0.02)	-0.08 (0.02)	-0.05 (-0.11, 0.01)	0.08
C-reactive protein (mg/L)	Complete case analysis	7 days	-35.2 (3.3)	-13.9 (3.5)	-21.4 (-30.9, -11.9)	<0.0001
	Multiple imputation	14 days	-24.6 (2.5)	-12.1 (2.6)	-12.4 (-19.7, -5.2)	0.001
	Multiple imputation	28 days	-23.5 (2.2)	-12.0 (2.2)	-11.5 (-17.5, -5.6)	0.0002
Neutrophil:lymphocyte ratio	Complete case analysis	7 days	0.52 (0.49)	2.28 (0.51)	-1.76 (-3.14, -0.38)	0.01
	Multiple imputation	14 days	0.35 (0.30)	1.67 (0.42)	-1.32 (-2.31, -0.33)	0.009
	Multiple imputation	28 days	-0.15 (0.42)	1.05 (0.34)	-1.19 (-2.26, -0.13)	0.03
Glucose (mmol/L)	Complete case analysis	7 days	0.35 (0.26)	0.21 (0.27)	0.15 (-0.60, 0.90)	0.70
	Multiple imputation	14 days	0.65 (0.19)	0.12 (0.17)	0.54 (0.02, 1.06)	0.04
	Multiple imputation	28 days	0.49 (0.21)	0.08 (0.12)	0.41 (-0.09, 0.91)	0.11
Creatinine (µmol/L)	Complete case analysis	7 days	-2.9 (1.7)	-5.8 (1.7)	2.9 (-1.8, 7.5)	0.23
	Multiple imputation	14 days	-1.0 (2.4)	-3.9 (1.1)	3.0 (-2.3, 8.2)	0.27
	Multiple imputation	28 days	-0.9 (1.8)	-2.9 (1.0)	2.1 (-2.3, 6.4)	0.35
Alanine aminotransferase (IU/L)	Complete case analysis	7 days	9.3 (3.4)	4.8 (3.4)	4.6 (-4.9, 14.1)	0.35
	Multiple imputation	14 days	9.1 (5.8)	6.1 (2.4)	3.1 (-9.4, 15.6)	0.63
	Multiple imputation	28 days	7.3 (2.9)	6.5 (1.9)	0.8 (-6.5, 8.2)	0.83

95% CI = 95% Confidence Interval
SE = Standard Error
[1]Adjusted for age and respiratory support group at randomisation

[back to main text]

Supplementary Table 86: Exploratory outcomes of daily rate of change in biological measurements in the first 7 days after randomisation in the RECOVERY-ISARIC baricitinib comparison population.

Daily rate of change in biological measurement	Baricitinib mean (SE)	Usual Care mean (SE)	Difference in adjusted means[1] (95% CI)	p-value
Ordinal scale score (categories)	-0.17 (0.04)	-0.02 (0.04)	-0.14 (-0.26 , -0.03)	0.01
C-reactive protein (mg/L)	-24.2 (3.8)	-35.0 (2.9)	10.9 (1.0 , 20.8)	0.03
Neutrophil:lymphocyte ratio	0.91 (0.63)	1.60 (0.38)	-0.69 (-2.10 , 0.72)	0.33
Glucose (mmol/L)	-0.25 (0.29)	0.11 (0.30)	-0.36 (-1.24 , 0.52)	0.41
Creatinine (µmol/L)	-4.7 (1.1)	-8.3 (0.9)	3.6 (0.9 , 6.2)	0.009
Alanine aminotransferase (IU/L)	6.2 (2.6)	8.9 (2.7)	-2.7 (-9.8 , 4.3)	0.44

SE = Standard Error
95% CI = 95% Confidence Interval
[1]Adjusted for age and respiratory support group at randomisation

[back to main text]

Supplementary Table 87: Results of sensitivity analyses of biological measurement outcomes in the RECOVERY-ISARIC baricitinib comparison population.

Daily rate of change in biological measurement	Analysis method	Follow-up time period	Baricitinib mean (SE)	Usual care mean (SE)	Difference in adjusted means[1] (95% CI)	p-value
Ordinal scale score (categories)	Complete case analysis	7 days	-0.63 (0.03)	-0.55 (0.03)	-0.08 (-0.16, 0.01)	0.08
	Multiple imputation	14 days	-0.16 (0.03)	-0.03 (0.04)	-0.13 (-0.24, -0.03)	0.01
	Multiple imputation	28 days	-0.52 (0.02)	-0.43 (0.02)	-0.08 (-0.13, -0.03)	0.001
C-reactive protein (mg/L)	Complete case analysis	7 days	-20.9 (4.1)	-33.6 (3.9)	12.7 (1.6, 23.9)	0.03
	Multiple imputation	14 days	-24.1 (3.9)	-34.9 (2.9)	10.8 (1.2, 20.3)	0.03
	Multiple imputation	28 days	-20.2 (2.4)	-29.5 (2.8)	9.2 (2.1, 16.3)	0.01
Neutrophil:lymphocyte ratio	Complete case analysis	7 days	1.44 (0.45)	1.91 (0.44)	-0.46 (-1.70, 0.77)	0.46
	Multiple imputation	14 days	0.86 (0.60)	1.58 (0.45)	-0.72 (-2.19, 0.74)	0.33
	Multiple imputation	28 days	0.47 (0.46)	0.90 (0.33)	-0.43 (-1.51, 0.65)	0.43
Glucose (mmol/L)	Complete case analysis	7 days	-0.10 (0.32)	-0.08 (0.33)	-0.02 (-0.95, 0.90)	0.96
	Multiple imputation	14 days	-0.25 (0.21)	0.14 (0.30)	-0.38 (-1.13, 0.36)	0.31
	Multiple imputation	28 days	-0.06 (0.19)	-0.38 (0.22)	0.32 (-0.29, 0.92)	0.30
Creatinine (µmol/L)	Complete case analysis	7 days	-4.5 (2.8)	-10.9 (2.7)	6.4 (-1.3, 14.1)	0.11
	Multiple imputation	14 days	-4.7 (1.0)	-8.3 (0.9)	3.6 (1.0, 6.3)	0.007
	Multiple imputation	28 days	-3.1 (0.9)	-5.4 (0.7)	2.3 (-0.0, 4.6)	0.05
Alanine aminotransferase (IU/L)	Complete case analysis	7 days	7.1 (2.6)	12.0 (2.5)	-4.9 (-12.2, 2.3)	0.18
	Multiple imputation	14 days	6.5 (2.6)	9.2 (2.7)	-2.8 (-10.2, 4.7)	0.46
	Multiple imputation	28 days	8.1 (1.9)	16.2 (5.2)	-8.2 (-19.2, 2.8)	0.14

SE = Standard Error
95% CI = 95% Confidence Interval
[1]Adjusted for age and respiratory support group at randomisation

[back to main text]

Supplementary Table 88: Differentially expressed genes between dexamethasone and usual care treatment groups.

