Trial Registries for Transparency and Accountability in Clinical Research

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Submitted for the degree of Doctor of Philosophy

Hilary Term, 2022

This thesis is dedicated to my parents, Joseph and Elizabeth, who set me down the path that led me here, and my wife, Regine, without whose love, patience, and support none of this would have been possible.

Acknowledgements

I am immensely grateful to my supervisors, colleagues, friends, and family who aided, guided, and supported me throughout this DPhil.

First and foremost, I thank my supervisors, Professor Carl Heneghan and Professor Ben Goldacre. Thank you, Carl, for your encouragement to pursue this degree, one of the many opportunities you've provided for me to grow and mature as a researcher. Your council and advice these past four years have ensured I considered all the little things that are necessary for a successful DPhil and, ultimately, a research career. You are constantly challenging me to think about how I can create impact with my work and advance my research down new and interesting paths. I always leave our chats excited and inspired about what will come next.

To Ben, it would take up far too much space to list all the things for which I'd like to thank you. Your energy, leadership, guidance, and friendship are the cornerstones of this thesis. You have been a constant source of support and inspiration since you took a chance on me as a research assistant six years ago. When you called to offer me that job you asked me "Do you really want to come work with us?" and emphatically saying "Yes!" was one of the best decisions I've ever made. Over that time, you've had a profound influence on me as a researcher, writer, and an advocate for better, more open, and rigorous science. You've also managed to build a bloody marvellous collection of talented people at the Bennett Institute that I look forward to working with every day. I can't thank you enough and I'm excited about what comes next. ONWARD!

Moving on to that truly bloody marvellous collection of talented people, I'd like to thank my daily comrades in this adventure at the Bennett Institute for Applied Data Science (née The DataLab).

I've seen this team grow massively over the past few years and yet the productivity, determination, intelligence, and good humour of the group has never wavered. Thank you all for being fountains of knowledge and support (tech and otherwise). Working on a thesis can be lonely at times but being embedded in this community has made a huge difference to my productivity and wellbeing. I can't wait to see what the future holds for the Bennett Institute. Special thanks for many years of collaboration, brainstorm sessions, coding tips, quick questions, pints at the pub, and an entire institutional history of jokes to Seb Bacon, Dr. Helen Curtis, Dr. Alex Walker, Brian MacKenna, Peter Inglesby, Richard Croker, Dave Evans, Dr. Caroline Morton, (future Dr.) Jess Morely, and Dr. Henry Drysdale.

Many thanks to my fellow DPhil students at the Nuffield Department of Primary Care Health Sciences for being a source of support, tips and tricks, commiseration, and inspiration throughout the DPhil. Hearing about the wonderful work being done by all of you is always fascinating and reinvigorating. I am particularly indebted to Dr. Georgia Richards, Dr. Beth Jakubowski, Dr. Oghenekome Gbinigie, (future Dr.) Jackie Walumbe, and Dr. Julian Treadwell for their advice and friendship throughout these past four years.

I've also had the pleasure to work with a host of excellent collaborators and colleagues who have helped and motivated me in innumerable ways throughout my DPhil. Thank you to (future Dr.) Maia Salholz-Hillel, Dr. Peter Grabitz, Molly Pugh-Jones, Nicole Hildebrand, Tjada Schult, Dr. Johannes Schwietering, and Dr. Daniel Strech of the DIRECCT project; Dr. Jeff Aronson, Ruth Davis, and Dr. Annette Plüddemann at CEBM; Dr. Marin McKee of the LSHTM; Dr. James Smith of NDORMS, and Dr. Síle Lane and Dr. Tracey Brown from the AllTrials Campaign. Thank you to Dr. Stephen Bradley for so often including me in your unwavering commitment to improving medical research; to Dr. Anthony Franchini for providing fresh eyes on my final chapters; and to Dr. Till Bruckner, who has been a constant colleague and companion in

championing the importance of transparency in clinical research and has helped bring meaning and impact to my work. Lastly, thank you to Dr. Susan Chimonas who helped me begin to realise my academic aspirations at CMAP and, when I moved to the UK, forwarded me a job opportunity at Oxford she saw, and thought would be a great fit. She was right.

And finally, thank you to all my family and friends whose love and support has fuelled my journey throughout life.

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Glossary of Common Terms and Abbreviations

Global Terms

International Clinical Trials Registry Platform (ICTRP): The ICTRP, hosted by the World Health Organisation, creates standards for registries, recognises primary registries that meet these standards, and maintains a meta-registry that ingests a standard dataset from all approved global registries

US-Specific Terms

Applicable Clinical Trial (ACT): An applicable clinical trial is any trial that is covered by the FDA Amendments Act 2007 and therefore subject to its registration and reporting requirements. In this thesis, I mirror the official terminology and call any trial that started prior to the implementation of the Final Rule, but ended after, a "probable Applicable Clinical Trial" (pACT) and any trial that started after the implementation of the Final Rule an ACT.

Department of Health and Human Services (DHHS or HHS): The executive department of the US Government specialising in the administration and regulation of medicine, public health, and social services. Most relevant to this thesis, DHHS houses both the FDA and the NIH.

Food and Drug Administration (FDA): The United States regulator for medical interventions. The FDA sits within the Department of Health and Human Services and is charged with enforcing the FDA Amendments Act and approving drugs, devices, and other products (e.g., tobacco products) for marketing.

FDA Amendments Act 2007 (FDAAA 2007): The current US law governing how various aspects of the research and marketing of medical interventions are regulated by the FDA

including requirements for the registration and reporting of clinical trials.

FDA Modernization Act (FDAMA): A precursor law to the FDAAA 2007 that established the first federal requirement to register certain clinical trials.

Final Rule on Clinical Trials Registration and Results Information Submission (the Final Rule, or 42 CFR Part 11): Unless otherwise specified, references to the Final Rule throughout this thesis are referring specifically to Final Rule 42 CFR Part 11 which implemented and clarified various aspects of the FDAAA 2007. This Final Rule came into effect in January 2017.

Investigational New Drug Application (IND) & Investigational Device Exemption (IDE): These are designations given to interventions being studied in support of an eventual marketing authorisation from the FDA. Whether a drug or device is currently under an IND or IDE is not publicly disclosed by the FDA.

National Institutes of Health (NIH): The NIH is a collection of US federal institutes that conduct, and fund, health and biomedical research.

National Library of Medicine (NLM): The NLM is a branch of the NIH that deals with information technology and runs various services including PubMed and ClinicalTrials.gov.

Primary Completion Date (PCD): Defined by ClinicalTrials.gov as “The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure.” Under the FDAAA, a trial is due to report results within a year of the PCD. A Study Completion Date (SCD) is when all subjects have completed follow-up for all outcomes.

EU-Specific Terms

Clinical Trial Application (CTA): The detailed tabular trial protocol submitted by a sponsor to a national authority, via the EudraCT system, for approval. These go on to form the individual parts of a public trial registration on the EUCTR.

Clinical Trial of Investigational Medicinal Product (CTIMP): The name for trials of drugs, vaccines, and biologics that are covered under EU clinical trial regulations. Despite leaving the EU, the UK still uses the CTIMP terminology.

Clinical Trial Information System (CTIS): The new EU clinical trial portal that will replace the EudraCT and EUCTR system under the 2014 European clinical trial regulations. The CTIS will become the sole source of new EU trial registrations in 2023.

European Medicines Agency (EMA): The EU body that, among other responsibilities, manages the clinical trial regulations, including the EudraCT and EUCTR. The EMA is the EU counterpart the US FDA.

European Union Drug Regulating Authorities Clinical Trials Database (EudraCT): The backend data management system for the former EU clinical trial directive where sponsors submit information about clinical trials to national authorities and the EMA.

European Union Clinical Trial Register (EUCTR): The public facing EU clinical trial registry populated with data from the EudraCT system.

National Competent Authority (NCA): The national regulator(s) for each EEA country that

provides regulatory approval for trials with planned enrollment in that country. For instance, the national competent authority for the UK was the Medicines and Healthcare products Regulatory Agency (MHRA) prior to Brexit.

UK-Specific Terms

Clinical Trial Units (CTUs): Academic research units that specialise in the conduct of clinical trials, usually connected to a university or other research institution.

Health Research Authority (HRA): The regulatory body in England responsible for overseeing the ethical conduct of health-related research. Their primary responsibility is managing and overseeing research ethics committees that consider and approve research. The HRA is an "arm's length body" of the Department of Health and Social Care.

ISRCTN: The ICTRP primary registry for the United Kingdom that accepts registrations from anywhere in the world. The ISRCTN is run by the publisher BMC (owned by SpringerNature). ISRCTN is the official name of the registry and does not stand for anything.

Medicines and Healthcare products Regulatory Agency (MHRA): The MHRA is the UK regulator responsible for ensuring the efficacy and safety of medicines and medical devices. Prior to Brexit, the MHRA acted as the national competent authority for the UK. For CTIMPs, trialists are required to get both ethics approval and regulatory approval from the MHRA.

House of Commons Science and Technology Committee (SciTech Committee): The select committee of the UK House of Commons that oversees the work of the Department for Business, Energy, and Industrial Strategy in the UK and has conducted inquiries into research integrity and the transparency of clinical trials.

Research Ethics Committee (REC): Groups that review and approve research proposals to ensure they are conducted to recognised ethical standards. Ethics approvals are required for most research and the REC system is managed by the HRA in England, and the HRA's sister agencies in the devolved nations of the UK. These are analogous to Institutional Review Boards in the US.

Abstract

Background: Over the past 30 years clinical trial registries have become a key institution aiming to reduce bias and waste within global clinical research. Funders, journals, and governments have made prospective trial registration a near universal requirement and a route for results dissemination. This thesis examines the use of registries within the current research landscape and examines how they function as tools for aiding and informing research.

Aims: To examine how clinical trial registries are used to promote transparency and accountability in clinical research and describe where improvements are needed to meet these goals.

Methods: I used a mixed-method approach to examine various aspects of the current function and usage of clinical trial registries. My first four results chapters focus on auditing various aspects of clinical trial registration and reporting to assess and describe the current registry environment. First, I conducted two studies that rely on registries to examine clinical trial reporting at the micro and macro level. Next, I examined how the current regulatory regimes requiring the use of registries in the US and EU have been implemented through examinations of compliance, data quality, and results reporting. These four studies relied on accessible registry data and drew on methods from epidemiology and bibliographic research for data collection and analysis. Lastly, I conducted qualitative interviews with key personnel from public research institutions in the UK about current policies and practice around clinical trial registration and reporting.

Results: Clinical trial registries allow for effective audits of transparency in reporting at both the level of individual studies and of entire research areas. Examinations of e-cigarette and Covid-

19 clinical trial reporting both were made possible through audits linked to registered clinical trial information. However, issues with the reliability and quality of registered data impacted these assessments. Regulations mandating the use of clinical trial registries have been unevenly implemented and enforced in the US and EU. Regulatory processes have not fully ensured that timely trial information is made available, including clinical trials results. Non-commercial sponsors have shown particularly poor compliance with transparency requirements. However, in the UK, political attention informed improvements in institutional transparency policy and practice that may be a model for future improvements elsewhere.

Conclusions: Effectively mandating clinical trial registration through various mechanisms has made registries a vital piece of research infrastructure. Registries both allow for insights into planned, ongoing, and completed trial research as well as form a valuable dataset for original metaresearch. However, additional effort is required to ensure registries are meeting their promise as tools to improve transparency and accountability in clinical research. Without assurances that registrations will be used as definitive sources of trial information by key stakeholders, their uptake will amount to little more than a tick-box bureaucratic measure. Journal editors, funders, and research sponsors all have key roles to play in ensuring that registrations occur prospectively, are properly maintained, and are clearly linked to study results. The incorporation of registries into regulatory schemes has the potential to further ensure meaningful use of registries however experiences in the US, EU, and UK show that without proper enforcement, compliance with these requirements will inevitably be deprioritised.

Statement of Contributions

I certify that this thesis contains my work. In all publications arising from this thesis, I am either the first or senior author. I detail substantial contributions from collaborators and colleagues below along with their initials, which are used for future reference throughout the thesis. My supervisors, Prof. Ben Goldacre (BG) and Prof. Carl Heneghan (CH), provided support and feedback throughout all aspects of the thesis.

Chapter 3: Dr. Henry Drysdale (HD) was the second searcher and extractor for trial information and Dr. Martin McKee (MM) provided valuable context and feedback concerning clinical and policy issues in the tobacco control space that informed the interpretation of the results.

Chapter 4: This chapter is based on an ongoing collaborative project. I am the lead researcher on the project owning the conceptualisation, development, implementation, analysis, and manuscript writing. For the Phase 1 results presented in this thesis, Dr. Peter Grabitz (PG) contributed to the conceptualisation, design, data collection, and interpretation. Maia Salholz-Hillel (MSH) contributed to the design, data collection, analysis, and interpretation, created and managed the data extraction and management infrastructure, and created two figures from the raw data that are reproduced with her permission. Molly Pugh-Jones (MPJ) contributed to data collection. Dr. Daniel Strech (DS) provided the funding and senior project oversight.

Chapter 5: Seb Bacon (SB) created the code to download and process data from the full ClinicalTrials.gov dataset as part of the FDAAA TrialsTracker project and provided final review of my code for identifying covered and due trials. I owned all processing and analysis of the raw data for the work presented in this thesis.

Chapter 6: Dr. Georgia Richards (GR) helped pilot the search strategy and Dr. James Smith (JS) served as the second searcher for trial results in the main analysis. Prof. Carl Heneghan (CH) provided senior support in resolving discrepancies in the extracted data. Seb Bacon (SB) and Francis Irving (FI) created the code that collects protocol data for the EU TrialsTracker which I supplemented with my own custom scrapers. Tom Ward (TW) currently maintains the EU TrialsTracker codebase. I owned all processing and analysis of the raw data for the work presented in this thesis.

Chapter 7: Jessica Morley (JM) contributed to the codebook development and interpretation of this analysis. Drs. Till Bruckner (TB) and Jennifer MacLellan (JM) provided initial feedback on my interview guide.

“Many excellent notions or experiments are, by sober and modest men, suppressed”

-Robert Boyle, 1661

Chapter 1: Overview and Structure of Thesis

1.1 Rationale of Thesis

Clinical trials are crucial to the generation of medical evidence and are relied on by stakeholders to inform guidelines, policies, and clinical decisoin-making.[1] In addition to being highly influential throughout general medical practice and health policy decision making, trial results also inform regulatory approvals of new treatments.[2] Therefore, much attention is paid to the design, tracking, management, and reporting of clinical trials and the creation of strategies to minimise bias in their conduct and interpretation.

Reporting biases concern the selective reporting of results and can impact the complete assessment of an evidence-base.[3] Throughout academia there is evidence that results are left unreported, hypotheses and outcomes are created or switched after results are already known, and lacklustre results can be exaggerated through spin.[4–7] While many disciplines are beginning to confront these issues, biomedical research has long standing research infrastructure, in the form of clinical trial registries, that is meant to help address these concerns.[8] This global network of registries has emerged over the past three decades to both combat reporting biases and inform the community about the current research environment in order to promote enrollment, prevent wasteful duplication, and share methods. A functional registry system is essential as clinicians, patients, and the public cannot make informed choices about treatments when information about clinical trials is routinely withheld or incompletely reported.

In the past decade, registration and reporting in clinical research has transitioned from best practice to a fundamental aspect of trial regulation and governance.[9,10] The research powerhouses of the US and the EU have both implemented requirements for the registration and reporting of clinical trials conducted under their regulatory purview.[11,12] This evolving legal,

ethical, and regulatory context provides the backdrop for this thesis. As the landscape rapidly changes, gaps in the evidence will inevitably occur. Major changes to the global research environment require close study to inform the ongoing development of these systems. Furthermore, the COVID-19 pandemic has tested the ability of the global research community to provide rapid, quality results under emergency conditions. This thesis will touch on each of these areas and offer recommendations to improve the value and utility of registries as a tool for accountability and transparency.

1.2 Overall Hypothesis

Clinical trial registries are currently not functioning optimally as tools for accountability and transparency in clinical research.

1.3 Overall Aim of Thesis

To assess how clinical trial registries are being used by regulators and research sponsors to ensure clinical trial information is provided in a timely, accurate, and complete manner.

1.4 Thesis Structure

1.4.1 Introduction, Background, and the Registry Environment

1.4.1.1 Chapter 1: Thesis overview

This chapter is an overview of the thesis covering its rationale, content, and context.

1.4.1.2 Chapter 2: Thesis Introduction and Background

For Chapter 2, I detail the history of the global system of clinical trial registries and examine their place in current ethical, legal, and regulatory frameworks. In addition, I review the existing evidence about the functionality of clinical trial registries, and explore their use as tools for

research, transparency, and accountability. Parts of this chapter informed two publications in *BMJ Evidence-Based Medicine*.[13,14]

1.4.2 Registries as Tools for Accountability and Transparency

1.4.2.1 Chapter 3: E-cigarette manufacturers' adherence with clinical trial reporting expectations

In Chapter 3, I adapted prior methods[6] to check the consistency of outcome reporting between registrations and results reports of e-cigarette trials sponsored by Juul Labs Inc., a major e-cigarette company. This project demonstrated how registries can be used as tools for critical evaluation of research and raised important questions about the intersection of trial reporting regulations and e-cigarette research in the US. A manuscript based on this chapter was published in the journal *Tobacco Control*.[15]

1.4.2.2 Chapter 4: DIssemination of REgistered Covid-19 Clinical Trials (The DIRECCT Study)

During my DPhil, I acted as the lead researcher on the DIRECCT study, examining the dissemination of Covid-19 clinical trials, with colleagues in Berlin. Chapter 4 reports the preliminary results from the first phase of this study and details the future of the project. Using registry data, I designed a comprehensive search strategy to locate trial results and examine reporting patterns of Covid-19 research and oversaw its implementation by the study team. The dynamics of trial reporting during a public health emergency, including the role registries have played in making results available, are key findings from this study. Additionally, the practical experiences in dealing with the quality and completeness of registry data is informative about the limitations of using these data at scale. The preliminary findings of this study, detailed in Chapter 4, were published in *BMJ Open*.[16]

1.4.3 Clinical Trial Registries and Regulations in the US and EU

1.4.3.1 Chapter 5: Tracking Compliance with Transparency Requirements of the FDA Amendments Act 2007

The remainder of my results chapters shift focus more explicitly to the legal and regulatory context around research transparency while continuing to examine the use and function of registries. In Chapter 5, I conducted a series of audits of compliance with various aspects of the FDA Amendments Act 2007 which governs trial registration and reporting in the US. These audits identified covered trials and assessed compliance across the entire ClinicalTrials.gov dataset using the most up-to-date interpretation of the law. I examined five areas starting with trial reporting, then expanding my automated assessment methods to four additional areas: timely registration, data verification, delayed reporting and trial document submission. For each area I also examined factors associated with compliance. Findings from this chapter were published in *The Lancet* and *JAMA Internal Medicine*.[17,18]

1.4.3.2 Chapter 6: Function and Utility of the EU Clinical Trials Register as a Source of Clinical Trial Information

Chapter 6 builds on prior work from my advisors and I examining EU trial reporting.[19] Here I address questions about how data quality on the registry impacts reporting assessments and how the availability of results on the EUCTR compares to the published literature. This chapter provides a comprehensive assessment of how EU transparency requirements operate, the value of the EUCTR as a data source, and offers lessons for stakeholders as they begin to implement the new EU trial regulations. The data quality and availability analysis from this chapter was published in the journal *Clinical Trials* and the results search study results are being prepared for submission.[20]

1.4.4 Institutional Transparency Practice

1.4.4.1 Chapter 7: Clinical Trials Transparency at UK Public Research Institutions

In Chapter 7, I report a qualitative study in which I interviewed research governance, clinical trial unit, and trial management staff at UK universities and NHS trusts. This study aimed to gain a better understanding of how these institutions manage the registration and reporting of clinical trials. Particular attention was paid to EU reporting requirements in the UK prior to Brexit. Understanding the response to these pressures offers valuable insights into transparency at public research institutions. Documenting and analysing these experiences can help identify best practices and barriers as the UK prepares to reform its newly independent regulatory infrastructure. This analysis is being prepared for journal submission.

1.4.5 Conclusions, Discussion, and Next Steps

1.4.5.1 Chapter 8: The Current Status and Future Direction of Clinical Trial Registries

The final chapter summarises the key findings from my five results chapters and reflects holistically on their strengths and limitations. I then consider how these findings can inform the improved use and management of trial registries and detail my own future research plans examining trial transparency and research integrity.

1.5 Personal Background and Motivation for Thesis

As an undergraduate, my degree focused on combining instruction in the biological sciences with humanities coursework examining the history, ethics, and meta-study of science and medicine. Throughout my studies I developed an interest in how public policy interacts with and influences science. Following my Bachelors, I undertook a Masters in Public Health (MPH) at the Yale School of Public Health in health policy to further pursue these interests. With advanced coursework in policy analysis, epidemiology, and biostatistics, my MPH would provide me with the building blocks of my research career. Additionally, my training in qualitative

methods as a Masters student influenced my development as a mixed-methods researcher as shown in this thesis.

Following my Masters, I began my first job in the private sector working in communications for a large pharmaceutical client. My main responsibility was to support the communications strategy around upcoming regulatory approvals. This experience, combined with an internship during my Masters with a global pharmaceutical company, gave a unique insight into both the regulation of the medical industry and the motivations, values, and goals of pharmaceutical industry professionals.

Working in transparency research has the potential to be antagonistic towards industry actors as there is a history of well-documented issues, some of which I explore in Chapter 2. However, spending time in industry provided invaluable experience and perspective about how the pharmaceutical industry functions day-to-day. I have found that it is important to remember my colleagues who genuinely wanted to help treat and educate patients. That said, the sometimes sordid history of some companies cannot be fully ignored even if the evidence shows that major pharmaceutical companies are leading the way in compliance with transparency provisions. It is important to be vigilant for bad actors in any policy context and work to understand the complex incentive structures that may distort decision making by commercial sponsors. That said, I have found that it is much easier to try and be a partner in improvement with industry and to communicate openly, professionally, and honestly with them, rather than demonise and instantly dismiss them as irredeemably corrupt. This mindset served me well in dealing with industry and academic colleagues who can both, at times, be critical or combative about the findings of my research.

Eventually, I became interested in returning to academia to pursue a career in research and explore many of the topics my education and work experience had raised. I began working at Columbia University's Center on Medicine as a Profession (CMAP) in 2014. I was the lead researcher on a project examining the recently launched Open Payments database, which documented payments from industry to physicians in the US. This would be the first steps in my research career examining topics at the intersection of health policy and transparency. My team's work included qualitative studies on physician attitudes to the Open Payments database, and usage and reactions to the Open Payments website by physicians and the public.[21]

Following my time at CMAP, I moved to the UK in 2016 and soon after began working as a researcher for Dr. Ben Goldacre at the DataLab in Oxford examining issues in trials transparency and research integrity, a natural extension of my past interests. My initial work on the TrialsTracker projects provided the skills, knowledge, data, and research questions that underlie this thesis. Entering this space coincided with major changes in the use and regulation of clinical trial registries across Europe and the US providing the perfect foundation for a DPhil at the intersection of my interests in policy, transparency, and healthcare research.

In addition to examining my key research questions, I also had personal goals to grow and mature as a researcher during my doctoral work. I aimed to employ a mixed methods approach that would challenge me to learn new skills, and hone my existing experience, in quantitative and qualitative methods. Reflecting on my work throughout this thesis allows me to appreciate how much I've accomplished and learned over the course of my degree.

1.6 Key Accomplishments & Reflections

1.6.1 Thesis Publications and Results Dissemination

As of my thesis submission I have published five first- or last-authored manuscripts based on original research from this thesis and written or contributed additional work on publication bias and preregistration based on Chapter 2.[13–18,20] In addition I have presented results from my thesis at academic conferences: a poster at the MetaScience 2019 Symposium based on Chapter 5,[22] which won a poster prize; a presentation on results reporting capabilities at ICTRP registries at the REWARD-EQUATOR 2020 conference based on data presented in Chapter 2;[23] and presentation on clinical trials registration results reporting at EBM Live 2019, and MetaScience 2021 drawing on my work throughout the thesis.[24,25] Additional results from the project presented in Chapter 4 have been accepted for an oral presentation at the World Conference on Research Integrity in May 2022.

1.6.2 Additional Work

During my DPhil, I have been fortunate enough to contribute to a wide range of projects and publications. Some of these were related to my thesis while some are relevant to my general interests in transparency, open science practices, and epidemiology. I contributed to a review on reducing bias in medical research in the *Journal of the Royal Society of Medicine*[26] and opioid prescribing in *BMC Medicine;*[27] co-wrote editorials on reporting of trials in dentistry, the necessity of sharing analytic code, EU trial regulations, and UK trial registration policy, the latter three appearing in *The BMJ;*[28–31] and wrote a methods piece on using web scrapers for research, a key data collection method for my DPhil, in *Nature*.[32] I have also authored or co-authored three published correspondences on topics in research transparency with another letter under review,[33–35] co-presented on open research methods at the *Evidence Live 2018* conference;[36] and presented on harms reporting on clinical trials registries at 4E's Forum in Erice, Sicily.[37]

Collaborations on original research include examining trial reporting in Poland[38] and the compliance of top non-commercial sponsors with EU reporting requirements.[39] For the first year of my DPhil, I was the primary author of the “Unreported Trial of the Week" series at *The BMJ* which highlighted individual trials with missing results.[40] Additionally, I have frequently served as a peer reviewer during my DPhil with over 40 verified reviews across over 30 publications.[a]

I have also contributed to projects related to the Covid-19 pandemic. I am a co-author on an accepted Stage 1 registered report assessing Covid-19 trial design at *Royal Society Open Science*[41] and have contributed to efforts led by my advisors. This includes co-first authorship on a publication in *The Lancet Rheumatology* examining hydroxychloroquine efficacy for Covid-19 in lupus and rheumatoid arthritis patients,[42] and input into additional analyses, as part of the OpenSafely project started by my advisor Prof. Ben Goldacre. I set up and ran the Covid-19 TrialsTracker (covid19.trialstracker.net) early in the pandemic, which aimed to clean and annotate information on registered Covid-19 trials for general use by the community and used this to contribute to the Covid-19 Evidence Service, run by my advisor Prof. Carl Heneghan.[43,44] This work eventually evolved into the DIRECCT project detailed in Chapter 4.

1.6.3 Public and Professional Engagement and Feedback

In addition to my conference presentations, I have been invited to speak about my research to various professional organisations including the UK Clinical Research Collaboration meeting of registered clinical trial units, and at the annual meeting of the UK Trial Managers Network. Forming relationships with these organisations was crucial to recruitment for Chapter 7. I’ve also spoken to colleagues in various other forums about my work including to colleagues at the

[a] Peer review history documented at: https://publons.com/researcher/1578220

University of Bristol, and the University College London Hospitals NHS Foundation Trust. I also appeared as a guest on the "Let's talk e-cigarettes" Podcast[b] which is run by Cochrane Tobacco Addiction researchers at Oxford to discuss the results of Chapter 3 of my thesis.

As the lead researcher on the TrialsTracker project, I am also continuously in touch with sponsors in the US and EU addressing questions about the TrialsTracker project and how best to address reporting issues. This engagement has been key to helping develop research questions, understand how registry data is managed by various stakeholders both inside and outside of industry, and provided crucial context to my findings. I also frequently provide comment to the media on topics related to my research.[45–47]

1.6.4 Grants and Funding Disclosure

I am grateful to my funders who made this thesis possible. My DPhil is funded by a studentship from the Naji Foundation. I have received additional support for conference travel and research materials from the Nuffield Department of Primary Care Health Sciences (REWARD-EQUATOR 2020; MetaScience Symposium 2019), The Centre for Evidence-Based Medicine (4-Es Forum), and Kellogg College (MetaScience Symposium 2019). I additionally received a grant from the Fetzer Franklin Memorial Fund primarily supporting the work in Chapter 7 of this thesis and support from the German Federal Ministry of Education and Research (BMBF) via the QUEST Centre in Berlin for my work on Chapter 4. During my DPhil I have also been employed as a researcher at the DataLab[c] with funding from the Laura and John Arnold Foundation and The Good Thinking Society.

[b] Episode available at: https://www.cochrane.org/news/lets-talk-e-cigarettes-podcast
[c] As of March 2022, The DataLab is now the Bennett Institute for Applied Data Science.

1.6.5 Teaching and Supervision

During my time as a DPhil student, I have participated as a co-instructor in a one-day course on using Python for health data science presented by the DataLab. I also successfully supervised a medical student project on trial reporting under the FDA Amendments Act 2007 that expanded on my existing examinations of the law.

1.6.6 Training and Skill Development

As part of my training, I participated in a one-day course run by the Health Experiences Research Group from the Department of Primary Care Health Sciences on qualitative interview skills. While I have experience conducting interviews from past research projects, this course served as a welcome refresher in advance of my own project and provided valuable guidance on creating interview guides and successfully conducting interviews. Self-teaching has been a large part of my DPhil. I have largely taught myself how to code in Python, with support from developer colleagues at the DataLab. This has been instrumental to the work in my thesis and many of my projects would not have been possible without this self-directed learning and skill development. Additionally, I have continuously endeavoured to improve and expand my knowledge of quantitative methods. Particularly notable during my DPhil has been better understanding and implementing survival analysis as a useful tool for modelling time to reporting for clinical trials.

1.6.7 Challenges

The primary challenge during my DPhil has been the Covid-19 pandemic. In addition to devoting attention to pandemic related research outside of my DPhil, some of my planned DPhil projects had to be altered or delayed due to the pandemic. Most notably, I had to delay data collection for my qualitative study to ensure I could successfully recruit personnel who, early in the pandemic, would have been extremely taxed in managing their research portfolios. I planned to

start recruitment in early Summer 2020 but did not actually begin until late-Autumn 2020. While I was able to manage these delays, it impacted how I prioritised and structured my time throughout the DPhil and required me to adapt my research plans.

Chapter 2: Thesis Introduction and Background

Features of this chapter are published in the following peer-reviewed journals:

- DeVito NJ, Goldacre B. Catalogue of bias: publication bias. *BMJ Evid Based Med* 2019; 24: 53–4. DOI: 10.1136/bmjebm-2018-111107
- Cashin AG, Richards GC, DeVito NJ, Mellor DT, Lee H. Registration of health and medical research. *BMJ Evid Based Med* 2021; published online Dec 21. DOI:10.1136/bmjebm-2021-111836.

This chapter also contains results presented at the REWARD-EQUATOR 2020 conference:

- DeVito NJ. Results reporting at ICTRP data-provider registries: a cross-sectional audit study (O 4-1). 2020; published online Feb 21. https://osf.io/xenkq/

2.1 Chapter Rationale and Overview

This introductory chapter will provide background and context for my thesis by exploring clinical trial registries as a key institution in clinical research. Since the 1980s, an expansive literature has arisen articulating why registries are needed, critiquing the practice, and researching its impact on research integrity and evidence synthesis. My overarching hypothesis is that these registries are not adequately performing their transparency and accountability roles and understanding the origins of these roles is an essential first step. I will do this through analysis of the history and development of registries, their use, and research to improve upon their applications in practice.

2.2 Introduction

Clinical trials are foundational to generating evidence in the biomedical sciences. Well designed and conducted trials are the “fair tests” necessary to inform clinicians, health officials, and the

public about the benefits and harms of interventions.[1] However the value of evidence generated by clinical trials can be compromised by the introduction of bias.[48] Bias can impact the research process at many points in the journey from design to dissemination.[49] Those creating, and interpreting, evidence need to be constantly aware of the risk of bias, understand how it can occur, and attempt to measure and minimise its influence.[50] Clinical trial registries, which collect and present information about planned, ongoing, and completed trials, are one tool to combat bias in clinical research. Through public registration, the intent, design, outcomes, responsible parties, and results of a study are housed in a single record within an open-source, searchable database. This system promises transparency into the clinical research endeavour and aims to reduce research waste and reporting biases.[3,51,52]

This thesis will examine how well clinical trial registries are currently providing accurate and timely information on clinical research. Trial registration has relatively quickly matured into a formalised institution within the medical research landscape.[53–55] Recent years have seen a swell of advocacy for preregistration in other disciplines, most notably in the field of psychology, in response to the "reproducibility crisis".[8,56,57] However, no other field has ingrained prospective registration as an institution within the discipline to the extent of clinical trials research. Major global registries are organised around internationally agreed upon standards for their design and implementation[58] and their use is increasingly being mandated by governments due to the unique intersection of healthcare, policy, and research.[59] The continuing emergence of this global system of legal, ethical, and practical requirements being placed on clinical research offers a rich opportunity to investigate the gaps this thesis aims to fill.

Various stakeholders are served by a functional registry system.[10,60] Those planning clinical trials can understand the current research landscape in an area, reference the design of similar studies, and prevent waste through minimising redundant research.[61–63] Regulators,

researchers, and clinicians performing evidence synthesis to inform approvals, guidelines and practice can also more easily survey a research area, and quickly and efficiently access results.[64–66] The public is provided access to details of the research that underlies health decision-making and is often supported through their tax dollars. Patients and clinicians may also benefit from more efficient matchmaking between potential participants and trials.[67]

The permanent registration record holds sponsors of trials publicly accountable to deliver on their ethical obligations to report results and honour the voluntary commitments of those who participated in producing new clinical knowledge.[68,69] Results cannot be expected for trials that are not known to exist.[70] Even when trials are fully reported, a registration should offer the simplest, most straightforward way to check that the study was conducted in accordance with the specified analysis and any deviations justified.[6,8]

In this chapter, I will detail the history of registries and their current place in the research landscape including their benefits and shortcomings. Research both on and using registries will be examined alongside the introduction of key context and background that frames the work presented in subsequent chapters.

2.3 Methods

Research for this chapter has been ongoing throughout my DPhil. I've collected a substantial library of relevant citations, within the Paperpile citation manager, in support of my published work. At the time of writing I reviewed my collection of citations and utilised a snowball method to locate primary documents, original sources for key claims, and used forward and backward citation searches to capture additional relevant literature.[71] In addition, while writing this chapter in August 2021, I conducted targeted searches in PubMed and Google Scholar using search

terms related to specific areas of interest where further detail was required.[d] I supplemented my literature review with brief original assessments of the results reporting capabilities of ICTRP registries as part of a larger planned project[72] and an informal update to the search strategy from the Schmucker et al. review on publication of registered studies.[73]

2.4 A History of Clinical Trial Registries

2.4.1 Early Research on Publication Bias Sets the Stage

The need for a system to catalogue and track clinical research emerged throughout the 1980s. References to the "file drawer problem" date back to at least the 1950s, however evidence for its impact on clinical trials research arose later.[74,75] In perhaps the earliest work demonstrating reporting bias in clinical research, Elina Hemminki demonstrated that 38% of 566 studies of psychotropic drug submitted to regulators in Sweden and Finland in the 1960s and 70s were not available in the literature making them invisible to clinicians and other stakeholders.[76] Required regulatory processes are an attractive route for examining potential biases in evidence.[77–82] However these records are not always publicly accessible, nor easily retrieved, and represent only the subset of trials that support regulatory submissions from industry.[83–87]

Soon after Hemminki's piece, Robert John Simes would show the quantitative threat of publication bias to the evaluation of clinical evidence. Simes compared the published literature for an ovarian cancer intervention to a results database and showed exaggerated efficacy in the literature due to incomplete data. Simes called for an international registry of clinical trials to manage selective dissemination.[88,89] Additional studies examining the publication status of known populations of trials began to emerge[90] and in the early 1990s a meta-analysis from Kay

[d] Examples of search terms: *publication bias; clinical trial registries AND reporting; clinical trial registries AND history; ClinicalTrials.gov and FDA Modernization Act; clinical trial registries AND bias; ICTRP AND [creation OR history]*

Dickersin and colleagues showed “a positive association between statistically significant results and publication” (unadjusted OR 2.88, 95% CI: 2.13-3.90).[74] The bias in the literature towards “positive” results remains a major issue throughout academia and was at the centre of arguments for trial registration as a method to detect and avoid selective dissemination.[91,92]

Attention to the issue of publication bias would continue to grow throughout the 1990s as the evidence-based medicine movement emphasised the “critical appraisal of the literature”.[93] Many of the leading advocates for registries were also key figures in evidence-based medicine.[94] The literature on publication bias continued to grow[73,95] including a landmark study on reporting issues in antidepressant trials published in the *New England Journal of Medicine*.[79] Researchers began to investigate reasons for publication bias[96–98] and registries were viewed as a key tool in understanding and combating the issue.[96,98–102] Related issues like outcome reporting bias, interpretive spin, and insufficiently detailed trial reports also emerged as major concerns that could be better detected and managed with the use of trial registries.[103–105]

2.4.2 The First Clinical Trial Registries

Calls for clinical trial registries were not solely driven by concerns about publication bias. Early supporters of registries wanted both improved research discovery and synthesis along with improved matchmaking of patients to trials.[106] Disease specific registries serving these purposes dated to at least the 1960s.[106] The 1994 *Handbook of Research Synthesis* included names and contact information for 26 registries of clinical research and other similar lists were maintained elsewhere.[107,108] The implementation and content of these registries varied by the intended audience. Registries aimed at professional audiences were not necessarily widely accessible while others focused on supporting trial enrollment in specific areas like HIV/AIDS and cancer trials.[65] Registration requirements also began to develop alongside regulatory processes.[109–111] At the eighth meeting of the Society for Clinical Trials in 1986, two early registries, The

International Committee on Thrombosis and Haemostasis (ICTH) registry and the Oxford Database of Perinatal Trials (ODPT), maintained by Ian Chalmers among others, were presented as exemplars in a session titled “The Case for Registers of Clinical Trials.”[112] The introduction to the 1986 version of the ICTH registry, disseminated via a physical report, is emblematic of the aim, scope, and barriers for early registries[113]:

“This is an annual report of multicenter, randomized, controlled trials in the field of thrombosis, haemostasis, and atherosclerosis. A register of planned and ongoing trials is thought to be of help to investigators who are planning or designing new trials, or performing meta-analysis. However, the Subcommittee does not have the wherewithal to distribute the details of protocols in the current or previous reports. It is recognized that not all trials have been listed in the registry; two drug companies did not agree to have their studies registered; some contacted investigators have not answered for various reasons. Therefore, the Subcommittee would appreciate receiving information on ongoing or planned multicenter controlled trials that can be included in the next report.”

The ODPT was developed with similar objectives[114]:

- *To provide a resource for reviews of the safety and efficacy of interventions used in perinatal care.*
- *To provide a register of ongoing and planned randomised trials to foster cooperative and coordinated efforts by researchers in the perinatal field.*
- *To encourage a scientifically based approach to the care of mother and babies throughout the world by making this resource available to all those interested.*

The utility of registries in aiding the planning, conduct, and assessment of research was clearly and consistently articulated by those promoting their development and use. Writing about the 1986 meeting, Dickersin noted that “although the discussion often centred on the difficulties of such an undertaking, the need to initiate the effort was emphasised."[112]

2.4.3 Momentum Towards an International Registry System

The early 90s saw major meetings in the US and Europe on trial registration.[106] In 1991 the Ad Hoc Working Party of the International Collaborative Group on Clinical Trial Registries met for the first time in Brussels, Belgium and adopted aims to promote clinical trial registries and

support those who wish to establish their own registries.[115] The US National Institutes of Health (NIH) convened a meeting in late 1993 to "review the rationale for registries, exchange information on existing registries, identify user needs, and explore the barriers to setting up and maintaining registries." A piece describing this meeting noted that "registry advocates envision a time when anyone will be able to obtain information on-line regarding international clinical trials, if not through one unified registry then through a directory of registries."[116]

The increased proliferation of registries spawned larger cross-disciplinary collections of trial records. In the late 1990s, Brown University operated a "register of registers" of clinical trials containing records from over 500 different clinical trial databases.[117] The Cochrane Collaboration, founded in the early 1990s, immediately took an interest in trial registries as a data source.[106,118] Cochrane began to curate the CENTRAL database to support Cochrane Review Groups and as of August 2021, CENTRAL contains nearly 1.8 million records from a variety of sources, including registries.[119]

In 1998, the Current Controlled Trials (CCT) service was launched by the publisher BioMed Central (BMC) as a platform to "facilitate the exchange of information about randomized trials worldwide and to publish an increasing number of trial protocols and trial results."[120] CCT included the metaRegister which brought together trial information under an International Randomized Controlled Trial Number, or ISRCTN, a single identifiable number for each clinical trial to improve cross-database matching. ISRCTN[e] would later become the BMC-run primary registry for the UK. The CCT services were recommended to member organisations throughout Europe by the European Science Foundation in 2001 and a subsequent meeting in 2002 led to calls for a comprehensive European registry.[106,121]

[e] Today, "ISRCTN" currently does not stand for anything. The official name of the registry is just the ISRCTN.

These various efforts were essential landmarks in the road towards a global system of trial registration but significant barriers to progress remained. Independent efforts by academics and other private stakeholders lacked any authority to mandate widespread adoption of registration. Attempting to bring together existing records inevitably created trade-offs between the available resources and the comprehensiveness of the database as funding for these efforts were lacking. Even for well curated existing registries, design differences did not guarantee interoperable datasets.[117] Industry was also slow to embrace registration for reasons of cost and commercial confidentiality.[53,67,106] Further advancing the registry movement would require standardisation and centralisation of the registration process and broad, meaningful requirements to register.[122]

2.4.4 The Creation of ClinicalTrials.gov

In 1997, the US Congress passed the FDA Modernization Act (FDAMA) which authorised the NIH to "establish, maintain, and operate a data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions."[123] These provisions followed pressure from scientists and advocates from the HIV/AIDS and breast cancer communities.[69,106,108]

Trials in support of new drug applications to the FDA that investigated a "severe or life-threatening disease"[f] would be required to register, partially addressing long-standing recommendations to make data on approved treatments held by the FDA public.[124] After three years of development by the National Library of Medicine (NLM), ClinicalTrials.gov launched in

[f] FDA documentation states that "The term life-threatening is defined as (1) diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and (2) diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analysis is survival (21 CFR 312.81(a))."

early 2000. Initially the database contained NIH trials and imported pre-existing government trial databases like the AIDS Clinical Trials Information System and Physician's Data Query.[125]

The first implementation guidance for industry was issued in 2002 and reiterated that new trials covered under the FDAMA must register within 21 days of first enrollment of the trial,[g] while existing trials were encouraged to register within 45 days of the notice.[108,126,127] Table 2.1 shows the original ClinicalTrials.gov public dataset as described in the "Industry Guidance" document and contemporaneous publications from NLM staff:[108,126,128] At the time, this was a more expansive dataset than had been collected by the CCT database.[106]

Table 2.1: Original Data Categories and Elements for ClinicalTrials.gov Registration

Category	Data Elements
Descriptive Information	● Brief and Official Title ● Brief Summary and study purpose ● Study Sponsor ● Study Design/Study Phase/Study Type ● Condition or Disease ● Intervention ● Study Start Date
Recruitment Information	● Study Status Information including: ○ Overall Study Status (e.g., recruiting, no longer recruiting) ○ Individual Site Status Eligibility ● Criteria/Gender/Age
Location and Contact Information	● Location of Trial ● Contact information (central contact or per-site)
Administrative Data	● Unique Protocol ID Number and other identifiers ● Study Sponsor ● Last Data Update and Verification dates ● Links to more information (either sponsor provided or through MEDLINE*plus)* and publications if available

A comprehensive US government run registry was a major step forward however the FDAMA was imperfect. While registration was now mandated, the legislation "provided neither funding nor a mechanism of enforcement" and compliance was a major issue.[106,129] Data presented at

[g] Note the FDAAA does not require prospective registration.

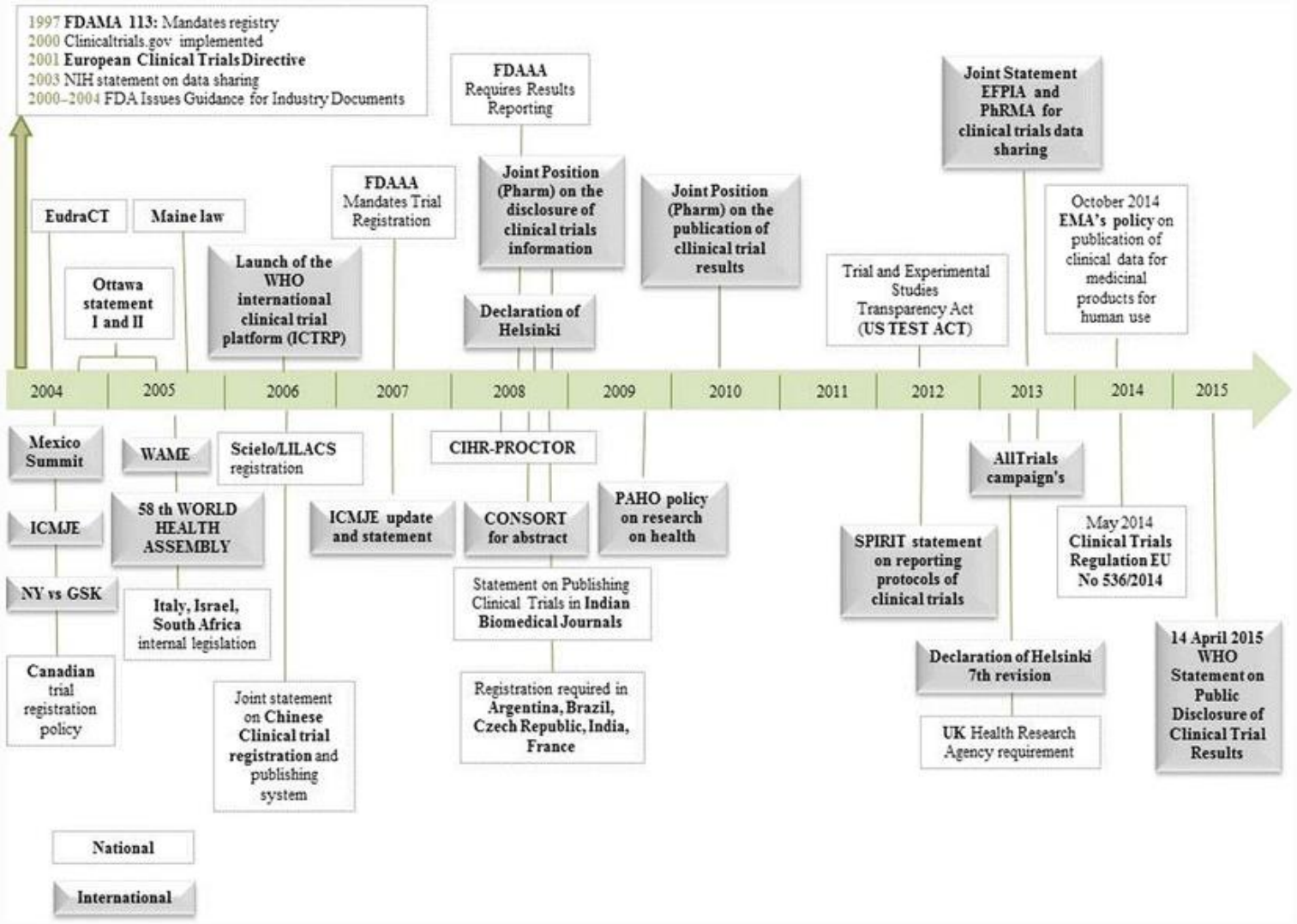
the 2003 FDA Science Forum indicated that just 61 of 127 (48%) industry protocols for cancer trials supporting FDA approvals in 2002 were located on the registry even after the industry guidance became available with instructions to register both new and ongoing trials.[83,106] ClinicalTrials.gov risked becoming just another entry on an ever-expanding list of incomplete registries. Despite criticisms of mandatory transparency measures from commercial interests their hand would soon be forced.[67,130]

2.4.5 "A Great Idea Switches from Ignored to Irresistible"

When Dickersin and Rennie lamented in a 2003 *JAMA* piece that the "relative obscurity of [trial registration] in the lay and biomedical press" conveyed "the message that [the scientific] community does not think registers are important",[106] they must not have known that they were standing on the cusp of a seismic shift in attention to transparency in clinical research and an explosion in the development and promotion of clinical trial registries (Figure 2.1). Drummond Rennie would publish another piece in the same journal just 14 months later titled "Trial Registration: A Great Idea Switches from Ignored to Irresistible."[9] The case of paroxetine brought the two decade fight for a global registration system to the public and political forefront.[67,131]

Paroxetine is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of depression in adults. Due to a lack of adequate disclosure rules, SmithKline Beechum (now GlaxoSmithKline, GSK) did not have to disclose results of studies for off-label usage in children.[132,133] However, clinicians and advocates were beginning to raise concerns about increased suicide risk in paediatric populations taking paroxetine as it was widely used off-label in these patients.[134]

Figure 2.1: Key Milestones in the Registration of Clinical Trials from Pansieri et al. 2015



Reprinted by permission from Springer Nature: Springer. European Journal of Clinical Pharmacology. The evolution in registration of clinical trials: a chronicle of the historical calls and current initiatives promoting transparency. Pansieri et al. 2015. Licence #5200761033832.

By the early 2000s, GSK had evidence that the drug both didn't work in children and increased their rate of suicide. "Study 377" was completed in 1998 and showed the drug was ineffective. It would not be published in the literature until 2006. "Study 329" was published in 2001 with positive safety and efficacy findings that could not be confirmed in later independent reanalysis.[135–137] Leaked internal GSK communications highlighted this strategy of suppression and spin with suicide risks downplayed in applications to regulatory agencies.[133,138] Regulators in the United Kingdom (UK) would go on to detect these safety signals when more data were provided. A systematic review published in the *Lancet* in early 2004 concluded that consideration of the unpublished data caused the harms of these drugs to outweighed any benefits in the paediatric context.[139] Physicians in the UK were soon warned against prescribing these drugs to children by regulators and other countries soon followed suit.[133,138,140]

Various lawsuits and investigations arose from the controversy. In the UK, a four year MHRA inquiry ultimately could not recommend any sanctions due to technicalities around the disclosure of data on off-label uses.[133,141] In the US, GSK would face criminal and civil action at both the state and federal levels for withholding essential safety data. Similar treatments from other companies were also put under scrutiny.[142] By the end of 2004, GSK had settled with New York State for $2.5 million in fines and an agreement to establish a company registry of trial results.[9,143] Other companies would soon begin to proactively establish public registries to host information on their trials despite initial objections.[9,106] GSK pled guilty to federal charges related to the missing safety data combined with various other infractions in 2012 and agreed to pay over $3 billion in criminal and civil penalties, the largest pharmaceutical fraud settlement in US history.[144]

This scandal put the public spotlight on transparency and accountability in clinical research and major advancements quickly followed. In mid-2004, the American Medical Association would

call for a fully comprehensive US register and enhanced access to data held by the FDA.[9] In November 2004, the World Health Organisation (WHO) hosted a summit on health research.[111] Meeting attendees supported the establishment of a "platform linking a network of international clinical trials registers to ensure a single point of access and the unambiguous identification of trials"[145,146] and that:

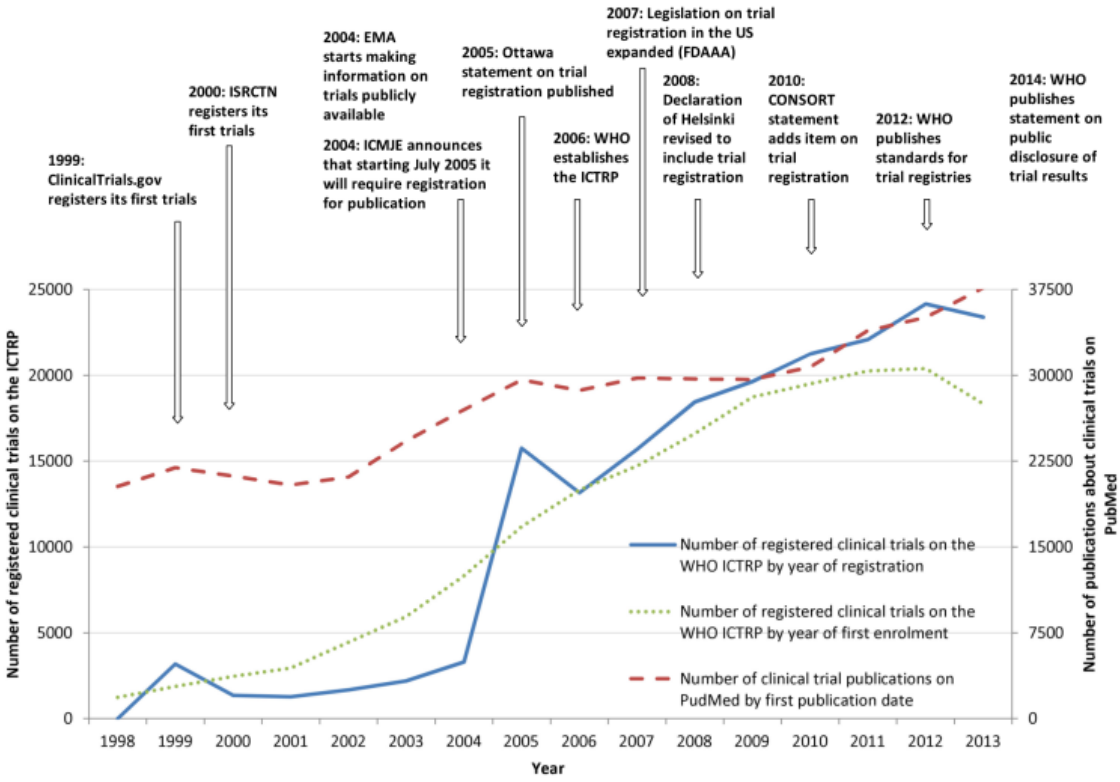
The findings of high-quality research should not only be accessible to decision-makers but also communicated in ways that effectively inform policy, public health, and health care decision-making. Research findings, including of clinical trials, need to be published, documented in internationally accessible registers and archives, and consolidated through systematic reviews. Dissemination of findings in this way can help to inform decisions about support for new research and to build public confidence in science.

The WHO's governing body would take up these recommendations and the International Clinical Trial Registration Platform (ICTRP) was established in 2005.[111,147] The ICTRP would soon release standards for the design, functionality, and governance of clinical trial registries including a minimum registration dataset.[110,148,149]

The International Committee of Medical Journal Editors (ICMJE), a consortium of top medical journals, announced in September 2004 that they would require proof of prospective clinical trial registration[h] as a condition of publication.[99,131,150–152] This was done "as a solution to the problem of selective awareness" of results to enhance "public confidence in the research enterprise." The ICMJE requirements were widely influential although not universally adopted.[153–155] Their impact on registration behaviour, however, was abrupt (Figure 2.2). In 2003 and 2004, ClinicalTrials.gov recorded 3,588 and 3,166 new trial registrations. In 2005, 12,798 new trials were registered -- a 304% increase.[156] Zarin and colleagues noted a 73% increase in registrations on ClinicalTrials.gov between May and October 2005.[157] This uptick in registration was seen across the global registry landscape.[158]

[h] At the time of the announcement, only registration on ClinicalTrials.gov met the minimum conditions for registration set by the ICMJE

Figure 2.2: Publications and Registrations of Clinical Trials 1998-2013 from Viergever & Li (2015)



Reproduced via CC-NC-BY licence. BMJ Open. Trends in global clinical trial registration: an analysis of numbers of registered clinical trials in different parts of the world from 2004 to 2013. Viergever RF, Li K. 2015.

Still, there was a desire for continued development and improvement of the registry system. In 2004, the Canadian Institutes of Health Research hosted a meeting aimed at fostering "international consensus on trial registration."[159] The Ottawa Statement consensus document arising from this meeting would outline basic "principles of trial registration" that would influence the ICTRP's efforts and lead to further guidance and recommendations on the development of registries.[130,159–161] The Ottawa Group was explicit in its calls for mandatory prospective registration and proposed a minimum registration dataset more ambitious than either the ICTRP or industry.[67,130]

2.4.6 Maturation of the Global Registry Landscape

Following these rapid international efforts, a number of national and regional registries were established throughout the 2000s and 2010s.[110,158] The ICTRP began to recognise "primary registries" with national or multinational mandates in 2007. These would have to meet the ICTRP standards and provide the minimum trial dataset for all registered trials to the ICTRP Clinical Trials Search Portal meta-registry. In 2007, the ICMJE expanded their existing registration requirements to specify that prospective registration in any ICTRP recognized primary registry would meet their conditions for publication.[162] The revised 2010 Consolidated Standards of Reporting Trials (CONSORT) guidelines, which promote better reporting of clinical trials, included an item on reporting trial registration numbers in articles.[163] In 2008, the ethical requirement for trial registration and reporting would be codified in the World Medical Association's Declaration of Helsinki which underlies the global conduct of medical research.[164,165]

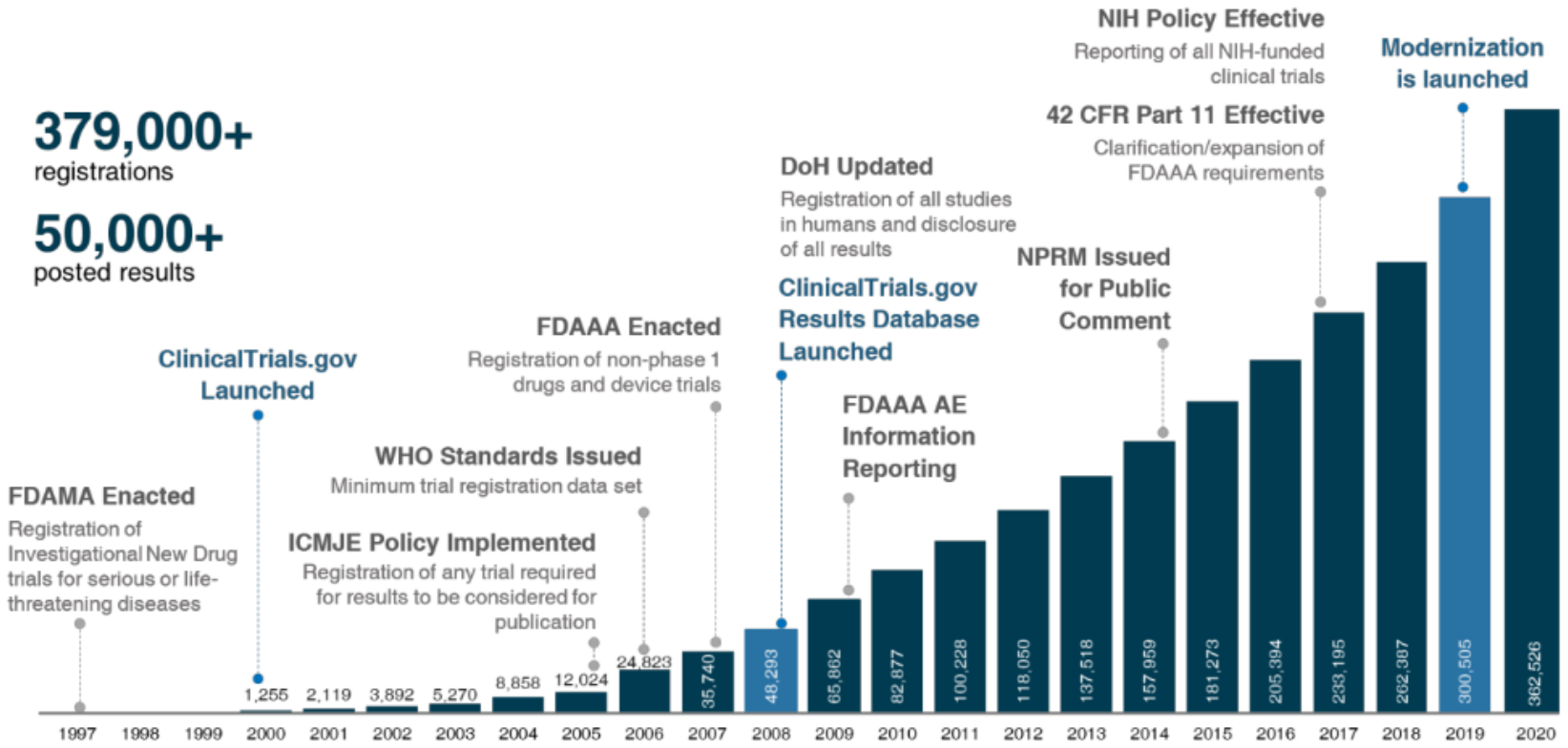
Legal and regulatory frameworks around trial registration and results reporting also began to mature. In 2007 the US Congress passed the FDA Amendments Act (FDAAA 2007) which strengthened and expanded the requirements of the FDAMA (Figure 2.3).[166] Requirements for registration were no longer limited to trials of "serious or life-threatening diseases." Now sponsors of any phase 2-4 trial on a drug, biologic, or device falling under FDA authority would be required to register and report their results directly to ClinicalTrials.gov in a standard tabular format. Results were due within one year of the completion of follow-up for the study's primary outcome(s) and non-compliance could result in monetary fines and additional sanctions.[167] The US government's centralised authority avoided issues that prior non-authoritative and piecemeal efforts were unable to address.[168,169]

The NLM added the public results database to ClinicalTrials.gov in 2008.[127] By 2010, ClinicalTrials.gov was receiving 330 new registrations and 2,000 revisions to existing records each week and contained over 3,000 trial results submissions.[170] This new law further elevated the importantance of ClinicalTrials.gov within the clinical research landscape and it is now the largest registry in the world by an order of magnitude (Table 2.2).[171] However the uptake, implementation, and enforcement of the FDAAA 2007 rules would be slow.[172,173] The US federal rulemaking process, which was necessary to clarify various ambiguities in the law's implementation, was only proposed and brought into full effect nearly a decade later.[11] As of 2021, the NLM is leading a ClinicalTrials.gov modernisation effort to update and improve the usability of the ClinicalTrials.gov.[174] Chapters 3 and 5 of this thesis will further consider the details of the FDAAA 2007 and its current implementation.

European clinical trials regulations also advanced throughout the 2000s. The 2001 Clinical Trials Directive, governing clinical research throughout the EU, included the establishment of a pan-European registry for clinical trials of investigational medical products (CTIMPs).[175] As opposed to ClinicalTrials.gov where the onus for registration fell on the individual sponsors and investigators, the EU system would automatically register protocols via national competent authorities[i] as part of the regulatory approval process for covered trials. The EudraCT database began accepting protocols in 2004.[176,177] The public facing portal to the EudraCT, the EU Clinical Trials Register (EUCTR), launched and became an ICTRP primary registry in 2011.[178,179]

[i] For instance, prior to Brexit the Medicines and Healthcare products Regulatory Agency (MHRA) was the national competent authority for the UK. See Table 6.1 for a list of all NCAs.

Figure 2.3: ClinicalTrials.gov Registrations and Key Milestones 1997-2020



Reprinted without copyright as an official US Government Work. National Library of Medicine. Report on the ClinicalTrials.gov Modernization Effort. 2021. NPRM: Notice of Proposed Rulemaking AKA the draft of the eventual Final Rule.

Additional EU regulations would soon follow, first requiring the reporting of paediatric trials, and eventually the reporting of all registered trials on the EU database. This included an expectation to retrospectively report trials completed before the launch of the results database in 2014.[180–184] New EU clinical trial regulations, originally passed in 2014, have begun to phase into effect as of January 2022 with the launch of a new clinical trials portal, the Clinical Trial Information Section (CTIS).[185,186] CTIS will replace the EudraCT/EUCTR system and is set to include more streamlined registration and concrete results reporting requirements.[187,188] These new regulations explicitly allow EU national governments to implement sanctions for noncompliance and move beyond the "soft legislation" of the current paradigm.[29,189,190] Chapter 6 of this thesis will examine the utility of the EUCTR as a reliable public source of information about clinical trials in the EU/EEA.

The UK, a major source of biomedical research, has also seen substantial changes in the regulation of clinical research in recent years. The completion of Brexit led to the country to leave the regulatory infrastructure of the EU and EMA including the trial registration process. In late 2021, it was announced that all UK clinical trials will be automatically registered on the ISRCTN as part of the routine ethics process beginning with drug trials in 2022.[191] This is part of the UK Health Research Authority's "Make It Public" strategy which arose from a Parliamentary committee investigation into trial transparency.[192,193] Registration requirements, however, are not unique to the US and Europe. The NIH ClinRegs website details clinical research regulations in 21 countries and, as of September 2021, 13 include some requirement for clinical trials to be registered[194] including countries with ICTRP primary registries across all global regions.[195–200] Smaller non-ICTRP registries also continue to exist usually linked to a specific public entity, funder, or institution.[201]

2.4.7 The Modern Registry Landscape

As of 2021, the ICTRP includes 17 primary registries and accepts data from ClinicalTrials.gov (Table 2.2). In addition to the ICTRP meta-registry, the WHO also manages the Universal Trial Reference Number system in which trial sponsors can apply for a single number to link trial documentation.[202] The third edition of the ICTRP standards were released in January 2018 and the minimum dataset now includes a results element (Table 2.3).[58] While registries are not required to implement separate tabular results sections like ClinicalTrials.gov and the EUCTR, they must include a field that links to results publications or other documentation with results details.

In January 2020, I examined how each of the 18 ICTRP data provider registries had implemented these new results standards and found that 13 (72%) had a dedicated results field while another two had partially implemented this requirement.[23] This has since grown to 15 (83%) leaving only the Iranian (IRCT), Peruvian (REPEC), and Brazilian registry (REBEC) without a dedicated results reporting field as of mid-2021. There was, however, considerable variation in how these results sections were implemented. Only two registries (11%) had a specific tabular results format, nine (50%) allowed for results documents to be uploaded locally, eight (44%) allowed free-text results, and 12 (67%) had a field for citations. Ten registries (56%) allowed results to be shared in at least two formats. The ability to search specifically for trials with results (n=5, 28%) and to download trial records in bulk (n=8, 44%) were uncommon.[j] Overall, results availability, discoverability, and registry functionality was highly variable.

[j] The Thai Clinical Trial Registry had a mass download option at the time this data was originally collected but this was removed in a recent redesign. They were not counted here as having this feature here.

Table 2.2: WHO ICTRP Primary and Data Provider Registries

Registry Name	Abbreviation	Year Founded	Became Primary Registry	Registrations[a]
Australian New Zealand Clinical Trials Registry	ANZCTR	2005[200]	2007[203]	21,711
Brazilian Clinical Trials Registry	ReBec	2010[204]	2011[204]	5,210
Chinese Clinical Trial Registry	ChiCTR	2005[205]	2007[206]	53,298
ClinicalTrials.gov (USA)	N/A	2000[127]	N/A[f]	397,275
Clinical Research Information Service (South Korea)	CRiS	2010[207]	2010[207]	6,787
Clinical Trials Registry - India	CTRI	2007[208]	2008[209]	38,461
Cuban Public Registry of Clinical Trials	RPCEC	2007[210]	2011[210]	399
European Union Drug Regulating Authorities Clinical Trials Database/EU Clinical Trials Register	EudraCT/ EUCTR	2004/2011[177,178]	2011[179]	41,233
German Clinical Trials Register	DRKS	2008[211]	2008[212]	13,045
Iranian Registry of Clinical Trials	IRCT	2008[213]	2008[213]	30,573
ISRCTN	ISRCTN	2000[120]	2007[214]	21,415
Japan Primary Registries Network[b]	JPRN	2007[215]	2008[215]	52,470
Lebanon Clinical Trials Registry	LBCTR	2018[216]	2019[217]	116
Thai Clinical Trials Registry	TCTR	2009[218]	2013[219]	6,175
The Netherland National Trial Register[c]	NTR	2004[e]	2007[214]	9,822
Pan African Clinical Trial Registry	PACTR	2009[220]	2009[220]	3,177
Peruvian Clinical Trial Registry[d]	REPEC	2011[195]	2016[195]	1,948
Sri Lanka Clinical Trials Registry	SLCTR	2006[221]	2008[221]	393

[a]As of December 2021

[b]Contains data from the JapicCTI, JMACCT CTR, jRCT, and UMIN CTR registries. UMIN was founded the earliest (2005).

[c]The NTR has ceased operation as of November 2021 and a new Dutch registry is planned.

[d]The REPEC database has existed since 1995 but the online registry was established in 2011

[e]Personal communication with NTR staff.

[f]ClinicalTrials.gov is an ICTRP data provider registry but has declined to become a primary registry.

Table 2.3: Required ICTRP Trial Registration Dataset Version 3 (2018)

Number	Item
1	Primary Registry and Trial Identifying Number
2	Date of registration in Primary Registry
3	Secondary identifying numbers
4	Source(s) of monetary or material support
5	Primary sponsor
6	Secondary sponsor(s)
7	Contact for public queries
8	Contact for scientific queries
9	Public title
10	Scientific title
11	Countries of recruitment
12	Health condition(s) or problem(s) studied
13	Interventions
14	Key inclusion and exclusion criteria
15	Study type (e.g., interventional, observational, and design characteristics)
16	Date of first enrollment
17	Sample size
18	Recruitment Status
19	Primary outcomes(s)
20	Key secondary outcome(s)
21	Ethics review
22	Completion date
23	Summary results[a]
24	Data sharing plan

[a]Must include Baseline Characteristics, Participant Flow, Adverse Events, and Outcomes

Prior systematic assessments of registry functionality, usability, and informational content support the need for updates and improvements across the registry landscape.[222–224] One analysis of the implementation of the current ICTRP standards concluded: “it is clear that some of the registries have much work to do, although even a few improvements would significantly improve them”.[224]

Funders can also incentivise and promote the use of registries. In 2017, major non-commercial funders and research organisations were convened by the WHO to discuss transparency measures. Attendees signed a joint statement pledging to implement clear standards for their funded and supported clinical research including preregistration and rapid results reporting to registries regardless of journal publication status. They also committed to continued monitoring and repercussions for poor compliance.[225,226]

Prior to my DPhil I had conducted an audit of transparency policies for the largest global funders of health research with criteria aligned to the WHO joint statement. There was substantial variation in whether funders explicitly required registration, summary results publication, and the sharing of individual patient data. Even when these were required, documented compliance monitoring or disclosure mechanisms were rare.[227] Many major funders have since strengthened their policies to align with the WHO statement including the Medical Research Council[228,229] and National Institute for Health Research in the UK[230] and INSERM in France.[231] There is also substantial variation among the transparency policies of commercial sponsors.[232]

Civil society and advocacy organisations have also played a key role in shaping the modern registry landscape. The AllTrials Campaign was started in 2013 by concerned academics, journal editors, and advocates including both of my thesis advisors. The campaign promoted a simple message that "All Trials Should be Registered and All Trials Should be Reported."[233] Through campaigning and lobbying efforts, the AllTrials pledge has been signed by over 95,000 individuals and 700 organisations globally as of October 2021. AllTrials forms one part of an international network of transparency and good science advocates including organisations like TranspariMED, Transparency International, Cochrane, and Universities Allied for Essential Medicines who promote higher standards for the reporting of clinical research.[234–236]

2.5 The Registry Research Agenda: Understanding the Benefits & Limits of Registration

Clinical trial registries have developed as a tool to support research as well as a subject of research. A primary motivation for the development of clinical trial registries was to assist evidence synthesis efforts. Registries are routinely used as a tool to survey and compare the research landscape in a given area.[237–242] ClinicalTrials.gov staff have published guidance on using the database for research.[243] The current *Cochrane Handbook for Systematic Reviews of Interventions* recommends searching ClinicalTrials.gov and the ICTRP search portal together to locate registered trials for reviews but this has not necessarily become routine practice.[244–246] Adding trial registries to search strategies has been shown to identify additional studies but does not consistently impact conclusions when examined.[66,247–250]

Results reported to ClinicalTrials.gov have repeatedly been shown to be more complete when compared to matched journal publications, especially concerning adverse event reporting.[251–255] While reporting to registries is not perfect, especially when compared to comprehensive regulatory documents like Clinical Study Reports,[256] the evidence supports that registries help to provide a more complete understanding of clinical trial results than solely relying on publication. Registration is also associated with higher overall reporting quality in journal publications and lower risk of bias.[257–260]

Following from Hemminki and Simes, registries have commonly been used for research into the extent of non-publication of clinical trials.[73,95] The most recent review of these studies was published in 2014 by Schmucker and colleagues and found a pooled reporting rate of just 54% (95% CI: 42%-66%) across 22 studies of registered trials, though with substantial heterogeneity.[73,95] These types of studies remain common in the literature. Informally repeating the Schmucker search strategy and title/abstract screening in January 2020, and adding other known publications, identified over 40 new studies. These include analyses of reporting by

academic medical centres in the US and Germany,[261,262] numerous examinations of reporting practices within specific disciplines or disease areas (e.g., heart failure[263], urology[264], epilepsy[265]) and other broad categories of trials (e.g., industry trials,[266,267] trials in children[268,269]).

As requirements for prospective registration increase, registry records also provide an opportunity to check for outcome-reporting issues in subsequent publications.[6,104,270] This thesis includes three studies examining the publication and outcome reporting of registered clinical trials (Chapters 3, 4 & 6).

The issues and shortcomings of clinical trial registries have also been widely documented. In 2007, ClinicalTrials.gov staff described various difficulties in running a clinical trial registry.[214] Box 2.1 reproduces the headline issues identified in the piece covering the logistics of managing, indexing, and feeding data back to users in a consistent, reliable, and simple manner. A registry is only as good as the underlying data it supplies, and so low quality data undermine the utility of the registration process. Viergever and colleagues showed in 2011 that across the nine ICTRP data provider registries at the time, there were substantial deficiencies in the provision of routine data about interventions, trial contacts, and outcomes with a follow-up in 2014 concluding that "problems with quality remain and continue to constitute an impediment to the meaningful utilisation of registered trial information."[271,272] Others have noted similar issues with the quality of the ClinicalTrials.gov dataset.[273–276]

Throughout the 2010s articles were published declaring that "trial registers cannot yet be relied upon as the sole means to locate trial for systematic review…[they] lag behind the major bibliography databases in terms of their search interfaces"[277] and "the amount of protocol information registered is often insufficient to judge the validity of reported results and the problem of identifying all relevant studies has not yet been solved."[169] While the registry

landscape has continued to evolve, these logistical, practical, and quality concerns remain across registries.[198,278–282] This thesis touches upon these quality issues throughout each analysis.

Box 2.1: Issues identified by Zarin et al. (2007) in the Registration of Clinical Trials

- Validating Trial Registry Data
- Establishing a Search Engine to Serve the Needs of Heterogeneous Users
- Preventing Duplicate Trial Registrations
- Defining and Naming Interventions
- Coordinating Trial Registration Internationally
- Extending Registries to Include Trial Results

How registries are used in practice is also frequently researched. Li and colleagues reported in a 2018 systematic review of 37 studies comparing registry entries and protocols to published findings that "inconsistent reporting...is frequent, prevalent, and suboptimal" suggesting inadequate registry checks by editors and reviewers.[270] A 2018 review found that across 19 studies, the pooled proportion of prospective registration for randomised trials was just 21% (95% CI: 15%-27%).[257] Once a study with issues has been published it becomes increasingly difficult to address even when standard post-publication review procedures are followed underlying the importance of building registry checks into pre-publication review.[6,283] Researchers who examine fraudulent clinical trial reporting believe that discrepancies between registration and publication can be a reliable indicator of fraud when considered alongside other issues.[284] Others have suggested that unregistered trials should be excluded from reviews all together.[285]

Lemmens and colleagues have written about common objections to the proliferation of increased clinical transparency regulations. These include increased administrative burden, impacts on innovation and discovery, the potential for public misinterpretation of results, and concerns over protecting sensitive or confidential information.[67,69] Carve outs for for registration

and reporting of Phase 1 trials, and provisions for delayed disclosure, are present in transparency regulations in the name of commercial confidentiality.[166,175] Many of these issues and concerns originate from industry but are mirrored in academia and explored further in Chapter 7 within the UK context.

Debates about the value of registration compared to the burden it imposes on research are not unique to clinical trials and efforts must continue to prove their value beyond transparency for transparency's sake.[286–289] In one debate piece, a director at a major US cancer centre was critical of further enforcement of ClinicalTrials.gov results reporting measures as "neither I nor my colleagues would typically go to ClinicalTrials.gov to look for data to guide management of our patients."[290] Adherence to the ICMJE registration recommendations has also met resistance from editorial boards who remain unconvinced that prospective registration offers more value than the publication of trials that registered retrospectively or not at all.[153,291]

2.6 Thesis in Context

The past 30 years have seen major advancements in clinical trial registration. Increasing uptake, enshrinement in ethical principles, and statutory requirements have solidified their widespread use in the clinical research community. Actors in academia, industry, civil society, and government have all played important roles in influencing how and why this global system of transparency, generally unique among the sciences, has come to fruition. However the story remains ongoing. The promise of transparency from registries is evident and broadly recognised but it is not clear their ability to provide reliable, valuable data to the community has been fully realised. There remains room for continued assessments of how registries are implemented, regulated, utilised, and maintained.

2.6.1 Gaps in the Literature

2.6.1.1 Clinical trial registries in the modern research landscape

Many of the arguments for clinical trial registration were articulated decades ago. With the proliferation of registries throughout the 2000s, the need to frequently reiterate these points became less of a necessity. However, as registration becomes routine it also risks becoming bureaucratic background noise, taken for granted, rather than an essential act of transparency and rigour.[292,293] It is important to revisit and re-examine the role of registries within the current research landscape and how they serve their envisioned functions at both the micro and macro levels.[158,294] Detailed examples of the utility of registries, and clear arguments for their place within the contemporary research landscape, justify continued investment in their development and adoption.

2.6.1.2 Increased regulatory use of clinical trial registries

While assessments of trial reporting and publication bias are common in the literature, specific examinations of regulatory transparency requirements are much rarer. At the start of my DPhil, comprehensive and systematic studies of new reporting regulations in the US and EU were essentially non-existent. There was no public information on recent compliance trends available in the literature or from regulators. For instance, studies investigating the impact of the FDA Amendments Act often only examine trials within a specific area with long delays between trial completion and the associated metaresearch project.[295,296] Even recent studies that have included post-Final Rule trials lack a robust enough sample of relevant studies for analysis.[297] The EU transparency regulations have been even more neglected outside of a few recent examples of studies mostly conducted by my advisors.[19,298,299]

2.6.1.3 Institutional management of clinical trials

Analyses examining the reasons for transparency issues focus on individual researchers, editors, or broad cross-sections of stakeholders.[96,98,300–303] Understanding the experiences of these individual's impact on transparency issues is essential however it is not the only perspective that must be considered. Clinical research institutions also take on a share of the responsibility for the ethical and regulatory oversight of their sponsored trials. They create the and manage the environment under which this research takes place and translate national and international transparency requirements into the local context through policies and standard operating procedures. Research examining the role of institutional governance in transparency practice is sparse with most examples coming from the US.[236,304–306] To my knowledge there has been no in-depth qualitative examination of these stakeholders published to date.

2.6.2 Key Research Questions

Advancing the use of registries for meaningful transparency and accountability across the entire research community will involve creating evidence that shifts perceptions of registration from required bureaucracy to a valuable exercise that improves scientific inquiry, and where improvements are needed to promote this value. This thesis closely examines how the current system functions and where it is failing to provide consistent, accurate, and timely information. My thesis is organised around three broad research questions that aim to address these gaps in the literature and better understand the current function of the continuously evolving registry environment.

2.6.2.1 How do registries function as tools for transparency and accountability?

My thesis begins with two studies that use trial registries, and the information they provide, to examine the quality and extent of clinical trial reporting. Both studies stand alone in examining important questions about how the results of registered trials are disseminated but in the context

of this thesis, they also serve a broader function in demonstrating both the promise of registries and the problems that impact their use. Chapter 3 uses trial registrations as a starting point to closely examine the reporting quality of e-cigarette trials from a single prominent sponsor. Chapter 4 moves the lens back to the entire trial registration landscape and reports preliminary results from a large project examining how and when the results of Covid-19 clinical trials are disseminated. Neither of these studies would have been possible without the global clinical trial infrastructure and the detailed records they hold. Having an existing, standardised dataset of registered trials to work from allowed me to relatively rapidly design and implement studies addressing timely public health concerns. However, issues with the accuracy and timeliness of trial registry data are an important methodological complication in both studies and demonstrative of larger issues.

2.6.2.2 How are regulatory systems that require registration and reporting of clinical trials functioning?

With clear demonstrations of the strengths and weaknesses of the global registry system it is important to consider how these can be addressed. One strategy has been to regulate the registration process. Laws requiring the use of clinical trials registries have continued to drive their rise within the clinical research landscape. Registries are now being seen by governments as vital tools to help assure the integrity of the clinical research that informs clinical and health policy decision making. Chapter 5 and 6 will examine how well the two most comprehensive and robust regulatory regimes in the world are working to fulfil the promise of trial registries. These studies build upon my work on the TrialsTracker project to describe trial reporting, registration quality, and availability of registry data under US and EU regulations. Recent developments in both regulatory environments make them a rich source of research questions and analysis. These results will describe how these requirements are functioning to provide trial information to

researchers and the public. As no public audit function from the responsible regulators exist, these studies also serve an independent audit and feedback function.

2.6.2.3 How do institutions manage their trial transparency responsibilities?

Chapter 7, the final results chapter of my thesis, examines perspectives on the use of registries through the lens of public research institutions in the UK. Informed by the findings from previous chapters, I used in-depth interviews to examine how governance staff universities and NHS trusts manage the transparency of their trial portfolios. Prior work has shown that non-commercial funders are often laggards in terms of proper registration and reporting behaviour, especially in the EU.[19] However, with recent attention to these issues from the UK Government, there has been a concerted effort to improve transparency in clinical research throughout the UK public sector. In addition, most UK public sponsors will have broad experience with the international registry system. These experiences, along with the emerging independent regulatory environment in the UK resulting from Brexit, offers a particularly compelling opportunity to understand how institutions have engaged with transparency issues while documenting the barriers that remain.

2.7 Conclusion

This chapter explores the history of clinical trial registries including the rationale for their development, the major milestones in their proliferation, and the research that has explored their use and value to the research community. This understanding of the origins and history of the global registry system is essential context that informs how the research throughout this thesis was designed, implemented, critically evaluated, and interpreted.

2.8 Chapter Summary

- Tracking the history of clinical trial registries reveals the rationale and motivations behind the current global registration environment and allows for an understanding of why ethical and legal transparency requirements exist.
- Despite their considerable promise, the effective use of registries to reduce bias faces well-documented obstacles in implementation, use, and acceptance by the broader research community.
- This thesis aims to examine the extent to which the current registry environment promotes transparency and accountability, specifically through the provision of accurate and timely information about clinical trials in the form of trial details and results.

Chapter 3: Transparency and Reporting of Industry Sponsored E-cigarette Clinical Trials

A case series of registered trials

A manuscript based on this chapter was published in the journal *Tobacco Control*:

- DeVito NJ, Drysdale H, McKee M, Goldacre B. E-cigarette manufacturers' compliance with clinical trial reporting expectations: a case series of registered trials by Juul Labs. *Tob Control* 2021; published online June 14. DOI:10.1136/tobaccocontrol-2020-056221.

Data for this project are available on Figshare:

- DeVito NJ. Juul Clinical Trial Reporting Assessments. 2021; published online June 15. DOI:10.6084/m9.figshare.14627346.

3.1 Chapter Rationale and Overview

Registries allow investigations of the research landscape at scale as well as assessments of the particulars of individual trials. This thesis contains analyses of both types, demonstrating the utility of registries as a tool for transparency and accountability. Here I draw on the capability of registries to identify expected trial results and allow for checks of registered information against available results as a form of post-publication review. This chapter provides a demonstration of the benefits of registration, their applied use, and ultimately a reflection on the implementation and interpretation of US trial reporting regulations. This chapter, along with Chapter 4, primarily address my first research question on how registries can be utilised as a tool to support transparency and accountability and what issues compromise this role.

In early 2020, e-cigarettes were often in the news following regulatory action against certain products by the US Food and Drug Administration (FDA). During routine searches related to the TrialsTracker project, I identified several unreported Juul Labs Inc. trials that appeared to be

covered under the FDA Amendments Act. I developed this study, based on similar prior work,[6] to closely examine the availability of results for these studies and how the registrations aligned with published work in the e-cigarette space. The small number of trials allowed me to share results as a case series offering in-depth analysis and explanations of my findings. It is well documented that outcome reporting bias occurs[104], however I believe a more detailed demonstration of how these issues manifest in practice offers additional value to the community. As the paroxetine scandal demonstrated in Chapter 2, real-world examples of poor practice can provide powerful impetus for change.

3.2 Introduction and Background

3.2.1 Introduction

The importance of complete reporting of clinical trial results is widely recognised.[165,307] However reporting must also be of sufficient quality to be useful. Quality reporting is promoted by guidelines such as CONSORT, which aims to improve the reporting of clinical trials through "complete, clear, and transparent information on…methodology and findings" The CONSORT guidelines are endorsed by over 500 academic journals.[163] Protocols and trial registrations should be published prospectively and referenced during peer review to avoid undisclosed "outcome-switching" and selective non-reporting. These biases can exaggerate benefits and obfuscate harms of interventions.[50,81,104,308] Clinical trials registers offer the opportunity to hold researchers and sponsors of clinical research accountable to their prespecified methods and outcomes and allow the public to expect results of completed trials.