Ensembl ID	Gene	Log_2 Fold Change[1]	Adjusted p-value[1]	Direction
ENSG00000179593	ALOX15B	4.16	<0.0001	UP
ENSG00000079215	SLC1A3	2.75	<0.0001	UP
ENSG00000152463	OLAH	4.71	<0.0001	UP
ENSG00000121454	LHX4	4.93	<0.0001	UP
ENSG00000135424	ITGA7	2.01	<0.0001	UP
ENSG00000115590	IL1R2	3.48	<0.0001	UP
ENSG00000169174	PCSK9	4.10	<0.0001	UP
ENSG00000259383	RP11-403B2.6	24.23	<0.0001	UP
ENSG00000180509	KCNE1	2.46	<0.0001	UP
ENSG00000121933	TMIGD3	2.74	<0.0001	UP
ENSG00000276289	LOC102723475	2.61	<0.0001	UP
ENSG00000279174	RP11-1099M24.9	2.39	<0.0001	UP
ENSG00000144820	ADGRG7	14.12	<0.0001	UP
ENSG00000078053	AMPH	2.83	<0.0001	UP
ENSG00000198585	NUDT16	1.28	<0.0001	UP
ENSG00000288156	nA	1.20	<0.0001	UP
ENSG00000222009	BTBD19	1.44	<0.0001	UP
ENSG00000258973	RP11-934B9.3	1.19	<0.0001	UP
ENSG00000105352	CEACAM4	1.55	0.0001	UP
ENSG00000185168	LINC00482	1.78	0.0001	UP
ENSG00000132259	CNGA4	2.27	0.0001	UP
ENSG00000278961	LOC107983987	2.10	0.0001	UP
ENSG00000281969	NA	4.40	0.0001	UP
ENSG00000172771	EFCAB12	1.63	0.0001	UP
ENSG00000096060	FKBP5	1.98	0.0001	UP
ENSG00000271806	RP5-892K4.1	1.34	0.0001	UP
ENSG00000146122	DAAM2	4.01	0.0001	UP
ENSG00000087116	ADAMTS2	3.09	0.0001	UP
ENSG00000171136	RLN3	2.92	0.0002	UP
ENSG00000140044	JDP2	1.36	0.0002	UP
ENSG00000189221	MAOA	2.96	0.0002	UP
ENSG00000258831	RP11-76E17.4	3.39	0.0002	UP
ENSG00000258476	LINC02207	3.05	0.0002	UP
ENSG00000160796	NBEAL2	1.07	0.0002	UP
ENSG00000203999	LINC01270	1.64	0.0002	UP
ENSG00000113719	ERGIC1	1.37	0.0003	UP
ENSG00000236785	SDR42E1P5	3.49	0.0004	UP
ENSG00000086544	ITPKC	1.27	0.0004	UP
ENSG00000103175	WFDC1	3.57	0.0004	UP
ENSG00000132965	ALOX5AP	1.30	0.0004	UP
ENSG00000144671	SLC22A14	1.70	0.0004	UP
ENSG00000258810	RP11-219E7.1	1.50	0.0004	UP
ENSG00000139572	GPR84	1.78	0.0004	UP
ENSG00000205085	GARIN1A	1.26	0.0004	UP
ENSG00000104883	PEX11G	1.74	0.0004	UP
ENSG00000161643	SIGLEC16	1.62	0.0004	UP
ENSG00000054598	FOXC1	2.24	0.0004	UP
ENSG00000228058	LINC01736	2.05	0.0005	UP
ENSG00000257411	RP11-603J24.9	18.44	0.0005	UP
ENSG00000140545	MFGE8	1.62	0.0005	UP
ENSG00000287733	NA	1.68	0.0005	UP
ENSG00000180316	PNPLA1	1.62	0.0006	UP
ENSG00000177675	CD163L1	2.80	0.0006	UP
ENSG00000183873	SCN5A	3.11	0.0006	UP
ENSG00000213903	LTB4R	1.15	0.0006	UP
ENSG00000007237	GAS7	1.26	0.0007	UP
ENSG00000107566	ERLIN1	1.70	0.0007	UP
ENSG00000109906	ZBTB16	1.90	0.0007	UP
ENSG00000157150	TIMP4	3.29	0.0007	UP
ENSG00000224397	PELATON	1.34	0.0007	UP
ENSG00000229648	RPSAP22	1.58	0.0007	UP
ENSG00000248780	RP11-632F7.1	2.11	0.0007	UP
ENSG00000267385	CTB-50L17.14	1.58	0.0007	UP
ENSG00000124588	NQO2	1.13	0.0007	UP
ENSG00000259687	LINC01220	1.40	0.0007	UP
ENSG00000273706	LHX1	3.13	0.0007	UP
ENSG00000004660	CAMKK1	1.08	0.0007	UP
ENSG00000220008	LINGO3	1.21	0.0008	UP
ENSG00000184389	A3GALT2	2.15	0.0008	UP
ENSG00000183160	TMEM119	2.42	0.0008	UP
ENSG00000164850	GPER1	2.21	0.0008	UP
ENSG00000049089	COL9A2	2.28	0.0008	UP
ENSG00000123119	NECAB1	3.80	0.0008	UP
ENSG00000155659	VSIG4	2.31	0.0008	UP
ENSG00000196209	SIRPB2	1.27	0.0008	UP

ENSG00000214456	PLIN5	1.53	0.0009	UP
ENSG00000167210	LOXHD1	1.93	0.0009	UP
ENSG00000172985	SH3RF3	1.30	0.0009	UP
ENSG00000186417	GLDN	3.49	0.001	UP
ENSG00000286127	NA	1.31	0.001	UP
ENSG00000018280	SLC11A1	1.47	0.001	UP
ENSG00000130518	IQCN	1.15	0.001	UP
ENSG00000137869	CYP19A1	2.88	0.001	UP
ENSG00000254248	RP11-320N21.2	1.96	0.001	UP
ENSG00000134463	ECHDC3	2.36	0.001	UP
ENSG00000282608	ADORA3	1.67	0.001	UP
ENSG00000157343	ARMC12	1.73	0.001	UP
ENSG00000181751	MACIR	1.59	0.001	UP
ENSG00000079277	MKNK1	1.33	0.001	UP
ENSG00000101307	SIRPB1	1.16	0.001	UP
ENSG00000177575	CD163	2.09	0.001	UP
ENSG00000228302	RP11-186N15.3	2.18	0.001	UP
ENSG00000287935	LOC124902606	1.15	0.001	UP
ENSG00000188959	C9orf152	3.20	0.001	UP
ENSG00000274008	Metazoa_SRP	1.31	0.001	UP
ENSG00000109047	RCVRN	2.16	0.001	UP
ENSG00000167434	CA4	1.76	0.001	UP
ENSG00000100906	NFKBIA	1.19	0.001	UP
ENSG00000139832	RAB20	1.43	0.001	UP
ENSG00000245080	MIR3150BHG	1.79	0.001	UP
ENSG00000258565	BLZF2P	1.23	0.001	UP
ENSG00000287737	NA	1.48	0.001	UP
ENSG00000183762	KREMEN1	1.69	0.001	UP
ENSG00000228705	LINC00659	1.70	0.001	UP
ENSG00000273084	RP11-1275H24.3	1.12	0.001	UP
ENSG00000189419	SPATA41	1.14	0.001	UP
ENSG00000257017	HP	1.83	0.001	UP
ENSG00000100336	APOL4	3.40	0.002	UP
ENSG00000287975	NA	1.31	0.002	UP
ENSG00000082014	SMARCD3	1.09	0.002	UP
ENSG00000115604	IL18R1	2.64	0.002	UP
ENSG00000288025	NA	2.22	0.002	UP
ENSG00000213937	CLDN9	1.34	0.002	UP
ENSG00000106070	GRB10	2.31	0.002	UP
ENSG00000272079	LA16c-380H5.5	1.38	0.002	UP
ENSG00000164105	SAP30	1.65	0.002	UP
ENSG00000230454	U73166.2	1.09	0.002	UP
ENSG00000121316	PLBD1	1.33	0.002	UP
ENSG00000257599	OVCH1-AS1	2.59	0.002	UP
ENSG00000012779	ALOX5	1.14	0.002	UP
ENSG00000115607	IL18RAP	1.86	0.002	UP
ENSG00000196296	ATP2A1	1.13	0.002	UP
ENSG00000150337	FCGR1A	2.01	0.002	UP
ENSG00000228463	RPL23AP21	1.71	0.002	UP
ENSG00000189325	BNIP5	3.10	0.002	UP
ENSG00000259319	RP11-293M10.6	1.22	0.002	UP
ENSG00000107738	VSIR	1.07	0.002	UP
ENSG00000204345	CD300LD	3.27	0.002	UP
ENSG00000160883	HK3	1.11	0.002	UP
ENSG00000238078	LINC01352	2.19	0.002	UP
ENSG00000152229	PSTPIP2	1.64	0.003	UP
ENSG00000163083	INHBB	2.27	0.003	UP
ENSG00000287771	NA	2.53	0.003	UP
ENSG00000113916	BCL6	1.69	0.003	UP
ENSG00000112333	NR2E1	3.48	0.003	UP
ENSG00000267780	RP11-154H12.3	2.71	0.003	UP
ENSG00000172179	PRL	2.65	0.003	UP
ENSG00000139178	C1RL	1.09	0.003	UP
ENSG00000163959	SLC51A	2.63	0.003	UP
ENSG00000244607	CCDC13	1.18	0.003	UP
ENSG00000196935	SRGAP1	1.95	0.003	UP
ENSG00000287317	LOC124901656	2.51	0.003	UP
ENSG00000068024	HDAC4	1.11	0.003	UP
ENSG00000134243	SORT1	1.40	0.003	UP
ENSG00000167680	SEMA6B	1.47	0.003	UP
ENSG00000185585	OLFML2A	1.46	0.003	UP
ENSG00000140538	NTRK3	2.26	0.003	UP
ENSG00000251139	RP11-701P16.2	2.28	0.003	UP
ENSG00000243696	RP5-966M1.6	1.14	0.003	UP
ENSG00000198915	RASGEF1A	1.14	0.003	UP
ENSG00000228295	LINC00392	2.60	0.003	UP
ENSG00000287216	NA	2.83	0.003	UP
ENSG00000265531	FCGR1CP	2.03	0.003	UP
ENSG00000276961	MIR7848	1.51	0.003	UP
ENSG00000075399	VPS9D1	1.38	0.003	UP
ENSG00000122025	FLT3	2.00	0.003	UP
ENSG00000183578	TNFAIP8L3	2.33	0.003	UP

ENSG00000242583	KMT5AP3	1.77	0.003	UP
ENSG00000258316	KLF17P1	1.50	0.003	UP
ENSG00000102010	BMX	2.00	0.003	UP
ENSG00000167676	PLIN4	1.48	0.003	UP
ENSG00000213386	RP11-779O18.2	2.35	0.003	UP
ENSG00000244731	C4A	1.24	0.004	UP
ENSG00000146094	DOK3	1.04	0.004	UP
ENSG00000174715	RP11-79L9.2	1.26	0.004	UP
ENSG00000285938	BCL6-AS1	1.88	0.004	UP
ENSG00000156113	KCNMA1	3.10	0.004	UP
ENSG00000167995	BEST1	1.08	0.004	UP
ENSG00000182511	FES	1.09	0.004	UP
ENSG00000183696	UPP1	1.27	0.004	UP
ENSG00000108352	RAPGEFL1	1.10	0.004	UP
ENSG00000259704	LOC105370969	1.22	0.004	UP
ENSG00000254470	AP5B1	1.21	0.004	UP
ENSG00000188523	CFAP77	3.68	0.004	UP
ENSG00000226125	LINC01907	1.38	0.004	UP
ENSG00000186205	MTARC1	1.39	0.004	UP
ENSG00000204936	CD177	3.18	0.004	UP
ENSG00000274536	MIR223HG	1.52	0.004	UP
ENSG00000145685	LHFPL2	1.52	0.004	UP
ENSG00000188305	PEAK3	1.25	0.004	UP
ENSG00000225313	RP11-415J8.3	2.45	0.004	UP
ENSG00000233013	FAM157B	1.41	0.004	UP
ENSG00000250608	NUDT16-DT	1.65	0.004	UP
ENSG00000175274	TP53I11	1.08	0.004	UP
ENSG00000123836	PFKFB2	2.42	0.004	UP
ENSG00000243273	LOC124909446	2.18	0.004	UP
ENSG00000271581	XXbac-BPG248L24.12	1.42	0.004	UP
ENSG00000244242	IFITM10	1.12	0.004	UP
ENSG00000136383	ALPK3	1.35	0.004	UP
ENSG00000253200	RP11-582J16.5	1.07	0.004	UP
ENSG00000100003	SEC14L2	1.66	0.005	UP
ENSG00000268262	CTC-246B18.8	1.22	0.005	UP
ENSG00000226091	LINC00937	1.09	0.005	UP
ENSG00000178175	ZNF366	1.48	0.005	UP
ENSG00000129038	LOXL1	1.54	0.005	UP
ENSG00000159339	PADI4	1.18	0.005	UP
ENSG00000185950	IRS2	1.48	0.005	UP
ENSG00000237094	RP4-669L17.10	1.16	0.005	UP
ENSG00000279400	CTD-2353F22.2	2.57	0.005	UP
ENSG00000221025	MIR1250	1.51	0.005	UP
ENSG00000232973	CYP1B1-AS1	1.31	0.005	UP
ENSG00000158825	CDA	1.15	0.005	UP
ENSG00000164106	SCRG1	2.03	0.005	UP
ENSG00000236308	RP11-316M21.7	2.27	0.005	UP
ENSG00000267394	CTB-175E5.7	1.74	0.005	UP
ENSG00000203812	HIST2H2AA4	14.83	0.005	UP
ENSG00000287255	LOC101929667	1.95	0.005	UP
ENSG00000168916	ZNF608	2.65	0.005	UP
ENSG00000174885	NLRP6	1.38	0.006	UP
ENSG00000173212	MAB21L3	2.03	0.006	UP
ENSG00000087157	PGS1	1.29	0.006	UP
ENSG00000278002	RP11-596C23.2	1.10	0.006	UP
ENSG00000231123	SPATA20P1	1.98	0.006	UP
ENSG00000115594	IL1R1	1.85	0.006	UP
ENSG00000196547	MAN2A2	1.07	0.006	UP
ENSG00000179299	NSUN7	1.69	0.006	UP
ENSG00000197903	H2BC12	1.13	0.006	UP
ENSG00000177191	B3GNT8	1.04	0.006	UP
ENSG00000246016	LINC01513	1.22	0.006	UP
ENSG00000266718	RP11-466A19.1	1.36	0.006	UP
ENSG00000063015	SEZ6	2.21	0.007	UP
ENSG00000276649	RP5-858L17.1	1.15	0.007	UP
ENSG00000273812	WI2-87327B8.2	1.47	0.007	UP
ENSG00000114268	PFKFB4	1.05	0.007	UP
ENSG00000077238	IL4R	1.14	0.007	UP
ENSG00000229647	MYOSLID	1.31	0.007	UP
ENSG00000228923	AP000355.2	1.52	0.007	UP
ENSG00000198019	FCGR1B	1.67	0.007	UP
ENSG00000203799	CCDC162P	1.52	0.007	UP
ENSG00000266913	LINC01841	1.33	0.007	UP
ENSG00000055955	ITIH4	1.23	0.007	UP
ENSG00000142657	PGD	1.03	0.007	UP
ENSG00000254814	RP11-535A19.1	2.09	0.007	UP
ENSG00000167046	RP11-93B14.6	1.32	0.007	UP
ENSG00000234617	SNRK-AS1	1.25	0.008	UP
ENSG00000157064	NMNAT2	1.65	0.008	UP
ENSG00000169385	RNASE2	1.29	0.008	UP
ENSG00000204577	LILRB3	1.11	0.008	UP
ENSG00000172367	NHERF4	1.25	0.008	UP

ENSG00000225062	CATIP-AS1	1.22	0.008	UP
ENSG00000120129	DUSP1	1.55	0.008	UP
ENSG00000282840	NA	2.31	0.008	UP
ENSG00000145491	ROPN1L	1.23	0.008	UP
ENSG00000155893	PXYLP1	1.34	0.008	UP
ENSG00000237879	LINC00398	1.60	0.008	UP
ENSG00000284154	MIR3605	1.94	0.008	UP
ENSG00000134686	PHC2	1.48	0.008	UP
ENSG00000185338	SOCS1	1.95	0.008	UP
ENSG00000135636	DYSF	1.18	0.008	UP
ENSG00000258785	LINC01580	2.94	0.009	UP
ENSG00000117115	PADI2	1.52	0.009	UP
ENSG00000284673	NA	1.15	0.009	UP
ENSG00000253320	KB-1507C5.2	1.03	0.009	UP
ENSG00000282572	NA	1.19	0.009	UP
ENSG00000260528	FAM157C	1.17	0.009	UP
ENSG00000173744	AGFG1	1.17	0.009	UP
ENSG00000228340	MIR646HG	1.06	0.009	UP
ENSG00000269877	CTD-3022G6.1	1.07	0.009	UP
ENSG00000178814	OPLAH	1.23	0.009	UP
ENSG00000185972	CCIN	1.48	0.009	UP
ENSG00000196843	ARID5A	1.03	0.009	UP
ENSG00000213285	RPL23AP45	13.11	0.01	UP
ENSG00000064932	SBNO2	1.10	0.01	UP
ENSG00000249309	RP11-153M7.5	2.13	0.01	UP
ENSG00000171236	LRG1	1.40	0.01	UP
ENSG00000256433	RP1-102E24.8	1.27	0.01	UP
ENSG00000117834	SLC5A9	1.92	0.01	UP
ENSG00000121270	ABCC11	2.66	0.01	UP
ENSG00000287431	RENO1	1.24	0.01	UP
ENSG00000287626	NA	1.85	0.01	UP
ENSG00000139890	REM2	1.25	0.01	UP
ENSG00000230149	RP3-508I15.19	1.39	0.01	UP
ENSG00000261471	RP11-61F12.1	1.23	0.01	UP
ENSG00000054523	KIF1B	1.20	0.01	UP
ENSG00000244491	RP3-508I15.18	1.09	0.01	UP
ENSG00000254017	IGHEP2	1.33	0.01	UP
ENSG00000112062	MAPK14	1.17	0.01	UP
ENSG00000198363	ASPH	1.60	0.01	UP
ENSG00000278276	RP3-324O17.8	1.73	0.01	UP
ENSG00000284642	NA	1.37	0.01	UP
ENSG00000129204	USP6	1.97	0.01	UP
ENSG00000241860	RP11-34P13.13	1.14	0.01	UP
ENSG00000102780	DGKH	1.87	0.01	UP
ENSG00000239732	TLR9	1.02	0.01	UP
ENSG00000253230	MIR124-1HG	2.87	0.01	UP
ENSG00000272941	RP11-134L10.1	1.33	0.01	UP
ENSG00000206344	HCG27	1.30	0.01	UP
ENSG00000240934	RP11-925D8.1	2.00	0.01	UP
ENSG00000238152	OR7E140P	1.07	0.01	UP
ENSG00000132170	PPARG	1.46	0.01	UP
ENSG00000241527	CA15P1	1.01	0.01	UP
ENSG00000112053	SLC26A8	1.66	0.01	UP
ENSG00000157613	CREB3L1	2.39	0.01	UP
ENSG00000182885	ADGRG3	1.35	0.01	UP
ENSG00000186431	FCAR	1.23	0.01	UP
ENSG00000169902	TPST1	1.82	0.01	UP
ENSG00000171786	NHLH1	1.09	0.01	UP
ENSG00000251456	RP11-436H11.5	3.43	0.01	UP
ENSG00000233791	BTG2-DT	1.45	0.01	UP
ENSG00000155307	SAMSN1	1.41	0.01	UP
ENSG00000188026	RILPL1	1.06	0.01	UP
ENSG00000222005	LINC01118	1.71	0.01	UP
ENSG00000181409	AATK	1.09	0.01	UP
ENSG00000111490	TBC1D30	1.11	0.01	UP
ENSG00000250548	LINC01303	1.33	0.01	UP
ENSG00000272540	XXbac-BPG252P9.9	1.04	0.01	UP
ENSG00000168404	MLKL	1.03	0.01	UP
ENSG00000287338	NA	1.52	0.01	UP
ENSG00000161640	SIGLEC11	1.62	0.01	UP
ENSG00000100985	MMP9	1.55	0.01	UP
ENSG00000130202	NECTIN2	1.88	0.01	UP
ENSG00000286004	NA	1.62	0.01	UP
ENSG00000272754	AL133245.2	1.14	0.01	UP
ENSG00000171658	RP11-443P15.2	2.03	0.01	UP
ENSG00000160781	PAQR6	1.17	0.01	UP
ENSG00000084070	SMAP2	1.22	0.01	UP
ENSG00000235888	AF064858.8	1.73	0.01	UP
ENSG00000253190	AC084082.3	2.36	0.01	UP
ENSG00000135407	AVIL	1.08	0.01	UP
ENSG00000240219	RP11-430C7.5	1.01	0.01	UP
ENSG00000008438	PGLYRP1	1.67	0.01	UP