Electronic nicotine delivery systems (ENDS, or e-cigarettes) are controversial. Some see them as an important weapon in the struggle against smoking.[309] Others question their real world effectiveness as quitting aids, their short and long-term safety, and their role in promoting nicotine addiction.[310,311] Over 40 countries have banned the sale of e-cigarettes, with others

restricting their marketing.[312] In early 2020 the US Government banned most flavoured e-cigarette cartridges amid concerns about uptake in non-smoking teenagers.[313] Given these ongoing questions, it is essential that e-cigarette research is made fully available in a timely manner to inform medical and public health decision-making.

3.2.2 Transparency Concerns in E-cigarette Research

There is a longstanding research literature on financial conflicts of interest and concerns around poor quality reporting of tobacco-industry research.[314–316] Recent reviews have concluded that conflicts of interest are important when interpreting the findings of e-cigarette research.[317,318] Many journals have policies to not publish research sponsored by the tobacco industry due to their notable history of past research distortion and misconduct.[319–321]

In an August 2019 commentary, Tan and colleagues raised concerns about industry sponsored vaping research.[322] They focus on JLI Science, a Juul Labs, Inc. (Juul Labs) research centre that supports e-cigarette studies. Juul Labs is a major e-cigarette company holding 27% of the US market share in 2017.[323] Tan and co-authors noted a lack of transparency around JLI Science's funding mechanisms, research processes, and potential conflicts of interest. When auditing the JLI Science website the authors could not locate details on governance, funding, study selection, or reporting of Juul Labs-supported research that would allow proper assessments of influence. These findings raise concerns that research arising from this centre may be used to "positively portray the tobacco industry and lobby against regulatory actions" as has occurred in the past. Examining these transparency concerns has only grown in importance given the June 2020 Premarket Tobacco Product Application submission to the FDA by Juul Labs that relies on their "comprehensive research program...examining the public health impact of the JUUL System."[324]

3.3 Aim and Objectives

3.3.1 Aim

Use ClinicalTrials.gov to determine whether results of e-cigarette clinical trials sponsored by Juul Labs, Inc. were reported in accordance with best practice.

3.3.2 Objectives

3.3.2.1 Identify registered trials by Juul Labs, Inc that appear covered under the FDA Amendments Act 2007

3.3.2.2 Assess the availability of results of registered e-cigarette trials sponsored by Juul Labs, Inc. in journal articles and conference presentations

3.3.2.3 Analyse the quality of reporting within available results by comparing registered and reported outcomes and present results both narratively and quantitatively

3.4 Methods

3.4.1 Inclusion Criteria for Assessment

I searched ClinicalTrials.gov for all interventional clinical trials in which Juul Labs was the primary sponsor and assessed whether each trial had registered data consistent with coverage under the FDAAA 2007, based on established inclusion logic derived from official documentation.[17,325–328] In the US the FDA Amendments Act (FDAAA) 2007 and its 2017 Final Rule requires the sponsors of certain trials to report results within one year of primary completion directly to the ClinicalTrials.gov registry.[11,328] Chapter 2 covers the history of the FDAAA, while Chapter 5 presents a comprehensive analysis of reporting under this law.

The “FDA-regulated Device Product” field, added to ClinicalTrials.gov when the Final Rule came into effect, denotes coverage by device regulations and is used to aid determinations of whether FDAAA reporting requirements apply to a given trial.[326,327] As with all information on

ClinicalTrials.gov, this field is attested to as accurate by the sponsor and reviewed during quality control by ClinicalTrials.gov staff before being made publicly available.[328,329] While official regulatory determination of coverage under FDAAA would not solely be based on registered data elements, the use of ClinicalTrials.gov data for public audit of potential FDAAA coverage is expressly encouraged in the Final Rule preamble[k] and has informed prior analyses.[17,172,173] As under the FDAAA 2007 and WHO ethical guidelines, results were expected to be available within one year from primary completion either on ClinicalTrials.gov or via any other dissemination routes.[307,330]

3.4.2 Results Searches

To assess each trial's reporting status a colleague (HD) and I searched 1) ClinicalTrials.gov 2) the academic literature via PubMed and Google Scholar and 3) the JLI Science "Research Library" database[l] for results of registered trials. For searches outside ClinicalTrials.gov, the trial ID, principal investigator (PI), and keywords derived from the trial title and design were used as search terms. Publications were matched to registrations using either the presence of a trial ID or a comparison of the study aims, authors/affiliations, design, sample size, and outcomes. Journal articles and conference materials were considered as results in the academic literature. Each assessor independently compared reported results with the current outcomes listed on ClinicalTrials.gov, based on CONSORT items 6 (i.e., disclose changes to trial outcomes), 17 (i.e., report all outcomes) and 18 (i.e., identify non-specified analyses performed).[163] Changes from the prespecified outcomes to current outcomes on the registry, obtained via the ClinicalTrials.gov archive site, were noted.

[k] "Public users of ClinicalTrials.gov, other than responsible parties, should be able to understand whether a registered trial is an applicable clinical trial"
[l] Located at https://jliscience.com/research-library

Each outcome was classed as: “fully reported”; “reported with issues” where there was a substantial undeclared deviation from how an outcome was specified; “properly declared” if unreported or changed, but with disclosure; “unreported” if it was not located; or “unclear” if it could not be assessed. Findings from searches and outcome assessments were discussed in committee and discrepancies resolved by consensus. Edge cases were resolved conservatively in favour of proper reporting as a rule. An annotated record was created for each trial detailing exact locations of results, outcomes, and additional trial information within the registry and any located results. The full record of these assessments is available on the project’s FigShare page. Figure 3.1 shows example assessment slides from the annotated data. I narratively report these assessments including any issues with outcome reporting and justifications for certain assessments. Summary statistics of the search results and outcome assessments are presented.

Figure 3.1: Example of Annotated Outcome Assessment Record for Trial NCT03605641

Primary Outcomes 1-4

Primary Outcome Measures :

1. Exhaled Breath Sample (EBS) - Nicotine [Time Frame: Clinic Visit (JUUL/VUSE: 2 days and 2 overnights; conventional cigarette: 1 day and 1 overnight)]

   Absolute change from baseline in nicotine levels in the EBS of subjects who use JUUL, VUSE Solo, or conventional cigarettes.

2. Exhaled Breath Sample (EBS) - Propylene glycol [Time Frame: Clinic Visit (JUUL/VUSE: 2 days and 2 overnights; conventional cigarette: 1 day and 1 overnight)]

   Absolute change from baseline in propylene glycol levels in the EBS of subjects who use JUUL, VUSE Solo, or conventional cigarettes.

3. Exhaled Breath Sample (EBS) - Vegetable Glycerin [Time Frame: Clinic Visit (JUUL/VUSE: 2 days and 2 overnights; conventional cigarette: 1 day and 1 overnight)]

   Absolute change from baseline in vegetable glycerin levels in the EBS of subjects who use JUUL, VUSE Solo, or conventional cigarettes.

4. Exhaled Breath Sample (EBS) - Carbonyls [Time Frame: Clinic Visit (JUUL/VUSE: 2 days and 2 overnights; conventional cigarette: 1 day and 1 overnight)]

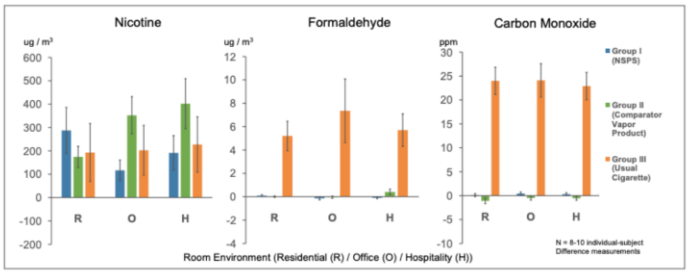
   Absolute change from baseline in carbonyl levels in the EBS of subjects who use JUUL, VUSE Solo, or conventional cigarettes. Carbonyl compounds include: formaldehyde, acetaldehyde, and acrolein.

Primary Outcomes 1-4

Results – Exhaled Breath
Nicotine and propylene glycol were elevated in exhaled breath for each product (Figure 2). After cigarette use, formaldehyde and carbon monoxide were consistently elevated ($p<0.05$). Comparatively, mean changes in formaldehyde and carbon monoxide in exhaled breath were reduced by 99% or more with vapor products vs. cigarettes (Figure 3).

Note: It is unclear why this section references Figure 3 which does not report any measures for exhaled breath.

Figure 2: Change in Content of Exhaled Breath Samples After *Ad Libitum* Product Use



Primary Outcomes 1-4

Assessments:

- Outcome 1: Fully Reported
- Outcome 2: Not Reported. The text reports Propylene glycol as “elevated” but provides no exact measure and it is not included in Figure 2
- Outcome 3: Not Reported. There is no mention of Glycerin in exhaled breath reported in the poster
- Outcome 4: Reported with Issues. This outcome groups “Carbonyls” and specifically mentions formaldehyde, acetaldehyde, and arcolein (and formerly carbon monoxide). Acetaldehyde and acrolein in exhaled breath are not reported anywhere in the poster. Carbon monoxide is reported.

3.5 Results

3.5.1 Study Population

On 1 August 2020, searching ClinicalTrials.gov for “Juul Labs, Inc”, the standardised sponsor name for the company, returned 11 registrations. One trial (NCT04452175) was excluded because Juul Labs was a collaborator, not the primary sponsor. Five further trials were excluded as their registrations were inconsistent with potential FDAAA coverage (NCT04143256, NCT04123041, NCT04107779, NCT04088175 & NCT03700112). None of these excluded trials had results available on ClinicalTrials.gov, and only NCT03700112 had completed over a year ago as of 1 August 2020 and could have potentially been included in our searches. Table 3.1 shows the title and primary completion dates (PCD) for all excluded trials with additional information available in the full dataset.

Five trials were registered consistent with the FDAAA Final Rule’s “Applicable Clinical Trial” (ACT) criteria.[17,327] My methods for identification of covered trials based on public data are further detailed in Chapter 5. All trials were interventional and on an “FDA-regulated Device Product”.[325] The reason Juul Labs inconsistently identified similar trials as being on FDA-regulated products was not immediately apparent at the time of the study. The meaning of this field is not ambiguous in ClinicalTrials.gov materials [326,327] and since data on ClinicalTrials.gov, especially those relating to FDAAA coverage, are attested to as accurate on submission, we maintained our original inclusion/exclusion criteria in line with the public data. Additional details of these discrepancies following the publication of this work is included in the Discussion. Results were expected for all five trials as the PCDs were more than one year ago as of 1 August 2020. Table 3.2 includes the key dates for each included trial.

Table 3.1: Details of Excluded Trials

NCT ID	Official Title	Primary Completion Date
NCT04143256	An Open-Label, Multi-Center Study to Evaluate Selected Constituents in the Exhaled Breath Samples From the Use of JUUL Nicotine Salt Pod System Product (5% and 3% Virginia Tobacco, Mint, Mango, Menthol) Users and Conventional Cigarettes (Non-Menthol and Menthol Flavors)	12 December 2019
NCT04123041	A Randomized, Open-Label, Cross-Over Study to Characterize the Nicotine Uptake and Subjective Effects With Use of JUUL Electronic Nicotine Delivery Systems With Multiple Flavors and Nicotine Concentrations, Usual Brand of Combustible Cigarettes, a Comparator E-Cigarette and Nicotine Gum in Adult Smokers	18 December 2019
NCT04107779	A Randomized, Open Label, Parallel Group Study in Adult Smokers to Evaluate Changes in Biomarkers of Cigarette Smoke Exposure After Switching Either Exclusively or Partly to Using JUUL Electronic Nicotine Delivery Systems With Two Different Nicotine Concentrations	17 February 2020
NCT04088175	A Randomized, Open-Label, Cross-Over Study to Characterize Puffing Topography With Use of JUUL Electronic Nicotine Delivery Systems (ENDS) in Adult, Closed-System ENDS Consumers	23 January 2020
NCT03700112	An Open Label, Randomized Crossover Study Comparing Nicotine Pharmacokinetics of Seven Electronic Cigarette Products and One Traditional Cigarette Across Two Delivery (10 Puff and Ad-libitum) Conditions, in Healthy Adult Smokers.	24 February 2019
NCT04452175	Cigarette Consumption After switchinG to High or Low Nicotine strENght E-cigaretteS In Smokers With Schizophrenia (GENESIS)	March 2022

Table 3.2: Included Trials and Key Dates

Trial ID	Registration First Submitted	Last Updated Posted	Study Start	Primary Completion	Study Completion	FDAAA Results Due
NCT03463837	7 Mar 2018	3 Jan 2019	4 Mar 2018	27 Jul 2018	13 Aug 2018	27 Jul 2019
NCT03605641	16 Jul 2018	5 Dec 2018	17 Sept 2018	2 Dec 2018	2 Dec 2018	2 Dec 2019
NCT03593239	1 Jun 2019	9 Jan 2019	29 Jun 2018	26 Jul 2018	26 Jul 2018	26 Jul 2019
NCT03596034	6 Jun 2018	2 Oct 2018	9 Aug 2018	26 Sept 2018	26 Sept 2018	26 Sept 2019
NCT03719391	17 Oct 2018	3 Jan2019	19 Oct 2018	21 Nov 2018	28 Nov 2018	21 Nov 2019

3.5.2 Results Searches

Searches were conducted in August 2020. None of the five trials had results reported to ClinicalTrials.gov. Literature searches located conference posters for four of the five trials on the JLI Sciences website and one publication in the literature reporting more in-depth results from one of the posters. Three of the posters were available under a year from the provided primary completion date. Details of available results and outcome discrepancies are narratively described below. Additional trial details are available in Appendix 3.1.

3.5.3 Trial Details

3.5.3.1 NCT03463837

This study examined “biomarkers of exposure” across various tobacco products including four Juul products. There were no meaningful changes to outcomes after first registration, however this trial was retrospectively registered by three days (Table 2) while the follow-up for the primary outcome was just five days meaning the registration could have occurred after data had already been collected.

We located two results outside of ClinicalTrials.gov: a poster presented at the 25th Annual Meeting of the Society for Research on Nicotine and Tobacco on 23 February 2019 and available on the JLI website; [331] and an article published online in the journal *Nicotine & Tobacco Research* on 5 November 2019.[332] As of writing, *Nicotine & Tobacco Research* has not endorsed the CONSORT guidelines.[333] The paper includes all the outcomes reported in the poster in addition to adverse events and a declaration that the three pharmacokinetic outcomes would be reported in a future publication. Across both publications: the primary outcome was fully reported; six (32%) of the 19 secondary outcomes were fully reported; five (26%) were reported with issues; three (16%) were not reported but properly declared; and one (5%) was unclear, leaving four (21%) entirely unreported.

Of the five outcomes reported with issues, four were measures of nicotine equivalents in the urine (nicotine, cotinine, trans-3'-hydroxycotinine, and glucuronides) specified separately but reported as a grouped measure. The fifth outcome was measuring "future intent to use" with no specified scale in the registry. The article reports the brief Wisconsin Inventory of Smoking Dependence Motives which includes some aspects that could be indicative of "intent to use" in combination with non-prespecified measures of dependence.[334] The three secondary outcomes related to blood or serum nicotine equivalents are noted in the paper's methods but could not be located anywhere in the results or appendices. Product malfunctions were grouped with adverse events. While no malfunctions were listed, there was no statement to confirm that none occurred despite being listed as a discrete outcome. In the absence of such a statement this outcome could not be properly assessed.

3.5.3.2 NCT03605641

This was an open label study examining emissions across three different environments for a Juul device, a competitor device (Vuse solo), and conventional cigarettes. Carbon monoxide (CO) was removed from two outcomes on 18 September 2018, the day after the provided start date. No results were found on ClinicalTrials.gov. Searches revealed no results in the academic literature. The JLI Science website contains a poster presented at the 6th Annual Global Forum on Nicotine on 14 June 2019.[335] Of the 12 prespecified primary outcomes on ClinicalTrials.gov eight (67%) are fully reported, two (17%) had reporting irregularities, and two (17%) are not reported.

In the poster, outcomes describing "room air samples" were not consistently and clearly reported for both use conditions despite identical specification in the registry entry. Select carbonyls in exhaled breath (acetaldehyde and acrolein) were not reported. Propylene glycol in

exhaled breath is mentioned in the results poster text as “elevated” and references “Figure 2” of the poster, but assessing this figure and all other figures in the poster did not reveal anything related to propylene glycol in exhaled breath.[335] We therefore considered this outcome unreported. Exhaled CO is reported in the poster, but room air CO is not; both were removed as outcomes on ClinicalTrials.gov. Lastly, measurements of particle size are missing for one of the group/setting pairs with no explanation.

3.5.3.3 NCT03593239

This study intended to examine the nicotine pharmacokinetics of various Juul 1.7% and 5% nicotine salt products across four primary and two secondary outcomes. No outcome definitions changed meaningfully from first registration. Searches revealed no results in the academic literature nor on the JLI Science research database.

3.5.3.4 NCT03596034

This study assessed “puff topography” (PT) in adult smokers using the “Juul 5% Electronic Nicotine Delivery Systems” product. No outcome definitions changed meaningfully from first registration. Searches revealed no results in the academic literature. The JLI Science website contains a poster with results presented at the 6th Annual Global Forum on Nicotine on 14 June 2019.[336] All five (100%) primary outcomes are reported, however only two of the seven (29%) secondary outcomes are reported. The secondary outcome “self-reported product use” was conservatively determined to be fully reported despite differences in how consumption was measured in the poster presentation compared to the prespecified outcome. The five unreported secondary outcomes were subjective measures, specifically: cigarette dependence, smoking urges, effect of nicotine, affect (via Positive and Negative Affect Scale), and nicotine withdrawal.

3.5.3.5 NCT03719391

This study examined the nicotine pharmacokinetics of various Juul 5% nicotine salt products, Vuse Solo e-cigarettes, Nicorette 4mg nicotine gum, and standard combustible cigarettes. The primary outcomes were vaguely specified pharmacokinetic measurements of nicotine uptake in the plasma referencing a statistical analysis plan (SAP) that could not be located during trial searches. No outcome definitions changed meaningfully from first registration. We located no results searching the academic literature but found a matching poster on the JLI Science website from the 2020 Annual Meeting of the Society for Research on Nicotine & Tobacco on 14 March 2020.[337] The primary outcome was reported however just two (20%) of the 10 secondary outcomes were fully reported without issue. One (10%) additional secondary outcome was partially reported and seven (70%) were unreported without any disclosure.

Various measures were reported that fit the broad "pharmacokinetic parameters" primary outcome. While we could not access the SAP we conservatively counted it as fully reported given there were pharmacokinetic details available. For one of the secondary outcomes, the complete modified Product Evaluation Scale (mPES) was specified but only a single sub-scale ("Satisfaction") was reported. Missing outcomes included measures of blood pressure, heart rate, product usage, and two additional subjective scales (Nicotine Withdrawal Questionnaire and Product Direct Effect Questionnaire).

3.5.4 Summary of Results and Outcomes Reporting Rates

Across all trials, 28 of 61 (46%) prespecified outcomes were reported or properly declared, and 8 (13%) additional outcomes were reported but with issues; by outcome type 15 of 23 (65%) primary outcomes and 13 of 38 (26%) secondary outcomes were accounted for in any results reports. Problematic outcomes tended to measure specific levels of molecules arising from tobacco use in various contexts (e.g., urine, breath, room air, plasma) or subjective measures. Among the eight outcomes reported with issues, six measured specific molecules and two were

subjective scales; among the 24 missing outcomes, 11 examined molecule concentrations and nine were subjective measures. Summary results for outcome assessments are presented in Table 3.3.

Table 3.3: Reporting of Juul Sponsored Clinical Trials

Measure	NCT03463837	NCT03605641	NCT03593239	NCT03596034	NCT03719391	Total (%)
Results reported on ClinicalTrials.gov	No	No	No	No	No	0
Results reported outside of ClinicalTrials.gov	Yes (Poster & Paper)	Yes (Poster)	No	Yes (Poster)	Yes (Poster)	4 (80%)
Prespecified primary outcomes required to report	1	12	4	5	1	23
Primary outcomes fully reported	1 (100%)	8 (67%)	0	5 (100%)	1 (100%)	15 (65%)
Primary outcomes partially reported	0	2 (17%)	0	0	0	2 (9%)
Prespecified secondary outcomes required to report	19	0	2	7	10	38
Secondary outcomes fully reported	6 (32%)	0	0	2 (29%)	2 (20%)	10 (26%)
Secondary outcomes reported with issues	5 (26%)	0	0	0	1 (10%)	6 (16%)
Outcomes unreported or switched but declared	3 (16%)	0	0	0	0	3 (8%)
Unable to assess	1 (5%)	0	0	0	0	1 (3%)

3.6 Discussion

3.6.1 Summary of Findings

None of the trials assessed reported results on ClinicalTrials.gov. Only one of five trials reported results in the academic literature, albeit with notable inconsistencies. Four trials were reported in conference posters shared on the JLI Science website which provided only brief methods and incomplete outcome reporting. Justifications or explanations for altered or unreported outcomes were rare.

3.6.2 Results in Context

Non-reporting and selective outcome reporting are well documented sources of bias in clinical research.[17,73,104] Results presented in Chapter 5 showed that among registrations consistent with FDAAA coverage, 74% of industry-sponsored trials and 63% of non-industry-sponsored trials had reported results to ClinicalTrials.gov at any time after becoming due.[17] The COMPare project found that among 67 trial manuscripts with 915 specified outcomes 524 (57.2%) outcomes were reported correctly and 5 were switched between primary and secondary designations.[6] Other studies have consistently shown more complete reporting of results to ClinicalTrials.gov compared to journal articles, for instance Riveros and colleagues reported that "trial results, especially serious adverse events, are more completely reported at ClinicalTrials.gov than in the published article."[251,252,254,255]

Given the questionable history of tobacco-industry, some may question the value of these industry funded trials. However, these trials occurred and are being used as evidence in regulatory proceedings. It is important that all trials, regardless of funding status, are reported fully and transparently so they can be critically interpreted, assessed for potential bias, and properly considered by the broader medical and public health community.

Results disseminated through JLI Science, in the form of conference posters with space limitations, cannot be counted on to convey complete results which may complicate or bias their inclusion in future evidence synthesis. This is consistent with prior evidence regarding the completeness of reporting in conference abstracts.[270,338–340] ClinicalTrials.gov provides a robust dissemination route, independent of journals and without space restrictions, in which this research can be freely shared. While this route lacks peer review and narrative methodological detail it also provides clear summary statistics in a standard discoverable format that can be updated with additional outcomes or long-term follow-up as these become available. ClinicalTrials.gov also only allows results to be presented as summary values without potential for narrative spin.[103]

Overall, Juul Labs has sponsored relatively few registered trials. Reasons for non-reporting can vary substantially.[96] Chapter 5 shows that reporting under FDAAA requirements increases with more sponsored trials on ClinicalTrials.gov; it is possible that more experienced sponsors have deeper knowledge of their obligations, ethical or legal, and can implement more robust reporting practices.[17] It should be noted, however, that Juul Labs is part owned by Altria, formerly Philip Morris, a major tobacco company with an established research programme.[322] We cannot speculate on what the unreported results from these clinical trials may be or why they occurred in this specific instance; prior research shows that trials with less favourable results are less likely to report;[79] and that even within reported trials, non-significant outcomes are less likely to be reported.[341] These are the very issues that the FDAAA 2007 set out to address.[11]

3.6.3 Strengths and Limitations

In reporting detailed examinations of each trial's outcomes, I aimed to provide insights into our evaluations and concrete examples of how outcome reporting bias occurs in the literature. Many studies have summarised the issue of outcome reporting bias and established it as an ongoing

concern, and this case series offers useful detail and examples of how this can occur in practice.[6,104]

This work has limitations. As with all studies reliant on bibliographic searches some results may exist but were not located. However, per ICMJE and CONSORT best practice, trial IDs should be clearly present in the abstracts and text of clinical trial publications.[163,342] If trial ID and keyword searches could not locate relevant publications across multiple databases, this low discoverability would represent a breach of best practice. In addition, searches were necessarily cross-sectional, and more results may become available in the future.

Accuracy and availability of registered data is another potential limitation. Study documents with more detail on outcomes may exist. I could not locate any public source of trial protocols or SAPs for Juul Labs sponsored research. If changes to outcomes occurred, they should be reflected on ClinicalTrials.gov and disclosed in any publications. Inaccurate or out-of-date data on the registry may lead to misclassification based on our inclusion or exclusion criteria and compromised outcome evaluations.

The availability of posters for four of the five trials further confirms that the trials did occur and full results could be made available. Sponsors have a clear ethical and, in the case of trials covered under FDAAA, legal responsibility to ensure their trial registrations are kept up to date and therefore should be held accountable to the public information they attest to as accurate.[343] While officially determining FDAAA coverage may require complex regulatory consideration consistent with the Final Rule, public accountability based on registered data on ClinicalTrials.gov has an important role to play in improving the quantity and quality of trial reporting. Registration data for all five trials were also “Verified” meaning the information was reviewed after registration and attested to as accurate. At minimum, it appears that incorrect

registry data have been consistently provided for some of Juul's registered trials and this was confirmed by post-publication statements from Juul discussed below.

3.6.4 Implications for Policy and Practice

There are consistent indications in regulatory documentation that tobacco products, like ENDS, are considered drug or device products under certain circumstances (e.g., smoking cessation claims).[344–346] Furthermore, the FDAAA Final Rule is clear that the intent to market a drug or device for a certain use has no bearing on the applicability of requirements to report the trial results of unapproved and uncleared treatments beholden to the law.[330] The FDAAA Final Rule discusses the similar dual-regulatory pathway of dietary supplements noting that "a substance characterised by a responsible party as a dietary supplement could be considered a 'drug' subject to section 505 of the [Federal Food, Drug, and Cosmetic Act] under the applicable drug clinical trial definition if the trial is studying a use that meets the drug definition under the FDC Act."[328]

Similarly, another Final Rule (21 CFR Parts 201, 801, and 1100) notes that coverage as a drug or device vs. a tobacco product would depend on aspects of the trial itself that can only be determined after evaluation of the "methods and measures" to determine "the purposes for which a product is being investigated."[347] The complexity of these various laws, regulatory pathways, and subjective legal precedents complicate the issue of FDAAA coverage for ENDS products and obstructs public transparency and accountability.

This ambiguity is apparent when examining this sample of e-cigarette trials. The uptake of nicotine in the body is an important component of nicotine addiction.[348] Three of the five trials examined nicotine biomarkers or pharmacokinetics. Trials excluded from this analysis share similar outcomes. It is unclear whether these outcomes aid in making claims about the "delivery

of a pharmacologically active dose of nicotine" which are generally exempted from drug and device regulations; investigate "modified risk tobacco product" designations that allow claims relative to other tobacco products outside of drug and device regulations; or fall under unapproved or uncleared drug and device rules due to their clinical subject matter and outcomes.

Additional Juul sponsored trials directly address smoking cessation with relevant outcomes like product use, dependency, urge to smoke, and aspects of withdrawal raising similar coverage questions. Clarity around their coverage under the FDAAA would require a more active approach to enforcement of the law. The FDA has only recently engaged in limited direct approaches to enforcing the registration and reporting requirements of the FDAAA amidst mounting public criticism.[17,45,349] Previous comments from President Joe Biden have shown support for active enforcement of federal results reporting requirements which may signal receptiveness of the current administration to these issues.[350] Still, engagement to date has been minimal and this lack of attention can lead to ambiguity about which trials are covered, lessening the impact of FDAAA reporting requirements.

Failing general efforts to make FDAAA coverage more definitive to the public, the FDA may consider specifically clarifying the reporting responsibilities of tobacco-industry sponsors under the law. If registered industry-sponsored clinical research into tobacco products supports various tobacco-specific regulatory pathways, instituting reporting requirements as a condition of these applications could bypass complicated FDAAA 2007 considerations entirely. The public and the scientific community have a clear interest in ensuring the results of research on tobacco products is made fully available and current dissemination routes appear lacking. In any case, setting aside legal obligations, there is also a strong ethical expectation that all clinical trial

results should be reported completely in a timely manner and this investigation also shows notable deficiencies with outcome reporting in available results.[165,307]

3.6.5 Implications for Future Research

In the context of my DPhil this chapter offered valuable experience in building a search strategy to examine the extent of reporting in an area. This was one of the first studies I designed for my DPhil and I had to consider specific methodological questions around where to search, how to search, rectifying data between searchers, and linkage of results back to registry entries. While I was familiar with similar studies in the literature, designing and performing these tasks and analysis myself was instructive for designing the search strategies for Chapters 4 and 6.

This study also showed that registries continue to be a valuable tool for research on outcome-switching and non-reporting of outcomes. The extent of selective reporting, and its impact on evidence, will vary by field and should be considered within any evidence-base.[50] Additional in-depth audits that focus on a single sponsor, funder, or institution, can better catalogue how and why these issues occur and where systemic gaps require attention. The ongoing TrialsTracker project allows for close tracking of trials from a specific sponsor or therapeutic area.

Additional research is also needed on ways to improve the use of registries in the assessment of the published research literature. Mandates on prospective registration or reporting guidelines like CONSORT can only be utilised to their full effect if they are checked to ensure complete and transparent reporting at the pre-publication stage. When peer reviewers and editors fail to incorporate this due diligence into routine journal processes, reporting biases are primed to enter the literature. Interventions in journal processes should be investigated to ensure improvements in transparent reporting. Post-publication methods, like sending letters to the

editor, have not been shown to adequately address reporting issues and are at times actively resisted by editors and authors.[6,283]

Emerging research has examined the feasibility of incorporating a "discrepancy review" into standard editorial processes to better ensure transparent and complete reporting. Dedicated reviewers were tasked to check the consistency between registrations and submitted manuscripts and provide feedback to authors. Piloting the process at two journals, including *Nicotine and Tobacco Research* which was assessed in this study, suggested this process was feasible as authors addressed most of the discrepancy review comments. Notably, however, the authors concluded that reviews for clinical trial registrations needed to be treated separately from other forms of registration as "the former are generally more precise, and the latter are generally more comprehensive."[351]

This is the type of interventional research I will propose to develop and study further as I move to the next stage of my career. Another potential avenue for research is to examine ways to improve reporting at academic conferences. Conference organisers should be prompted to do more to ensure their accepted abstracts of clinical trial results properly represent and disclose the completeness of accepted posters and presentations. This is especially important as some results may only be shared at conferences.[352–355] While abstract space is often limited, there may be cause to amend current conference reporting guidelines to avoid potential biases.[356]

3.7 Reflection

This study presented a fascinating opportunity to focus in-depth on how registries can address bias. The COMPare study provided a model to assess reporting bias in individual studies that I was able to modify and apply to e-cigarette trials to investigate an area of substantial interest to global public health policy.

Originally this study was designed to be a relatively straightforward assessment of FDAAA reporting compliance of a single sponsor with additional investigations of outcome reporting. However, during the review process one reviewer offered considerable resistance to the idea that tobacco products are covered under the FDAAA. This led to a very constructive back and forth in which the analysis remained unchanged, but the framing and interpretation shifted to explore the uncertainty around coverage of tobacco product trials and the unresolved regulatory questions. In my opinion, this led to a substantially richer discussion. During this process I reached out to both ClinicalTrials.gov and the FDA and while neither could comment on the status of individual trials, both provided additional information and context that improved my understanding of the issues.

Following publication of this study Dr. Snigdha R Mishra, a representative from Juul, posted a rapid response to the journal noting that since the final searches in August 2020, two additional pieces had appeared in the literature increasing their overall reporting performance and the FDA has all data from these studies as part of Juul's regulatory submissions.[337,357] In addition, Juul claims that the registration information on all five trials was incorrect and none are actually covered under FDAAA and have since updated their registrations accordingly.[358] In my response, I noted that while Juul should be commended for any additional disclosure they neither disputed nor addressed any of the outcome-reporting bias we found in the one publication that was public as of our analysis and note that disclosure to the FDA is not the equivalent of disclose to the public. In addition, I reiterated that the question of FDAAA coverage of tobacco products appears to be an open regulatory question and cited exact regulatory language to support my interpretation.[359] However, it should be noted that voluntary reporting to ClinicalTrials.gov gov would avoid any of these considerations.

3.8 Conclusion

Both publication and outcome reporting bias are well-established issues in the medical literature. While this chapter focuses on issues with e-cigarette reporting, these are not unique in their lack of full and transparent reporting practices. They do, however, provide a useful case study demonstrating how registration can and should interact with the publication, interpretation, and regulation of clinical research. The rest of this thesis substantially expands the scope of analyses and methods used but builds on the basic ideas about the utility and value of registries discussed here.

3.9 Chapter Summary

- Among five registered e-cigarette trials sponsored by Juul Labs Inc., no results were made available on ClinicalTrials.gov nor were full results made available in a timely manner in the literature.
- None of the trials assessed fully reported their outcomes across available results.
- Ambiguities in the FDAAA regulatory process limits the ability of the public to use ClinicalTrials.gov as a tool for transparency and accountability when assessing industry sponsored e-cigarette research likely requiring further action from the FDA or the US Congress.
- Reporting complete results to a registry can avoid incomplete reporting in short conference posters and delays inherent to journal publications.

Chapter 4: DIssemination of REgistered Covid-19 Clinical Trials (The DIRECCT Study)

A cross-sectional examination of Covid-19 results reporting

A publication based on this chapter was preprinted on *MedRxiv* and published in the journal *BMJ Open*:

- Salholz-Hillel M, Grabitz P, Pugh-Jones M, Strech D, DeVito NJ. Results availability and timeliness of registered Covid-19 clinical trials: interim cross-sectional results from the DIRECCT study. *BMJ Open* 2021; 11: e053096. DOI: 10.1136/bmjopen-2021-053096

This study was preregistered on the *Open Science Framework* with data available via *Zenodo*:

- DeVito NJ, Salholz-Hillel M, Grabitz P. A Protocol for Analysing the Results Dissemination of Registered Covid-19 ClinicalTrials. *Open Science Framework* 2020; published online June 30. https://osf.io/5f8j2
- Salholz-Hillel M, Grabitz P, Pugh-Jones M, Strech D, DeVito NJ. Dataset for the DIssemination of REgistered Covid-19 Clinical Trials (DIRECCT) Study. 2021; published online April 7. DOI:10.5281/zenodo.4669937.

The study code is available across two *GitHub* repositories covering code in Python and R.

- Python Repository: https://github.com/ebmdatalab/covid19_results_reporting
- R Repository: https://github.com/maia-sh/direcct

4.1 Chapter Rationale and Overview

In Chapter 3 I examined trials from a single sponsor demonstrating how registries can be used as a tool to check for presence of publication and outcome-reporting bias. This chapter broadens the scope of analysis to the entire International Clinical Trials Registry Platform

(ICTRP) infrastructure to assess the dissemination of Covid-19 clinical trials. As with Chapter 3, this study examines an important research question around how results are disseminated in public health emergencies, but also provides key insights into the use of registry data for research at scale.

In March 2020, I used my experience in working with registry data to develop Python code[m] that extracted, standardised, and normalised key fields from the ICTRP dataset of registered Covid-19 clinical trials. This allowed more convenient use of fields like sponsor name and phase. I also supplemented the data with additional registry information that wasn't part of the standard ICTRP dataset like details of intervention types, completion dates, results, and transparent cataloguing of cross-registrations. These data were collected using a mix of registry scrapers and manual extraction. Using the Datatables framework[n], I created a basic website[o] that hosted the dataset and some simple visualisations made using Python and Tableau. These resources saw some initial use,[43,44,360,361] however as the scale of the pandemic grew, by the end of 2020 maintaining this resource as a side-project was not feasible.

The website, however, led to conversations with colleagues at the QUEST Centre at the Charité – Universitätsmedizin Berlin about how to build on this idea. Initial conversations quickly evolved into the DIssemination of REgistered Covid-19 Clinical Trials (DIRECCT) project which aimed to combine automated and manual methods to understand how and when the results of registered Covid-19 research entered the literature. I co-designed the project with colleagues at QUEST and was made the lead researcher for the design, conduct, and analysis. QUEST would provide additional funding and personnel support as collaborators.

[m] Original code available at: https://github.com/ebmdatalab/covid_trials_tracker-covid
[n] More information on Datatables available at: https://datatables.net/
[o] https://covid19.trialstracker.net/

The pandemic created a unique environment in which significant global clinical research resources were focused on the treatment and prevention of a single disease. It also created a research opportunity to document how the scientific community reacts and responds to a pandemic. This chapter addresses how Covid-19 clinical trials were reported while providing valuable real-world insights into the global role and function of trial registries.

4.2 Introduction and Background

4.2.1 Introduction

Soon after its initial identification in Wuhan, China in early 2020, the Covid-19 pandemic would quickly grow to dominate international research efforts aiming to treat and prevent the disease. On 25 March 2020, the World Health Organisation (WHO) ICTRP listed 668 registered Covid-19 studies, a year later that number had grown to 8,798 studies and surpassed 12,000 by 2022.[362] Similarly, over 5,400 reviews of Covid-19 studies in humans are registered on the PROSPERO database as of October 2021.[363] These require timely and complete trial reporting for rapid evidence synthesis. Throughout this process trial registrations became crucial to informing the academic community about the trajectory of pandemic research.[364–367]

Expectations for sharing of trial results change during public health emergencies. The WHO noted in a 2015 consultation that "every researcher that engages in generation of information related to a public health emergency or acute public health event with the potential to progress to an emergency has the fundamental moral obligation to share preliminary results once they are adequately quality controlled for release."[307,368,369] Early on in the Covid-19 pandemic, various health publishers, funders and organisations signed a public statement reiterating their commitment to the WHO statement.[370] Guideline 20 of the *International ethical guidelines for health-related research involving humans* reiterates the need to "generate knowledge quickly" in

emergency situations while maintaining ethical standards and public trust.[371] Further development of principles for sharing data in public health emergencies have been published by the Global Research Collaboration for Infectious Disease Preparedness (GLOPID-R).[372,373]

However, none of these guidelines specify an exact timeframe for reasonable dissemination in emergencies. For instance, the WHO statement expressed that the usual expectation to report primary results within 12 months "should be greatly shortened," and the GLOPID-R calls for timely sharing in a "logical, efficient and rapid manner" without expectations about what this means in practice. Every public health emergency is unique and brings its own realities as to how, when, and where results may become available; however, the need for rapid yet accurate dissemination of information remains constant. Clinical trial registries should provide one of the most efficient and rapid dissemination routes for results. Understanding how and when trial results are shared in a global pandemic can inform future policy discussions around research management during emergency situations.

4.2.2 Prior research on pandemic reporting

Past investigations of pandemic reporting show lackluster reporting performance. One analysis of the 2009 H1N1 pandemic found just 29% of randomised trials examining H1N1 were reported in the literature within 18 months of trial completion, and just 12% of H1N1 vaccine trials published within a year of completion, rising to 30% within two years.[374,375] Across the H1N1, Ebola, and Zika outbreaks, less than half (42%) of all trials met either of the WHO reporting standards for non-emergency situations (i.e., 12 months for a registry, 24 months for journal publication).[376]

However, the global scale and scope of the Covid-19 pandemic, and its accompanying explosion in clinical research, distinguishes it from other modern disease outbreaks.[377] The

rapid rise in the usage of preprint servers for the clinical and biomedical sciences is also a distinct feature of the research response to the current pandemic.[378–381] The DIssemination of REgistered Covid-19 Clinical Trials (DIRECCT) study was designed as a multi-phase, living examination of results dissemination throughout the Covid-19 pandemic to examine these facets of the research response.

4.3 Aim and Objectives

4.3.1 Aim

Examine the results dissemination of registered clinical trials during the Covid-19 pandemic.

4.3.2 Objectives

4.3.2.1 Create a method to combine automated and manual searches for the results of registered Covid-19 clinical trials

4.3.2.2 Describe the availability of results for trials completed during the first six months of the Covid-19 pandemic across dissemination routes

4.3.2.3 Assess the timeliness reporting of clinical trial results in a public health emergency setting

4.3.2.4 Test the robustness of findings to alternate assumptions about the completion and reporting of clinical trials

4.4 Methods

4.4.1 Project Overview

This study was originally designed to take part in three phases. Each phase would involve creating a population of registered completed trials through a set cut-off date and then conducting searches for those trials. This chapter contains data from Phase 1, examining trials completed through the first six months of the pandemic. Phases 2 and 3 were meant to cover

trials completed during the first 12 and 18 months respectively. However, delays to trial searchers for Phase ,1 and the unforeseen growth in new trials, led to the decision to combine Phases 2 and 3. Methods details for Phase 1 follow below with additional details on the future direction of the project available in the Discussion. Code for collection, cleaning, and analysis of data for the project was written by me in Python v3 (Python Software Foundation), and the study database was managed by my colleague (MSH) in R v4 (R Foundation for Statistical Computing). The project's current protocol, with amendments, is available on the OSF page linked above and the full status of the project is detailed in the Discussion.

4.4.2 Study Population

The WHO ICTRP maintains a list of registered Covid-19 studies across 18 global registries (See Table 2.2, Chapter 2). For Phase 1 of the project, I downloaded this curated database on 1 July 2020 (last updated 29 June 2020). Data on trial completion from all registries were collected during the first week of July 2020 via custom web scrapers or manual extraction, as this was not available in the ICTRP dataset. ICTRP fields (e.g., phase, study type) were cleaned, standardised, and combined with data scraped from registries. A list of known cross-registrations (i.e., same trial on multiple registries) was maintained throughout the project and used to collapse duplicate entries to a single record, preferring a ClinicalTrials.gov entry when available, unless another registration is deemed more complete or relevant by the study team.

4.4.3 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria for trials were assessed twice. First using automated screening based on fields extracted directly from the ICTRP and registries between 30 June 2020 and 5 July 2020, and then via a manual assessment of each trial passing automated screening. Trial completion was defined as a trial that had reached its registered completion date regardless of listed trial status. Two additional *post hoc* exclusion criteria arose during coding reconciliation

discussions informed by the focus on trials for the direct treatment or prevention of acute infection with Covid-19; trials were excluded that focused exclusively on treating side-effects (e.g., reducing pain or mental distress experienced during or because of Covid-19) or those on post-acute Covid-19 experiences, (e.g., rehabilitation) (Table 4.1).

Table 4.1: Inclusion and Exclusion Criteria

Inclusion Criteria	Trial assessed an intervention for treatment or prevention of Covid-19 infection and subsequent acute disease.
	Trial included a primary completion date, or overall completion date if no primary completion date was available, on or before 30 June 2020.
Exclusion Criteria	Registration was found, at any time, to indicate that the trial was withdrawn before enrollment and therefore never occurred.
	Registration prior to 1 January 2020.
	Trial exclusively on symptomatic treatment of Covid-19 disease side-effects (e.g., fatigue, anosmia) (*post hoc*)
	Trial on rehabilitation after acute disease (*post hoc*)

4.4.4 Search Strategy

4.4.4.1 Automated Searches

On 30 June 2020, I programmatically searched PubMed with code using a PRESS Peer Reviewed search strategy for Covid-19 trial publications from the Covid-evidence project [382] and downloaded the XML records for all results. I also downloaded the CORD-19 database, a collection of open access coronavirus-related literature. This includes metadata and full-text articles including the PubMed Commons (PMC).[383,384] Both datasets were limited to only those publications on or after 1 Jan 2020 and either (1) matched a regular expression pattern for an ICTRP-approved primary registry ID, prefix, and/or name in either the abstract, metadata, or full

text[p] (full-text available for the CORD-19/PMC sample only) , or (2) was designated as a clinical trial “publication type” in PubMed.