ENSG00000287655	NA	1.47	0.01	UP
ENSG00000119888	EPCAM	2.84	0.01	UP
ENSG00000241666	RP3-455J7.4	1.10	0.01	UP
ENSG00000114270	COL7A1	1.07	0.01	UP
ENSG00000186583	SPATC1	1.66	0.01	UP
ENSG00000236525	AC007278.2	2.03	0.01	UP
ENSG00000176749	CDK5R1	1.35	0.01	UP
ENSG00000260859	RP11-254F19.2	1.43	0.01	UP
ENSG00000222112	RN7SKP16	1.84	0.01	UP
ENSG00000112195	TREML2	1.09	0.01	UP
ENSG00000283683	MYOCOS	1.44	0.01	UP
ENSG00000246082	NUDT16P1	1.06	0.01	UP
ENSG00000154227	CERS3	1.40	0.01	UP
ENSG00000273076	RP3-508I15.22	1.36	0.01	UP
ENSG00000218226	TATDN2P2	1.26	0.01	UP
ENSG00000261997	RP11-212I21.4	1.39	0.01	UP
ENSG00000252577	SCARNA20	1.29	0.02	UP
ENSG00000180712	LINC02363	1.26	0.02	UP
ENSG00000230724	LINC01001	1.10	0.02	UP
ENSG00000248727	LINC01948	1.15	0.02	UP
ENSG00000266265	KLF14	2.59	0.02	UP
ENSG00000271344	RP11-274B21.9	1.02	0.02	UP
ENSG00000137962	ARHGAP29	1.50	0.02	UP
ENSG00000236953	ZDHHC20-IT1	1.20	0.02	UP
ENSG00000223914	AC079630.2	1.76	0.02	UP
ENSG00000184005	ST6GALNAC3	1.39	0.02	UP
ENSG00000282508	NA	1.11	0.02	UP
ENSG00000287064	NA	1.39	0.02	UP
ENSG00000172146	OR1A1	1.48	0.02	UP
ENSG00000248592	STIMATE-MUSTN1	1.08	0.02	UP
ENSG00000261504	LINC01686	1.74	0.02	UP
ENSG00000008516	MMP25	1.36	0.02	UP
ENSG00000203907	OOEP	1.39	0.02	UP
ENSG00000258819	LINC02289	1.95	0.02	UP
ENSG00000262362	LA16c-380H5.2	1.78	0.02	UP
ENSG00000215196	BASP1-AS1	1.43	0.02	UP
ENSG00000239961	LILRA4	1.71	0.02	UP
ENSG00000236409	NRADDP	1.15	0.02	UP
ENSG00000158089	GALNT14	1.33	0.02	UP
ENSG00000235655	H3F3AP4	12.70	0.02	UP
ENSG00000169131	ZNF354A	1.24	0.02	UP
ENSG00000246548	LINC02288	1.56	0.02	UP
ENSG00000130222	GADD45G	1.34	0.02	UP
ENSG00000183598	H3C13	1.50	0.02	UP
ENSG00000116991	SIPA1L2	1.41	0.02	UP
ENSG00000205176	REXO1L1P	3.28	0.02	UP
ENSG00000141574	SECTM1	1.42	0.02	UP
ENSG00000100218	RSPH14	1.41	0.02	UP
ENSG00000225873	LINC00694	1.56	0.02	UP
ENSG00000281162	LINC01127	1.55	0.02	UP
ENSG00000230492	RP4-753D10.5	1.94	0.02	UP
ENSG00000136630	HLX	1.25	0.02	UP
ENSG00000243544	RN7SL172P	1.06	0.02	UP
ENSG00000204338	CYP21A1P	1.31	0.02	UP
ENSG00000233431	LINC02596	1.23	0.02	UP
ENSG00000172940	SLC22A13	1.04	0.02	UP
ENSG00000268500	SIGLEC5	1.22	0.02	UP
ENSG00000073150	PANX2	1.09	0.02	UP
ENSG00000188559	RALGAPA2	1.08	0.02	UP
ENSG00000217083	MTCO2P33	1.63	0.02	UP
ENSG00000286796	NA	1.08	0.02	UP
ENSG00000142609	CFAP74	1.38	0.02	UP
ENSG00000187554	TLR5	1.41	0.02	UP
ENSG00000256690	STX5-DT	1.03	0.02	UP
ENSG00000137462	TLR2	1.13	0.02	UP
ENSG00000221869	CEBPD	1.09	0.02	UP
ENSG00000124215	CDH26	1.06	0.02	UP
ENSG00000163754	GYG1	1.04	0.02	UP
ENSG00000227766	HCG4P5	1.74	0.02	UP
ENSG00000279721	RP11-416H1.2	1.16	0.02	UP
ENSG00000258082	RP11-443B7.3	1.04	0.02	UP
ENSG00000276644	DACH1	1.44	0.02	UP
ENSG00000233461	LOC122526782	1.17	0.02	UP
ENSG00000280407	RP13-516M14.8	1.57	0.02	UP
ENSG00000288582	NA	1.37	0.02	UP
ENSG00000170439	TMT1B	1.65	0.02	UP
ENSG00000232807	RP11-536K7.3	1.05	0.02	UP
ENSG00000255801	RP11-561P12.5	2.15	0.02	UP
ENSG00000121060	TRIM25	1.23	0.02	UP
ENSG00000203666	EFCAB2	1.46	0.02	UP
ENSG00000222179	RN7SKP26	1.89	0.02	UP
ENSG00000246430	LINC00968	1.08	0.02	UP

ENSG00000225213	RP11-197M22.2	1.08	0.02	UP
ENSG00000164708	PGAM2	1.03	0.02	UP
ENSG00000152766	ANKRD22	2.08	0.02	UP
ENSG00000223629	DEFA8P	2.60	0.02	UP
ENSG00000090376	IRAK3	1.51	0.02	UP
ENSG00000182541	LIMK2	1.25	0.02	UP
ENSG00000184985	SORCS2	1.11	0.02	UP
ENSG00000286633	NA	2.06	0.02	UP
ENSG00000168140	VASN	1.35	0.02	UP
ENSG00000146592	CREB5	1.09	0.02	UP
ENSG00000156968	MPV17L	1.14	0.02	UP
ENSG00000168062	BATF2	2.05	0.02	UP
ENSG00000254477	AP000640.10	1.11	0.02	UP
ENSG00000279858	RP11-618M23.5	1.58	0.02	UP
ENSG00000232938	FLJ43681	1.49	0.02	UP
ENSG00000234389	AC007278.3	1.90	0.02	UP
ENSG00000213373	LINC00671	1.23	0.02	UP
ENSG00000249437	NAIP	1.13	0.02	UP
ENSG00000204634	TBC1D8	1.28	0.02	UP
ENSG00000204805	FAM27E4	1.66	0.02	UP
ENSG00000257210	NACAP3	1.52	0.02	UP
ENSG00000224950	RP5-1086K13.1	1.02	0.02	UP
ENSG00000271377	RP11-33I11.3	1.78	0.02	UP
ENSG00000279359	RP11-36D19.9	2.67	0.02	UP
ENSG00000251179	TMEM92-AS1	1.44	0.02	UP
ENSG00000162407	PLPP3	1.02	0.02	UP
ENSG00000102794	ACOD1	2.35	0.02	UP
ENSG00000198216	CACNA1E	1.57	0.02	UP
ENSG00000284830	LOC101928718	1.22	0.02	UP
ENSG00000234534	CSNK1G2P1	1.23	0.02	UP
ENSG00000275210	AC008984.2	1.13	0.02	UP
ENSG00000225422	RBMS1P1	1.85	0.02	UP
ENSG00000070371	CLTCL1	1.11	0.02	UP
ENSG00000234076	TPRG1-AS1	1.07	0.02	UP
ENSG00000009950	MLXIPL	1.31	0.02	UP
ENSG00000105392	CRX	1.42	0.02	UP
ENSG00000248863	RP11-83A24.1	1.01	0.02	UP
ENSG00000116793	PHTF1	1.02	0.02	UP
ENSG00000189120	SP6	1.76	0.02	UP
ENSG00000267344	CTB-39G8.3	2.69	0.02	UP
ENSG00000126603	GLIS2	1.50	0.02	UP
ENSG00000236754	LOC101929372	1.00	0.02	UP
ENSG00000113749	HRH2	1.20	0.02	UP
ENSG00000250982	RP11-159J3.1	4.00	0.02	UP
ENSG00000256751	PLBD1-AS1	1.24	0.03	UP
ENSG00000160471	COX6B2	1.51	0.03	UP
ENSG00000230423	XX-C2158C6.1	1.52	0.03	UP
ENSG00000259803	SLC22A31	1.22	0.03	UP
ENSG00000171051	FPR1	1.09	0.03	UP
ENSG00000267546	RP11-666A8.8	1.01	0.03	UP
ENSG00000284471	NA	1.39	0.03	UP
ENSG00000131379	C3orf20	1.33	0.03	UP
ENSG00000100024	UPB1	1.02	0.03	UP
ENSG00000179967	PPP1R14BP3	1.06	0.03	UP
ENSG00000267365	KCNJ2-AS1	1.43	0.03	UP
ENSG00000214688	C10orf105	1.10	0.03	UP
ENSG00000133800	LYVE1	1.38	0.03	UP
ENSG00000138185	ENTPD1	1.02	0.03	UP
ENSG00000240527	RP11-429G19.3	1.63	0.03	UP
ENSG00000276488	CTD-2537I9.18	1.40	0.03	UP
ENSG00000104611	SH2D4A	1.69	0.03	UP
ENSG00000203721	LINC00862	1.25	0.03	UP
ENSG00000273247	RP11-83A24.2	1.06	0.03	UP
ENSG00000215156	RP11-1023L17.2	1.42	0.03	UP
ENSG00000196917	HCAR1	1.23	0.03	UP
ENSG00000260366	CTD-2639E6.4	1.43	0.03	UP
ENSG00000230257	NFE4	1.17	0.03	UP
ENSG00000261305	RP4-584D14.7	1.16	0.03	UP
ENSG00000285737	NA	1.08	0.03	UP
ENSG00000198736	MSRB1	1.06	0.03	UP
ENSG00000179094	PER1	1.44	0.03	UP
ENSG00000128641	MYO1B	1.86	0.03	UP
ENSG00000227080	CTD-2021A8.3	1.64	0.03	UP
ENSG00000163958	ZDHHC19	2.10	0.03	UP
ENSG00000172216	CEBPB	1.02	0.03	UP
ENSG00000166839	ANKDD1A	1.16	0.03	UP
ENSG00000229314	ORM1	1.83	0.03	UP
ENSG00000272589	ZSWIM8-AS1	1.16	0.03	UP
ENSG00000132518	GUCY2D	1.32	0.03	UP
ENSG00000280181	RP11-629N8.4	1.12	0.03	UP
ENSG00000184106	TREML3P	1.28	0.03	UP
ENSG00000147408	CSGALNACT1	1.42	0.03	UP

ENSG00000166741	NNMT	2.15	0.03	UP
ENSG00000287192	NA	1.60	0.03	UP
ENSG00000241886	RP11-242C19.2	1.21	0.03	UP
ENSG00000251161	RP11-540O11.1	1.18	0.03	UP
ENSG00000140795	MYLK3	1.13	0.03	UP
ENSG00000201988	Y_RNA	1.10	0.03	UP
ENSG00000275888	RP13-516M14.10	1.45	0.03	UP
ENSG00000228719	RP5-1119A7.14	1.19	0.03	UP
ENSG00000232133	IMPDH1P10	2.01	0.03	UP
ENSG00000234290	AC116366.6	1.29	0.03	UP
ENSG00000073737	DHRS9	1.27	0.03	UP
ENSG00000116774	OLFML3	1.15	0.03	UP
ENSG00000257506	PLA2G10HP	5.09	0.03	UP
ENSG00000260256	AP001063.1	1.31	0.03	UP
ENSG00000166523	CLEC4E	1.21	0.03	UP
ENSG00000267293	LOC100422497	1.56	0.03	UP
ENSG00000084110	HAL	1.05	0.03	UP
ENSG00000262408	RP11-670E13.3	1.32	0.03	UP
ENSG00000140986	RPL3L	2.47	0.03	UP
ENSG00000248559	RP11-215P8.3	1.04	0.03	UP
ENSG00000236438	FAM157A	1.13	0.03	UP
ENSG00000239887	C1orf226	1.54	0.03	UP
ENSG00000285444	NA	1.40	0.03	UP
ENSG00000137393	RNF144B	1.02	0.03	UP
ENSG00000274026	FAM27E3	1.01	0.03	UP
ENSG00000205517	RGL3	1.07	0.03	UP
ENSG00000199933	RNY1P16	1.29	0.03	UP
ENSG00000079393	DUSP13B	1.39	0.03	UP
ENSG00000257878	RP11-256L6.3	1.20	0.03	UP
ENSG00000138315	OIT3	1.06	0.03	UP
ENSG00000287193	NA	1.14	0.03	UP
ENSG00000138207	RBP4	1.58	0.03	UP
ENSG00000238061	RP4-635A23.4	1.02	0.03	UP
ENSG00000164379	FOXQ1	2.82	0.03	UP
ENSG00000266368	RP11-1096G20.5	1.16	0.04	UP
ENSG00000264400	RN7SL491P	1.52	0.04	UP
ENSG00000239605	STPG4	1.23	0.04	UP
ENSG00000181458	TMEM45A	1.04	0.04	UP
ENSG00000276651	AC007950.2	1.10	0.04	UP
ENSG00000163697	APBB2	1.24	0.04	UP
ENSG00000119138	KLF9	1.02	0.04	UP
ENSG00000146955	RAB19	1.16	0.04	UP
ENSG00000105609	LILRB5	1.23	0.04	UP
ENSG00000229832	RP11-384C4.2	1.03	0.04	UP
ENSG00000232528	RP4-673D20.3	1.04	0.04	UP
ENSG00000101638	ST8SIA5	1.48	0.04	UP
ENSG00000183638	RP1L1	1.72	0.04	UP
ENSG00000259070	LINC00639	1.17	0.04	UP
ENSG00000224216	RP13-228J13.1	1.22	0.04	UP
ENSG00000232599	RP1-161N10.1	2.20	0.04	UP
ENSG00000179862	CITED4	1.09	0.04	UP
ENSG00000277545	RP11-73M11.3	1.11	0.04	UP
ENSG00000184557	SOCS3	1.33	0.04	UP
ENSG00000152932	RAB3C	1.50	0.04	UP
ENSG00000237372	LINC03062	1.34	0.04	UP
ENSG00000235321	AC007556.3	1.65	0.04	UP
ENSG00000236567	TCF3P1	1.17	0.04	UP
ENSG00000286045	NA	1.66	0.04	UP
ENSG00000249274	PDLIM1P4	1.05	0.04	UP
ENSG00000280017	RP11-54F2.9	1.36	0.04	UP
ENSG00000187513	GJA4	1.41	0.04	UP
ENSG00000254639	CTD-2589M5.5	1.11	0.04	UP
ENSG00000266970	SOCS3-DT	1.39	0.04	UP
ENSG00000149575	SCN2B	1.41	0.04	UP
ENSG00000274173	RP4-568C11.4	1.72	0.04	UP
ENSG00000012171	SEMA3B	1.06	0.04	UP
ENSG00000108950	FAM20A	1.44	0.04	UP
ENSG00000165181	SHOC1	1.87	0.04	UP
ENSG00000286999	NA	2.48	0.04	UP
ENSG00000157152	SYN2	1.38	0.04	UP
ENSG00000159496	RGL4	1.11	0.04	UP
ENSG00000206177	HBM	3.13	0.04	UP
ENSG00000136315	RP11-84C10.2	1.02	0.04	UP
ENSG00000133116	KL	1.43	0.04	UP
ENSG00000257322	RP11-511B23.2	1.24	0.04	UP
ENSG00000130656	HBZ	2.17	0.04	UP
ENSG00000115457	IGFBP2	1.71	0.04	UP
ENSG00000232450	RPS2P14	1.23	0.04	UP
ENSG00000128917	DLL4	1.30	0.04	UP
ENSG00000011201	ANOS1	1.32	0.04	UP
ENSG00000168126	OR2W6P	1.21	0.04	UP
ENSG00000108984	MAP2K6	1.24	0.04	UP