Following de-duplication, we manually screened all potential results hits to determine whether they represented *bona fide* primary trial results that matched the registered trial characteristics, like trial name and ID, investigators, treatment, enrollment, and dates. All potential hits were screened by two reviewers. Matched results had to achieve consensus agreement between reviewers for inclusion in addition to reasonably matching registered characteristics. Issues not resolved by reviewer pairs were referred to the full study team for a final determination.

4.4.4.2 Manual Searches

Following automated exclusion of non-interventional, pre-2020, and non-completed clinical trials, remaining records were manually reviewed to assess their inclusion status. Trials meeting the inclusion criteria were searched using a strategy adapted from Wieschowski and colleagues[262] in which PubMed, Europe PMC, Google Scholar, and Google were searched in a stepwise fashion for results. Wieschowski and colleagues searched Web of Science but not Europe PMC and Google; Web of Science was excluded to ensure all searches were conducted in openly accessible databases and Europe PMC and Google were added for better coverage of preprint publications.[385]

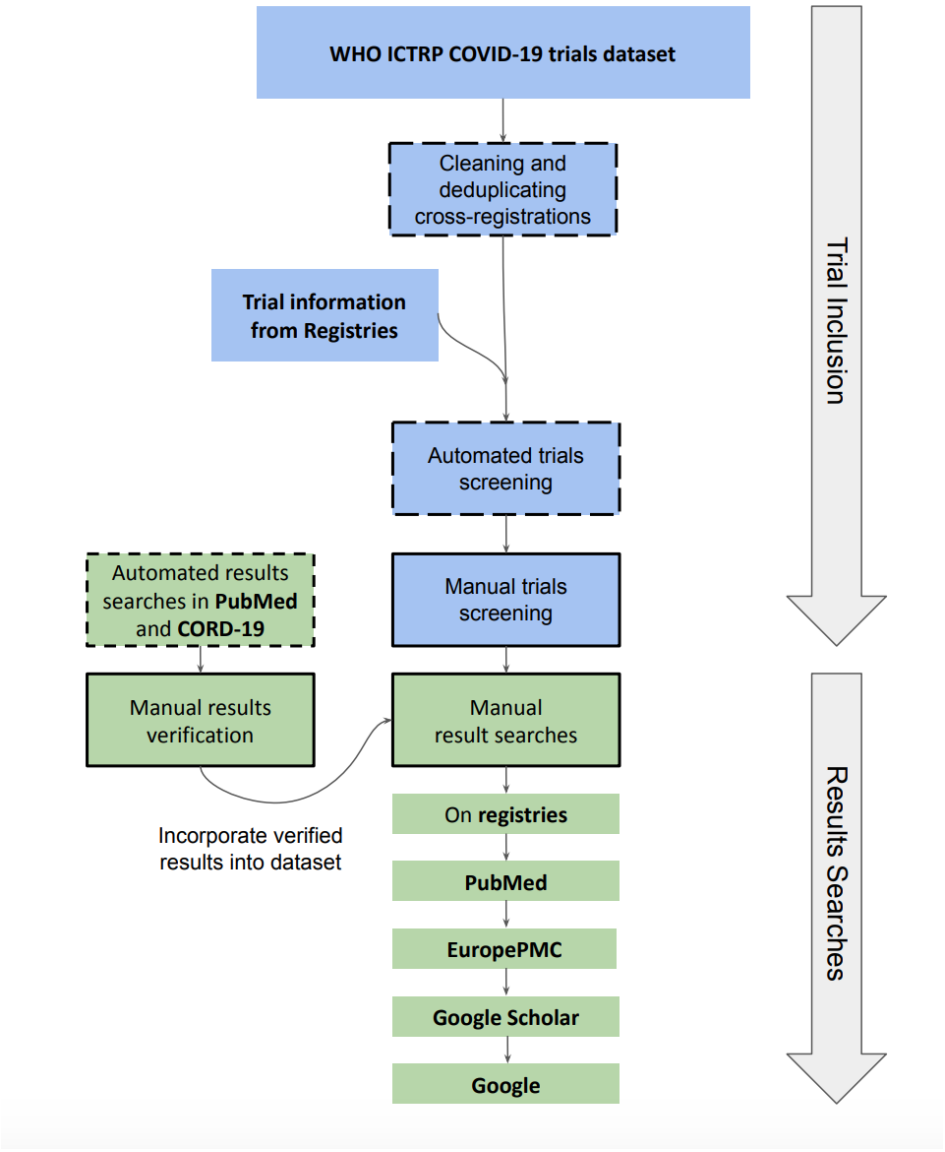
I led the search team made up of myself and three colleagues (MSH, PG, MPJ). All searches were performed by at least two reviewers. Each database was first searched using the trial ID(s) and keywords derived from the trial registration; then keyword searches using combinations of the titles and abbreviation of the trial, investigator names and affiliations, and the intervention

[p] Full-text available for the CORD-19/PMC sample only.

and population under study. Searchers also had discretion to create additional relevant keywords from the registry. This flexibility, rather than only repeating fixed keyword searches, should maximise search coverage. Date filters could be applied as necessary and the first 30 results in each database search were screened for results.

Searches took place between 21 October 2020 and 18 January 2021. If a full-results preprint and journal publication were located for a given record, no additional searches beyond a review of the registry entry were performed. For each manual search, we recorded any results located, the date of publication, and whether the publication contained a “last patient, last visit” date for the primary outcome. As with automated searches, publications were matched to registry entries on key study criteria and discrepancies were resolved by consensus between either the two reviewers or the full study team. Data collected manually was entered into Qualtrics forms,[386] and reviewer reconciliation conducted via the Numbat Systematic Review Manager.[387] A methods flowchart is available in Figure 4.1.

Figure 4.1: Methods Flowchart



All sources of data are highlighted in bold text. Blue colouring indicates the flow of registered trials; green indicates the flow of results. Automated steps have a dashed outline, manual steps have a solid outline. Figure co-created with Maia Salholz-Hillel and reproduced with permission.

4.4.5 Outcomes

4.4.5.1 Outcome Definitions

Results were recorded as either a journal publication, preprint publication, result on a registry, or other type of result. Other result types (e.g., secondary analyses, conference abstracts, grey literature) were not considered for this analysis. In addition, we recorded whether the publication included the complete results of any primary outcome(s), or if the results were interim results without completed follow-up. The inclusion of the primary outcome was assessed as described in the publication and did not have to match the registered primary outcome(s). The main results are based on publication of complete, non-interim results.

4.4.5.2 Outcome Reporting

Per protocol, outcome assessments are based on registry data as they stood on 30 June 2020. Subsequent updates to the completion date are not reflected in our main analysis. The only exception is if a results publication clearly included a specific “last patient, last visit” date that contradicted the registered completion date. If this occurred, the published completion date was used in all analyses.

For all trials included in the per-protocol analysis, I report overall results availability in any format by 15 August 2020 (six weeks after our cut-off) and each specific dissemination route along with a breakdown by registry and recruitment country. Additionally, I fit cumulative incidence curves using the Kaplan-Meier method for time to any results availability and time to journal publication censoring follow-up on 15 August 2020. Cumulative incidence for time to preprint publication was fit using the Aalen-Johansen method with journal publication as a competing risk and ties broken by nominal offsets.[388] For trials with multiple publications, the earliest publication date for the dissemination route(s) relevant to each analysis were selected. The median and IQR for time to publication among only those trials with a result were separately calculated.

4.4.6 Sensitivity Analyses

Following data collection, I assessed the robustness of our per-protocol analyses to changes in completion date and results definitions. I report the change in the rate when the analysis is repeated using: completion dates extracted from our later manual searches rather than from 30 June 2020; full completion dates rather than primary completion dates when available; and an expanded definition of first results to include interim results. Since manual results searches did not begin until October 2020, an expanded follow-up of three months could also incidentally be reported beyond the 6-week minimum.

4.4.7 Protocol Deviations

In addition to the *post hoc* sensitivity analyses described above the following protocol deviations occurred. Ensuring all trials had six full weeks to report (i.e., by 15 August 2020) was not specified in the protocol but was decided during study set-up to be a reasonable minimum follow-up time to allow time for rapid results reporting. The first round of searches began 15 weeks following our cut-off due to extensive development and pilot testing of our search and extraction methods. The 6-week search buffer will be maintained as a minimum follow-up time for searches and analysis moving forward.

The protocol also called for continuous checking of inter-rater reliability for each reviewer pair. This was difficult and impractical to implement into the final workflow for assessing results availability. The study team created an alternate system in which each reviewer-pair would attempt to reconcile any differences on study inclusion or results availability and categorisation through discussion. If consensus could not be reached, the issue was referred to the larger study team for further discussion, a final consensus decision, and if necessary, a specific rule

addressing similar situations moving forward. Two *post hoc* exclusion criteria based on these adjudications are detailed above.

4.5 Results

As of 30 June 2020, the ICTRP Covid-19 database contained information on 3,844 registrations. Following all automated and manual exclusions, the final analysis dataset included 285 completed clinical trials. Details of all exclusions are available in Figure 4.2. Brief descriptive details of the 285 trials are included in Table 4.2.

Figure 4.2: Flow Chart for Trial Inclusion

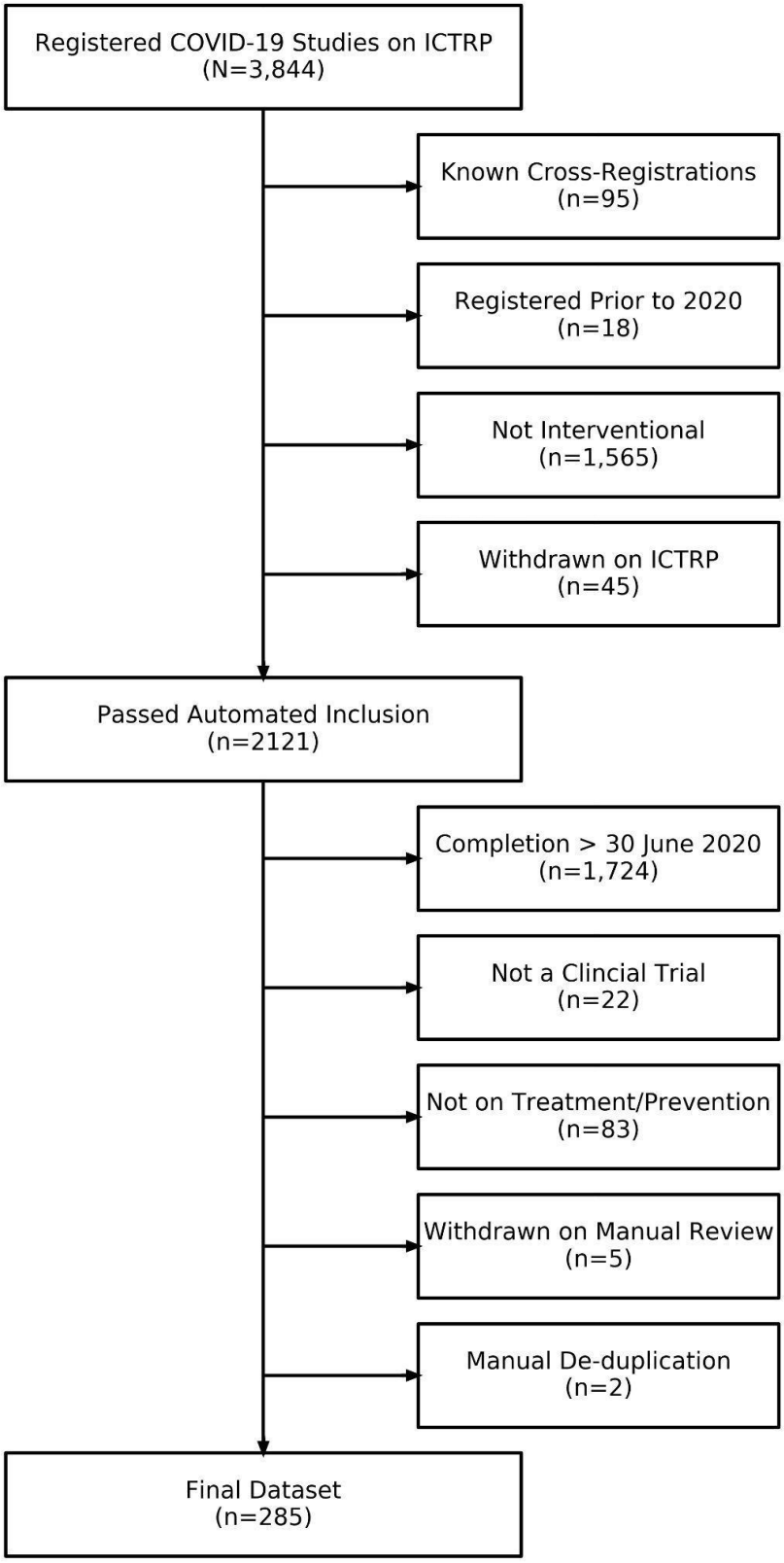


Table 4.2: Characteristics of Included Trials

Characteristics		Results Status		
		Overall (N = 285)	With Results (N = 41)	Without Results (N = 244)
Target Enrollment Median (IQR)		86 (40, 200)	60 (30, 127)	90 (40,200)
Phase n (%)	Not Applicable	109 (38%)	16 (39%)	93 (38%)
	Phase 1	13 (4.6%)	1 (2.4%)	12 (4.9%)
	Phase 1/2	13 (4.6%)	1 (2.4%)	12 (4.9%)
	Phase 2	46 (16%)	5 (12%)	41 (17%)
	Phase 2/3	16 (5.6%)	2 (4.9%)	14 (5.7%)
	Phase 3	38 (13%)	8 (20%)	30 (12%)
	Phase 4	50 (18%)	8 (20%)	42 (17%)
Registry n (%)	Cross-registered	22 (7.7%)	2 (4.9%)	20 (8.2%)
	ClinicalTrials.gov	134 (47%)	18 (44%)	116 (48%)
	ChiCTR	105 (37%)	17 (41%)	88 (36%)
	IRCT	9 (3.2%)	1 (2.4%)	8 (3.3%)
	EudraCT	3 (1.1%)	0 (0%)	3 (1.2%)
	RPCEC	3 (1.1%)	1 (2.4%)	2 (0.8%)
	Other Registries (<3 trials)	9 (3.2%)	2 (4.9%)	7 (2.9%)
Countries n (%)	China	130 (46%)	20 (49%)	110 (45%)
	Iran	22 (7.7%)	1 (2.4%)	21 (8.6%)
	United States	19 (6.7%)	1 (2.4%)	18 (7.4%)
	Italy	11 (3.9%)	4 (9.8%)	7 (2.9%)
	Spain	9 (3.2%)	1 (2.4%)	8 (3.3%)
	Egypt	7 (2.5%)	0 (0%)	7 (2.9%)
	France	7 (2.5%)	0 (0%)	7 (2.9%)
	Multinational	5 (1.8%)	3 (7.3%)	2 (0.8%)
	Countries with <5 trials	51 (18%)	9 (22%)	42 (17%)
	No Country Given	24 (8.4%)	2 (4.9%)	22 (9.0%)

4.5.1 Availability of Trial Results

Among the 285 trials registered as completed on 30 June 2020 or earlier, 41 trials (14%) had results available by 15 August 2020 spread across 47 individual results publications. Minimum follow-up for unreported trials was 46 days (i.e., six full weeks from our cut-off) and the longest trial follow-up time from completion was 196 days. Details on the screening of included results are included in Figure 4.3. The breakdown of results by dissemination route is detailed in Figure 4.4. Figure 4.5 shows the reporting of results by registry.

Figure 4.3: Results Inclusion Flowchart

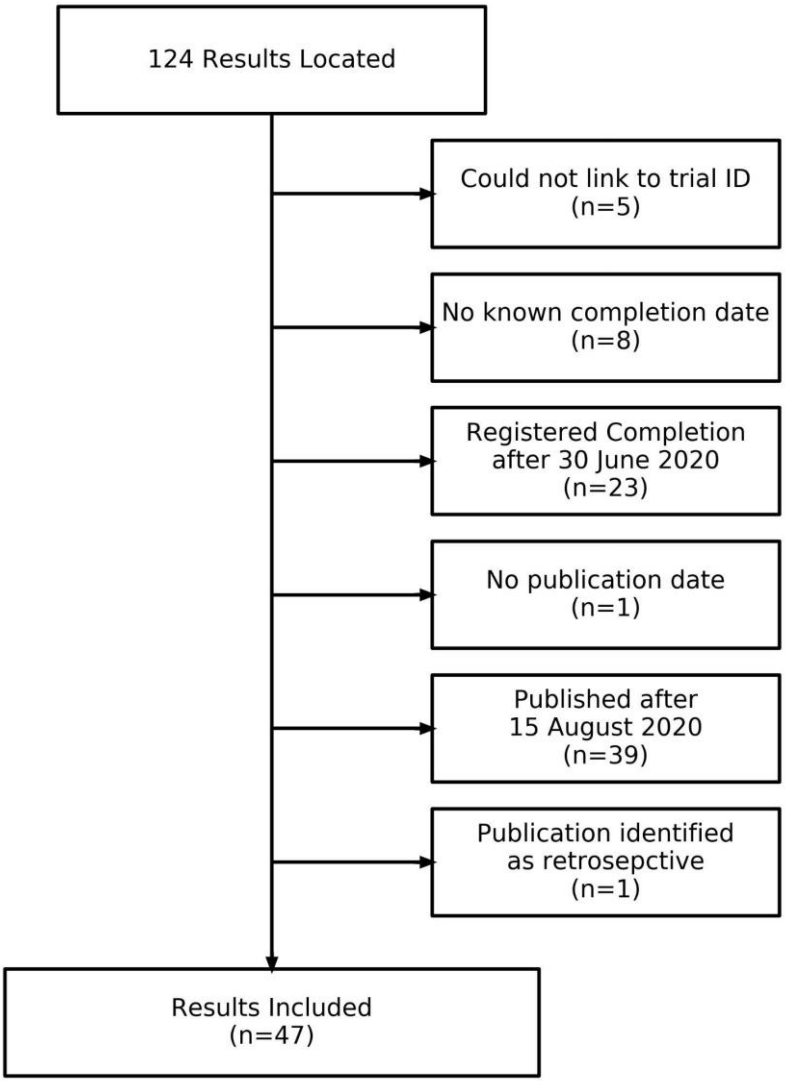
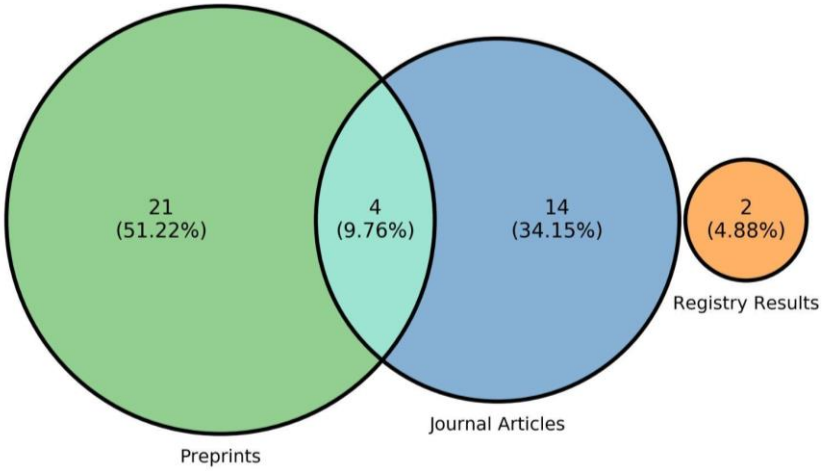
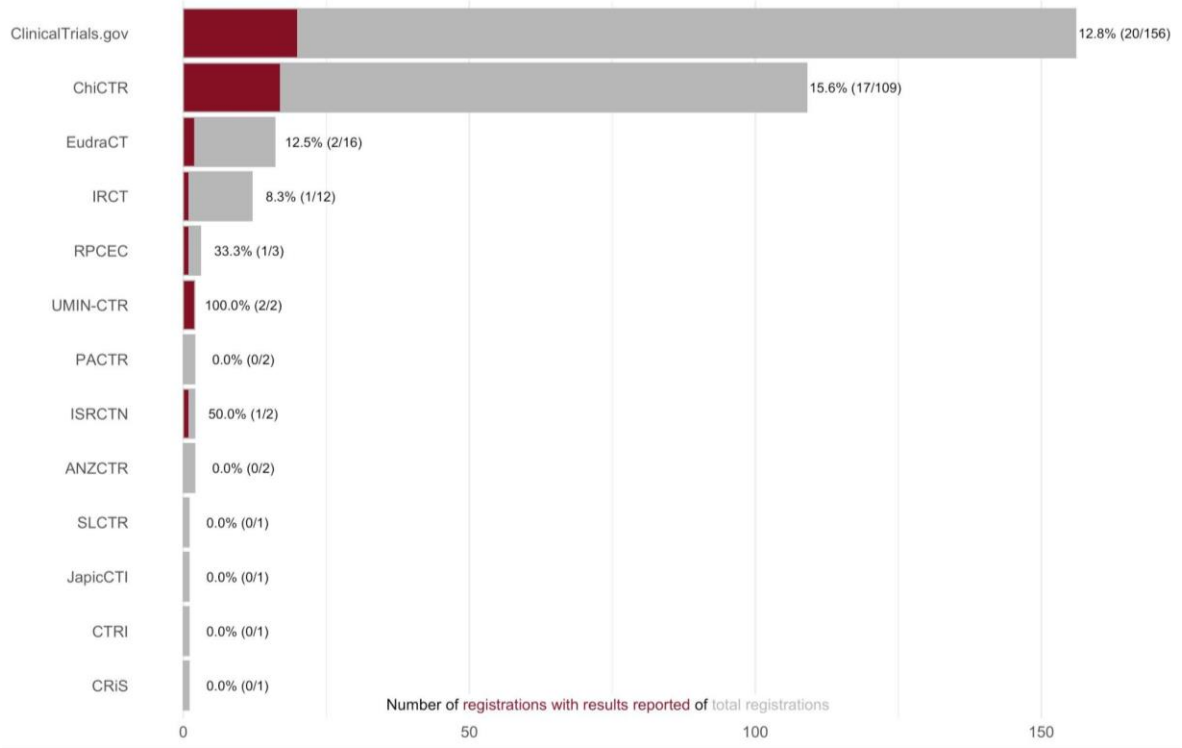


Figure 4.4: Covid-19 Clinical Trial Results by Dissemination Route



Preprints were the dominant mode of dissemination among Covid-19 clinical trials early in the pandemic with few rapidly converting to journal publications and little use of registries.

Figure 4.5: Result Reporting Rate per Clinical Trial Registry



The count of registrations is inclusive of known cross-registrations for included trials, therefore the denominators will sum to >285. Figure created by Maia Salholz-Hillel and reproduced with permission.

4.5.2 Timeliness of Trial Results

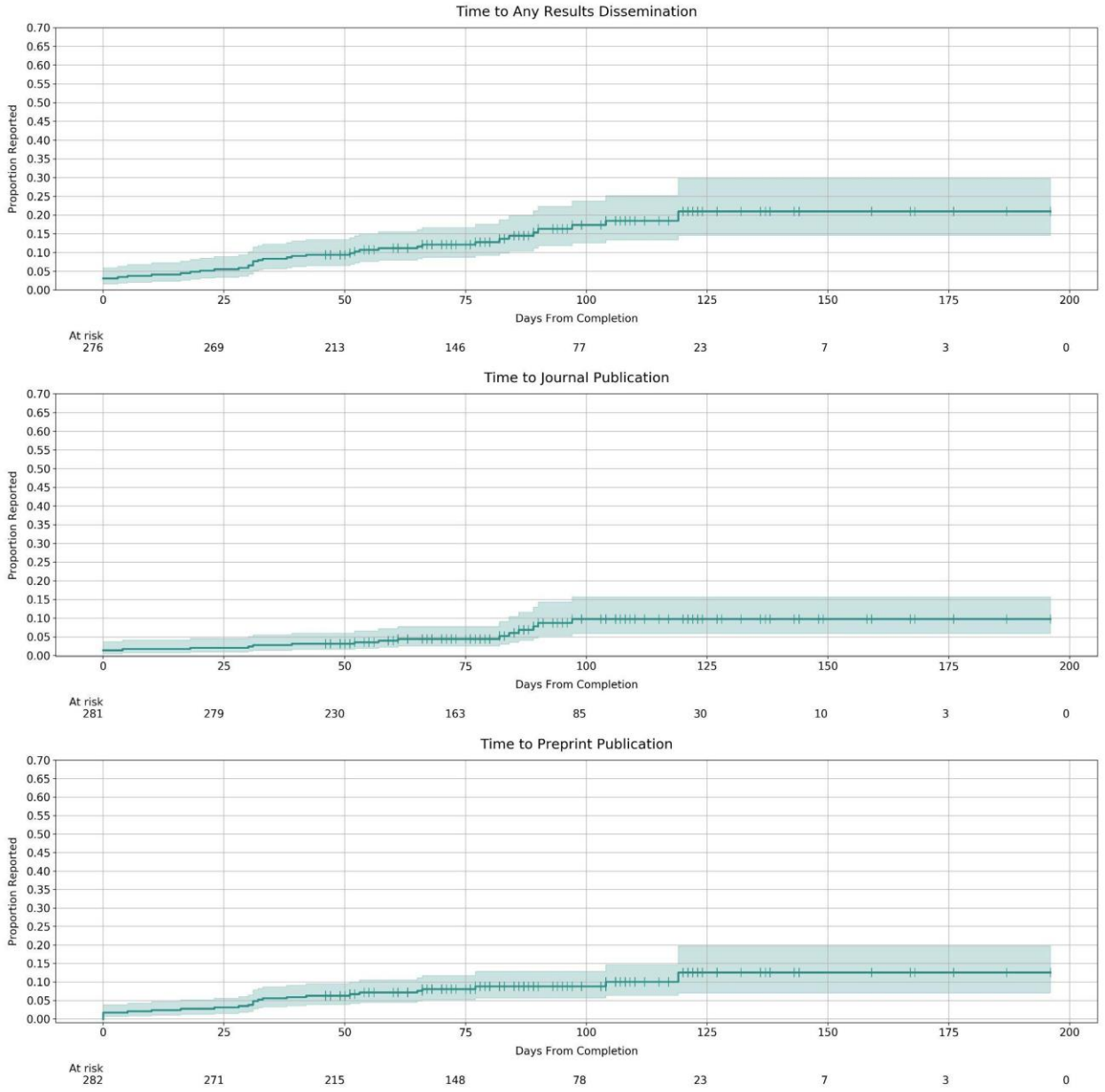
Figures 4.6a-c shows cumulative incidence plots for time-to-publication and 95% CIs. Trials with a publication date prior to the available completion date (across all results, n = 8 of 41 trials, 19.5%) were considered reported at time 0.[q] A date from a full results publication replaced the registered completion date (i.e., last patient, last visit), in 4 of 31 trials (9.8%). These figures show the cumulative incidence of a) first publication across any dissemination route, b) earliest journal publication, and c) earliest preprint publication. The medians for all cumulative incidence plots were undefined as no curve crossed 50%. The cumulative incidence of any results availability, accounting for right-censorship, surpassed 20% at 119 days from completion.

As only two trials reported results to a registry no plots were generated for this route. Summary results for these two trials were published on ChiCTR 3- and 20-days following completion. For the four trials that had both a preprint and a journal publication, the median time from preprint publication to journal publication was 24.5 days (IQR: 14.2, 36.2). For the 21 trials that had only a preprint, preprints had been published a median of 90 days (IQR: 76, 136) without a matched publication by completion of follow-up.

Trials with only a preprint (n = 21) published the preprint with a median of 32 days of completion (IQR: 10, 53), whereas trials with both a preprint and a journal article (n = 4) published the preprint with a median of 31 days (IQR: 19.5, 31); trials with only a journal article (n = 14) published the article with a median of 45.5 days (IQR: 0.8, 83.5), whereas trials with both a preprint and a journal article published the article with a median of 46 days (IQR: 24.2, 67.2). Due to the small number of trials with both preprint and journal publications, no statistical comparisons were made.

[q] The Aalen-Johanssen plot used nominal offsets to break ties at 0.

Figure 4.6a-c: Time to Results Across Dissemination Routes



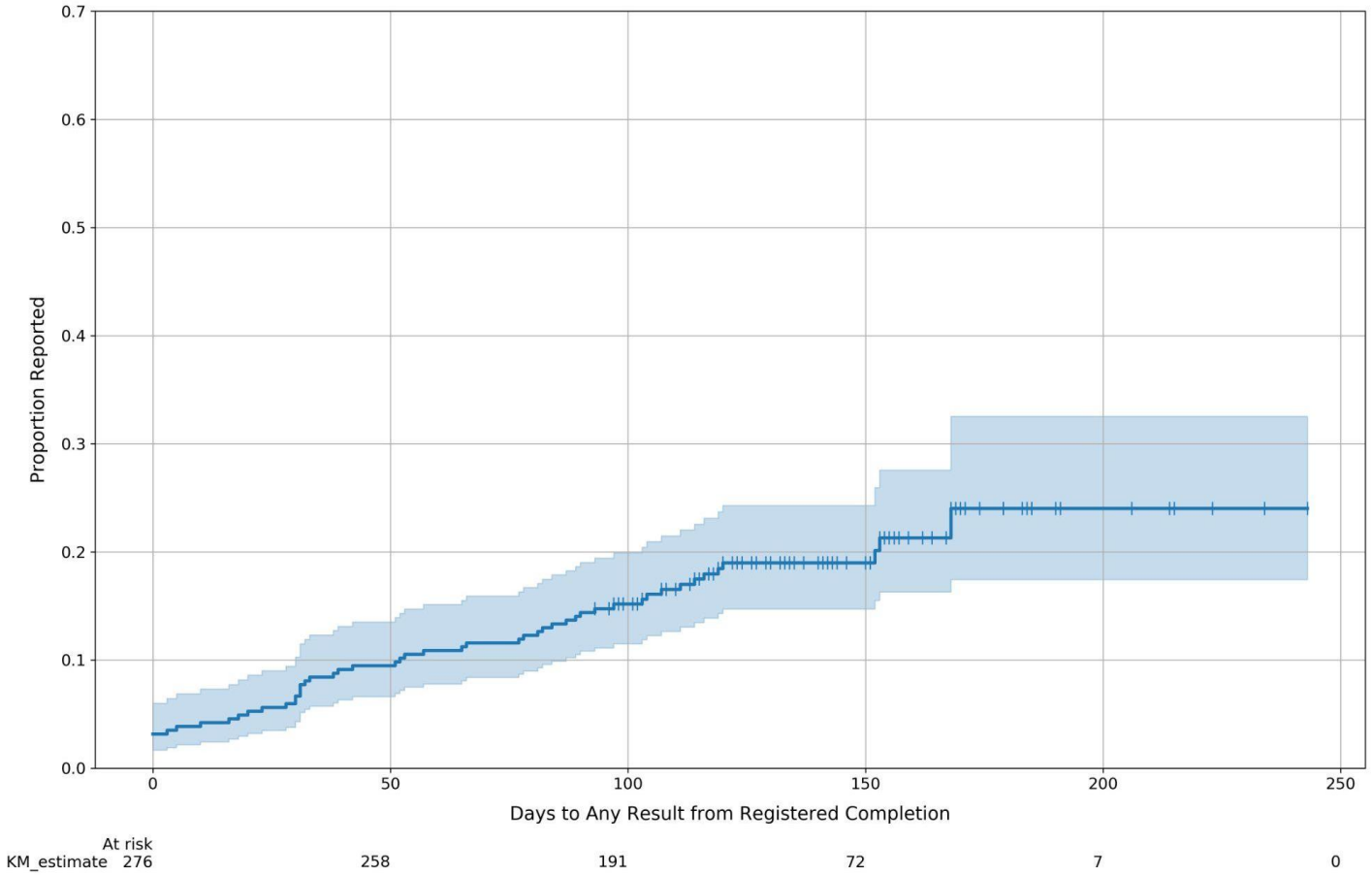
Cumulative incidence curves for the time to any results dissemination and to journal publication were created using the Kaplan-Meier method. Time to preprint publication was created using the Aalen-Johansen method with journal publication as a competing risk and nominal offsets to break ties.

4.5.3 Sensitivity Analyses

Each sensitivity analysis changed only a single aspect of the main analysis; the changes were not cumulatively applied. First, new completion dates were recorded for 48 trials during manual searches, 33 of which moved the completion date post-June 2020. Using this updated trial population (n = 252) leads to a reporting percentage of 16% with a minimum of six weeks of follow-up. Second, restricting our original sample to only those trials that reached full completion by 30 June 2020 showed 38 of 212 (18%) trials reported with a minimum of six weeks of follow-up. Third, adding interim results to our per-protocol findings yielded only one additional results publication for a reporting percentage of 15%.

Lastly, extending the six-week minimum follow-up window to three-months (i.e., counting any results reported by 1 October 2020), aligned with when the searches for this phase of our project actually began, added an additional 17 results for a reporting rate of 54/285 (19%). Figure 4.7 includes a cumulative incidence plot for any results from expanded follow-up time.

Figure 4.7: Time to Results Dissemination from Registered Completion Date - Extended Follow-up



Since data collection took longer than expected to begin, the minimum follow-up time between the cut-off for trial completion and the start of searches was actually 3-months rather than the original 6-week cut-off reported as the primary outcome.

4.6 Discussion

4.6.1 Summary of Findings

Of 285 registered trials for the treatment or prevention of Covid-19 completed during the first six months of the pandemic, 14% had a result available in either a preprint, journal article, or posted to a clinical trials registry after a minimum follow-up time of six weeks. Sensitivity analyses using alternate dates and definitions of results for assessments did not appreciably change the reporting percentage. Extending the minimum follow-up time to three months yielded 19% of registered completed trials with results. Preprints have played an important role in results dissemination with the most unique results of any route. These preprint results did not rapidly enter the peer reviewed literature as just four preprints in our sample had a matched journal publication. There was low use (5%) of clinical trial registries for results dissemination.

4.6.2 Results in Context

Registered and reported Covid-19 trials have been well-described in the literature.[240,377,389–392] These results add to these examinations of the design, focus, and outcomes of the Covid-19 research response. Janiaud and colleagues searched a single database for results of all registered Covid-19 RCTs from the first 100 days of 2020 and conducted outreach to trial contacts in October 2020. They located results for 53 of the 516 trials (10.3%) but did not match results to only completed trials. Of the 516 trials in their sample, 155 (30%) had not started or were discontinued, per either the registry or trial team outreach.[393]

Reporting for Covid-19 trials may be accelerated compared to non-pandemic trials even if rapid reporting assessed here is low. A 2014 meta-analysis showed pooled reporting of 54.2% in studies with a minimum of 24 months of follow-up. Reporting percentages in the 22 individual studies, often examining trials in a single specialty, ranged from 23% to 76%; five of these studies with data on time to publication showed a 30% pooled probability of reporting at 24

months of follow-up.[73] Subsequent large examinations of reporting registered trials from academic medical centres in the US and Germany showed 35.9% and 39% of results published in the literature within two years of completion and overall reporting did not surpass 20% in either study until well after six months of follow-up.[261,262]

Low reporting rates have also been seen in previous pandemics; vaccine trials during the H1N1 pandemic showed <20% probability of reporting within 5 months of completion.[375] Jones and colleagues examined the extent and timeliness of reporting during the H1N1, Zika, and Ebola outbreaks. As in these findings, registries were less commonly used to disseminate results compared to journal publications (47% to 68% available at 24 months). Overall, there was a median delay from completion of 42 months (IQR: 16-76) for results posting to registries and 21 months (IQR: 9-34) for journal publication. H1N1 trials were substantially slower to publish results compared to Ebola and Zika trials; however, Zika trials showed the lowest overall reporting percentage across both routes. No negative findings were reported among 44 non-vaccine drug or biologic trials. [376]

Preprints grew modestly during prior outbreaks;[378] however their rise has been substantial since the Covid-19 pandemic began, including for clinical trials.[380,394] Preprints represented the most popular dissemination route, and often the only route, in which results were available in our sample. The low conversion of preprints to journal articles is consistent with other research on preprints from early in the pandemic.[395,396] The final analysis of DIRECCT will cover a wider population of trials and provide additional follow-up to be considered alongside emerging evidence on the relationship between preprints and the peer-reviewed Covid-19 academic literature.[381,397] A preprint from Kapp and colleagues assessed the quality and completeness Covid randomised controlled trial reports located through 31 May 2021. Overall, they located 124 preprints, of which 76 (61%) had converted to full journal publication with a median delay of

95 days (IQR 59-171) at the completion of follow-up. Additionally, of 158 trials that could post summary results to a registry, just 27 (17%) had done so. This study also showed poor congruence between registered and reported outcomes with just 51% of trials assessed adequately reporting “results for the primary outcome.”[398]

4.6.3 Strengths and Limitations

This work had several strengths. The broad definition of interventional clinical trials beyond just randomised controlled trials, and use of the ICTRP database covering all primary registries, gave a complete picture of the Covid-19 landscape in comparison to other efforts that focused on randomised controlled trials to inform evidence synthesis.[382,399,400] Publication searches were performed using multiple strategies and databases with dual-coded manual verification. Analysis using alternate assumptions confirmed these findings as robust.

However, this work has limitations. Missing, incomplete, inaccurate, or outdated data all likely impacted this analysis to varying degrees that would be difficult to quantify. Deviations from best practices for discoverability (e.g., inclusion of registration IDs in abstracts and metadata), publications in non-indexed journals or preprint servers, and articles not available in English language may have made some results difficult to locate despite our extensive search strategy. Lastly, these methods may under-represent some aspects of how results have been shared during the pandemic in practice. For instance, large adaptive trials like the RECOVERY trial or master protocol trials like SOLIDARITY have reported numerous influential results under a single registration and will only be represented as a single interim datapoint in our analysis that remains ongoing until the end of follow-up for the final arm.[401,402]

4.6.4 Implications for Policy and Practice

The huge increase in trial registrations reflects the fragmentation of the global Covid-19 response. As others have noted, this rush to register research without coordination or consideration of the work of others may compromise progress towards answering crucial questions.[403] A disparate research environment may lead to considerable research waste as unnecessary duplication, disjointed outcomes, and competition for participants slows evidence generation.[404–407] It is essential that the scientific community reflects on the Covid-19 research response and how and why it evolved as it did.

A complete assessment of Covid-19 trial results dissemination would require accurate registry data on both trial completion and the overall status of the trial. The availability of completion dates, planned or actual, in registries ranged from never (e.g., REBEC), to sometimes (e.g., ANZCTR), to always (e.g., ClinicalTrials.gov). Other registries, like the EUCTR, only make completion dates available retrospectively.

Additionally, data collection revealed substantial variation in registration quality both between and within registries. Searches for results, choices on inclusion, and comparisons of registrations to results are complicated by poor registration and reporting practice. Failure to include trial IDs in publications, or keep registry entries updated, clear, and consistent with the methods and outcomes in the final manuscript were all prevalent issues. Even including study dates in a publication, which would aid the precision of our analysis, was often missing despite being a CONSORT reporting item.[163]

Issues with missing, incomplete, and outdated data on registries have been detailed in prior investigations and in other chapters of this thesis.[271,272,298] Registries were rarely used as a dissemination route for clinical trial results. The US National Institutes of Health have since

called for the rapid publication of Covid-19 study results on ClinicalTrials.gov and instituted expedited reviews of these results submissions moving forward.[408] While this research project would not have been possible in its current form without the global registry system, issues with the current implementation of that system also prevent its use to obtain precise and accurate accounts of the research environment.

It is difficult to conclude from these preliminary results whether these findings show true potential for publication bias from unpublished results, poor management of trial registrations, or some combination of both. The larger sample and extended follow-up of next phases of this study should provide additional clarity around pandemic reporting practices. The stakes of a global pandemic only amplify the importance of minimising reporting issues that may impact evidence synthesis, guideline development, and ultimately clinical practice. Failure to update registry entries compromises an important tool for transparency and accountability in the Covid-19 research response. Searching for or anticipating results that will never come hampers crucial efforts to efficiently collect and examine the evidence around Covid-19 interventions.

4.6.5 Implications for Future Research

The DIRECCT study team has expanded and throughout 2021 I led a group of five researchers in continued results searches. In early January 2021 the dataset was refreshed to include all trials registered as completed during the first year of the pandemic. Searches for these commenced in March 2021 however the number of trials added to the dataset was unexpectedly large. Rather than continue Phase 2 data collection past the planned Phase 3 cut-off date, the decision was made to combine the data from Phase 2 and 3 for the final analysis. The dataset was refreshed for a final time in July 2021 to include all trials registered completed during the first 18 months of the pandemic.

All trials from Phase 2 would be searched twice; Phase 3 trials would be searched once and then searched again if a searcher flagged any issues or uncertainties around their extraction. All trials in the Phase 2/3 combined dataset would be searched at least once after the six weeks of minimum follow-up time in mid-August 2021. Trial searches of >2600 trials completed in early 2022. In addition, I created a method for manually extracting standardised details about the intervention and control arms to further enrich the final analysis.

The original protocol included planned analyses of factors associated with timely publication of results, an examination of the directionality of results, and outreach to investigators. However, the study team decided to refocus our efforts on assessing the primary reporting outcomes given the high number of required searches and examine additional areas in separate analyses. I am working to locate additional funding to support these analyses using the DIRECCT dataset and continue the collaboration with my colleagues in Berlin. Openly sharing this dataset will also allow other groups to build on this work and open up avenues for future collaborations. These data form one part of a robust landscape of curation, examination, and synthesis of Covid-19 research and literature, through platforms like Covid-NMA, Cochrane, Covid-evidence, and Epistimonikos.[382,399,400,409]

The continued examination of publication rates over time will help place Covid-19 results reporting data in further context and inform expectations for reasonable dissemination timelines in public health emergencies. Future studies may also wish to examine additional forms of dissemination, such as press releases or other grey literature findings. These efforts allow for rapid evidence synthesis and the ability to efficiently examine pandemic research output to inform strategies for improved management and coordination of the global scientific community both during global health emergencies and otherwise.

4.7 Reflection

While the Covid-19 pandemic has been a hurdle to overcome throughout the second half of my thesis, it also presented opportunities for original research using my skills and experience with registry data. Typically, discrete analyses of trial reporting behaviour are conducted months to years after the final trials are completed. However, my colleagues and I were able to create and execute a study plan that allowed for more rapid assessments. What began as a side project early in the pandemic grew into a funded collaborative research study that I designed, implemented, and led while still a DPhil candidate.

This opportunity was an invaluable experience for my professional development and an unexpected addition to my thesis work. Up until this point, most of my time involved individually working with large trial datasets with occasional input from colleagues. This project grew into an exciting and extensive collaboration with the Charité – Universitätsmedizin Berlin that allowed me to act as a project lead and work through the benefits and challenges of remote cross-border collaborations. Managing junior colleagues, weighing the allocation of resources, building and adapting study plans, and responding to external pressures were an invaluable part of this experience.

4.8 Conclusion

Chapters 3 and 4 present valuable examples of the role registries play in the current global research environment. Their values as tools for research, transparency, and accountability cannot be understated. However, while registration is the status quo, maintaining data on registries and their use for dissemination is not yet the norm. Even during the Covid-19 pandemic when rapid reporting is of paramount importance, registries were rarely used for timely dissemination. Chapters 5 and 6 will explore the role regulations have played in beginning to address registration and reporting practice in the US and EU.

4.9 Chapter Summary

- When a cohort of completed trials from the first six months of the pandemic were given a minimum follow-up of six weeks to report results, 14% made results available; expanding minimum follow-up for the same cohort to three months increased reporting to 19%.
- Registries were not typically used for rapid dissemination early in the pandemic as preprints became the dominant mode of results reporting.
- Major shortcomings in the quality and availability of registration data complicate more precise assessments of trial reporting during the Covid pandemic.

Chapter 5: Tracking Compliance with Transparency Requirements of the FDA Amendments Act 2007

A cohort study

Manuscripts based on this chapter were published in the journals *The Lancet* and *JAMA Internal Medicine*:

- DeVito NJ, Bacon S, Goldacre B. Compliance with legal requirement to report clinical trial results on ClinicalTrials.gov: a cohort study. *Lancet* 2020; 395: 361–9. DOI: 10.1016/S0140-6736(19)33220-9
- DeVito NJ, Goldacre B. Evaluation of Compliance With Legal Requirements Under the FDA Amendments Act of 2007 for Timely Registration of Clinical Trials, Data Verification, Delayed Reporting, and Trial Document Submission. *JAMA Intern Med* 2021; 181: 1128–30. DOI: 10.1001/jamainternmed.2021.2036

Code and data for this chapter are available on *GitHub* and the *Open Science Framework*:

- *The Lancet*:
    - Code: https://github.com/ebmdatalab/fdaaa_trends
    - Data: https://doi.org/10.17605/OSF.IO/X8NBV
- *JAMA Internal Medicine*:
    - Code & Data: https://github.com/ebmdatalab/fdaaa_requirements

5.1 Chapter Rationale and Overview

The FDA Amendments Act 2007 (FDAAA) covers thousands of trials connected to the regulation of medical treatments in the United States. Since the FDAAA Final Rule came into effect in 2017, over 30,000 registered trials are covered under the most recent reporting rules. The requirement to register and report trials of new and existing treatments on the world's

largest register has major implications for how details of clinical research are shared. In Chapter 2, I detailed the passage of the FDAAA as a landmark legislation in the ongoing maturation of the global registry landscape. In Chapter 3 I explored the implications of lax enforcement and vague interpretations of the law in relation to e-cigarette trials. This chapter contains the most comprehensive examination of compliance with multiple facets of the FDAAA to date. This chapter, and Chapter 6, build on Chapter 3 and 4 by continuing to demonstrate the utility, and ongoing issues, with trial registries but shifts focus to the regulatory context around trial registration and reporting to address the second major research question of my thesis.

In 2018, I began development of the FDAAA TrialsTracker which examines compliance with FDAAA reporting requirements across the entire ClinicalTrials.gov dataset.[325,410] Though past studies have quantified FDAAA compliance, especially with the results reporting provisions, this work is the first to do so following the implementation of the Final Rule while also extending assessments to additional areas of compliance. I combined audit methods with quantitative epidemiological methods to describe FDAAA compliance. Since no official US regulatory accounting of FDAAA compliance exists, the analyses presented here provide independent public accountability and a baseline against which to measure the evolution of sponsor behaviour over time. Opportunities for improvement in the use of ClinicalTrials.gov, and compliance under FDAAA, can only advance with a comprehensive understanding of how these provisions are being implemented and which populations of sponsors require additional attention, outreach, and investment in order to improve.

5.2 Introduction and Background

5.2.1 Introduction

Shortly after the FDAAA 2007 was passed, Deborah Zarin and Tony Tse of the NLM wrote that the law “should transform the degree of public access to critical clinical trial information from

publicly and privately funded clinical research."[411] By 2007, approximately 70% of all global clinical trial registrations were being uploaded to ClinicalTrials.gov. In 2013, trials registered on the ICTRP with a US location (n=5,906) rivalled those in all of Europe (n=6,225) or East Asia (n=5,553).[158] Given the position of the US as a leader in both academic and industry sponsored clinical research, the law had enormous potential to increase the public availability of clinical trial information.

The FDAAA expanded the registration requirements of the FDA Modernization Act **(**FDAMA) to all trials on therapies under the regulatory purview of the FDA -- a wider scope than the FDAMA's trials of "serious or life-threatening diseases and conditions" standard.[123,166] Under the FDAAA, sponsors would have to register covered trials (i.e., applicable clinical trials or ACTs) within 21 days of the first enrollment of a participant and report results within a year of their primary completion date or PCD (i.e., the last date of data collection for the last primary outcome). In practice, the FDAAA requirements would cover most non-Phase 1 interventional medical trials of drugs, devices, and biologics conducted in the US while also extending to non-US trials conducted in support of potential FDA approvals and those containing products produced and exported from the US.

Full implementation of the law has been slow. US legislation often requires "rulemaking" by relevant executive agencies to fully clarify and implement all or parts of a law. In the FDAAA, Congress instructed the Department of Health and Human Services (DHHS), which houses the National Institutes of Health (NIH) and the FDA, to clarify certain aspects of the law within three years. This included reporting requirements for trials of unapproved therapies, whether the one year deadline for reporting should be expanded to 18 months, and various details and definitions of required information. The US rulemaking process involves the proposal of a draft rule, an open public comment period, and finally the publication of the official "Final Rule" in the

US Federal Register. This Final Rule clarified which trials are covered by the FDAAA 2007, when and how they should register and report, and how to request allowable delays to reporting and included an extensive preamble discussing the background, rationale, and interpretation of the rule.[11,412] The characteristics of covered trials were more robustly described using concrete inclusion criteria with direct links to data on ClinicalTrials.gov including newly created fields. The FDA was empowered to enforce the law by levying various sanctions on non-compliant sponsor, including fines of up to $10,000 per day after sufficient notice.[328]

5.2.2 The TrialsTracker Project and the FDAAA TrialsTracker

My work on trial transparency began in the year prior to starting my doctorate. I joined the Research Integrity team at the DataLab in early 2017 under my advisor Prof. Ben Goldacre. One major project was to launch the TrialsTracker research programme which would form the basis for much of the work presented in this thesis. This project aimed to take newly implemented trial reporting requirements in the US and EU and create automated, real-time, compliance tracking websites that monitored the entire population of registered trials. As opposed to one-off studies, these trackers would apply code that could re-assess the reporting status of all trials at regular intervals and automatically update the audit of compliance.

The FDAAA TrialsTracker was launched in early 2018 as the first trials covered under the Final Rule, completed in early 2017, became due. The Tracker was driven by code I developed in late 2017 and early 2018 to identify covered trials in the public data and track their reporting status. A few months later I started my thesis work with the intent to continue refining and expanding the tracker methods and code while conducting comprehensive analyses using the Tracker's data.

5.2.3 Prior Work on FDAAA Compliance

The clarity of the Final Rule was necessary to advance the goals of the law and allowed for more precise independent public audit. ACTs are not proactively publicly identified by any US regulatory entity due in part to commercial confidentiality concerns so independent audit requires a robust and defensible method of identifying regulated trials.

Prior to the Final Rule, there were three large-scale audits that attempted to comprehensively audit compliance with FDAAA requirements: Prayle and colleagues found that 163 of 738 (22%) trials that completed in 2009 had reported results by 2011; Gill found that 1,285 of 7,427 (17.3%) of trials completed between September 2007 and June 2010 had posted results by 2011; and Anderson reported that 1,790 of 13,327 (13.4%) “highly likely applicable clinical trials” completed between January 2008 and August 2012 had reported results within the one-year deadline and 5,110 (38.3%) reported results at any time as of 2013. Gill also examined a broader population of trials, including those likely covered under the FDAMA, to assess timely registration and found high rates of late registration, with 55% of all trials registering late, but increasing compliance over time. [129,172,173]

These studies all faced limitations due to the pre-rule lack of clarity (Table 5.1). Prayle and colleagues employed a labour-intensive manual process to match trial interventions to an approved drug database excluding trials of other interventions covered under FDAAA. This team also lacked information on whether certificates to delay reporting requirements had been granted as this was not yet public information. The FDA was quick to point out these limitations following the study publication.[413,414]

The Gill analysis also had no data on certificates of delay and included other issues such as conflation of funding and sponsorship of a trial, stating that only industry sponsored trials as part

of an IND were covered by the FDAAA requirements, and anchoring reporting deadlines to the full study completion date rather than the primary compilation date. The registration analysis did not appear to include any exclusion criteria beyond having a US location.[r]

Anderson and colleagues covered a longer timeframe and used more expansive criteria that would more closely match the eventual Final Rule criteria. They also had access to what was, at the time, non-public data about reporting delays. However, the methodology included the very conservative step to only assess trials in a "Completed" or "Terminated" status as due to report despite this not being required by the law. This means sponsors who simply did not update their trial to a completed status in a timely manner were excluded from the study. This removed over 16,000 trials from the analysis. The uncertainty in identifying due trials, especially around the handling of delays for unapproved treatments, would present ongoing difficulties in conducting robust analyses of FDAAA compliance.[415,416]

Other assessments of FDAAA compliance usually focus on specific samples or subsets of clinical trials. The Good Pharma Scorecard project has applied the FDAAA reporting standards to trials supporting FDA approvals in 2012 and 2014-17 showing mixed performance. The most recent findings showed that just 58% of drugs and biologics approved in 2016-17 were supported by trials fully compliant with FDAAA requirements.[415,417–419] The FDAAA has also been shown to impact transparency measures among trials supporting approvals in specific disease areas.[296,297,420] Others have assessed FDAAA reporting for select groups of trials but not within the post-Final Rule landscape.[263,265,421] In-depth evaluations of FDAAA compliance at a single institution has also been reported.[422]

[r] While the Gill paper included a link to the underlying data for the study, the link is no longer active which unfortunately precluded a more in-depth assessment.

Table 5.1: Inclusion Criteria for Pre-Final Rule Audits of FDAAA Results Reporting

Paper	Criteria
Prayle et aa. 2012	● Completed in 2009 per registered Primary Completion Date (or Study Completion Date if PCD not available) ● Interventional study ● Phase 1/2 or higher ○ Excludes no phase ● Has a US location ● Study contains a drug, biologic, or device ● Studies required to report had to include a treatment of an approved indication from the FDA (per the Drugs@FDAAA database)
Gill 2012	● Completed between September 2007 and June 2010 by the Completion Date (PCD if Study Completion not available) ● Interventional Study ● Phase 1/2 or higher ● Has a US location
Anderson et al. 2015	● Completed between January 2008 and August 2012 per registered Primary Completion Date (or Study Completion Date if PCD not available) ○ If both missing, included if last verified between 2008 and 2012. ● Interventional study ● Phase 1/2 or higher ● Has US location ● Study contains a drug, biologic, device, genetic, or radiation treatment ● US FDA oversight field is "No" ● Trial status of Completed or Terminated as of 31 August 2012

Since there is no official public record of FDAAA compliance, independent audits can aid in filling this gap and ensuring accountability. While perfect public identification of ACTs likely cannot currently exist, the current public ClinicalTrials.gov dataset can support the most robust estimates of true compliance to date owing to the Final Rule.[s] This chapter examines longitudinal data from the TrialsTracker project to describe and characterise reporting behaviour across all identified covered trials. These comprehensive methods are then extended and applied to additional areas of the final rule.

[s] As stated in Chapter 3, public assessments of compliance are actively encouraged in the preamble to the FDAAA Final Rule: "Public users of ClinicalTrials.gov, other than responsible parties, should be able to understand whether a registered trial is an applicable clinical trial"

5.3 Aim and Objectives

5.3.1 Aim

To analyse compliance behaviour of sponsors with multiple aspects of the FDA Amendments Act 2007 and its 2017 Final Rule.

5.3.2 Objectives

5.3.2.1 Analyse trends in compliance with the FDAAA 2007 results reporting requirements.

5.3.2.2 Identify additional areas of the FDAAA that can be assessed for compliance across the ClinicalTrials.gov dataset using computational methods and describe current levels of compliance.

5.3.2.3 Describe factors associated with compliance across reporting requirements

5.3.2.4 Assess compliance at the level of individual sponsors.

5.4 Methods

5.4.1 Data Acquisition

As part of the FDAAA TrialsTracker project, the full ClinicalTrials.gov dataset is downloaded in XML format and archived each working day. The project includes ClinicalTrials.gov archives dating to February 2018. The original cross-sectional analysis of results reporting was performed on data extracted from ClinicalTrials.gov on 16 September 2019; monthly trends analysis used archived data closest to the 15th day of each month from March 2018 to September 2019. The subsequent cross-sectional analysis of compliance with additional areas of FDAAA were performed on data extracted from ClinicalTrials.gov on 18 January 2021. All code for data collection and analysis in this chapter was written in Python v3 (Python Software Foundation).

5.4.2 Determining Applicable Clinical Trial Status

I developed code for identifying applicable clinical trials under the FDAAA Final Rule as part of the TrialsTracker project with full details of this process published in a methods preprint.[325] Development of this code followed an extensive review of the Final Rule, official documentation from ClinicalTrials.gov, and communication with ClinicalTrials.gov staff.[325–328] The official criteria for identifying applicable trials is included in Table 5.2 and the final ACT identification logic is included in Box 5.1.

ACTs are trials started and completed after the implementation of the Final Rule on 18 January 2017. Relevant fields were added to the dataset in early 2017 alongside the Final Rule and post-Rule trials should always include a “Yes” or “No” response in the required “FDA Regulated Drug” or “FDA Regulated Device” section. Through communication with ClinicalTrials.gov staff I confirmed that either “FDA regulated” field containing a “Yes” should indicate that the trial was either conducted as part of an “IND/IDE”, has a US location, or includes a drug, biological, or device manufactured in and exported from the US.[325] One of these must be true to indicate FDAAA coverage (Table 5.2). This was a key finding in developing my methodology as the Investigational New Drug (IND) or Investigational Device Exemption (IDE) fields are not available in the public dataset for reasons of commercial confidentiality. Rather than compromise the analysis with incomplete data, I instead relied on the “FDA regulated” fields as a proxy for this aspect of coverage. The overall criteria are similar to the Anderson et al. criteria described in Table 5.1, however with increased precision and fidelity to the law.

Table 5.2: Official ClinicalTrials.gov ACT and pACT Identification Criteria

Criteria	ACT	pACT
Study Type	Interventional	
Intervention Type	N/A	Drug, Device, Biological/Vaccine, Radiation, Genetic, Combination Product, or Diagnostic Test
US FDA-regulated Drug/Device Product	Yes	N/A
Study Phase	Not Phase 1	
Primary Purpose	Not Device Feasibility	
Primary Completion Date	On or after January 2008 or not specified	
Study Completion Date	On or after January 2008, if Primary Completion Date not specified	
Overall Recruitment Status	Not Withdrawn	
Study Start Date	On or after January 18, 2017	Before January 18, 2017
Any of the following apply:		
At least 1 US location or location on specified	True	
US FDA IND/IDE	True	
Product Manufactured in and Exported from the U.S.	True	N/A

Box 5.1: FDAAA TrialsTracker ACT and probable ACT Identification Logic

ACT[a] logic ***(trials started on or after Jan 18, 2017)***	***Probable ACT logic*** ***(trials started before, but completed on or after Jan 18, 2017)***
"Study Type" is Interventional AND ("FDA Regulated Drug" OR "FDA Regulated Device") is Yes AND "Phase" is (1/2, 2, 2/3, 3, 4 OR N/A) AND "Primary Purpose" is NOT Device Feasibility AND "Study Status" is NOT Withdrawn.	"Study Type" is Interventional AND "Phase" is (1/2, 2, 2/3, 3, 4 OR N/A) AND "Primary Purpose" is NOT Device Feasibility AND "Study Status" is NOT Withdrawn. *IF ("FDA Regulated Drug" OR "FDA Regulated Device") field is available:* ("FDA Regulated Drug" OR "FDA Regulated Device") is Yes. *IF ("FDA Regulated Drug" OR "FDA Regulated Device") field is NOT available:* "Intervention Type" is (Biological OR Drug OR Device OR Genetic OR Radiation OR Combination Product OR Diagnostic Test) AND "Study Location" includes (United States OR US Territories) AND "Is FDA Regulated" is (True OR Null).

[a]*ACT: applicable clinical trial*

Trials that began prior to the Final Rule, but finished after, are officially referred to as probable Applicable Clinical Trials (pACTs). While sponsors may update pre-Final Rule registrations to include the new "FDA Regulated Drug/Device" fields, they are not required to do so. In the absence of these fields, an alternate set of official pACT criteria are used to identify trials likely covered under the law. No matter which criteria are used to determine coverage status, all applicable trials that started prior to, but ended after, the Final Rule are referred to as pACTs throughout.

5.4.3 Identifying Trials Due to Report Results

The first analysis deals solely with the requirement for covered trials to report results directly to ClinicalTrials.gov within one year of the primary compilation date.[t] My code first identified all trials meeting the ACT/pACT criteria then assessed whether each trial had reached primary completion more than one year prior to the data's extraction date. Trials were excluded where a time-limited "certificate of delay" had been granted: these are available for interventions or new clinical indications that have not yet received a marketing authorisation by the FDA, or under "exceptional circumstances". Due to lack of details concerning these delays, I conservatively give all trials with a certificate the maximum additional two years to report for unapproved therapies even though they may be due sooner[u] or later for "good cause". Using this method, no trials with certificates of delay could have been due to report at the time of the analysis so all were excluded.[v]

[t] The study completion date is used if the primary completion date is unavailable.
[u] For instance, when a therapy is approved for a given indication, the delay ends and results for trials of the intervention for that indication are due within 30 days. There is currently no simple, automated way to connect FDA approvals directly to ClinicalTrials.gov data.
[v] The earliest any trial with a certificate could have come due to report under our standard would have been January 2020, therefore certificates of delay were only relevant to the creation of the dataset for examination of additional areas of compliance in January 2021.

Per the official criteria, I did not impose any requirement that a trial be in a "Completed" trial status to enter our population of due trials as Anderson and colleagues had done. Where missing or inconsistent registry data obstructed ascertainment of whether a trial was due to report, my methods would exclude that trial; where perfect ascertainment of due date was obstructed by a missing "day of the month" field, I conservatively assumed the trial was due to report at the latest possible date.[w]

A trial was considered "reported" if results had been submitted and were either publicly available or undergoing quality control (QC) review at ClinicalTrials.gov; a trial was considered "compliant" if these results were first submitted within one year of the primary completion. I calculated the overall number of trials due and the proportion reported on time as well as for each individual sponsor with more than 30 due trials on the registry. ClinicalTrials.gov defines a sponsor as "the organization or person who initiates the study and who has authority and control over the study". The sponsor may or may not also be the funder—however, the sponsor is legally responsible under FDAAA 2007 for the accuracy of registry data, and for reporting the results of the trial; the funder has no such responsibilities. Each trial has only a single lead sponsor who may also designate responsibilities to a primary investigator, however only primary sponsorship was considered in this analysis. I also calculated the trends in compliance and overall reporting over time for each month from March 2018[x] to September 2019.

To examine trial characteristics associated with reporting, my supervisor (BG) and I *a priori* selected explanatory variables on the basis of clinical and methodological interest which could be robustly derived from registry data and examined them in both univariable and multivariable models. Table 5.3 details the included variables. For each exposure variable I calculated the

[w] For instance, a completion date of March 2018 would become 31 March 2018.
[x] March 2018 is the first full month of data held by the FDAAA TrialsTracker project.

proportion of trials reported and compliant; I additionally conducted two logistic regressions with any reporting and compliant reporting as outcome variables to identify potential associations. Lastly, I generated Kaplan-Meier survival curves to model time from the date of primary completion to results submission for all due trials, and separately for industry and non-industry sponsored trials, censoring follow-up at the date of final extraction of data.

Table 5.3: Data Dictionary for Regression Analysis

Name	Type	Values
Sponsor Class	Categorical	Industry, non-industry, US government
Industry Collaborator	Binary	Yes/No
US Government Collaborator	Binary	Yes/No
Phase	Categorical	1/2, 2, 2/3, 3, 4, NA[a]
Trial Terminated	Binary	Yes/No
Contains Drug	Binary	Yes/No
Contains Device	Binary	Yes/No
Contains Biologic or Vaccine	Binary	Yes/No
Contains Diagnostic Test	Binary	Yes/No
Contains Radiation Treatment	Binary	Yes/No
Contains Combination Treatment	Binary	Yes/No
Contains Genetic Treatment	Binary	Yes/No
Trial Location	Categorical	US only, US + Outside US, Outside US, No data
Total Trial Sponsorship on ClinicalTrials.gov[b]	Categorical (split into quartiles)	Q1, Q2, Q3, Q4
Trial Fully Completed[c]	Binary	Yes/No

[a]NA, or not applicable, usually represents early stage device trials.
[b]This accounts for the sponsor's experience conducting trials.
[c]Study completion date is in the past.

5.4.4 Identifying Additional Requirements For Audit

Following my results reporting work, I examined the Final Rule for additional areas that could be assessed using only public ClinicalTrials.gov data and identified four areas: trial registration

within 21 days of first enrollment of a participant (timely registration), verification of the accuracy of registration data within the last year (annual data verification), requesting delays for results reporting on-time (requests for certificates for delayed reporting), and the submission of protocols and statistical analysis plans (SAPs) with results (document submission). Each of these areas impacts the quality, availability, and transparency of data on the registry. References to each section of the Final Rule[328] examined in this chapter are shown in Table 5.4.

Table 5.4: Section and Page References for Final Rule Requirements

Area	Final Rule Reference
Results Reporting	*Final Rule §11.40-11.44, pp. 65146-8*
Timely Trial Registration	*Final Rule §11.24, p. 65143*
Data Verification	*Final Rule §11.64, pp. 65155-6*
Certificates of Delay	*Final Rule §11.44, pp. 65146-8*
Document Submission	*Final Rule §11.48, p. 65148*

5.4.5 Assessment Methods for Additional Requirements

Identification of covered and due trials for additional areas of compliance used identical methods to the original reporting analysis. Timely registration was assessed by comparing trial start date to the date of first registration submission to ClinicalTrials.gov. The annual data verification check included all trials first registered more than a year ago and therefore should have verified their data at least once since registration. Trials with a study completion date in the past with results were excluded as they are no longer beholden to the verification requirement. Trials with results currently pending were excluded as it could not be confirmed if the results submission also included a record verification update.

Timeliness of requests for certificates of delay was assessed by comparing the date a certificate was applied for to the due date of the clinical trial results. While ClinicalTrials.gov does not publicly distinguish the exact type of delay granted, the Final Rule requires all delays to be requested prior to the trial otherwise becoming due. Lastly, for each applicable trial due to report results I checked for the presence of required documents that should be reported alongside results. The Final Rule requires protocols and statistical analysis plans to be provided alongside results and this is reflected in the ClinicalTrials.gov dataset. Details on document submission dates were scraped from the ClinicalTrials.gov archive website using a custom web scraper available in the project's GitHub repository.

5.4.6 Statistical Analysis

For each additional area assessed, I report the proportion of eligible trials in compliance and determined factors associated with compliance using univariable and multivariable logistic regression. The covariates were slightly modified and simplified from the results reporting analysis detailed in Table 5.3. These included: regulatory status (ACT or pACT), sponsor status (industry or non-industry), whether the trial contains a drug, phase (Early phase: 1/2, 2; Late phase: 2/3, 3, 4; and NA); and number of trials registered by the sponsor separated into quartiles. A conservative Bonferroni-corrected significance threshold of $p<.001$ was used to account for multiple covariates across multiple models and I report 99.5% CIs in line with this corrected alpha level.

For each area I identified the "major" sponsors with the highest proportion of trials out of compliance (i.e., all trials with at least 50 covered trials as of the analysis date). The denominator for each proportion was taken from the sub-population of trials relevant to that analysis. For late certificates, I limited the population to only those sponsors who have received

at least five certificates of delay to ensure only those who make repeated, rather than one-off, use of the system are captured.

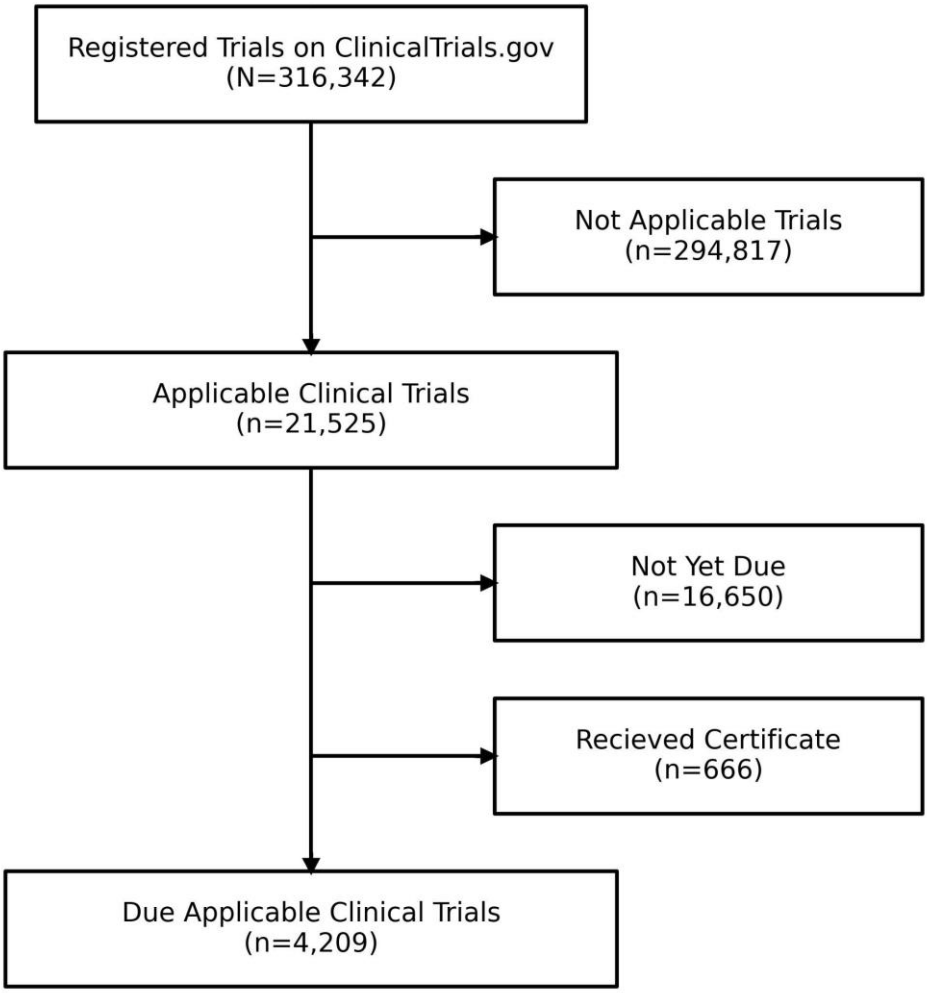
5.5 Results - Trial Reporting under the FDAAA Final Rule

5.5.1 Study Population

On Sept 16, 2019, the ClinicalTrials.gov database contained 316,342 trials in total. I excluded 294,817 trials as they did not meet FDAAA coverage criteria. A further 16,650 trials were excluded as they were not yet due to report results; 666 trials were excluded as they were due, but had received a certificate of delay from ClinicalTrials.gov. Therefore, 4,209 trials were identified as due to report results onto ClinicalTrial.gov. Figure 5.1 shows a flow diagram for the analysis population starting from all trials on ClinicalTrials.gov.

Overall, 3,326 (79.0%) due trials were pACTs and 883 (21.0%) were ACTs. Table 5.5 includes characteristics of the due cohort: approximately half had non-industry, non-US Government sponsors (n=2,178, 51.8%), and most included a drug intervention (n=2,968, 70.5%) and were conducted solely in the USA (n=3,000, 71.3%). The majority of included trials had a start date of 2015 or later (n=2,657, 63.1%); detailed information on start year is available in Appendix 5.1.

Figure 5.1: Flowchart for Inclusion in Analysis Population



5.5.2 Trial Reporting and Compliance

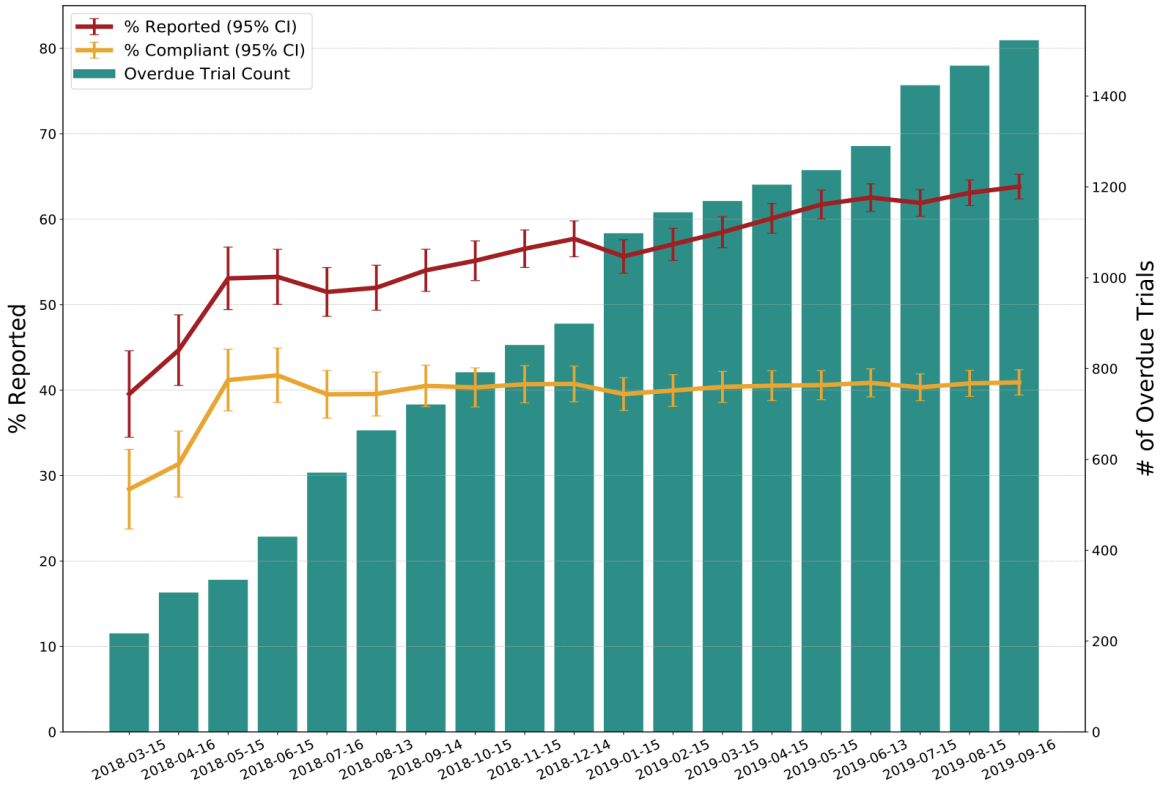
There were 1,722 (40.9%; 95% CI 39.4–42.2) trials with results submitted in compliance with the law, meaning 2,487 trials breached the law through late or non-reporting; 2,686 (63.8%; 62.4–65.3) trials had results submitted at any time. Table 5.5 also includes the proportion of trials reported, and compliant, for each variable of interest. Figure 5.2 shows the number of overdue trials, the proportion of compliant trials, and the proportion of reported trials at each month from March 2018 to September 2019. While overall reporting has increased gradually over time, compliance has remained stable at approximately 40% since July, 2018.

Table 5.5: Reported and Completed Applicable Clinical Trials by Trial Category

Variables		Total Trials (% of Total)	Trials with Any Results (%; 95% CI)	Compliant Trials (%; 95% CI)
Trials		4209	2686 (63.8%; 62.4-65.3)	1722 (40.9%; 39.4-42.4)
Sponsor Class	Non-Industry	2178 (51.8%)	1358 (62.4%; 60.3-64.4)	737 (33.8%; 31.9-35.9)
	Industry	1837 (43.6%)	1184 (64.5%; 62.2-66.6)	924 (50.3%; 48.0-52.6)
	US Gov	194 (4.6%)	144 (74.2%; 67.6-79.9)	61 (31.4%; 25.3-38.3)
Industry Collaborator		715 (17.0%)	482 (67.4%; 63.9-70.8)	310 (43.4%; 39.8-47.0)
US Gov Collaborator		461 (11.0%)	330 (71.6%; 67.3-75.5)	180 (39%; 34.7-43.6)
Phase	Phase 1/2	327 (7.8%)	191 (58.4%; 53.-63.6)	117 (35.8%; 30.8-41.1)
	Phase 2	1329 (31.6%)	916 (68.9%; 66.4-71.4)	575 (44.3%; 40.6-45.9)
	Phase 2/3	99 (2.4%)	56 (56.6%; 46.6-66.0)	40 (40.4%; 31.2-50.4)
	Phase 3	750 (17.8%)	557 (74.3%; 71.0-77.3)	415 (55.3%; 51.8-58.9)
	Phase 4	600 (14.3%)	392 (65.3%; 61.4-69.0)	242 (40.3%; 36.5-44.3)
	N/A	1104 (26.2%)	574 (52.0%; 49.0-54.9)	333 (30.2%; 27.5-32.9)
Terminated		663 (15.8%)	475 (71.6%; 68.1-74.9)	301 (45.4%; 41.6-49.2)
Reached Full Completion		3811 (90.5%)	2434 (63.9%; 62.3-65.4)	1547 (40.6%; 39.0-42.2)
Trial Contains a Drug		2968 (70.5%)	2025 (68.2%; 66.5-69.9)	1320 (44.5%; 42.7-46.3)
Trial Contains a Biological/Vaccine		369 (8.8%)	265 (71.8%; 67.0-76.2)	180 (48.8%; 43.7-53.9)
Trial Contains a Device		1020 (24.2%)	533 (52.3%; 49.2-55.3)	314 (30.8%; 28.0-33.7)
Trial Contains a Diagnostic Test		25 (0.6%)	14 (56.0%; 36.2-74.0)	7 (28.0%; 13.8-48.7)
Trial Contains a Radiation Treatment		103 (2.5%)	64 (62.1%; 52.4-71.0)	34 (33.0%; 24.6-42.7)
Trial Contains a Combination Product		13 (0.3%)	7 (53.8%; 27.3-78.4)	2 (15.4%; 3.6-46.6)

Trial Contains a Genetic Treatment		11 (0.3%)	5 (45.5%; 19.4-74.3)	4 (36.4%; 13.6-67.5)
Trial Location	US Only	3000 (71.3%)	1843 (61.4%; 59.7-63.2)	1046 (34.9%; 33.2-36.6)
	US and Other County	876 (20.8%)	700 (79.9%; 77.1-82.4)	565 (64.5%; 61.3-67.6)
	No US Location	242 (5.8%)	99 (40.9%; 34.9-47.2)	79 (32.6%; 27.0-38.8)
	No Location Data Available	91 (2.2%)	44 (48.4%; 38.2-58.6)	32 (35.2%; 26.0-45.5)
Total No. of Trials on Register for Sponsor	First Quarter (1-12)	1128 (26.8%)	451 (40.0%; 37.2-42.9)	241 (21.4%; 19.1-23.9)
	Second Quarter (13-219)	1119 (26.6%)	601 (53.7%; 50.8-56.6)	362 (32.4%; 29.7-35.2)
	Third Quarter (221-910)	1004 (23.9%)	766 (76.3%; 73.6-78.8)	491 (48.9%; 45.8-52.0)
	Fourth Quarter (925-3276)	958 (22.8%)	868 (90.6; 88.6-92.3)	628 (65.6%; 62.5-69.5)

Figure 5.2: Rolling Percent of Reported, Compliant, and Count of Overdue Trials by Month



The percent of trials reported (red), and reporting in compliance (orange), and the cumulative number of overdue trials (green) was assessed across the entire population of trials using archived data from ClinicalTrials.gov as it stood on each listed date.

5.5.3 Reporting and Compliance by Sponsor

Reporting and compliance performance for the 13 sponsors with more than 30 trials due is given in Table 5.6; performance for all 78 sponsors with at least ten due trials is given in Appendix 5.6.

Table 5.6: Reporting Performance of Sponsors with more than 30 Due Trials

Sponsor	Trials Due	Trials with any results (%)	Compliant Trials (%)
MD Anderson Cancer Center	85	71 (83.5%)	39 (34.1%)
National Cancer Institute	79	65 (82.3%)	24 (30.4%)
Massachusetts General Hospital	58	46 (79.3%)	32 (55.2%)
Mayo Clinic	47	45 (95.7%)	10 (21.3%)
Novartis Pharmaceuticals	46	46 (100%)	46 (100%)
Gilead Sciences	45	45 (100%)	43 (95.6%)
GlaxoSmithKline	43	43 (100%)	42 (97.7%)
Pfizer	42	42 (100%)	39 (92.9%)
Hoffmann-La Roche	38	38 (100%)	36 (94.7%)
University of California - San Francisco	38	26 (68.4%)	6 (15.8%)
AstraZeneca	37	37 (100%)	37 (100%)
Memorial Sloan Kettering Cancer Center	36	34 (94.4%)	33 (91.7%)
University of North Carolina, Chapel Hill	32	32 (100%)	26 (81.3%)

5.5.4 Factors Associated with Trial Reporting and Compliance

Crude univariable and adjusted multivariable odds ratios (ORs) for reporting and compliance across all explanatory variables are presented in Table 5.7. In the adjusted analyses, industry sponsors were significantly more likely to report results (OR 1.62, 95% CI 1.35–1.96) and be compliant (OR 3.08, 2.52–3.77) than non-industry, non-US Government sponsors. Similarly, the presence of an industry collaborator regardless of sponsor class increased the adjusted odds of reporting (OR 1.29, 1.06–1.58) and compliance (OR 1.30, 1.08–1.58). Trials that had reached full completion date for all trial outcomes were more likely to report results (OR 1.67, 1.29–2.17) and be in compliance with the Final Rule (OR 1.28, 1.00–1.65). Sponsors who have a large number of trials (range: 887–3254) registered on ClinicalTrials.gov were significantly more likely

to report results (OR 17.11, 13.00–22.54) and report in compliance (OR 11.84, 9.36–14.99) than sponsors with a small number of trials (range: 1–12). Trials with sites both inside the US and in other countries were more likely to report results than trials with only US sites (any results OR 1.85, 1.48–2.32; compliant OR 1.93, 1.57–2.38). Trials outside of the US (OR 0.44, 0.32–0.60) and with no location data available (OR 0.42, 0.26–0.70) were less likely to report results than trials located in the USA only.