ENSG00000165115	KIF27	1.20	0.04	UP
ENSG00000111058	ACSS3	1.22	0.04	UP
ENSG00000174705	SH3PXD2B	1.24	0.04	UP
ENSG00000218713	RP1-34L19.1	1.15	0.04	UP
ENSG00000178342	KCNG2	1.53	0.04	UP
ENSG00000280213	UCKL1-AS1	1.04	0.04	UP
ENSG00000175445	LPL	1.92	0.04	UP
ENSG00000223387	LINC02068	2.13	0.04	UP
ENSG00000276017	AC007325.1	1.33	0.04	UP
ENSG00000231794	AC009542.2	1.76	0.04	UP
ENSG00000214772	RP11-174G6.1	1.44	0.04	UP
ENSG00000111261	MANSC1	1.05	0.04	UP
ENSG00000187553	CYP26C1	1.41	0.04	UP
ENSG00000286231	NA	1.27	0.04	UP
ENSG00000170160	CCDC144A	2.14	0.04	UP
ENSG00000133063	CHIT1	1.54	0.04	UP
ENSG00000102796	DHRS12	1.02	0.04	UP
ENSG00000124785	NRN1	1.62	0.04	UP
ENSG00000233060	AC016700.2	1.29	0.04	UP
ENSG00000271821	XXbac-BPG299F13.14	3.35	0.04	UP
ENSG00000253720	RP11-473O4.3	2.05	0.04	UP
ENSG00000073734	ABCB11	1.10	0.04	UP
ENSG00000253139	RP11-17A4.3	1.05	0.04	UP
ENSG00000276754	RP11-461A8.5	1.18	0.04	UP
ENSG00000254632	RP11-21L23.4	1.61	0.04	UP
ENSG00000118160	SLC8A2	1.88	0.04	UP
ENSG00000163357	DCST1	1.08	0.04	UP
ENSG00000271304	DPRXP2	1.51	0.04	UP
ENSG00000157322	CLEC18A	1.15	0.04	UP
ENSG00000281106	TMEM272	1.22	0.05	UP
ENSG00000099985	OSM	1.12	0.05	UP
ENSG00000270393	AC000095.9	1.04	0.05	UP
ENSG00000168779	SHOX2	1.58	0.05	UP
ENSG00000073331	ALPK1	1.08	0.05	UP
ENSG00000285534	NA	2.34	0.05	UP
ENSG00000244265	SIAH2-AS1	1.12	0.05	UP
ENSG00000270641	TSIX	1.68	0.05	UP
ENSG00000232265	LINC02805	1.43	0.05	UP
ENSG00000254870	ATP6V1G2-DDX39B	1.57	0.05	UP
ENSG00000233750	CICP27	2.00	0.05	UP
ENSG00000100583	SAMD15	1.35	0.05	UP
ENSG00000157514	TSC22D3	1.02	0.05	UP
ENSG00000198673	TAFA2	1.23	0.05	UP
ENSG00000142178	SIK1	2.62	0.05	UP
ENSG00000259293	LIPC-AS1	1.60	0.05	UP
ENSG00000225450	RP3-508I15.14	1.12	0.05	UP
ENSG00000286256	NA	1.63	0.05	UP
ENSG00000243607	RPL35AP26	1.25	0.05	UP
ENSG00000224513	AC109309.4	2.43	0.05	UP
ENSG00000285210	NA	1.27	0.05	UP
ENSG00000145284	SCD5	-2.13	<0.0001	DOWN
ENSG00000123358	NR4A1	-2.23	0.0004	DOWN
ENSG00000198182	ZNF607	-1.03	0.0004	DOWN
ENSG00000126016	AMOT	-1.35	0.0005	DOWN
ENSG00000066468	FGFR2	-3.04	0.0005	DOWN
ENSG00000153563	CD8A	-1.97	0.0006	DOWN
ENSG00000078589	P2RY10	-1.34	0.0007	DOWN
ENSG00000147138	GPR174	-1.52	0.0007	DOWN
ENSG00000159618	ADGRG5	-1.24	0.0009	DOWN
ENSG00000166886	NAB2	-1.20	0.0009	DOWN
ENSG00000101096	NFATC2	-1.18	0.001	DOWN
ENSG00000131437	KIF3A	-1.01	0.001	DOWN
ENSG00000026751	SLAMF7	-1.33	0.001	DOWN
ENSG00000139116	KIF21A	-1.47	0.001	DOWN
ENSG00000161905	ALOX15	-3.43	0.001	DOWN
ENSG00000069702	TGFBR3	-1.63	0.001	DOWN
ENSG00000160791	CCR5	-1.49	0.001	DOWN
ENSG00000211799	TRAV19	-1.62	0.002	DOWN
ENSG00000082458	DLG3	-1.21	0.002	DOWN
ENSG00000112149	CD83	-1.03	0.002	DOWN
ENSG00000198934	MAGEE1	-1.06	0.002	DOWN
ENSG00000172058	SERF1A	-2.64	0.002	DOWN
ENSG00000129116	PALLD	-1.66	0.002	DOWN
ENSG00000185697	MYBL1	-1.54	0.002	DOWN
ENSG00000091181	IL5RA	-2.15	0.002	DOWN
ENSG00000111537	IFNG	-2.62	0.002	DOWN
ENSG00000213809	KLRK1	-1.65	0.002	DOWN
ENSG00000168329	CX3CR1	-1.47	0.002	DOWN
ENSG00000168824	NSG1	-1.90	0.002	DOWN
ENSG00000172059	KLF11	-1.00	0.003	DOWN
ENSG00000050405	LIMA1	-1.16	0.003	DOWN
ENSG00000107485	GATA3	-1.38	0.003	DOWN

ENSG00000136111	TBC1D4	-1.26	0.003	DOWN
ENSG00000276023	DUSP14	-1.28	0.003	DOWN
ENSG00000183918	SH2D1A	-1.66	0.003	DOWN
ENSG00000211795	TRAV8-6	-1.70	0.003	DOWN
ENSG00000116791	CRYZ	-1.28	0.003	DOWN
ENSG00000276597	TRBV11-3	-2.45	0.003	DOWN
ENSG00000259834	RP11-284N8.3	-1.01	0.004	DOWN
ENSG00000150687	PRSS23	-1.65	0.004	DOWN
ENSG00000176049	JAKMIP2	-1.45	0.004	DOWN
ENSG00000078596	ITM2A	-1.06	0.004	DOWN
ENSG00000129422	MTUS1	-1.89	0.004	DOWN
ENSG00000164483	SAMD3	-1.41	0.004	DOWN
ENSG00000142875	PRKACB	-1.09	0.004	DOWN
ENSG00000256039	LINC02446	-2.20	0.004	DOWN
ENSG00000197077	KIAA1671	-1.72	0.004	DOWN
ENSG00000091127	PUS7	-1.01	0.005	DOWN
ENSG00000122188	LAX1	-1.05	0.005	DOWN
ENSG00000163600	ICOS	-1.27	0.005	DOWN
ENSG00000135631	RAB11FIP5	-1.15	0.005	DOWN
ENSG00000172116	CD8B	-1.82	0.005	DOWN
ENSG00000100450	GZMH	-1.90	0.005	DOWN
ENSG00000133818	RRAS2	-1.13	0.005	DOWN
ENSG00000211786	TRAV8-2	-1.62	0.005	DOWN
ENSG00000198780	FAM169A	-1.36	0.005	DOWN
ENSG00000164323	CFAP97	-1.06	0.006	DOWN
ENSG00000117560	FASLG	-1.46	0.006	DOWN
ENSG00000125245	GPR18	-1.15	0.006	DOWN
ENSG00000163536	SERPINI1	-1.18	0.006	DOWN
ENSG00000168758	SEMA4C	-1.11	0.006	DOWN
ENSG00000204116	CHIC1	-1.03	0.006	DOWN
ENSG00000253522	MIR3142HG	-1.46	0.006	DOWN
ENSG00000127152	BCL11B	-1.07	0.006	DOWN
ENSG00000132932	ATP8A2	-1.23	0.006	DOWN
ENSG00000196169	KIF19	-2.12	0.006	DOWN
ENSG00000139187	KLRG1	-1.47	0.007	DOWN
ENSG00000211777	TRAV3	-1.68	0.007	DOWN
ENSG00000142627	EPHA2	-1.85	0.007	DOWN
ENSG00000261655	CTD-3064M3.3	-3.05	0.007	DOWN
ENSG00000127334	DYRK2	-1.06	0.007	DOWN
ENSG00000127995	CASD1	-1.05	0.007	DOWN
ENSG00000160654	CD3G	-1.23	0.007	DOWN
ENSG00000229656	ITGB1-DT	-2.55	0.007	DOWN
ENSG00000172673	THEMIS	-1.32	0.007	DOWN
ENSG00000163508	EOMES	-1.48	0.007	DOWN
ENSG00000166428	PLD4	-1.56	0.007	DOWN
ENSG00000187601	MAGEH1	-1.14	0.007	DOWN
ENSG00000181847	TIGIT	-1.25	0.008	DOWN
ENSG00000137441	FGFBP2	-1.70	0.008	DOWN
ENSG00000124920	MYRF	-1.74	0.008	DOWN
ENSG00000140006	WDR89	-1.06	0.008	DOWN
ENSG00000100916	BRMS1L	-1.04	0.009	DOWN
ENSG00000188322	SBK1	-1.46	0.009	DOWN
ENSG00000073861	TBX21	-1.46	0.009	DOWN
ENSG00000163001	CFAP36	-1.03	0.009	DOWN
ENSG00000169429	CXCL8	-1.52	0.009	DOWN
ENSG00000188042	ARL4C	-1.11	0.01	DOWN
ENSG00000198885	ITPRIPL1	-1.03	0.01	DOWN
ENSG00000144451	SPAG16	-1.03	0.01	DOWN
ENSG00000174171	LOC105370792	-1.21	0.01	DOWN
ENSG00000156017	CARNMT1	-1.00	0.01	DOWN
ENSG00000171246	NPTX1	-1.93	0.01	DOWN
ENSG00000151376	ME3	-1.15	0.01	DOWN
ENSG00000131016	AKAP12	-2.01	0.01	DOWN
ENSG00000135736	CCDC102A	-1.05	0.01	DOWN
ENSG00000211776	TRAV2	-1.32	0.01	DOWN
ENSG00000151135	TMEM263	-1.06	0.01	DOWN
ENSG00000171954	CYP4F22	-1.97	0.01	DOWN
ENSG00000103522	IL21R	-1.02	0.01	DOWN
ENSG00000184227	ACOT1	-1.15	0.01	DOWN
ENSG00000159713	TPPP3	-1.85	0.01	DOWN
ENSG00000220793	RPL21P119	-3.31	0.01	DOWN
ENSG00000170962	PDGFD	-1.25	0.01	DOWN
ENSG00000254837	LIPT2-AS1	-1.13	0.01	DOWN
ENSG00000211714	TRBV7-3	-1.71	0.01	DOWN
ENSG00000183134	PTGDR2	-1.77	0.01	DOWN
ENSG00000226508	LINC01918	-2.95	0.01	DOWN
ENSG00000103355	PRSS33	-2.84	0.01	DOWN
ENSG00000275004	ZNF280B	-1.02	0.01	DOWN
ENSG00000109944	JHY	-1.13	0.01	DOWN
ENSG00000173208	ABCD2	-1.25	0.01	DOWN
ENSG00000165929	TC2N	-1.02	0.01	DOWN
ENSG00000180739	S1PR5	-1.59	0.01	DOWN