Table 5.7: Crude and Adjusted ORs for Factors Associated with Reporting Under the FDAAA 2007

Variables		Any Results Crude OR (95% CI; p value)[a]	Any Results Adjusted OR (95% CI; p value)[b]	Compliant Crude OR (95% CI; p value)[a]	Compliant Adjusted OR (95% CI; p value)[b]
Sponsor Class	Non-Industry	Ref	Ref	Ref	Ref
	Industry	1.09 (0.96-1.25; 0.17)	1.62 (1.35-1.96; <0.0001)	1.98 (1.74-2.25; <0.0001)	3.08 (2.52-3.77; <0.0001)
	US Gov	1.74 (1.25-2.43; 0.0011)	0.82 (0.54-1.23; 0.34)	0.90 (0.65-1.23; 0.50)	0.48 (0.33-0.69; <0.0001)
Industry Collaborator		1.21 (1.02-1.44; 0.028)	1.29 (1.06-1.58; 0.013)	1.13 (0.96-1.33; 0.14)	1.30 (1.08-1.58; 0.0065)
US Gov Collaborator		1.49 (1.20-1.84; 0.00025)	1.45 (1.12-1.87; 0.0049)	0.92 (0.75-1.12; 0.39)	1.19 (0.94-1.51; 0.15
Phase	Phase 1/2	0.49 (0.37-0.64; <0.0001)	0.65 (0.47-0.90; 0.0086)	0.45 (0.34-0.59; <0.0001)	0.91 (0.66-1.24; 0.55)
	Phase 2	0.77 (0.63-0.94; 0.010)	0.99 (0.78-1.25; 0.90)	0.62 (0.51-0.74; <0.0001)	1.05 (0.84-1.30; 0.69)
	Phase 2/3	0.45 (0.29-0.69; 0.00028)	0.52 (0.32-0.86; 0.0097)	0.55 (0.36-0.84; 0.0056)	0.94 (0.58-1.51; 0.78)
	Phase 3	Reference	Reference	Reference	Reference
	Phase 4	0.65 (0.52-0.83; 0.00037)	1.01 (0.75-1.34; 0.97)	0.55 (0.44-0.68; <0.0001)	1.15 (0.88-1.52; 0.31)
	N/A	0.38 (0.31-0.46; <0.0001)	0.65 (0.46-0.92; 0.014)	0.35 (0.29-0.42; <0.0001)	0.87 (0.62-1.21; 0.40)
Terminated		1.53 (1.27-1.83; <0.0001)	1.42 (1.16-1.74; 0.00078)	1.24 (1.05-1.47; 0.011)	1.16 (0.96-1.41; 0.11)
Reached Full Completion		1.02 (0.83-1.27; 0.83)	1.67 (1.29-2.17; 0.00011)	0.87 (0.71-1.07; 0.19)	1.28 (1.00-1.65; 0.050)
Trial Contains a Drug		1.88 (1.65-2.16; <0.0001)	1.71 (1.20-2.44; 0.0030)	1.67 (1.45-1.92; <0.0001)	1.45 (1.05-2.01; 0.024)
Trial Contains a Biological/Vaccine		1.49 (1.18-1.89; 0.00087)	1.64 (1.14-2.35; 0.0074)	1.42 (1.15-1.76; 0.0013)	1.51 (1.11-2.08; 0.0098)
Trial Contains a Device		0.53 (0.46-0.61; <0.0001)	1.90 (1.30-2.77; 0.00093)	0.56 (0.48-0.65; <0.0001)	1.35 (0.95-1.92; 0.099)
Trial Contains a Diagnostic Test		0.72 (0.33-1.59; 0.42)	1.51 (0.60-3.79; 0.38)	0.56 (0.23-1.34; 0.19)	1.14 (0.43-3.01; 0.80)
Trial Contains a Radiation		0.93 (0.62-1.39; 0.72)	0.81 (0.50-1.32; 0.40)	0.71 (0.47-1.07; 0.10)	1.00 (0.63-1.59; 0.99)

Treatment					
Trial Contains a Combination Product		0.66 (0.22-1.97; 0.46)	1.48 (0.44-5.00; 0.53)	0.26 (0.06-1.18; 0.081)	0.48 (0.10-2.30; 0.36)
Trial Contains a Genetic Treatment		0.47 (0.14-1.55; 0.22)	0.94 (0.25-3.54; 0.93)	0.82 (0.24-2.82; 0.76)	1.73 (0.46-6.41; 0.42)
Trial Location	US Only	Reference	Reference	Reference	Reference
	US and Other County	2.5 (2.08-2.99; <0.0001)	1.85 (1.48-2.32; <0.0001)	3.39 (2.90-3.97; <0.0001)	1.93 (1.57-2.38; <0.0001_
	No US Location	0.43 (0.33-0.57; <0.0001)	0.44 (0.32-0.60; <0.0001)	0.91 (0.68-1.20; 0.49)	0.77 (0.55-1.06; 0.11)
	No Location Data Available	0.59 (0.39-0.89; 0.013)	0.42 (0.26-0.70; 0.0074)	1.01 (0.65-1.57; 0.95)	0.67 (0.40-1.13; 0.13)
Total No. of Trials on Register for Trial's Sponsor	First Quarter (1-12)	Reference	Reference	Reference	Reference
	Second Quarter (13-225)	1.74 (1.47-2.06; <0.0001)	1.72 (1.44-2.06; <0.0001)	1.76 (1.46-2.13; <0.0001)	1.76 (1.44-2.16; <0.0001)
	Third Quarter (229-874)	4.83 (4.00-5.83; <0.0001)	6.09 (4.93-7.53; <0.0001)	3.52 (2.92-4.25; <0.0001)	6.18 (4.94-7.73; <0.0001)
	Fourth Quarter (887-3254)	14.48 (11.3-18.54; <0.0001)	17.11 (13.00-22.54; <0.0001)	7.00 (5.76-8.51; <0.0001)	11.84 (9.36-14.99; <0.0001)
Start Year (Increase of one year)		0.91 (0.90-0.94; <0.0001)	1.00 (0.97-1.04; 0.82)	1.00 (0.97-1.04; 0.82)	1.05 (1.02-1.08; 0.00090)

[a]*Odds ratios in these columns were from univariable analysis and contained no further adjustments.*
[b]*Odds ratios in these columns were from the full adjusted analysis. All listed variables were included in the model.*

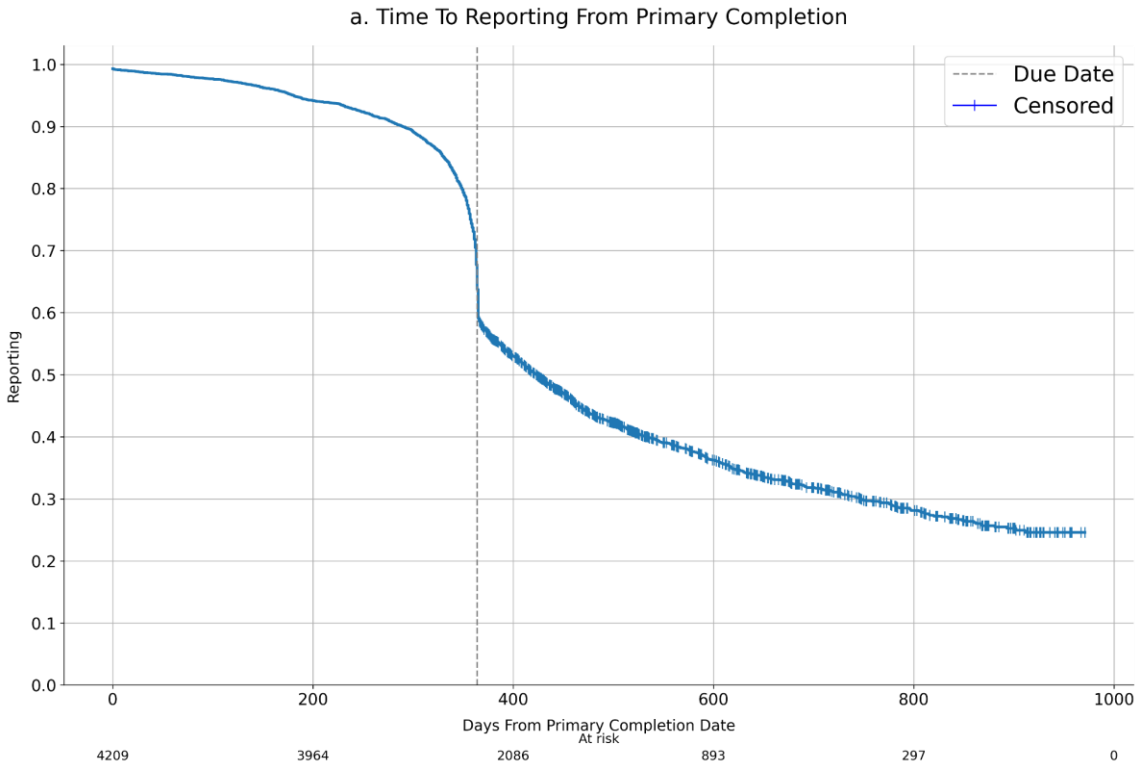
5.5.5 Sensitivity Analyses

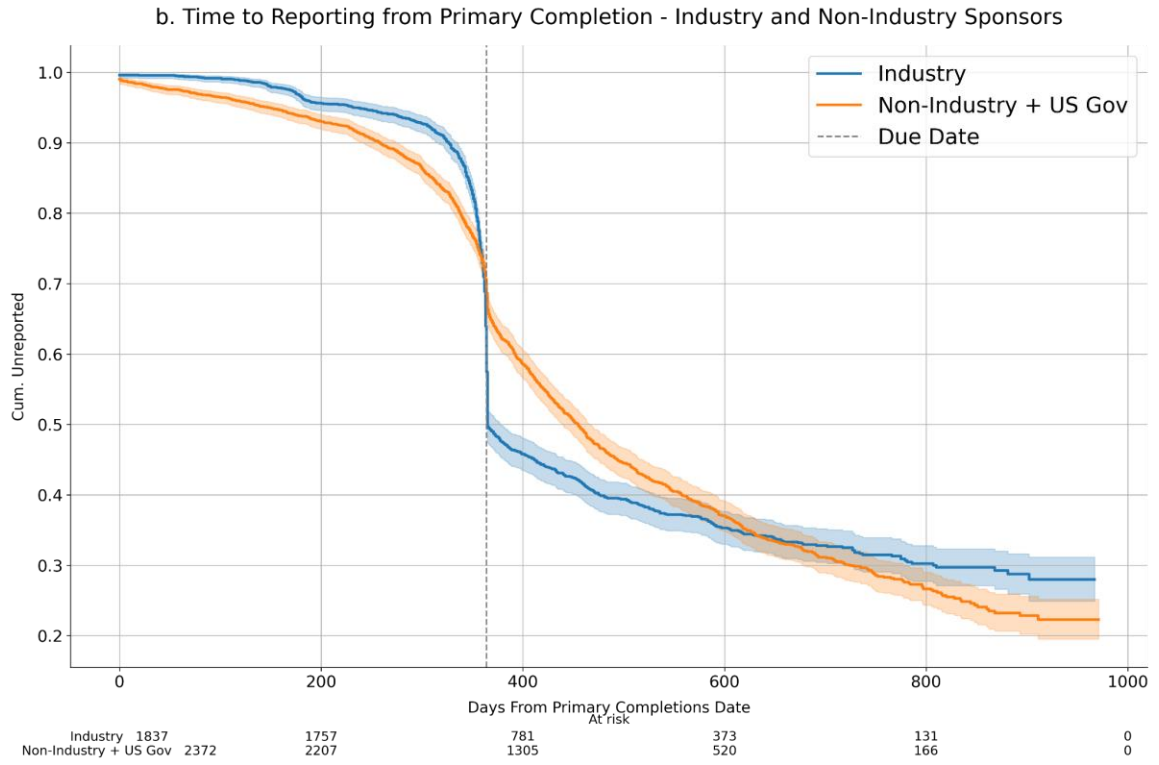
During the peer review at *The Lancet*, reviewers requested two *post hoc* sensitivity analyses: one examining only the ACT-only population of 883 trials, and one in which ACT or probable ACT status was included as an additional explanatory variable in the original regression. Only one finding changed substantially from our primary analyses (presence of an industry collaborator was no longer significant) in the ACT-only model; adding ACT status as a variable to the adjusted models showed that ACTs are less likely to report at all (OR 0.66, 0.54–0.81) but no less likely to be compliant than probable ACTs (OR 0.84, 0.69–1.03). Full results tables for these analyses are available in Appendices 5.2-5.5.

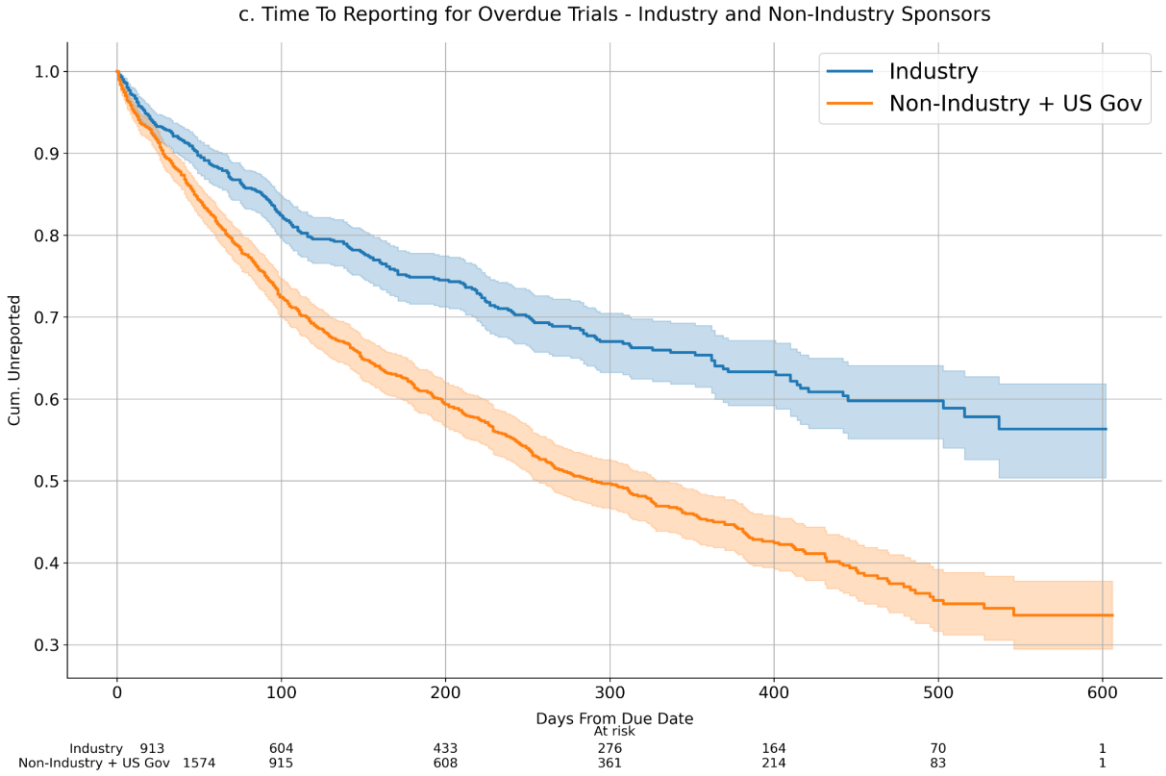
5.5.6 Time to Reporting from Trial Completion

Figure 5.3a shows the survival curve representing the delay from primary completion date to results submission for all due trials. The 27 (0.6%) due trials that submitted results prior to their PCD were counted as reporting at time 0. The median delay from PCD to results submission date was 424 days (95% CI: 412–435), 59 days longer than the legal reporting requirement of one year. Figure 5.3b shows the delay in results submission for trials by industry sponsors and non-industry sponsors. For this analysis non-industry sponsors and US Government sponsors were combined since only 194 government-sponsored trials were due. Although both groups substantially increase their trial reporting as they approach their due date, this increase is more apparent among industry-sponsored trials. Figure 5.3c focuses on the late, non-compliant reporting behaviour of industry and non-industry sponsors. After trials become overdue, an industry-sponsored trial is more likely to remain unreported.

Figures 5.3a-c: Time to Reporting from Primary Completion Date







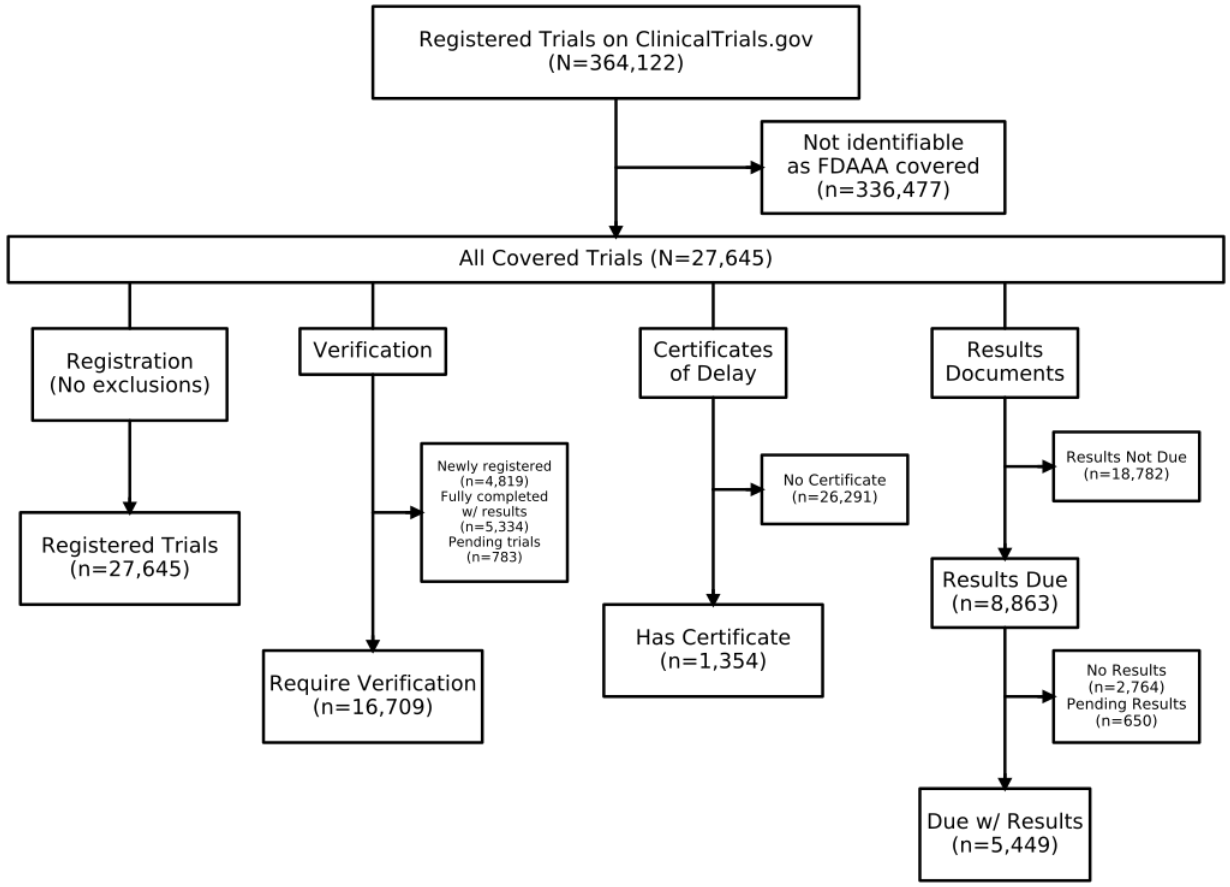
The dotted line in panels a and b represents the 1-year deadline by which trials should report under the FDAAA 2007; 95% CIs are provided for panels B and C. While industry is more likely to compliantly report (panel b), once a trial becomes overdue industry trials then become less likely to ever report than their non-commercial counterparts (panel c).

5.6 Results - Compliance with Additional Areas of the FDAAA 2007

5.6.1 Study Population

From the January 2021 ClinicalTrials.gov dataset, I identified 27,645 trials that appeared covered by FDAAA representing a 28% increase from the September 2019 dataset. Figure 5.4 shows a flow diagram for generating the relevant population for each analysis.

Figure 5.4: Flowchart for Inclusion in Assessment of Additional Areas of Compliance



5.6.2 Additional Compliance Results

Table 5.8 details compliance in each area overall and broken down by relevant covariates. Repeating the assessment of reporting compliance detailed above on this population showed 8,863 trials due to report. Of these, 3,499 (39.5%) did so within the 1-year deadline, and 6,099 (68.8%) reported at any time. Across the new compliance areas, the proportion of trials in

compliance ranged from 66.0% for on-time requests for delayed reporting to 99.1% for document submission with results (Table 1). Trials registered late were a median of 111 (IQR: 28-354) days late, trials with delayed annual data verification were a median of 275 (IQR: 122-550) days late, and trial with dilatory requests for delayed reporting were a median of 72 (IQR: 22-174) days late. Of the 5,449 due trials with full results posted to the registry (i.e., completed quality control checks), 5,401 (99.1%) accounted for all required documents; only 107 (3.1%) of the 3,414 due trials that had not submitted results had any documents available.

5.6.3 Factors Associated with Compliance

Table 5.9 shows the unadjusted and adjusted odds ratios for compliance. In the adjusted models, industry sponsors were more likely to register trials on time (OR 2.03, 99.5% CI, 1.74-2.37), verify data annually (OR 1.52, 1.31-1.76), and request reporting delays (OR 4.71, 2.19-10.15) within the required time frames. Likewise, sponsors with more registered trials were more likely to register on time (quartile 3: OR 1.76, 1.47-2.11; quartile 4: OR 2.74, 2.23-3.36), verify data annually (quartile 3: OR 4.35, 3.60-5.25; quartile 4: OR 8.70, 6.92-10.93), and request reporting delays on time (quartile 3: OR 6.07, 2.77-13.32; quartile 4: OR 10.58, 4.53-24.7). Applicable clinical trials were also more likely to meet registration (OR 2.14, 1.87-2.44) and verification (OR 1.99, 1.74-2.28) requirements than probable applicable clinical trials.

5.6.4 Compliance by Sponsor

Table 5.10 shows the top ten large sponsors with the most trials in violation of each requirement as a percentage of all applicable trials from that sponsor.

Table 5.8: FDAAA Compliance and Characteristics in Assessment Areas

		Compliant Results Reporting		Timely Registration[a]		Annual Data Verification		Certificate of Delay Requests		Document Submission[b]	
Cohort Size		8,863		27,645		16,709		1,354		5,449	
Trials in Compliance (%)		3,499 (39.5%)		24,429 (88.4%)		12,632 (75.6%)		893 (66.0%)		5401 (99.1%)	
Detailed Compliance Data											
		Total (%)	***compliant (%)***	***Total (%)***	***compliant (%)***	***Total (%)***	***compliant (%)***	***Total (%)***	***compliant (%)***	***Total (%)***	***compliant (%)***
Covered Status	**Is a pACT**	5,484 (61.9%)	2,249 (41.0%)	9,282 (33.6%)	7,818 (84.2%)	5,180 (31.0%)	3,586 (69.2%)	770 (56.9%)	505 (65.6%)	3,812 (70.0%)	3.764 (98.7%)
	Is an ACT	3,379 (38.1%)	1,250 (37.0%)	18,363 (66.4%)	16,611 (90.5%)	11,529 (69.0%)	9,046 (78.5%)	584 (43.1%)	388 (66.4%)	1,637 (30.0%)	1,647 (100%)
Industry Sponsor		3,951 (44.6%)	1784 (45.2%)	11,444 (41.4%)	10,516 (91.9%)	6,603 (39.5%)	5,001 (75.7%)	1,204 (88.9%)	814 (67.6%)	2,522 (46.3%)	2,509 (99.5%)
Trial Contains a Drug		6,069 (68.5%)	2,632 (43.2%)	19,074 (69.0%)	17,358 (91.0%)	11,492 (68.8%)	9,004 (78.4%)	1,061 (78.4%)	713 (67.2%)	4,008 (73.6%)	3,969 (99.0%)
Phase	**Early Phase**	3,487 (39.3%)	1,456 (41.8%)	12,415 (44.9%)	11,533 (92.9%)	7,802 (46.7%)	6,297 (80.7%)	649 (47.9%)	418 (64.4%)	2,276 (41.8%)	2,254 (99.0%)
	Late Phase	1,770 (20.0%)	869 (49.1%)	5,513 (19.9%)	5,102 (92.5%)	3,247 (19.4%)	2,611 (80.4%)	510 (37.7%)	357 (70.0%)	1,266 (23.2%)	1,257 (9.3%)
	N/A	3,606 (40.7%)	1174 (32.6%)	9,717 (35.1%)	7,794 (80.2%)	5,660 (3.9%)	3,724 (65.8%)	195 (14.4%)	118 (60.5%)	1,907 (35.0%)	1,890 (99.1%)
Number of Trials Registered[c]	**Quartile 1 (1-11)**	2,357 (26.6%)	458 (19.4%)	7,128 (25.8%)	6,135 (86.1%)	4,526 (27.1%)	2,788 (61.6%)	315 (23.3%)	162 (51.4%)	830 (15.2%)	821 (98.9%)
	Quartile 2 (12-220)	2,390 (27.0%)	709 (29.7%)	6,710 (24.3%)	5,759 (85.8%)	4,095 (24.5%)	2,747 (67.1%)	613 (45.3%)	374 (61.0%)	1,278 (23.5%)	1,268 (99.2%)
	Quartile 3 (221-987)	2,102 (23.7%)	993 (47.2%)	6,955 (25.2%)	6,153 (88.5%)	4,128 (24.7%)	3,464 (83.9%)	196 (14.5%)	157 (80.1%)	1,577 (28.9%)	1,563 (99.1%)
	Quartile 4 (988-3341)	2,014 (22.7%)	1,339 (66.5%)	6,852 (24.8%)	6,382 (93.1%)	3,960 (23.7%)	3,633 (91.7%)	230 (17.0%)	200 (87.0%)	1,764 (32.4%)	1749 (99.2%)

[a]All trials in the cohort were included in this analysis.

[b]This includes trials that proactively declared having no statistical analysis plan.

[c]The range of the number of registered trials on ClinicalTrials.gov in each quartile is provided below each quartile name.

Table 5.9: Unadjusted and Adjusted Odds Ratios for Factors Associated with Compliance

		Timely Registration		Annual Data Verification		Certificate of Delay Requests		Document Submission	
Odds Ratios (99.5% CI, p-value)		**Crude OR**	**Adj OR**	**Crude OR**	**Adj OR**	**Crude OR**	**Adj OR**	**Crude OR**	**Adj OR**
Is an ACT		1.78 (1.57-2.01, <.001)	2.14 (1.87-2.44, <.001)	1.62 (1.43-1.83, <.001)	1.99 (1.74-2.28, <.001)	1.04 (0.71-1.52, .743)	1.17 (0.78-1.76, .202)	DNC[a]	N/A
Industry Sponsor		1.86 (1.63-2.13, <.001)	2.03 (1.74-2.37, <.001)	1.01 (0.9-1.14, .736)	1.52 (1.31-.76, <.001)	1.88 (1.06-3.33, <.001)	4.71 (2.19-10.15, <.001)	2.34 (0.8-6.83, .009)	2.54 (0.76-8.54, .011)
Trial Contains a Drug		2.15 (1.89-.43, <.001)	1.35 (1.16-1.57, <.001)	1.59 (1.4-1.79, <.001)	0.94 (0.8-1.1, .205)	1.29 (0.82-2.02, .066)	1.08 (0.6-1.94, .666)	0.64 (0.19-2.17, .228)	0.62 (0.16-2.44, .251)
Phase	**Early Phase**	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Late Phase	0.95 (0.77-1.16, .402)	0.8 (0.65-0.99, <.001)	0.98 (0.82-1.17, .719)	0.92 (0.77-1.11, .158)	1.29 (0.85-1.96, .045)	1.14 (0.73-1.79, .322)	1.36 (0.37-5.04, .435)	0.96 (0.24-3.83, .922)
	N/A	0.31 (0.27-0.36, <.001)	0.38 (0.23-0.44, <.001)	0.46 (0.40-0.52, <.001)	0.46 (0.39-0.54, <.001)	0.85 (0.49-1.47, .322)	0.97 (0.47-2, .896)	1.09 (0.37-3.16, .801)	0.95 (0.29-3.09, .876)
Number of Trials Registered[b]	**Q1 (1-11)**	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Q2 (12-220)	0.98 (0.83-0.15, .682)	1.04 (0.88-1.23, .48)	1.27 (1.09-1.47, <.001)	1.36 (1.17-1.59, <.001)	1.48 (0.93-2.34, .005)	1.42 (0.89-2.28, .014)	1.39 (0.3-6.35, .476)	1.19 (0.26-5.57, .707)
	Q3 (221-987)	1.24 (1.05-1.47, <.001)	1.76 (1.47 - 2.11, <.001)	3.25 (2.74-3.86, <.001)	4.35 (3.6-5.25, <.001)	3.8 (1.9-7.62, <.001)	6.07 (2.77-13.32, <.001)	1.22 (0.3-5.03, .638)	1.57 (0.37-6.58, .301)
	Q4 (988-3341)	2.20 (1.81-2.67, <.001)	2.74 (2.23 - 3.36, <.001)	6.93 (5.59-8.59, <.001)	8.7 (6.92-10.93, <.001)	6.3 (2.99-13.24, <.001)	10.58 (4.53-24.7, <.001)	1.28 (0.32-5.15, .562)	1.58 (0.39-6.44, .287)

[a] *Perfectly predicted compliance therefore did not converge (DNC). Dropped from the adjusted regression.*

[b] *The range of the number of registered trials on ClinicalTrials.gov in each quartile is provided below each quartile name*

Table 5.10: Major Sponsors with the Highest Rates of Non-compliance (min 50 covered trials)

Late Registration[a]	% non-compliant (n)	Late Verification[b]	% non-compliant (n)	Late Certificates[c]	% non-compliant (n)	Results Documents[e]	% non-compliant (n)
University of California, Davis	36.4 (20)	University of Southern California	61.8 (34)	Virginia Commonwealth University	66.7 (4)	Milton S. Hershey Medical Center	6.7 (1)
Southwest Oncology Group	34.6 (18)	University of Virginia	58.3 (28)	University of California, San Francisco	60 (6)	University of Utah	5.9 (1)
Icahn School of Medicine at Mt. Sinai	30.7 (31)	Ohio State University	57.6 (19)	Sanofi	33.3 (3)	Weill Medical College of Cornell University	5.6 (1)
Ohio State University	30.0 (15)	Columbia University	41.4 (24)	Uni. of Texas Health Science Center at San Antonio	30.0 (3)	University of Wisconsin, Madison	5.26 (1)
Indiana University	24.7 (24)	Oregon Health and Science University	40.9 (22)	Incyte Corporation	28.6 (2)	University of Minnesota	4.0 (1)
Children's Hospital Medical Center, Cincinnati	23.9 (16)	City of Hope Medical Center	34.4 (22)	Vertex Pharmaceuticals Incorporated	25.0 (3)	University of California, San Francisco	4.0 (2)
Northwell Health	22.2 (12)	Brigham and Women's Hospital	31.8 (20)	University of Michigan	25.0 (2)	Dana-Farber Cancer Institute	3.9 (1)
University of California, Los Angeles	21.8 (19)	Massachusetts General Hospital	30.64 (53)	Emory University	22.2 (2)	Massachusetts General Hospital	3.7 (3)
Uni. of Texas Health Science Center at San Antonio	21.6 (11)	University of California, Los Angeles	28.9 (15)	T-3 sponsors[d]	20.0 (1)	T-3 sponsors[f]	3.7 (1)
Columbia University	21.4 (24)	University of Chicago	28.2 (20)	Eli Lilly	14.8 (4)	T-2 sponsors[g]	3.6 (1)

[a] *Denominator is all covered trials registered to that sponsor.*
[b] *Denominator is all trials currently requiring verification from that sponsor.*
[c] *Denominator is all trials with a certificate of delay from that sponsor. Only includes sponsors who have received at least five certificates.*
[d] *Celgene, VA Office of Research and Development, National Cancer Institute (NCI).*
[e] *Denominator is all due trials with results.*
[f] *New York State Psychiatric Institute, Columbia University, Wake Forest University Health Sciences.*
[g] *University of Texas Southwestern Medical Center, University of Washington*

5.7 Discussion

5.7.1 Summary of Findings

Compliance with the FDAAA 2007's requirement to report results within one year of a trial's primary completion was poor in September 2019 and has not improved over time. In my first analysis only 40.9% of due trials have submitted results within the legal 12-month deadline; and only 63.8% have submitted results at any point after one year from primary completion. Re-examining the rates in January 2021 showed little change as compliant reporting decreased to 39.5% while overall reporting increased to 68.6%. While compliance in other areas assessed is generally higher, there is an ongoing need to ensure sponsors are aware of and meet their legal responsibilities to ensure the quality of data on the registry. Across all areas, industry sponsorship, and sponsorship of many trials were most commonly associated with higher compliance.

5.7.2 Results in Context

The most recent audit of FDAAA reporting from Anderson and colleagues in 2015, found much lower rates of compliance. Just 13.4% of "highly likely applicable clinical trials" completed between 2008 and 2012 reported on time and 38.3% reported at all compared to 39.5% and 68.6% in the January 2021 analysis.[173] Though the methods used were not entirely equivalent, this large disparity indicates that reporting under the FDAAA likely has improved over time. The attention brought to the regulation by the Final Rule may have raised awareness and signalled action from regulators that had previously been lacking. Improved reporting behaviour from industry sponsors compared to their non-industry counterparts was consistent across multiple areas of compliance assessed. Anderson et al. found that industry sponsored trials were significantly more likely to compliantly report (OR: 1.62, 95% CI: 1.34-1.97), and other government or academic institutions were less likely to compliantly report (OR: 0.58, 0.45-0.75) when compared to NIH sponsored trials. Other recent work on industry reporting has also

shown high FDAAA compliance.[418] The only other area from this chapter that has been comprehensively addressed in prior work to my knowledge is the requirement for timely registration. Gill found that overall, 55% of trials from between 1999 and 2011 registered late but with notable increases over time.[129] By 2007, ~60-70% of new registrations met this requirement. For the January 2021 population, which includes trials dating to 2010 and later, over 80% registered within 21 days of their start date.

5.7.3 Strengths and Limitations

The analyses in this chapter offer the most complete public accounting of which trials are covered under the FDAAA 2007, and its Final Rule, to date. Using a transparent and reproducible analytic pipeline based on official criteria and publicly available data, I show that compliance checks can be automated across the entire ClinicalTrials.gov dataset allowing for ongoing tracking. The methodology used to identify ACTs has been public since the launch of the FDAAA TrialsTracker in 2018 and with positive feedback from sponsors.[423] The comprehensiveness and reproducibility of this analysis facilitates the conduct of future research. Appendix 5.7 contains an updated version of Figure 5.2 reporting trends through June 2021 showing that the proportion of all trials that compliantly report remains at ~40% while overall reporting continues to slowly increase over time.

There are limitations to these analyses. Assessments relying on sponsor-provided data from the registry is subject to the accuracy and availability of those fields. Usefully, however, FDAAA requires sponsors to maintain their registered information and data submitted to the registry are attested to as accurate under penalty of law.[328] As described in this study, sponsors must validate registry data at least once a year, and the majority do, however certain fields are held to much stricter update standards. For instance, the primary completion date is a key field for enforcement of the law and is required to be updated “no later than 30 calendar days after the

clinical trial reaches its actual completion date." However, even in the absence of timely updates, sponsors are held liable using the information provided on the registry, even if it is out of date or inaccurate. The text of the FDAAA 2007 is clear: results for applicable trials are due "after the earlier of the estimated completion date...or the actual completion date."[166] This means a sponsor is therefore in breach of the law if they have failed to report on time, or if they appear to have failed to report on time due to their own negligence in maintaining their registry data. While the precision of these analyses may be impacted by issues with data, the letter of the law allows for confidence in asserting that a breach has occurred in some capacity. It is a strength of the legislation that sponsors are held accountable for the accuracy of their own data.

In one situation, legally withheld data on ClinicalTrials.gov can block ascertainment of whether a trial is applicable: specifically, ClinicalTrials.gov declines to make public whether a trial is part of a "New Drug Application" or "Investigational Device Exemption" (see Glossary) due to commercial confidentiality concerns. However, given the criteria outlined by ClinicalTrials.gov for ACTs, the absence of this field should only impact a small number of trials initiated prior to the Final Rule without a US location. Based on my research and communications with ClinicalTrials.gov staff and other colleagues working in this area, I am confident that the "FDA-regulated Drug or Device" fields should operate as a sufficient indicator of FDAAA coverage when available. In cases where this field is missing but would be the deciding factor for inclusion, my code would conservatively exclude the trial from our analysis in order to avoid incorrectly asserting that a trial is in breach of the law.

Another area where ClinicalTrials.gov withholds information is the provision of certificates of delay. The exact reason for the delay impacts the reporting deadline but is not provided in the public dataset. Delays for unapproved therapies are time-limited to a maximum of two additional years; however, delays for "good cause" can apparently persist long beyond that. In either case,

though, the law states that any form of delay must be applied for prior to the trial becoming due. In early 2021, ClinicalTrials.gov stated their intent to enforce this standard for trials of unapproved therapies moving forward and extended this standard to delays for good cause in early 2022.[343,424] While the previous choice to not enforce this standard could impact these analyses, it would generally only effect rare edge cases.

Lastly, while this analysis covers a wide range of requirements, it does not cover all possible requirements of the law. In choosing which areas to focus on, I aimed for requirements which could be unambiguously assessed within the public dataset and reduced to binary determinations on compliance. More complex assessments, such as examining quality or completeness of results reporting, would require either more sophisticated computational methods or high resource manual review.

5.7.4 Implications for Policy and Practice

These results highlight the need for more robust public enforcement of regulations around clinical research. Clinical trials are not abstract research projects: they are large, expensive, practical, and necessary evaluations that aim to directly inform clinical practice. Ensuring that sponsors are meeting their legal and ethical responsibilities is of paramount importance. Both publications arising from this chapter were accompanied by independent commentaries from colleagues highlighting the need for enforcement to ensure mandated transparency measures are meeting their goals.[425,426] While progress has been made in recent years there remains room for improvement.

At the time of these analyses the FDAAA had been US law for well over a decade and the Final Rule implemented since 2017. While the Final Rule was considerably delayed and offered useful clarifications it did not fundamentally alter the reporting, timely registration, and data

verification provisions. While industry sponsors may have had to adapt to new requirements on reporting trials of unapproved therapies, this does not excuse the overall lack of compliance with the law to date, especially among non-commercial sponsors. Every trial in this analysis was completed or is set to complete after the Final Rule came into effect. Each trial sponsor had ample time to prepare to meet the requirements and yet less than half of all trials have managed to comply with the headline results reporting requirements of the law. As the Final Rule was coming into effect, Mayo-Wilson and colleagues surveyed academic institutions in the US about their preparations for the new regulations and concluded that "most organisations appear to be unprepared to meet the new requirements" foreshadowing this poor compliance.[304]

The lack of any regulatory momentum around the enforcement of FDAAA has been an ongoing issue. The delay in the final rulemaking can be seen as a symptom of an overall institutional lethargy in ensuring the transparency goals of the FDAAA were being met. Even after the Final Rule finally came into effect it took over three years for the FDA to announce an official enforcement strategy.[427] The proposed process required multiple rounds of notifications before sanctions are considered. The emphasis on voluntary compliance is consistent with the TrialTracker project's prior communications with the FDA[y], however the prioritisation of enforcement is unclear.

The FDA claims they monitor compliance through the Bioresearch Monitoring Program.[428] This links enforcement of FDAAA to a program described in the guidance as "associated with the submission of a research or marketing application or…the Agency's investigation of a complaint." This process risks being slow and *ad hoc* with no comprehensive strategy for compliance monitoring across all sponsors. I co-wrote the AllTrials Campaign's comments on

[y] Personal Communication, Office of Good Clinical Practice, 21 May 2018.

the draft guidance and was joined by advocates and colleagues, like TranspariMED and the Yale University Collaboration for Research Integrity and Transparency, in raising similar concerns.[429] Many expressed frustration when the eventual final guidance remained mostly unchanged.[45]

5.7.4.1 An update on FDAAA compliance since publication

At the time of these analyses, there was no indication that any enforcement action had been taken over the course of the entire life of the FDAAA. In April 2021 the first official "Notice of Noncompliance", the final warning for sponsors to comply within 30 days or face potential monetary sanctions, was sent to Acceleron, a small biotech company, for their failure to report a drug trial that was nearly three years overdue. In the FDA's statement about the letter they divulged publicly, for the first time, that ~40 pre-notices of non-compliance have been sent over the life of the FDAAA despite thousands of overdue trials appearing just since the advent of the Final Rule.[430]

The trial in question was already two years past due at the time of Acceleron's pre-notice and the FDA waited an additional eight months to send the Notice of Non-compliance. Acceleron quickly complied by submitting results the very next day. As of early 2022, the FDA has sent two more public Notices of Noncompliance.[431] The details of all three letters are shown in Table 5.11. I downloaded TrialsTracker data in June 2021 following the Acceleron letter and in the week following the Notice of Noncompliance, 91 trials newly reported results representing the highest weekly total ever. This began a sudden surge in reporting, as four straight weeks reached the level of ≥70 trials reports submitted. In contrast, only four previous weeks saw ≥70 trials reported in total since the first results started becoming due under the Final Rule in 2018.[432]

Table 5.11: Details of Notices of Non-Compliance Sent by FDA

Sponsor	Trial ID	Primary Completion Date	Pre-Notice Date	Notice Date	Results Submitted to ClinicalTrials.gov
Acceleron Pharma, Inc.	NCT01727336	June 2017	20 July 2020	27 April 2021	28 April 2021
Accuitis Inc.	NCT03064438	5 June 2018	26 October 2020	26 July 2021	17 August 2021
Andrey Petrikovets[a]	NCT03052816	1 June 2018	20 July 2020	31 August 2021	1 September 2021

[a]Dr. Petrikovets' trial was sponsored by University Hospitals Cleveland Medical Center, however he was designated as the "Responsibly Party" of the trial as the primary investigator and therefore received the notice of noncompliance.

Though the reporting levels quickly returned to normal, the burst in reporting around discrete enforcement activity, combined with the rapid reporting of all sponsors receiving a letter, shows the promise of more active enforcement. The entire FDAAA TrialsTracker project is proof-of-concept that comprehensive monitoring can be established as a means to provide early warning to potential non-compliant sponsors. While the FDA treats the question of applicable trial status as a "complex legal question" requiring individual consideration,[z] enforcement can be encouraged even before investigation into individual trials. This system can also aid in prioritising enforcement better than seemingly random and inconsistent inspections based on unrelated complaints or issues.

In the absence of statutory enforcement, open public audit is widely recognised as a valuable tool to increase accountability and improve quality.[433,434] While this work, and the larger TrialsTracker project, independently serves this purpose, the probable impact of more proactive and widespread FDA enforcement cannot be understated as they hold all regulatory power under the FDAAA. Rapidly encouraging voluntary compliance at scale, perhaps first through

[z] Personal Communication, FDA Office of Good Clinical Practice, 15 March 2021.

preliminary reminder letters prior to any official notification, could be a powerful proactive tool to improve reporting in the hands of the FDA. This is consistent with prior work showing that reminders can increase reporting.[349,435] This would also meet the FDAs stated goals to improve voluntary compliance with the law without resorting to enforcement action.

While the FDA has only focused on compliance with the results reporting provisions of the law to date, this analysis shows other areas ensuring timely registration and the upkeep of registry data may also deserve the attention of regulators. The success in attaching key study documents to results is a testament to how routine interaction with processes like ClinicalTrials.gov QC review can promote compliance. The previously inconsistent stance by ClinicalTrials.gov in issuing certificates of delay caused issues for public identification of non-compliance. This demonstrates the downside of lax and obscured procedures reiterating the findings from Chapter 2.

There remains a need for non-commercial sponsors, primarily made up of US academic institutions, to better ensure they are prepared to meet the FDAAA requirements. While these institutions may lag behind industry in terms of resources and dedicated compliance personnel, the disparity in compliance is notable even when considering these limitations. Some major US academic institutions have openly published their methods for increasing compliance under FDAAA and the Clinical Trials Registration and Reporting Taskforce provides resources and support to institutions around best practice in managing these areas.[305,436,437] Other investigators have shared technical limitations of the current system, including in response to our analysis published in *The Lancet*.[438] However recent coverage of the third non-compliance letter shows that even a decade after FDAAA some institutions remain unclear about their responsibilities under the law.[439]

5.7.5 Implications for Future Research

Overall, the findings presented here clearly show additional attention is needed to ensure widespread compliance with the FDAAA and trial transparency requirements in general. I am currently involved in additional projects around FDAAA including aiding colleagues at Yale University to analyse the set of pre-Notice letters sent by the FDA which were acquired via freedom of information requests.[349] This project will aim to better categorise the FDA's approach to compliance. I also supervised a medical student project examining how reporting to ClinicalTrials.gov compared to the literature. These findings will help understand which route has led to more timely reporting of results and the impact of the law on selective publication. We are currently preparing a manuscript for publication of these findings. Examining reporting performance on other registries is also necessary; my piece in *The Lancet* inspired a Chinese team to investigate and highlight deficiencies in reporting on the Chinese trial registry[282] and I have registered a study that will examine these practices across all ICTRP registries.[72] Chapter 6 closely examines reporting on the EU Clinical Trial Registry.

This work defined and set the basis for using the FDAAA TrialsTracker to monitor ACT compliance and reporting. The next step is to seek fundings to expand the Tracker's capabilities including tracking of additional data and measures, visualisations, and automated reporting reminders for sponsors. There is also potential scope to expand the Tracker methodology to pre-Final Rule trials, especially in the wake of a US federal court ruling on the reporting of these trials.[440] My work with the ClinicalTrials.gov dataset has raised a number of additional interesting research questions like how the quality control process impacts results availability,[441] how reporting practice changes over time, and which interventions can improve reporting.

The work in this chapter deals with compliance as a largely binary question and uses epidemiological methods to understand the area at scale. There is ample opportunity to further

examine the quality and completeness of reporting, as in Chapter 3, and how this interacts with legal and ethical requirements. Prior work has compared reporting between registries and the published literature, but never in the context of the legal implications of the differences that arise.[251,252,254,255] The utility of ClinicalTrials.gov as a repository of results information also needs to be further investigated and described so that researchers can better understand, and feel confident in, using ClinicalTrials.gov to fill evidence gaps in the literature.[290] There is also considerable scope to better understand how updates to ClinicalTrials.gov records occur, not only from a data quality perspective, but also in examining how registered details change over time and how this is reflected in publications.[442] I am well positioned to create methods and software that can directly aid in facilitating or automating these evaluations.[443] Creating automated tools that efficiently search and subset the full FDAAA dataset to examine reporting in specific areas of interest, such as Covid-19 trials as examined in Chapter 4, is another area I plan to pursue.

Lastly, mixed-methods approaches can also help understand sponsor-level deficiencies in meeting the reporting requirements and collecting best practices for dissemination to the broader community. Additional work on barriers to compliance, such as those presented in Chapter 7 of this thesis, are needed to better understand the FDAAA reporting landscape following up on the prior survey work from Mayo-Wilson and colleagues.[304] The next chapter also explores both registry-wide and in-depth examinations of registry data and regulatory responsibilities this time focusing on the EU Clinical Trials Register.

5.8 Reflection

As the first major project of my thesis, this work greatly influenced the remaining studies and my own development as an academic. The opportunity to expand upon my existing work on the TrialsTracker project was a major motivation for pursuing my doctorate in the first place. The

experiences of developing the FDAAA and EU TrialsTrackers has either directly led to, or greatly influenced, every chapter in this thesis. Without the FDAAA TrialsTracker, I could not have easily identified sponsor-level reporting to investigate as in Chapter 3; the skills gained from collecting and analysing ClinicalTrials.gov data allowed me to lead the research in Chapter 4; Chapter 6 is a direct extension of my prior EU TrialsTracker work; and the motivation for Chapter 7 arose from repeated interactions with sponsors through running the TrialsTracker project.

I wrote my first SQL queries in 2017 while developing the EU TrialsTracker and my first lines of Python code in February 2019 in order to improve the FDAAA TrialsTracker pipeline.[410,444] By the end of 2019, I had completed the entire results reporting analysis presented here entirely in Python through a combination of self-teaching and the support of my colleagues. Developing my computational and data science skills has been a major part of my professional development as a DPhil student and my progression can be tracked through the chapters of this thesis. Overall this work epitomises the type of research I will pursue as a post-doctoral researcher that brings together methods from policy evaluation, metascience, and epidemiology to improve research integrity and public health.

During the peer review process for my piece in *JAMA Internal Medicine*, one of my peer reviewers was an experienced former US Government official and expert in the FDAAA who, in evaluating the work, noted:

…it is quite difficult to tease apart the various legal requirements (especially since they have changed over time as various components have been implemented and/or as regulations took effect), and to try to evaluate compliance based on publicly available data. The authors have done an excellent job in dealing with the large number of critical details.

Receiving this high praise and recognition for the long hours spent ensuring attention to the minutiae of the law was incredibly humbling and motivating as I continued my thesis.

5.9 Conclusion

The FDA Amendments Act has the potential to ensure that thousands of trials supporting clinical interventions are reported in a timely manner. To achieve this goal, attention is required from regulators to ensure trial sponsors are aware of their responsibilities and face potential repercussions when they fail to comply. Even with an aversion to issuing penalties, the FDA should improve their efforts to reach non-compliant sponsors and encourage reporting. Chapter 6 will further examine the global regulatory context by examining how registration and reporting function on the EU Clinical Trials Register. Across both contexts, the need for regulatory attention, trustworthy data, and timely results is essential.

5.10 Chapter Summary

- Implementing checks for compliance with various aspects of the FDAAA 2007 in code is feasible using only the public ClinicalTrials.gov dataset.
- While overall reporting has steadily increased, there is no indication sponsors are improving at meeting statutory reporting deadlines as of January 2021.
- Sponsors have shown higher levels of compliance with other areas of the FDAAA concerning timely registration, data validation, delay requests, and document reporting; however, the FDA's limited attention to FDAAA compliance is a barrier to improved performance and the completeness and reliability of data on ClinicalTrials.gov.
- Non-industry sponsors have notably poor reporting practice compared to industry and should be prioritised for outreach, education, and potential enforcement activities from the FDA.

Chapter 6: Function and Utility of the EU Clinical Trials Register as a Source of Clinical Trial Information

A cohort study and bibliographic analysis

The data quality analysis from this chapter was preprinted on *MedRxiv* and published in the journal *Clinical Trials*:

- DeVito NJ, Goldacre B. Trends and variation in data quality and availability on the European Union Clinical Trials Register: A cross-sectional study. *Clin Trials* 2022; : 17407745211073483. DOI: 10.1177/17407745211073483

The bibliographic analysis of results availability was preregistered on the *Open Science Framework* and all study data and code are available on *GitHub* and the *OSF*:

- DeVito NJ. Cross-registration and results availability of trials registered on the EUCTR. Open Science Framework 2020; published online April 22. https://osf.io/r3vc5/.
- *Data Quality Code:*
    - https://github.com/ebmdatalab/euctr_data_quality
- *Results Search Code:*
    - https://github.com/ebmdatalab/euctr_pub_search

6.1 Chapter Rationale and Overview

The European Union's regulation of clinical trials transparency is second globally only to the US regime. However, despite covering tens of thousands of trials across the major clinical research hubs of Europe, and being directly integrated to EU regulatory processes, there is little primary research on and using the EU Clinical Trials Registry (EUCTR). This is especially true when compared to ClinicalTrials.gov which has been the subject of countless studies examining various aspects of registration and reporting.

The research in this chapter builds on and extends prior work on reporting and data quality on the EUCTR. Similar to the analysis of FDAAA from Chapter 5, the first EU TrialsTracker analysis published in 2018 in *The BMJ* examined compliance with guidelines requiring the reporting of all trials on the EUCTR.[19] The TrialsTracker, launched alongside this analysis, provides an ongoing monthly audit of compliance. This, and related advocacy efforts, have brought substantial attention to reporting practices.[445,446] However some view these requirements as superfluous reporting within an onerous system.[189,447,448]

The analyses presented in this chapter aim to provide clear evidence of how the EUCTR functions as a data source. For the registry to reliably contribute to evidence synthesis, or analyses like those in Chapters 3 and 4, there must be confidence among users that the data are timely, accurate, and complete. Otherwise, it fails to meet both its public and regulatory function. Past work has suggested that data on the EUCTR may be unreliable,[19,298] however many aspects of the registry have never been sufficiently examined. Together, the analyses presented in this chapter consider key issues about the function of registries as a regulatory tool and their role in promoting transparency and accountability.

6.2 Introduction and Background

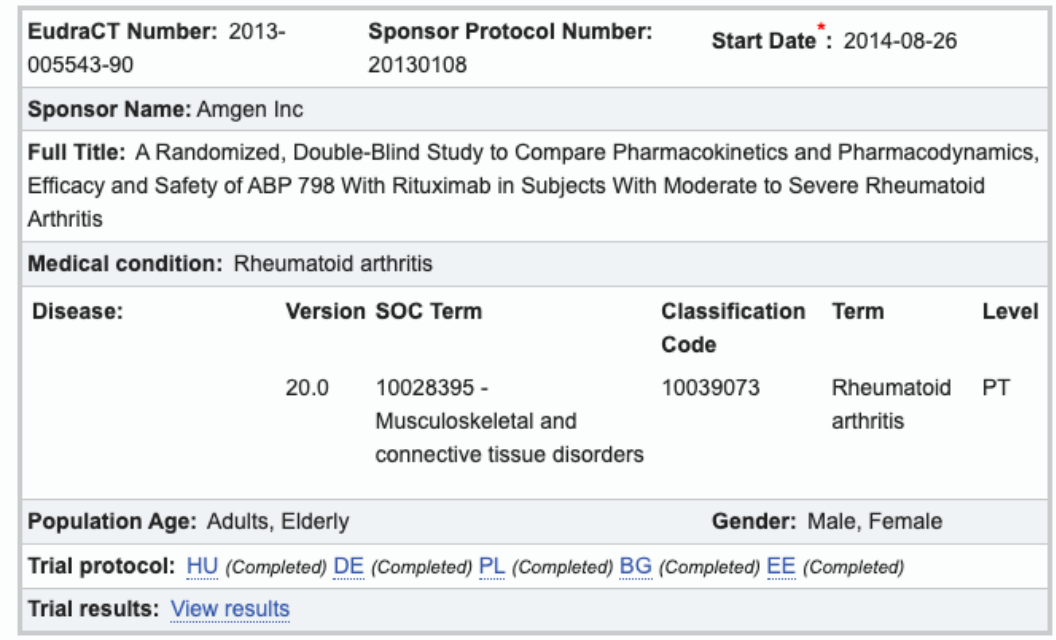
6.2.1 Introduction

The 2001 EU Clinical Trial Directive required the establishment of a pan-European registry to house details of clinical trials of medicinal products (CTIMPS) throughout the European Economic Area.[175] This is detailed in Chapter 2, but to briefly recap, the EudraCT database, managed by the European Medicines Agency (EMA), was created in 2004 to hold regulated trial information from member states. The public facing repository of this information, the EU Clinical Trials Register (EUCTR), would launch in 2011. The EU regulatory process requires trial

sponsors to submit a clinical trial application (CTA) in each country with planned enrollment in a given trial. This is essentially a standardised tabular protocol submitted to each national regulator (i.e., national competent authority) via the EudraCT system.[176,449] Once regulatory and ethics approvals are entered by the regulator, the country protocol is made public on the EUCTR under a single parent record.[177] At the end of the trial, details of the trial's completion are filed with the regulator and this information is then added to the registry.[182,449,450] The EMA has acknowledged issues with early EUCTR trial data through March 2011 (i.e., historical data) due to validation and institutional linkage issues and is working with national regulators "to ensure key data on the status of existing trials is complete."[451,452] Progress on this front, however, is undocumented and appears inconsistent.

In 2012, guidelines were issued requiring sponsors to report results within a year of trial completion directly to the registry. These guidelines applied not only to newly completed trials but also retrospectively to completed trials dating back to the start of the registry.[182,453] These requirements would come into full effect in late 2016 and regulators were expected to follow-up with the sponsors to ensure they add results.[182,184] Results can be added either in a tabular summary format, or as a document upload (i.e., a synopsis or journal article) for older trials. As of December 2021, the EUCTR contains over 41,000 trials. An example EUCTR trial record is shown in Figure 6.1.

Figure 6.1: An Example EUCTR Trial Record



EudraCT Number: 2013-005543-90	**Sponsor Protocol Number:** 20130108		**Start Date*:** 2014-08-26		
Sponsor Name: Amgen Inc					
Full Title: A Randomized, Double-Blind Study to Compare Pharmacokinetics and Pharmacodynamics, Efficacy and Safety of ABP 798 With Rituximab in Subjects With Moderate to Severe Rheumatoid Arthritis					
Medical condition: Rheumatoid arthritis					
Disease:	**Version**	**SOC Term**	**Classification Code**	**Term**	**Level**
	20.0	10028395 - Musculoskeletal and connective tissue disorders	10039073	Rheumatoid arthritis	PT
Population Age: Adults, Elderly			**Gender:** Male, Female		
Trial protocol: HU *(Completed)* DE *(Completed)* PL *(Completed)* BG *(Completed)* EE *(Completed)*					
Trial results: View results					

This is the master trial record displayed for a public registration on the EUCTR. Each protocol can be accessed via the links in the "Trial Protocol" section and results, if available via the "View Results" link.

6.2.2 Prior Research and the EU TrialsTracker

Existing research using the EUCTR is rare. None of the studies in the most recent systematic review covering searches for publications of registered trials used the EUCTR despite many collecting data after the public launch of the registry in 2011.[73] More recently, studies examining reporting of trials from Polish and German academic medical centres used ClinicalTrials.gov and the German Clinical Trials Registry but not the EUCTR even though it is the only mandatory registry in these countries.[262,454,455]

Deane and colleagues examined the reporting of trials for all EMA approved drugs from 2009-2013 and did include EUCTR registrations, finding in one study that the EUCTR returned 903 records compared to 2,852 on ClinicalTrials.gov prior to deduplication.[456–458] Other recent studies that could have used the EUCTR as a data source showed mixed usage with inclusion usually only via the ICTRP dataset.[268,374,459–466] Efforts examining registration quality have focused on ClinicalTrials.gov or include very few studies from the EUCTR.[271,272,276,467–469] While

the comparative size of the registries likely plays a role in these decisions, this lack of usage also may come down to technical differences.[470,471] Since the EUCTR does not have a comprehensive data export feature my colleagues and I have designed custom web scrapers to collect data from the registry that facilitated these analyses.[444,472]

Much of the existing work on the EUCTR originates from my advisors. One study examined the prevalence of completion status discrepancies between 10,492 matched EUCTR and ClinicalTrials.gov studies; 16.2% of all records were discrepant most commonly as “ongoing” trials on the EUCTR marked as completed on ClinicalTrials.gov.[298] I led the development of the EU TrialsTracker which conservatively assesses the results status of completed trials across the entire EUCTR. In data from January 2018, just 49.5% of all completed and due trials had reported results.[19] Consistent with the findings from Chapter 5, commercial sponsors were substantially more likely to report than non-commercial sponsors (Adj. OR: 23.25, 95% CI: 19.15-29.24) as were more active sponsors (Adj. OR largest vs smallest sponsors: 18.38, 15.31-22.06).[19] Even with the Tracker’s conservative methodology, and in light of substantial shortcomings of the EUCTR data, the results reporting issues were clear. Working on the EU TrialsTracker continued to reveal additional issues with the data and led to my interest in more holistically documenting their occurrences. The value of the EUCTR, and its reporting requirements, has been questioned by stakeholders.[189] Evidence was required to discuss where improvement was needed.

In the original EU TrialsTracker piece, I identified data quality issues as a major barrier to more complete ascertainment of reporting compliance. Additionally, reviewers asked how often reporting on the EUCTR matched the availability of results in the literature. In response, I conducted a preliminary search of 100 trials identified as due and unreported trials in our analysis and found 46 with results locatable on PubMed, Google Scholar and Google.[19]

Expanding these areas into a full investigations will provide evidence about the quality and availability of data on the registry and the extent of non-compliance. The results presented in this chapter will help describe the strengths and weaknesses of the EUCTR as a tool for transparency in clinical research and understand more completely how trial regulations have functioned in the EU over the past decade. With new EU regulations coming into effect starting in 2022, the lessons and experiences with the EUCTR can help prepare for more complete and robust transparency efforts under the new system.

6.3 Aim and Objectives

6.3.1 Aim

To assess the value of the EUCTR as a tool for providing accurate and timely information about clinical trials.

6.3.2 Objectives

6.3.2.1 Describe the availability and quality of trial data routinely collected as part of the regulatory process in the EU.

6.3.2.2 Examine the availability of results on the EUCTR compared to other registries and the peer reviewed literature.

6.4 Methods

6.4.1 Data Acquisition

Trial protocol and results information was collected from the EUCTR in December 2020. This is the last month in which updated data from the UK were available on the EUCTR prior to leaving the EU allowing for straightforward comparisons. As of 1 January 2021 UK sponsors may still add results to the EUCTR for existing registrations but protocol adjustments, including updates on trial completion, are not possible.[473] Information on each national competent authority as of

December 2020 are available in Table 6.1.[474] All data collection, handling, and analysis for was performed in Python v3 (Python Software Foundation).

Table 6.1: Details of Country-Level Regulators

Country	Regulator	Abbrev.	# Trial Protocols	First Record Entered
Austria	Austrian Federal Office for Safety in Health Care	BASG	4146	2004-07-16
Belgium	Federal Agency for Medicines and Health Products	FAMHP	5946	2004-07-07
Bulgaria	Bulgarian Drug Agency	BDA	2007	2007-02-02
Croatia	Croatian Ministry of Health	MIZ	401	2014-01-24
Cyprus	Ministry of Health Pharmaceutical Services	MoH PS	5	2009-02-24
Czechia	State Institute for Drug Control	SÚKL	4304	2004-06-24
Denmark	Danish Medicines Agency	DKMA	4069	2004-08-10
Estonia	Republic of Estonia Agency of Medicines	SAM	1020	2004-11-26
Finland	Finnish Medicines Agency	FIMEA	2533	2004-05-26
France	Agence Nationale de Sécurité du Médicament et des Produits de Santé	ANSM	5852	2005-06-21
Germany	Federal Institute for Drugs and medical Devices	BfArM	8324	2004-09-16
Germany	Paul-Ehrlich Institut	PEI	3193	2004-09-10
Greece	National Organization for Medicines	EOF	1791	2005-11-04
Hungary	The National Institute of Pharmacy & Nutrition	OGYEI	4473	2004-06-15
Iceland	Icelandic Medicines Agency	IMA	133	2004-09-07
Ireland	Health Products Regulatory Authority	HPRA	1169	2004-06-18
Italy	Italian Medicines Agency	AIFA	7559	2004-07-16
Latvia	State Agency of Medicines of the Republic of Latvia	ZVA	1079	2004-08-03
Liechtenstein	Amt für Gesundheit	AG	0	N/A
Lithuania	The State Medicines Control Agency	VVKT	1237	2004-06-22
Luxembourg	Ministère de la Santé	MS	8	2013-07-26
Malta	Medicines Authority	MDA	18	2005-10-10
Netherlands	Centrale Commisseei Mensfebonden Onderzoek	CCMO	5692	2006-03-16
Norway	Norwegian Medicines Agency	NoMA	683	2004-05-25
Poland	The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products	URPL	3242	2007-03-29
Portugal	Infarmed	N/A	1591	2005-08-18
Romania	National Agency for Medicines and Medical Devices	ANMDM	239	2009-07-14
Slovakia	State Institute for Drug Control	SUKL	1791	2004-06-02
Slovenia	Agency of the Republic of Slovenia for Medicinal Products and Medical Devices	JAZMP	388	2005-06-13
Spain	Agencia Española de Medicamentos y Producto Sanitarios	AEMPS	9566	2004-06-14
Sweden	Medical Products Agency	MPA	3893	2004-05-13
UK[a]	Medicines and Healthcare Products Regulatory Agency	MHRA	10975	2004-07-01

[a]*The UK has left the EU and no longer participates in the EMA system as of January 2021.*

6.4.2 Analysis Populations

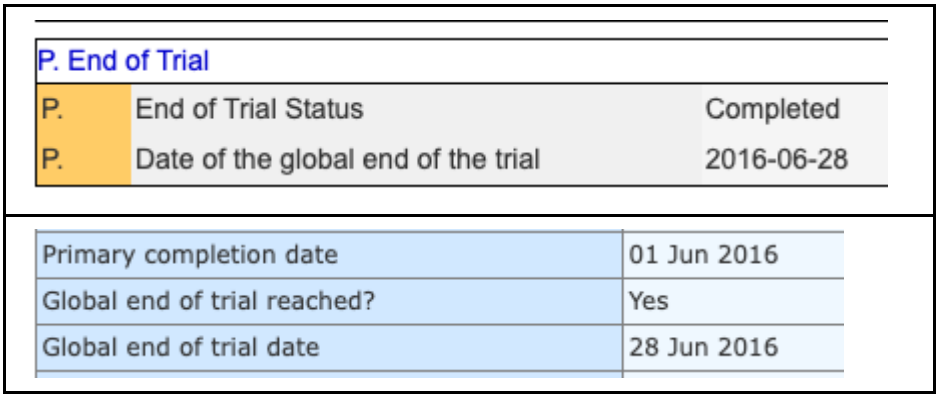
6.4.2.1 Data Quality and Availability

From the full December 2020 dataset, all trial records from an EU-regulated country were used in this analysis including non-EU members of the European Economic Area (i.e., Norway, Iceland, and Liechtenstein) beholden to EU regulations. Certain paediatric trials include non-EU protocols; these were excluded as they are not linked to any individual regulator and lack detailed information on trial completion by design. Phase 1 trials in healthy adults were excluded as these are not available on the public registry.[182] Germany has two independent regulators that manage trial records, and these were examined separately throughout unless otherwise noted.

6.4.2.2 Results Searches

For the results search analysis, all trials in status “Not Authorised” or “Prohibited by Competent Authority” and those with ethical approval dates from prior to the creation of the registry or later than the data extraction date were removed from the full December 2020 dataset. The remaining trials were checked for the presence of a completion date in either the individual trial protocols or in the results section, with the results completion date preferred when available (Figure 6.2). In contrast to parts of the data quality analysis, described below, this analysis did consider completion dates from the results section as they should more reliably represent the completion of the entire trial and the distinction between how completion dates are added to the registry was not relevant here. For trials with differing protocol completion dates and no results completion date, the latest date across all country-level protocols was used.

Figure 6.2: Example Completion Date Information on the EUCTR



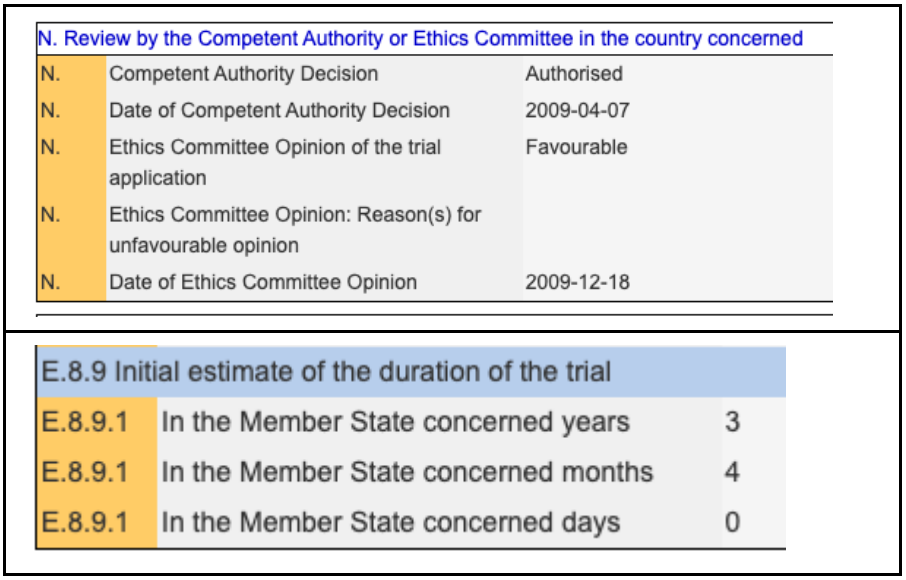
P. End of Trial		
P.	End of Trial Status	Completed
P.	Date of the global end of the trial	2016-06-28

Primary completion date	01 Jun 2016
Global end of trial reached?	Yes
Global end of trial date	28 Jun 2016

Completion information on the EUCTR appears in two locations: within each EU country protocol (top), which is tied to the filing of official documentation indicating the end of a trial; and in the results section (bottom) which is not tied to any formal submission of trial documentation.

In order to derive a more comprehensive sample of completed trials, I developed a method to infer trial completion dates for records that had no dates available in the public data. Each trial protocol in the data was assigned a start date, based on the later of the provided ethics and regulatory start dates, and an expected duration in days calculated from section E.8.9. (Figure 6.3)

Figure 6.3: Examples of Fields Used to Derive Trial Completion Dates



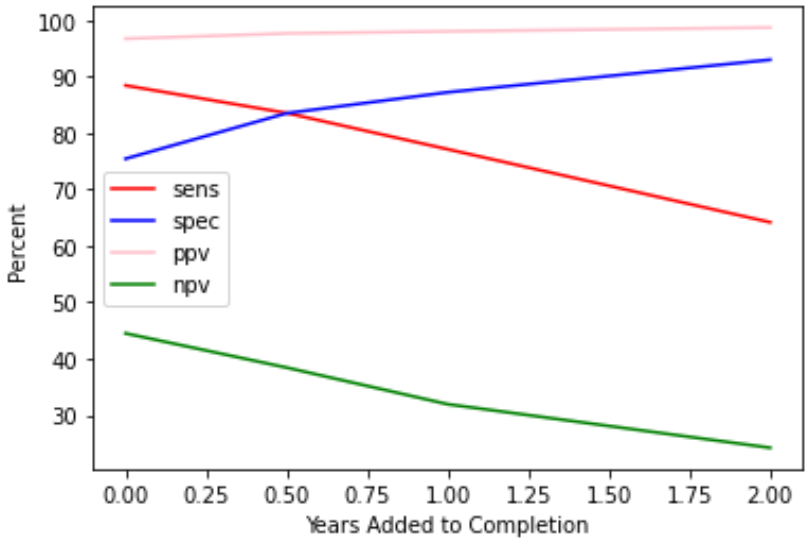
N. Review by the Competent Authority or Ethics Committee in the country concerned		
N.	Competent Authority Decision	Authorised
N.	Date of Competent Authority Decision	2009-04-07
N.	Ethics Committee Opinion of the trial application	Favourable
N.	Ethics Committee Opinion: Reason(s) for unfavourable opinion	
N.	Date of Ethics Committee Opinion	2009-12-18

E.8.9 Initial estimate of the duration of the trial		
E.8.9.1	In the Member State concerned years	3
E.8.9.1	In the Member State concerned months	4
E.8.9.1	In the Member State concerned days	0

The latest available date of the component authority and ethics committee sign-off (top) can be used as a general proxy for the start date of the clinical trials. For trials without a completion date, the duration of the trial can be inferred based on the estimated trial duration provided in protocol section E (bottom).

All protocols from a trial record were then grouped into a single entry in which the longest estimated duration was added to the latest start date. Another year was conservatively added to this date, to allow for any delays in the start-up and conduct of the trial, resulting in a final inferred completion date. Analysis code fully detailing this approach and its validation is available on the project's OSF repository using data from November 2020. Briefly, I applied my date inference method to protocols of trials with known start and completion dates from a tabular results submission. I then assessed whether this correctly identified completed trials. The additional year was added after considering potential date offsets of 0, 6, 12 and 24 months to conservatively ensure a trial was actually completed. I prioritised specificity and positive predictive value, over sensitivity, to minimise the inclusion of false positives (i.e., trials that are not actually completed) in the final sample. One year provided a specificity of 87% and a positive predictive value of 98% while maintaining a sensitivity above 75% (Figure 6.4).

Figure 6.4: Estimating the Impact of Date Offsets to Identify Completed Trials



Each line represents a different measure of accuracy in identifying whether a trial that was actually completed, per results on the EUCTR, was identified as completed using the methods I developed to infer a completion date. The measures were assessed at various additional time offsets added to the raw estimated completion date. sens: Sensitivity; spec: Specificity; ppv: Positive Predictive Value; npv: Negative Predictive Value.

Lastly, only trials with an inferred or extracted completion date at least 2 years in the past (i.e. before 1 December 2018) were included in the population to be sampled allowing time for reporting across dissemination routes.[261,262] From the population of all eligible trials, a random sample of 500 trials was taken using the Pandas package in Python. This sample size was chosen based on achieving point estimates with a maximum 95% confidence interval of ±5%. Using .7 as an estimate for prevalence of a result based on the pilot and the EU TrialsTracker (p), we can calculate the necessary sample size (n) for a 95% CI (z=1.96) and a precision (d) of .05 (i.e, ±5%) with the following formula:

$$n = \frac{z^2 * p(1-p)}{d^2}$$

This called for a sample size of at least 323 trials. Lowering the expected prevalence of any results proportion to .5 required a sample of 384 trials for this level of precision. I choose to assess 500 trials as this comfortably achieved these minimum sample sizes, with room for added precision among subpopulations, and aligned with my available resources.

6.4.3 Evaluation of Quality Metrics

For the data quality analysis, metrics were created to reflect protocol components most clearly linked to EU regulatory processes and public accountability efforts. These included the posting of expected trial protocols, the provision of data about trial completion, and the availability of results. Each area could be assessed in code using only EUCTR registry data. The “National Competent Authority” and “Trials Status” fields were taken from the “Summary” section of each protocol. For analyses involving time trends, the field “Date on which this record was first entered in the EudraCT database” was used as this represents the date the regulator entered the trial record into the EudraCT database.[475] This field was validated by comparison to the

regulatory approval date listed in the registry for alignment (Appendix 6.1). Lastly, the results status was identified by the presence of a “View Results” link in a protocol.

6.4.3.1 Protocol Availability

All recruitment countries from trials with tabular results available on the EUCTR were extracted via a custom web scraping program.[476] These results include a standard data field indicating which countries enrolled participants in the trial (Figure 6.5). This field was then compared to the EU protocols available for that trial. Authorities are required to approve trials recruiting in their country so every EU location with confirmed enrollment in the results should have an associated public protocol. A country was only expected to have a protocol available if the trial start date, from the tabular results, was after the earliest available record entry date for that country on the entire registry (Table 6.1) confirming an established link between the regulator and the EMA. This ensured that protocols were not expected from countries before they joined the EU or before the data linkages were made to the EMA system, which occurred piecemeal over the first years of the EudraCT system. The count of expected vs. actual protocol registrations is reported for each country and over time and compared to overall trends in new registrations.

Figure 6.5: Recruitment Countries in an EUCTR Tabular Result

Population of trial subjects	
Number of subjects enrolled per country	
Country: Number of subjects enrolled	Poland: 115
Country: Number of subjects enrolled	Bulgaria: 30
Country: Number of subjects enrolled	Hungary: 23
Country: Number of subjects enrolled	Estonia: 8
Country: Number of subjects enrolled	United States: 117
Country: Number of subjects enrolled	Germany: 18
Worldwide total number of subjects	311
EEA total number of subjects	194

Recruitment for all countries, whether an EU/EEA member or not, are shown in the tabular results section of an EUCTR record.

6.4.3.2 Quality of Trial Status and Completion Date Fields

Each protocol on the EUCTR should reflect the current status of the trial and the date it completed in all countries once available.[449] This date is officially called the "date of the global completion of the trial" and is referred to here as the "global completion date." Trial completion information entered in the results section was not considered in this analysis, in contrast to the results search analysis, as it only exists for trials that have results, and its provision is not linked directly to the regulatory process. The distribution of trial statuses and the availability of global completion dates in protocols are reported overall, by country, and over time. Trials with conflicting trial completion information were also described.

6.4.3.3 Results Availability

Trials were separated into those that have a single EU protocol, and those that have multiple protocols. Since reporting on the EUCTR occurs at the trial level and not the country level, for trials registered in a single country the responsibility for reporting follow-up falls solely within the remit of that country's regulator. I report on the availability of results by country, and over time, with a focus on trials with a single protocol.

6.4.4 Results searches for registered trials

6.4.4.1 Search Strategy

To inform my final search strategy I conducted a pre-registered pilot in 50 random trials. Following independent data extraction of 12 trials by myself and a colleague (GR), there was high percent agreement overall and discrepancies were easily resolved through discussion. Extraction of information from registries showed perfect agreement. Assessing whether the trial was cross-registered on ClinicalTrials.gov (87.5%) and the ISRCTN (100%) also showed high agreement. Whether a matched journal article was located showed the lowest agreement

(79.1%) however each extractor noted their confidence in matches and three of the five discrepant journal article findings were flagged as “low confidence” and therefore would have been considered for further review. I searched the remainder of the trials to further refine the search strategy and extraction sheet. The addition of proprietary databases (i.e., Scopus, Ovid) did not yield substantial additional value in locating results so the final search strategy used only open databases to allow for easier reproducibility of searches. Full data and results from the pilot are available in the protocol and on the project’s OSF repository.

For the final search strategy all data were recorded in a Google Forms extraction sheet. Each EUCTR trial record was reviewed for results on the registry and any other information about duplicate registrations or results publications. ClinicalTrials.gov and the ISRCTN were then cross-referenced for matched registrations and results information. ClinicalTrials.gov is the largest registry in the world (an order of magnitude bigger than the EUCTR) and has regulatory reporting requirements that should overlap for some trials. The ISRCTN is the primary registry for the UK, and while it accepts global registrations, it predominantly contains trials located in Europe indicating potential overlap with the EUCTR.[477] The EUCTR also contains specific fields denoting cross-registration on these two registries. Like the EUCTR, both registries also allow summary results to be uploaded and hosted directly within a trial record.

Registries were first searched using the EUCTR ID and then the trial title, name or acronym, intervention, condition, sponsor, and any additional secondary IDs available. A result on a registry was defined as summary data or a file included directly within the trial record; only including links to external papers or documents was not counted as registry results. Trials that did not post results but declared that the trial ended with very low enrollment, and justified why no analysis was possible in lieu of results, were counted as reporting since this would provide interested parties with enough detail to understand the fate of the trial.

Lastly, PubMed and Google Scholar were searched for journal publications using all known trial IDs, the trial title, acronym, interventions, conditions studied, and any investigator names and affiliations if available. Searchers had freedom to combine these terms, or add additional terms, to searches at their discretion. Results in the literature were included if they were in a peer reviewed journal, reported a final primary outcome, and were longer than 500 words in length, consistent with prior methods.[262] In practice, this meant longer conference abstracts could be counted as results. If multiple potentially relevant publications were located, the earliest was recorded. Only results published prior to the commencement of searches were included in the final analysis.

Article and registry matches were confirmed through comparison of ID numbers, study design, indication, intervention, planned enrollment, and the registered outcomes.[261] No specific threshold was set to define a match, however any issues were referred to the full study team for additional discussion. If, during any point in the searches, a trial was found to either be withdrawn without enrollment, still ongoing, or if the record is currently inaccessible on the EUCTR, it was excluded from the analysis sample and replaced with another random trial from the population. Trials with any amount of enrollment, even if terminated, were expected to have some form of results or a summary of why results could not be made available.

6.4.4.2 Details of Dual Searches

I was the lead searcher and searched all 500 trials. Due to resource constraints, a lower proportion of trials than specified were dual searched. A collaborator (JS) dual-searched 20% of the sample (n=100 trials) to assess congruence in data extraction and application of the search strategy. Any issues were examined by both searchers and resolved through discussion. Where

consensus could not be reached, or single-extracted trials were flagged for issues, I consulted one of my advisors (CH) to make final adjudications.

Overall, the two searchers displayed high agreement (>98%) for information extracted from registries requiring only minor corrections for typos or decisions on edge cases. Agreement on trial publication status was 97% and among the trials with results the same publication was located in 90% of cases. The most common issues were in the extraction of publication dates of journal articles with 79% congruence among the 58 located articles due to differing publication dates listed between databases, publications, and journal websites. I plan to manually review all these dates prior to submitting this study for peer review.

6.4.4.3 Analysis Plan and Outcomes

The primary outcome was the proportion of trials with results across any examined dissemination route, and for each route individually. Pre-specified secondary outcomes were the number and proportion of unique results from each dissemination route and frequency in which each dissemination route contained the first results available. Differences in reporting statistics between the inferred and extracted populations were also assessed using a two-proportion z-test (unadjusted alpha = .05, corrected using the Holm-Bonferroni method). One additional secondary outcome was added *post hoc* assessing the presence of trial IDs in journal publication. This was extracted during data collection and added as an outcome as it provides insights into how the published literature links back to the EUCTR registration.

The analysis of which dissemination route had the first results for a given trial was altered from the per-protocol description. Originally, I intended to look at when trials first reported across the entire dataset, and for the subset of trials that completed after the EUCTR launched their results section in March 2014, and assess these distributions for goodness-of-fit. On further

consideration, naively examining which route had the earliest result, without taking into consideration where a result could have appeared, did not provide a useful comparison. Additionally, using completion dates was not the most sensible way to divide the population as they do not reflect when results actually became available.

Instead, I separated all trials into two groups: those that had any result available prior to, and after, the launch of the EUCTR results section. For each of these sub-populations I examined the number of trials that reported to the EUCTR at any point. Then, taking into consideration where trials could have been published, I examined the fastest dissemination routes for all relevant combinations. For pre-EUCTR results, I compare trials available on ClinicalTrials.gov to the literature; for trials first reporting after the EUCTR results section, I first compared earliest results for all trials with registrations on both the EUCTR and ClinicalTrials.gov to the literature, then I compare the remaining EUCTR-only trials just to the literature. Due to the low number of results on the ISRCTN, the registry was excluded from this analysis. Additionally, to further describe the population of trials missing results I examined the distribution of start years for trials with missing results on the EUCTR and with missing results across all dissemination routes considered.

6.4.4.4 Exploratory Analyses

There were two pre-specified exploratory analyses. For trials with results available in any route, factors associated with results appearing on the EUCTR were examined using uni- and multivariable logistic regression. The following factors were considered: whether the completion date was reported or inferred, trial start year, sponsor type, number of EU protocols registered, the final enrollment (intent to treat), and whether the trial was EU-only or multinational. I extracted trial start year, final enrollment, and the location variable manually from trial registration and results available following searches. If contradictions between sources arose,

and no more complete or recent data were available from another source, the EUCTR data were preferred. The remaining variables were directly extracted from EUCTR data in code. Significance for the univariable and multivariable models was determined using the Holm-Bonferroni method (unadjusted alpha = .05).

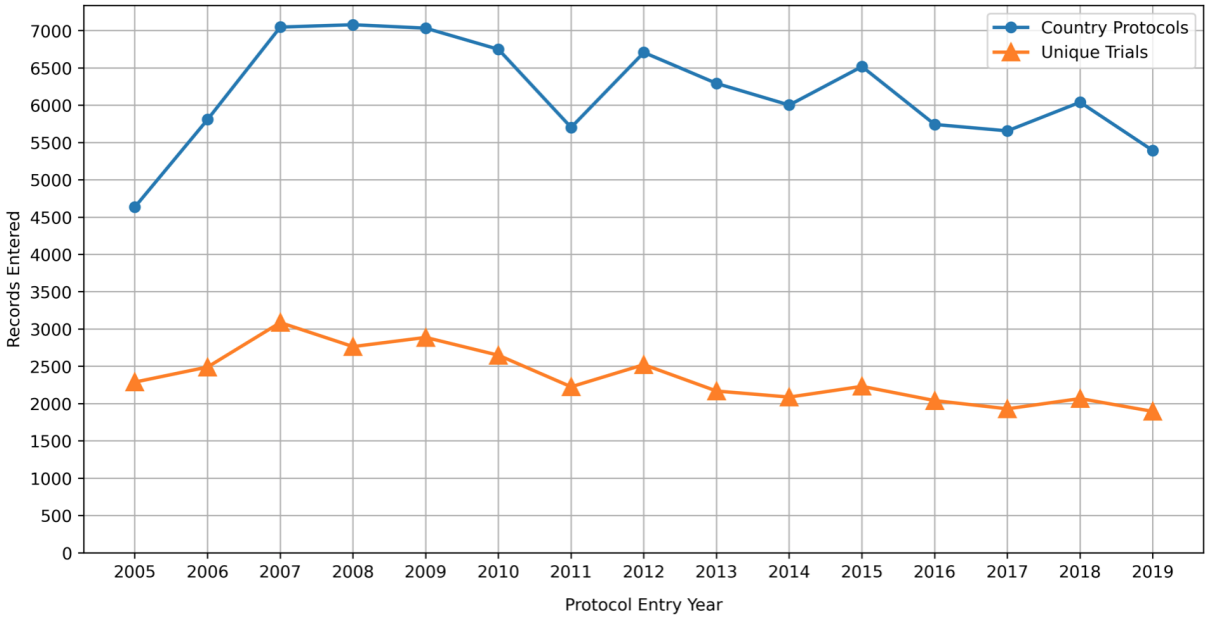
The second exploratory analysis examined variation in reporting behaviour by sponsor country. The sponsor "Country" field (B.1.3.4 on the EUCTR) was extracted for all country-level protocols for each trial. This is not necessarily the same country for all protocols within an EUCTR trial registration. For this analysis I used the sponsor country that appeared the most frequently for each trial. If no single country appeared most frequently, the trial was coded as having "multi-country" sponsorship. The percent of trials reported to the EUCTR, other registries, and the literature was reported for each sponsor country represented in the sample.

6.5 Results - Trends and Variation in Data Quality and Availability on the EUCTR

6.5.1 Study population

As of 1 December 2020, the EUCTR contained 98,622 country-level protocols across 38,566 registered trial records since 2004. Excluding all protocols from outside the direct regulatory purview of the EMA left 97,227 protocols across 37,520 trials for assessment. The overall trend in new registrations on the EUCTR is available in Figure 6.6. Small countries with very low registered trial counts (Cyprus (n=5), Luxembourg (n=8), Malta (n=18), and Liechtenstein (n=0)) are not shown for some analyses as no meaningful trends could be established.

Figure 6.6: Overall Registration Trends on the EUCTR

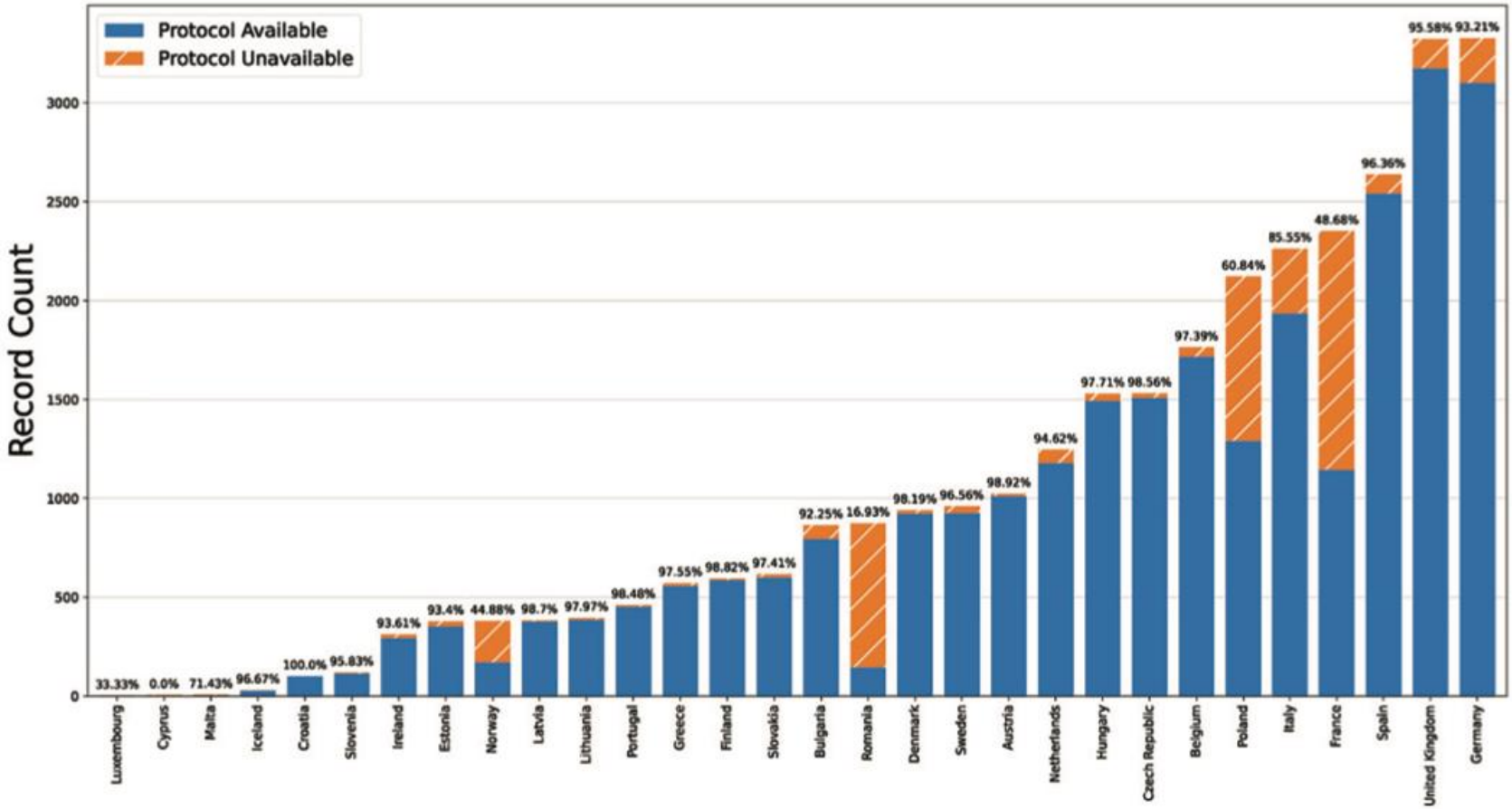


The overall trend in the number of new EU/EEA protocol and full-trial registrations for all years with full data (i.e., excluding 2004 and 2020). A single trial registration on the EUCTR is made up of individual EU/EEA protocols for countries with current or planned recruitment.