ENSG00000085563	ABCB1	-1.17	0.01	DOWN
ENSG00000115526	CHST10	-1.08	0.01	DOWN
ENSG00000169992	NLGN2	-1.04	0.01	DOWN
ENSG00000184293	CLECL1	-1.45	0.01	DOWN
ENSG00000242732	RTL5	-1.30	0.01	DOWN
ENSG00000119714	GPR68	-1.24	0.01	DOWN
ENSG00000131634	TMEM204	-1.20	0.01	DOWN
ENSG00000171476	HOPX	-1.28	0.01	DOWN
ENSG00000173917	HOXB2	-1.02	0.01	DOWN
ENSG00000205927	OLIG2	-2.65	0.01	DOWN
ENSG00000211778	TRAV4	-1.47	0.01	DOWN
ENSG00000119514	GALNT12	-1.05	0.01	DOWN
ENSG00000250696	LOC105377267	-2.30	0.01	DOWN
ENSG00000211694	TRGV10	-1.43	0.01	DOWN
ENSG00000211716	TRBV9	-1.34	0.01	DOWN
ENSG00000143185	XCL2	-1.75	0.02	DOWN
ENSG00000228495	LINC01013	-2.36	0.02	DOWN
ENSG00000265185	SNORD3B-1	-3.03	0.02	DOWN
ENSG00000159714	ZDHHC1	-1.47	0.02	DOWN
ENSG00000128656	CHN1	-1.02	0.02	DOWN
ENSG00000176055	MBLAC2	-1.15	0.02	DOWN
ENSG00000104427	ZC2HC1A	-1.03	0.02	DOWN
ENSG00000196586	MYO6	-1.32	0.02	DOWN
ENSG00000118922	KLF12	-1.12	0.02	DOWN
ENSG00000275993	LOC102724428	-1.31	0.02	DOWN
ENSG00000111728	ST8SIA1	-1.21	0.02	DOWN
ENSG00000166707	ZCCHC18	-1.09	0.02	DOWN
ENSG00000211797	TRAV17	-1.40	0.02	DOWN
ENSG00000176083	ZNF683	-2.03	0.02	DOWN
ENSG00000183691	NOG	-1.79	0.02	DOWN
ENSG00000153130	SCOC	-1.09	0.02	DOWN
ENSG00000211790	TRAV8-4	-1.48	0.02	DOWN
ENSG00000240184	PCDHGC3	-1.55	0.02	DOWN
ENSG00000204186	ZDBF2	-1.46	0.02	DOWN
ENSG00000104432	IL7	-1.23	0.02	DOWN
ENSG00000183439	TRIM61	-1.45	0.02	DOWN
ENSG00000145649	GZMA	-1.81	0.02	DOWN
ENSG00000185875	THNSL1	-1.09	0.02	DOWN
ENSG00000164930	FZD6	-1.34	0.02	DOWN
ENSG00000164037	SLC9B1	-1.09	0.02	DOWN
ENSG00000255819	KLRC4-KLRK1	-1.57	0.02	DOWN
ENSG00000089692	LAG3	-1.73	0.02	DOWN
ENSG00000180543	TSPYL5	-1.14	0.02	DOWN
ENSG00000152969	JAKMIP1	-1.17	0.02	DOWN
ENSG00000139626	ITGB7	-1.00	0.02	DOWN
ENSG00000211961	IGHV1-45	-3.13	0.02	DOWN
ENSG00000099822	HCN2	-1.09	0.02	DOWN
ENSG00000198821	CD247	-1.03	0.02	DOWN
ENSG00000234493	GS1-421I3.2	-2.33	0.02	DOWN
ENSG00000166780	BMERB1	-1.18	0.02	DOWN
ENSG00000100385	IL2RB	-1.09	0.02	DOWN
ENSG00000269226	TMSB15B	-1.10	0.02	DOWN
ENSG00000211791	TRAV13-2	-1.28	0.02	DOWN
ENSG00000147234	FRMPD3	-1.36	0.02	DOWN
ENSG00000211958	IGHV3-38	-3.44	0.02	DOWN
ENSG00000211805	TRAV24	-1.36	0.02	DOWN
ENSG00000235946	LL0XNC01-240C2.1	-1.66	0.02	DOWN
ENSG00000133067	LGR6	-1.57	0.02	DOWN
ENSG00000178162	FAR2P2	-1.41	0.02	DOWN
ENSG00000287682	NA	-2.89	0.02	DOWN
ENSG00000205221	VIT	-1.78	0.02	DOWN
ENSG00000074590	NUAK1	-1.54	0.02	DOWN
ENSG00000259080	RP11-158I13.2	-3.58	0.02	DOWN
ENSG00000118156	ZNF541	-1.46	0.02	DOWN
ENSG00000286313	LOC101928373	-1.76	0.02	DOWN
ENSG00000151835	SACS	-1.11	0.02	DOWN
ENSG00000185915	KLHL34	-1.29	0.02	DOWN
ENSG00000277734	TRAC	-1.19	0.02	DOWN
ENSG00000211801	TRAV21	-1.16	0.02	DOWN
ENSG00000116667	C1orf21	-1.10	0.02	DOWN
ENSG00000105366	SIGLEC8	-2.66	0.02	DOWN
ENSG00000007402	CACNA2D2	-1.33	0.02	DOWN
ENSG00000270379	HEATR9	-1.18	0.02	DOWN
ENSG00000110448	CD5	-1.12	0.02	DOWN
ENSG00000138311	ZNF365	-1.58	0.02	DOWN
ENSG00000179639	FCER1A	-1.93	0.02	DOWN
ENSG00000243926	TIPARP-AS1	-1.30	0.02	DOWN
ENSG00000246228	CASC8	-3.43	0.02	DOWN
ENSG00000272763	RP11-357H14.17	-1.94	0.02	DOWN
ENSG00000069667	RORA	-1.18	0.02	DOWN
ENSG00000129757	CDKN1C	-1.87	0.03	DOWN
ENSG00000156463	SH3RF2	-1.79	0.03	DOWN

ENSG00000240954	RPL4P1	-1.34	0.03	DOWN
ENSG00000174928	C3orf33	-1.24	0.03	DOWN
ENSG00000111344	RASAL1	-1.81	0.03	DOWN
ENSG00000007350	TKTL1	-1.37	0.03	DOWN
ENSG00000174600	CMKLR1	-1.11	0.03	DOWN
ENSG00000111249	CUX2	-1.26	0.03	DOWN
ENSG00000130433	CACNG6	-2.26	0.03	DOWN
ENSG00000103056	SMPD3	-1.31	0.03	DOWN
ENSG00000134489	HRH4	-1.66	0.03	DOWN
ENSG00000169740	ZNF32	-1.06	0.03	DOWN
ENSG00000114993	RTKN	-1.17	0.03	DOWN
ENSG00000233476	EEF1A1P6	-1.12	0.03	DOWN
ENSG00000211800	TRAV20	-1.22	0.03	DOWN
ENSG00000144824	PHLDB2	-1.05	0.03	DOWN
ENSG00000167123	CERCAM	-1.14	0.03	DOWN
ENSG00000130558	OLFM1	-2.02	0.03	DOWN
ENSG00000162804	SNED1	-1.09	0.03	DOWN
ENSG00000170298	LGALS9B	-1.71	0.03	DOWN
ENSG00000128536	CDHR3	-1.07	0.03	DOWN
ENSG00000136014	USP44	-1.17	0.03	DOWN
ENSG00000162543	UBXN10	-1.24	0.03	DOWN
ENSG00000235833	AC159540.14	-1.71	0.03	DOWN
ENSG00000267472	LOC440461	-1.78	0.03	DOWN
ENSG00000125864	BFSP1	-1.28	0.03	DOWN
ENSG00000227191	TRGC2	-1.38	0.03	DOWN
ENSG00000061337	LZTS1	-1.45	0.03	DOWN
ENSG00000020633	RUNX3	-1.09	0.03	DOWN
ENSG00000102471	NDFIP2	-1.12	0.03	DOWN
ENSG00000276819	TRBV15	-1.53	0.03	DOWN
ENSG00000158286	RNF207	-1.15	0.03	DOWN
ENSG00000174255	ZNF80	-1.77	0.03	DOWN
ENSG00000177465	ACOT4	-1.08	0.03	DOWN
ENSG00000274376	ADAMTS7P1	-1.36	0.03	DOWN
ENSG00000204455	TRIM51BP	-2.65	0.03	DOWN
ENSG00000181036	FCRL6	-1.41	0.03	DOWN
ENSG00000211720	TRBV11-1	-1.46	0.03	DOWN
ENSG00000185933	CALHM1	-1.47	0.03	DOWN
ENSG00000233411	RP11-104L21.2	-1.50	0.03	DOWN
ENSG00000274611	TBC1D3	-11.54	0.04	DOWN
ENSG00000238222	MKRN4P	-5.21	0.04	DOWN
ENSG00000233093	LINC00892	-1.26	0.04	DOWN
ENSG00000256427	RP11-118B22.4	-1.41	0.04	DOWN
ENSG00000170486	KRT72	-1.84	0.04	DOWN
ENSG00000178538	CA8	-1.47	0.04	DOWN
ENSG00000182963	GJC1	-1.30	0.04	DOWN
ENSG00000232434	AJM1	-1.00	0.04	DOWN
ENSG00000215148	PRSS41	-2.95	0.04	DOWN
ENSG00000114405	CEP15	-1.06	0.04	DOWN
ENSG00000182534	MXRA7	-1.28	0.04	DOWN
ENSG00000167286	CD3D	-1.33	0.04	DOWN
ENSG00000161681	SHANK1	-1.77	0.04	DOWN
ENSG00000237248	LINC00987	-1.07	0.04	DOWN
ENSG00000133739	LRRCC1	-1.09	0.04	DOWN
ENSG00000185920	PTCH1	-1.04	0.04	DOWN
ENSG00000250654	RP11-834C11.7	-1.23	0.04	DOWN
ENSG00000124507	PACSIN1	-1.38	0.04	DOWN
ENSG00000157985	AGAP1	-1.21	0.04	DOWN
ENSG00000255569	TRAV1-1	-1.66	0.04	DOWN
ENSG00000184545	DUSP8	-1.11	0.04	DOWN
ENSG00000100453	GZMB	-1.17	0.04	DOWN
ENSG00000167748	KLK1	-1.46	0.04	DOWN
ENSG00000155265	GOLGA7B	-1.04	0.04	DOWN
ENSG00000164114	MAP9	-1.12	0.04	DOWN
ENSG00000286640	NA	-1.74	0.04	DOWN
ENSG00000261754	CTC-523E23.1	-1.06	0.04	DOWN
ENSG00000163923	RPL39L	-1.12	0.04	DOWN
ENSG00000263155	MYZAP	-1.54	0.04	DOWN
ENSG00000137501	SYTL2	-1.03	0.04	DOWN
ENSG00000211751	TRBC1	-1.17	0.04	DOWN
ENSG00000229203	AC103564.7	-1.66	0.04	DOWN
ENSG00000286895	NA	-1.21	0.04	DOWN
ENSG00000130035	GALNT8	-1.06	0.04	DOWN
ENSG00000211792	TRAV14DV4	-1.24	0.04	DOWN
ENSG00000135898	GPR55	-1.10	0.04	DOWN
ENSG00000107954	NEURL1	-1.36	0.04	DOWN
ENSG00000167600	CYP2S1	-1.37	0.04	DOWN
ENSG00000214745	GOT2P6	-1.42	0.04	DOWN
ENSG00000104833	TUBB4A	-1.18	0.04	DOWN
ENSG00000255833	TIFAB	-1.30	0.04	DOWN
ENSG00000116824	CD2	-1.10	0.04	DOWN
ENSG00000240204	SMKR1	-1.38	0.04	DOWN
ENSG00000165091	TMC1	-1.74	0.04	DOWN

ENSG00000253291	TRBV7-7	-1.86	0.04	DOWN
ENSG00000040199	PHLPP2	-1.00	0.04	DOWN
ENSG00000241657	TRBV11-2	-1.06	0.04	DOWN
ENSG00000137876	RSL24D1	-1.11	0.04	DOWN
ENSG00000008517	IL32	-1.12	0.05	DOWN
ENSG00000165895	ARHGAP42	-1.28	0.05	DOWN
ENSG00000211746	TRBV19	-1.24	0.05	DOWN
ENSG00000187243	MAGED4B	-1.23	0.05	DOWN
ENSG00000156395	SORCS3	-1.69	0.05	DOWN
ENSG00000004799	PDK4	-1.13	0.05	DOWN
ENSG00000152207	CYSLTR2	-1.03	0.05	DOWN
ENSG00000211779	TRAV5	-1.29	0.05	DOWN
ENSG00000260302	RP11-973H7.1	-1.26	0.05	DOWN
ENSG00000117215	PLA2G2D	-1.37	0.05	DOWN
ENSG00000108691	CCL2	-3.00	0.05	DOWN
ENSG00000179841	AKAP5	-1.13	0.05	DOWN
ENSG00000285535	NA	-1.69	0.05	DOWN

[1]Differentially expressed genes defined as an adjusted p-value threshold of <0.05 and log_2 Fold Change of < -1 or > 1

[back to main text]

Supplementary Table 89: Over-represented Gene Ontology Biological Processes in differentially expressed genes between dexamethasone and usual care treatment groups in the dexamethasone comparison.

Pathway	Adjusted p-value[1]
lipoxygenase pathway	0.0002
positive regulation of toll-like receptor signaling pathway	0.0002
humoral immune response	0.0003
phospholipid metabolic process	0.0009
cellular response to tumor necrosis factor	0.0009
response to estrogen	0.0009
activation of GTPase activity	0.001
cellular response to interleukin-1	0.001
positive T cell selection	0.001
development of primary female sexual characteristics	0.001
negative regulation of type II interferon production	0.001
negative regulation of natural killer cell activation	0.001
chemotaxis	0.002
response to wounding	0.002
cellular response to fibroblast growth factor stimulus	0.002
endoderm formation	0.003
endochondral ossification	0.003
uterus development	0.003
positive regulation of oligodendrocyte differentiation	0.003
lipoxin A4 biosynthetic process	0.003
cellular response to redox state	0.003
negative regulation of lymphangiogenesis	0.003
leukotriene production involved in inflammatory response	0.003
positive regulation of natural killer cell activation	0.004
positive regulation of fatty acid beta-oxidation	0.004
killing of cells of another organism	0.005
defense response	0.006
cellular response to calcium ion	0.006
neuropeptide signaling pathway	0.006
lipopolysaccharide-mediated signaling pathway	0.007
embryonic digestive tract morphogenesis	0.007
ureter morphogenesis	0.007
norepinephrine biosynthetic process	0.007
negative regulation of T-helper 2 cell differentiation	0.007
acute-phase response	0.008
motor neuron axon guidance	0.008
negative regulation of transcription by RNA polymerase II	0.009
T cell receptor signaling pathway	0.009
negative regulation of myotube differentiation	0.009
[1]Over-represented pathways defined as an adjusted p-value of <0.01	

[back to main text]