6.5.2 Availability of Protocols for Countries with Known Enrollment

Of 31,118 expected protocols, 26,932 (86.5%) were available on the EUCTR and 22 of 30 (73%) countries had more than 90% of expected protocols available; 17 of 30 (56%) had >95% available (Figure 6.7). Setting aside small countries with very few trials, the lowest proportion of expected protocols were seen in France (48.7%), Norway (44.9%), and Romania (16.9%). Overall two-thirds (66.0%) of all missing protocols are from three countries: France, Norway, and Poland. Italy (85.6%) was the only other high-output country with <90% availability.

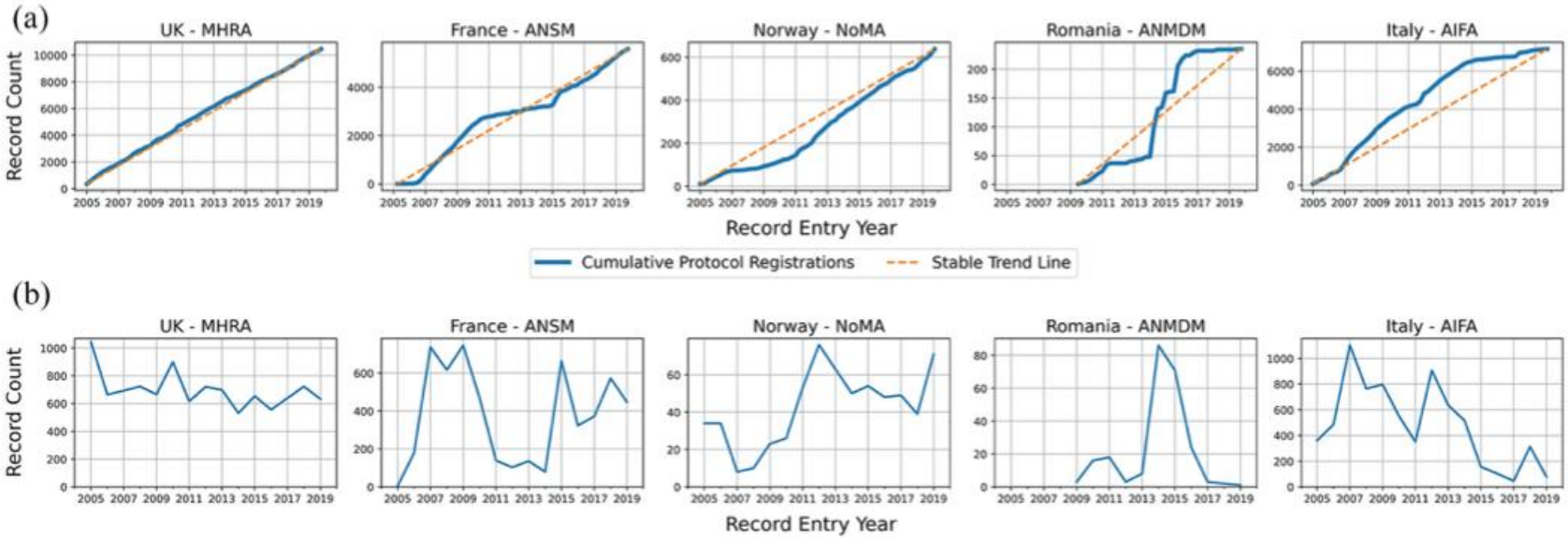
Figure 6.7: Protocol Availability on the EUCTR by Country



The number, and percentage, of protocols that should be publicly available for all trials with tabular results on the EUCTR. The actual protocols available for each country were compared to detailed tabular results, where available, that contain information on which specific countries enrolment was reported to have occurred.

Evidence of these missing protocols can also be seen in the trends in new registrations by country. In most countries, between 2005 and 2019 (i.e., all full years in the dataset) new registrations remain relatively constant over time (e.g., the UK), while countries with many missing protocols inconsistently added new registrations (Figure 6.8, Appendices 6.2 & 6.3). Missing protocols were not limited to the “historic” pre-2011 dataset as most were from records entered between 2012 and 2015 with a relatively low concentration of missing protocols from 2004 to 2009. (Appendix 6.4). According to the enrollment figures provided in the results section, missing protocols covered 1,265,740 enrolled trial participants.

Figure 6.8a & b: Trends of New Trial Registrations in Select Countries



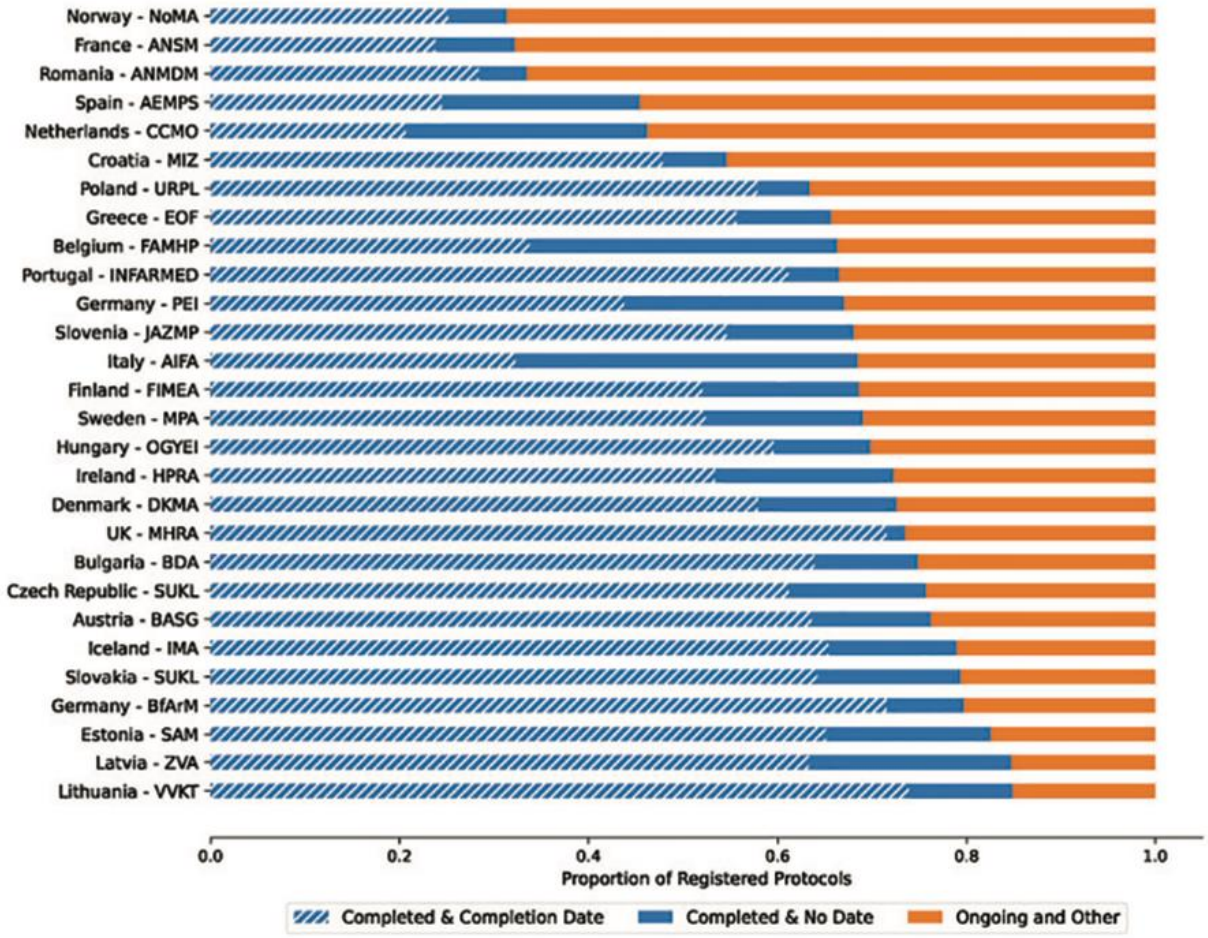
The (a) cumulative trend in new trials and (b) absolute trend in new trials for five countries. The United Kingdom is shown as a typical comparator country with a relatively stable rate of new trials, while the other four countries all have pronounced deviations in the registration of new protocols over time. The trends of all regulators are available in the Appendices 6.2 & 6.3.

6.5.3 Completion Status

Across all included trials on the EUCTR, 63,434 protocols (65.2%) are in a completed status, however 21 of 28 (75%) regulators exceeded this mark across their registered protocols. Five regulators (Norway, France, Romania, Spain, and the Netherlands) had <50% of their covered protocols in a completed status (Figure 6.9). There is a relatively consistent and expected pattern to the proportion of completed protocols in the database over time. From 2004-2013 the proportion of completed protocols among those first entered in that year ranged from 76.6% to 83.5% before dropping off rapidly from 2014 as more recently registered trials remain ongoing (Appendix 6.5).

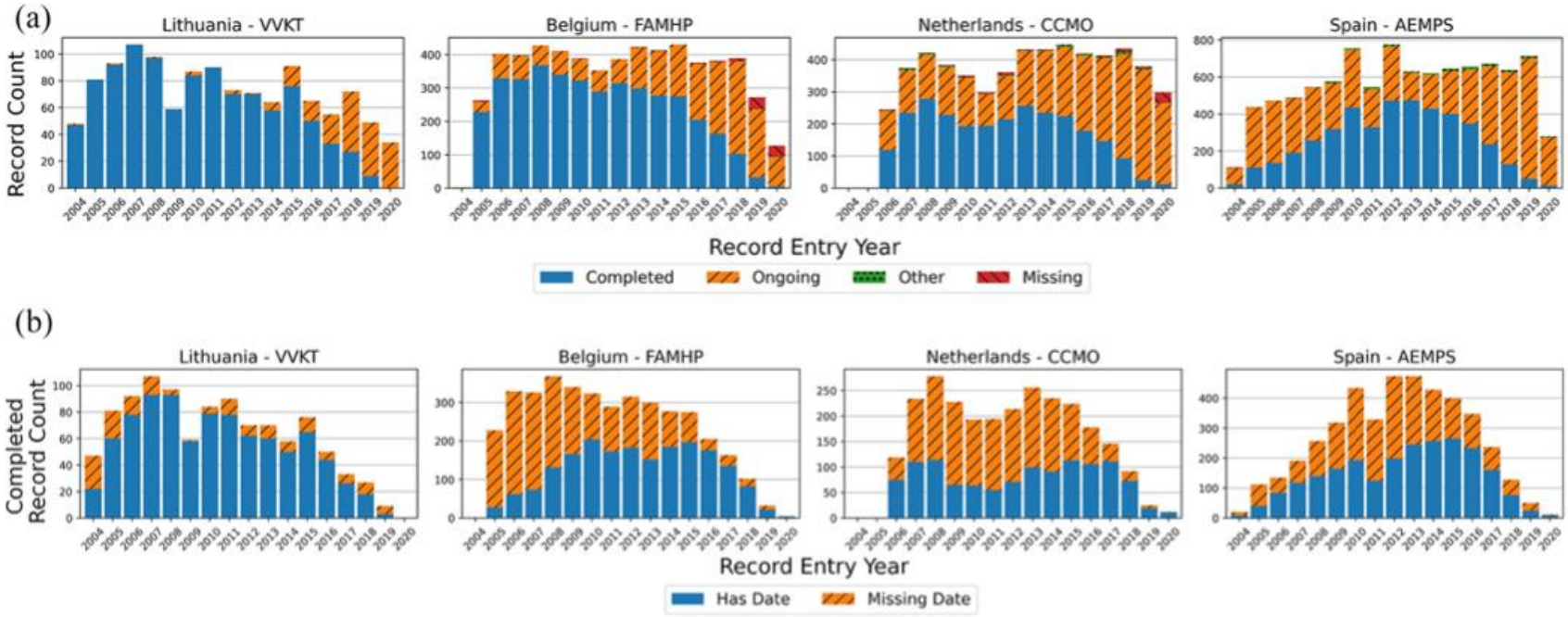
Time trends by regulator generally follow this expected pattern (e.g., Lithuania) and deviations from this trend were minor, but consistent, in some countries (e.g., Belgium) and pronounced in others (e.g., the Netherlands, Spain) (Figure 6.10a, Appendix 6.6). Of the 13,897 trial records with more than one country protocol, 4,520 (32.5%) contain protocols in both a Completed and Ongoing status with older trials having the highest proportion of trials with conflicts (Appendix 6.7). For single-protocol trials, 6,089 of 16,552 (36.8%) trials entered prior to 2015 are still in an “Ongoing” status.

Figure 6.9: Availability of Trial Completion Information by Country



The proportion of trials in each regulator's portfolio in a 'Completed' status (i.e. Completed or Prematurely Ended) is represented by the blue area and is broken down by those with a completion date (hashed blue) and without a completion date (solid blue). The number of 'Ongoing and Other' trials (in orange) in a status other than 'Ongoing' is nominal (see Appendix 6.5).

Figure 6.10a & b: Trends in Trial Completion Information



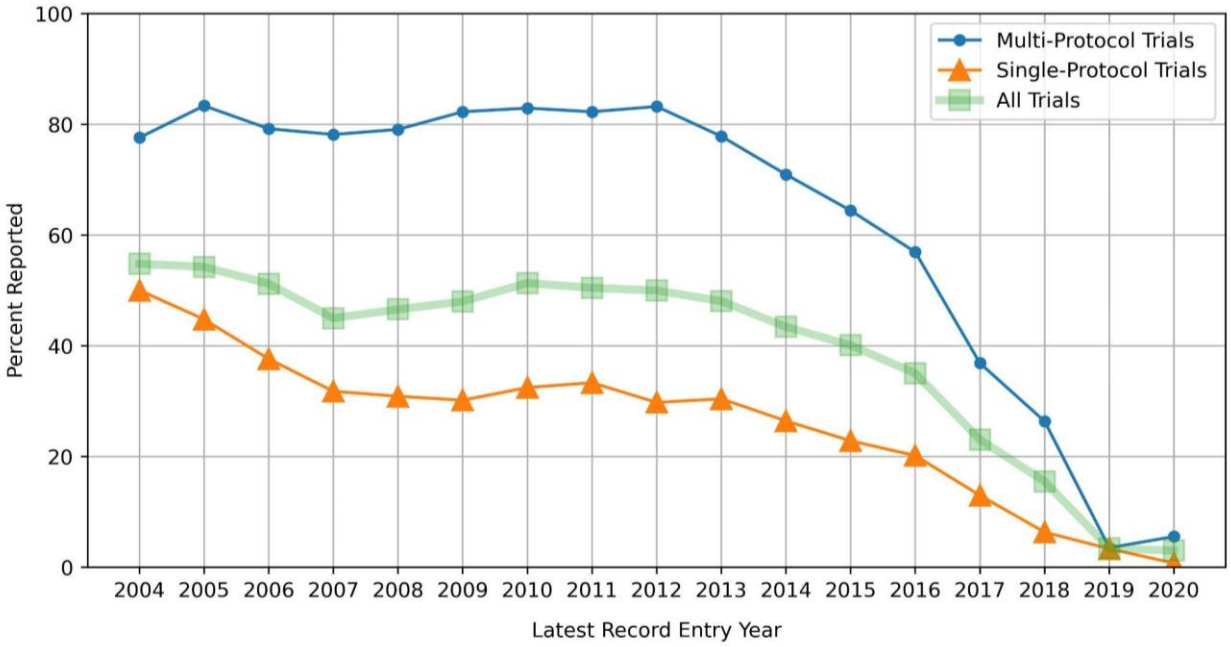
The (a) distribution of trial statuses of protocols first entered in each year and (b) trend in the proportion of completed protocols with a completion date across four selected countries. Lithuania is indicative of the standard expected trend, while Belgium, the Netherlands and Spain represent issues in the availability of trial completion information.

The overall availability of completion dates for completed protocols has remained consistent over time. Across the whole database, 75.6% of completed protocols have a global completion date available. From 2005-2018, the proportion of completed protocols first entered in that year that have a completion date never deviated far from this overall rate (range: 71.6%-79.2%) with an expected drop-off in 2019 and 2020 as recent studies may not have completed at all sites (Appendix 6.8). There is, however, variability among regulators: 20 of 28 (71.4%) exceeded the overall rate of global completion date availability and another three were within 2 percentage points (Appendix 6.9). The remaining six countries had a global completion date availability of <70%: Germany - PEI (65.3%), Spain (53.9%), Belgium (50.9%), Italy (47.2%) and the Netherlands (44.8%) (Figure 6.9, 6.10b). Of the 8,566 trials with multiple protocols and at least one global completion date, just 2,002 (23.4%) have provided the same date across all protocols.

6.5.4 Trends in Results Availability

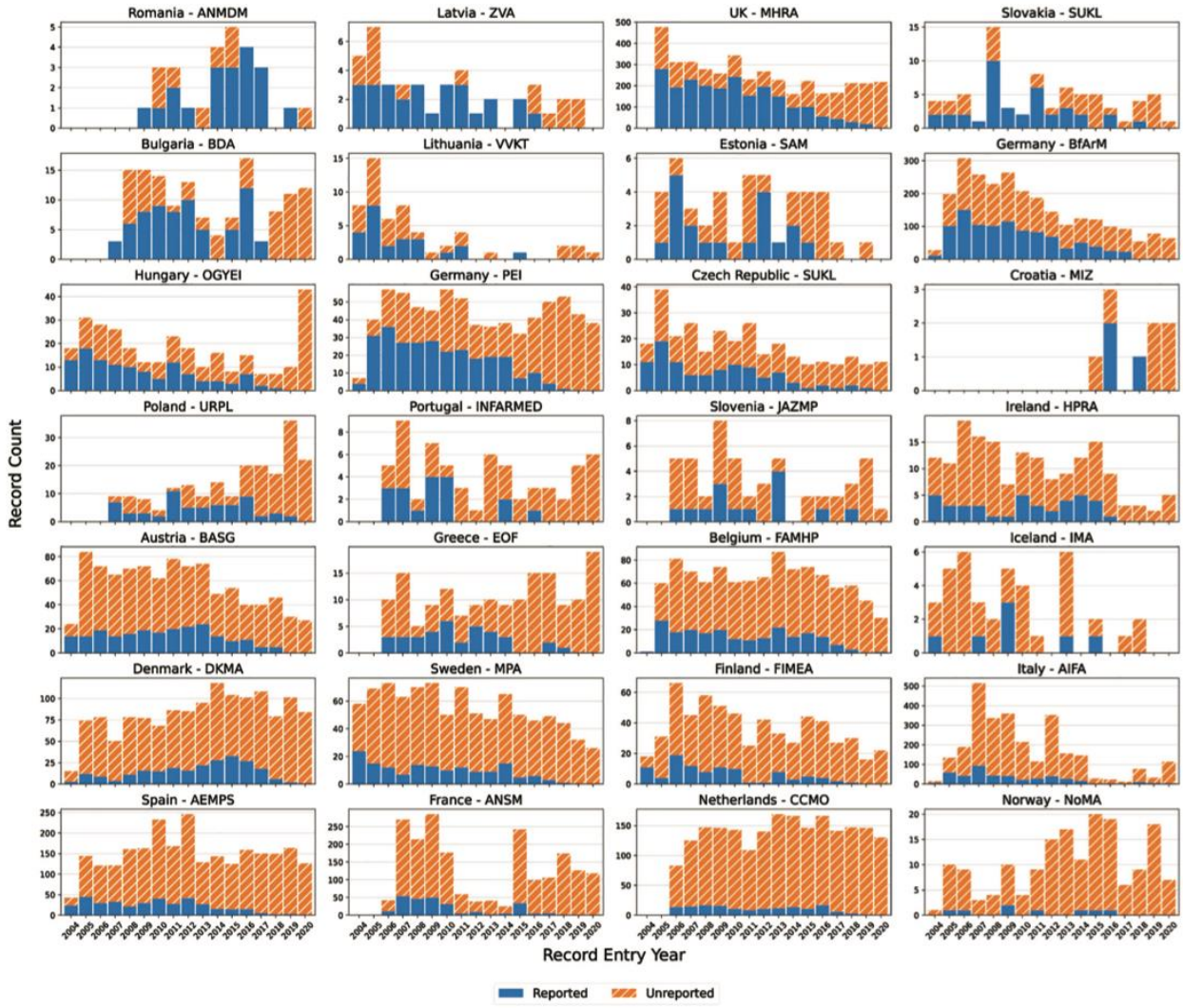
Overall the EUCTR contains 23,623 trials with a single EU protocol and 13,897 with multiple EU protocols. Results reporting for single protocol trials was lower overall (26.5%) compared to multi-protocol trials (60.6%) and across all years in which protocols were submitted (Figure 6.11). Only two regulators, Romania (70.4%) and Latvia (64.3%) exceeded a 60% reporting rate of single protocol trials, but this represented just 69 reported trials across both countries. The next highest reporting country, the UK, reported 53.8% of 4,057 trials. All high-research output peers of the UK fell below 40% of studies reported. Two countries had less than 10% of single-protocol trials reported: the Netherlands (7.5%) and Norway (4.7%) (Figure 6.12).

Figure 6.11: The Trend in Results Availability on the EUCTR Over Time



The trend of results availability for all trials on the EUCTR and separated by multi- and single-EU protocol trials. The availability of results for single-protocol trials is substantially lower than multi-protocol trials for all years through 2019.

Figure 6.12: Results Availability of Single-Protocol Trials on the EUCTR



The trend in completed, single EU protocol trials that have results across responsible national regulators and over time. Regulators are ordered by percentage of all protocols reported. Since these trials fall under the oversight of a single regulator, there is no ambiguity in where enforcement of EU rules on trial reporting would sit.

6.6: Results - Results Availability of Clinical Trials Registered on the EU Clinical Trials Registry

6.6.1 Study population and Sample

From the same starting population as the data quality analysis, exclusions for this study reduced the population to 66,833 individual protocols spread across 27,241 trials. Figure 6.13 shows a flow diagram detailing the creation of the population and final sample. During searches, 19 trials

were found to either be withdrawn without enrollment (n=15), still ongoing (n=2), or were no longer publicly accessible on the EUCTR (n=2) and were replaced in the final sample. Characteristics of the final sample of 500 trials drawn from this population are included in Table 6.2. Primary searches began on 11 December 2020 and continued through July 2021, with dual searches completing in November 2021.

Across the entire EUCTR, an end date was extracted for 21,766 (56.4%) trials and inferred for 16,051 (41.6%) trials. The remaining 749 (1.9%) trials either had insufficient information about completion or never started across all locations. Excluding trials that completed after 1 December 2018 (i.e., 2 years before data extraction) left a population of 27,241 trials eligible to be sampled made up of 19,182 (70.4%) trials with extracted end dates and 8,059 (29.6%) with inferred end dates. The random sample of 500 trials, taken from the full eligible population of trials, contained 353 (70.6%) trials with extracted completion dates, and 147 (29.4%) with inferred completion dates closely aligned to the overall rates.

Figure 6.13: Flow Diagram for Results Search Study

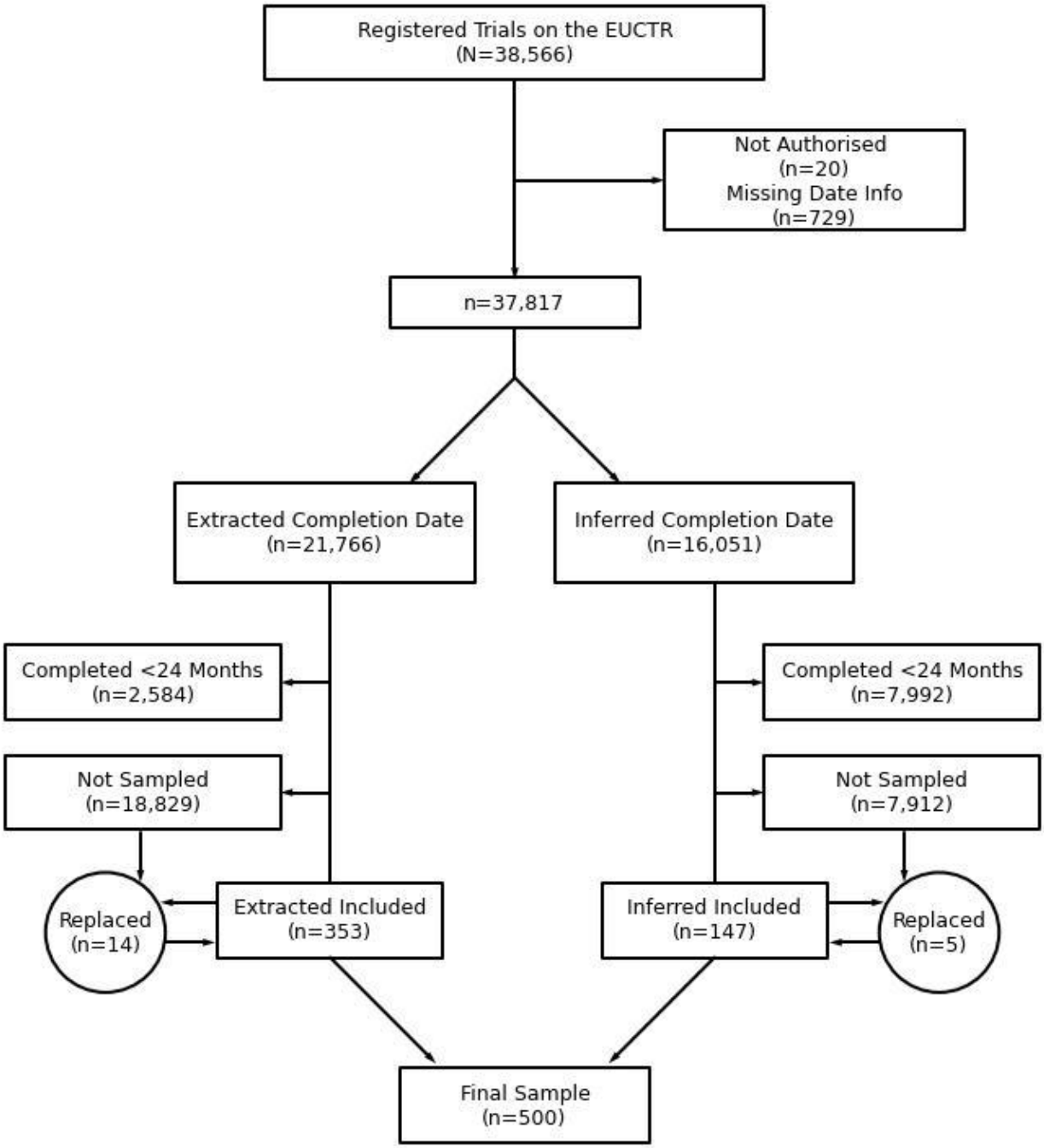


Table 6.2: Characteristics of Sample

	Characteristic	Count (Percent)
Sponsor Status	Commercial	276 (55.2%)
	Non-Commercial	223 (44.6%)
	Unknown	1 (.2%)
Enrollment	Median (IQR)	71.5 (36-196)
	Range	1-16000
Location	EEA Only	320 (64%)
	EEA & Non-EEA	166 (33.2%)
	Non-EEA Only	14 (2.8%)
Number of EU Protocols	Median, IQR	1 (1-3)
	Range[a]	0-16
Trial Start Year	<2004[b]	3 (.6%)
	2004	14 (2.8%)
	2005	28 (5.6%)
	2006	49 (9.8%)
	2007	43 (8.6%)
	2008	60 (12%)
	2009	47 (9.4%)
	2010	46 (9.2%)
	2011	49 (9.8%)
	2012	52 (10.4%)
	2013	35 (7%)
	2014	33 (6.6%)
	2015	20 (4%)
	2016	17 (3.4%)
	2017	3 (.6%)
	2018	1 (.2%)

[a]*Value is 0 when trial only contains an "Outside EU/EEA" protocol, for example 2014-003401-15.*
[b]*One each in 1999, 2002, and 2003. Earlier start dates found in other sources.*

6.6.2 Registration and Results Reporting

Of the 500 trials registered on the EUCTR, 264 (52.8%, 95% CI: 48.4-57.2) had results on the registry and 54 (20.5%, 15.6-25.3) of these were unique to the EUCTR (i.e., no results in any other dissemination route). This was similar to the overall availability of results in the literature (n=292, 58.4%, 54.1-62.7). Of the 264 results on the EUCTR, 116 (43.9%, 38.0-49.9) were uploaded in the EUCTR's native tabular format, 131 (49.8%, 43.8-55.8) were available as documents, and 17 (6.4%, 3.5-9.4) had both tabular results and a results document. Uploaded results documents were most commonly Clinical Study Report synopses (n=86) and copies of results submissions to ClinicalTrials.gov (n=24) with the rest made up of miscellaneous results reports (n=13) and journal articles (n=8).

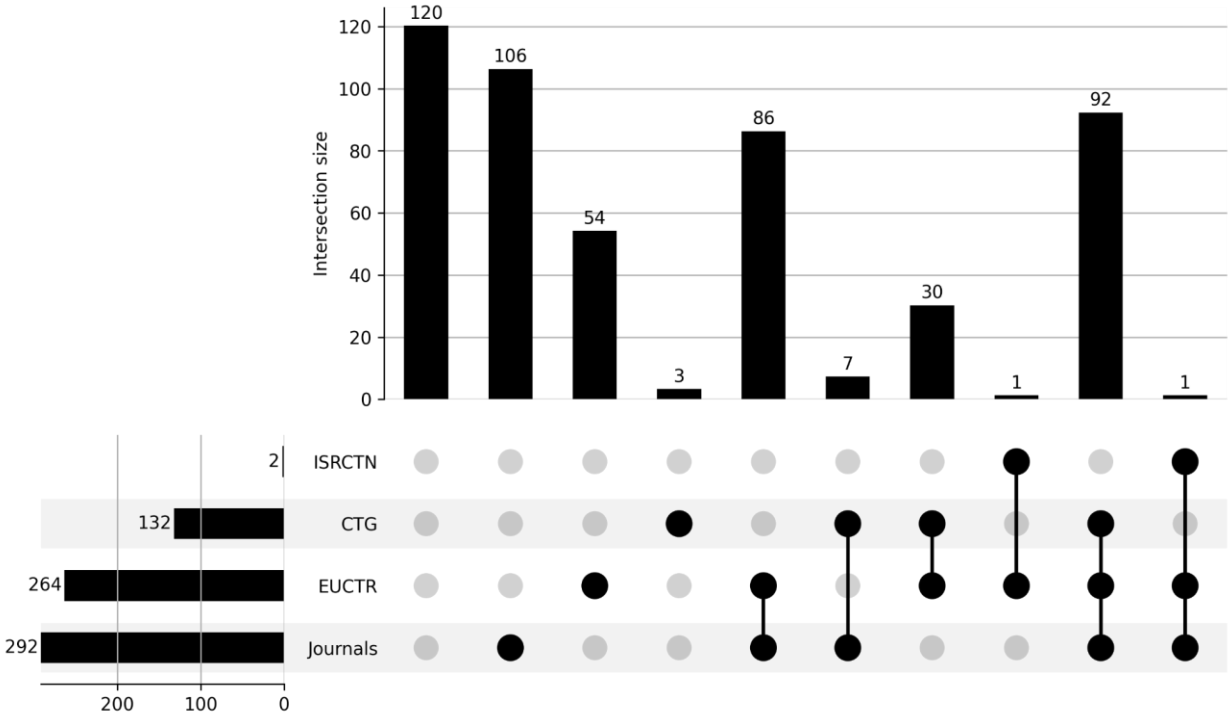
Table 6.3 details the availability of results across all examined registries and the peer reviewed literature. Overall, 690 results were located for 380 (76%, 72.3-79.7) trials in our sample of registered trials. Figure 6.14 shows an UpSet chart[478] with the frequency of each dissemination route combination. The most common dissemination combinations were available only in a journal (n=106), in a journal along with both the EUCTR and ClinicalTrials.gov (n=92), and in a journal and the EUCTR (n=86). No results were found for 120 (24.0%, 20.3-27.7) trials and 116 (23.2%, 19.5-26.9) trials had results elsewhere but not on the EUCTR. These 236 trials represent failures to report under EU guidelines. The 120 unreported trials enrolled or planned to enrol 33,844 participants.

Table 6.3: Availability of Results Overall and by Dissemination Route

Dissemination Route	Overall			Known Completion Date		Inferred Completion Date		p-value[a]
	Total Eligible to Report	Reported N (%, 95% CI)	# Unique N (%, 95% CI)	Total	Reported N (%, 95% CI)	Total	Reported N (%, 95% CI)	
Any Result	500	380 (76.0%, 72.3-79.7)	-	353	311 (88.1%, 84.7-91.5)	147	69 (46.9%, 38.9-55.0)	p<0.0001
EUCTR	500	264 (52.8%, 48.4-57.2)	54 (20.5%, 15.6-25.3)	353	264 (4.8%, 70.3-79.3)	147	0	p<0.0001
ClinicalTrials.gov	340	132 (38.8%, 33.6-44.0)	3 (2.3%, 0-4.8)	270	130 (48.2, 42.2-54.1)	70	2 (2.9%, 0-6.8)	p<0.0001
ISRCTN	32	2 (6.3%, 0-14.6)	0	29	2 (6.9, 0-16.1)	3	0	p=.639
Journals	500	292 (58.4%, 54.1-62.7)	106 (36.3%, 30.8-41.8)	354	224 (63.3%, 58.3-68.3)	147	68 (46.3%, 38.2-54.3)	p=0.0004

[a]*Comparing known to inferred reporting rates. Other than the ISRCTN, p-values for all z-tests met the holm-bonferroni corrected threshold for significance using an uncorrected alpha = .05*

Figure 6.14: Results Availability by Dissemination Route



Combinations of dissemination routes not shown had zero counts. CTG: ClinicalTrial.gov.

6.6.3 EUCTR Completion Status and Reporting

Trials with a known end date were significantly more likely to have results available in any route compared to those with an inferred end date (88.1% vs. 46.9%, p<.0001) and among all individual dissemination routes except the ISRCTN (Table 6.3). Trial results outside the EUCTR were also more likely for trials with extracted vs. inferred end dates (72.8% vs. 46.9%, p<.0001). While none of the trials with inferred end dates had results available on the EUCTR this aligns with the methods used to extract and infer completion dates.

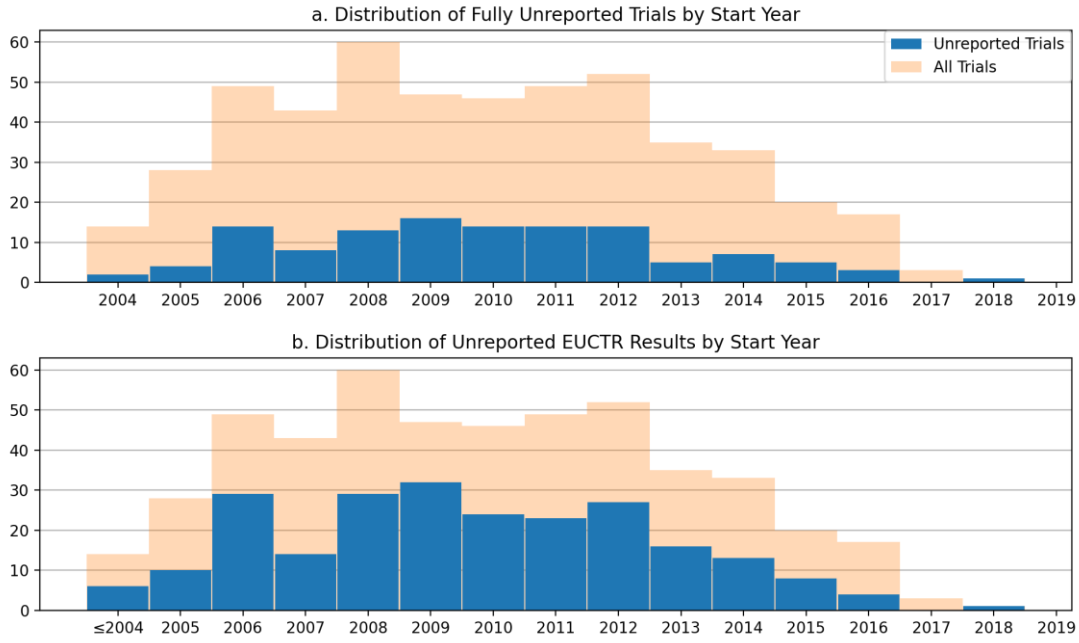
6.6.4 Timing and Characteristics of Results Availability

Prior to the addition of the results section to the EUCTR in March 2014, 135 trials had published a result via another dissemination route; 95 (70.4%, 62.7-78.1) of these would go on to publish a result on the EUCTR. Among these 135 trials, 99 were also registered on ClinicalTrials.gov

and therefore could have first posted their results to either ClinicalTrials.gov or a journal; 67 (67.7%, 58.5-76.9) of these first appeared on a journal, and 32 (32.3%, 23.1-41.5) on ClinicalTrials.gov.

After the launch of the EUCTR results section, 245 trials in the sample published a first result via any dissemination route and 171 (69.8%, 64.1-75.6) had a result appear on the EUCTR at any point. A total of 191 trials could have had their first result appear in either the EUCTR, ClinicalTrials.gov, or a journal article: 89 (46.6%, 39.5-53.7) of these first appeared in a journal; 83 (43.5%, 36.4-50.5) on the EUCTR; and 19 (10.0%, 5.7-14.2) on ClinicalTrials.gov. For the 53 trials with a result but no ClinicalTrials.gov registration, 22 (41.5%, 28.2-54.8) appeared on the EUCTR first and 31 (58.5%, 45.2-71.8) appeared in a journal first. Figures 6.15a and b show the distribution of start years for the trials with no results in any route and no results on the EUCTR.

Figure 6.15: Distribution of Start Years for Trials Missing Results



In both charts the distribution of start years, as collected from all available registrations and results, is shown in orange while the count of those trials that are unreported is shown in blue.

6.6.5 Reporting of Trial IDs

Of the 292 trials in which a matched journal article could be located, an EUCTR trial ID was included in 66 (22.6%, 17.8-27.4). Trials with registrations elsewhere included those IDs in publications at a much higher rate. ClinicalTrials.gov IDs were present in 186 of 222 (83.8%, 78.9-88.6) publications and ISRCTN IDs were available in 15 of 24 (62.5%, 43.1-81.8). No IDs were included in 57 publications (19.5%, 15.0-24.1).

6.6.6 Exploratory Analyses

For the exploratory risk factor analysis, it was necessary to exclude whether the trial had an inferred or extracted end date as a potential risk factor, despite pre-specification, as this was a perfect predictor of non-reporting of results to the EUCTR (Table 6.3). In the univariable models, being a commercial sponsor, an increasing number of registered EU protocols, and having trial location both inside and outside of the EEA compared to having only EEA locations increased the likelihood of results appearing on the EUCTR. In the fully adjusted multivariable analysis, only commercial sponsorship remained significant (Table 6.4).

Table 6.4: Factors Associated with Reporting to the EUCTR

		Reported to EUCTR Crude OR (95% CI; p value)	Reported to EUCTR Adjusted OR (95% CI; p value)
Commercial Sponsorship		13.44 (7.94-22.76; p<.001)[a]	9.31 (4.84-17.93; p<.001)[a]
Enrollment (continuous)		1.00 (1.00-1.00; p=0.54)	1.00 (1.00-1.00; p=0.60)
Location:	**EEA only**	Ref	Ref
	EEA & Non-EEA	5.60 (3.23-9.72; p<.001)[a]	1.15 (0.53-2.50; p=.72)
	Non-EEA Only	10.49 (1.35-81.60; p<.02	3.10 (0.37-26.21; p=.30)
Num. EU Protocols		1.52 (1.29-1.78; p<.001)[a]	1.20 (1.00-1.44; p=.05)
Trial Start Year (continuous)		1.05 (0.98-1.12; p=.18)	1.08 (1.00-1.18; p=.06)

[a]Reached significance after Holm-Bonferroni correction with unadjusted alpha=.05

The second exploratory analysis examined dissemination by sponsor country. Table 6.5 includes the 12 countries with more than ten sponsored trials in the sample. An expanded list of all countries (n=27) is available in Appendix 6.10. There was substantial heterogeneity in the use of different dissemination routes for results. In half of the countries with >10 sponsored trials the dissemination rates were highest on the EUCTR. The two lowest reporting countries to the EUCTR, Italy (17.4%) and Spain (14.3%), also had the lowest results availability across all dissemination routes.

Table 6.5: Dissemination by Sponsor Country

	Any Result		EUCTR		ClinicalTrials.gov		ISRCTN		Journal	
Sponsor Country	Total	# Reported (%)	Total	# Reported (%)	Total	# Reported (%)	Total	# Reported (%)	Total	# Reported (%)
USA	68	57 (83.8%)	68	49 (72.1%)	65	41 (63.1%)	0	N/A	68	45 (66.2%)
UK	61	55 (90.2%)	61	46 (75.4%)	32	14 (43.8%)	21	1 (4.8%)	61	45 (73.8%)
Germany	59	44 (74.6%)	59	30 (50.8%)	41	7 (17.1%)	3	0	59	31 (52.5%)
France	49	36 (73.5%)	49	28 (57.1%)	39	11 (28.2%)	1	0	49	22 (44.9%)
Italy	46	25 (54.3%)	46	8 (17.4%)	16	3 (18.8%)	0	N/A	46	21 (45.7%)
Spain	35	18 (51.4%)	35	5 (14.3%)	20	0	0	N/A	35	17 (48.6%)
Netherlands	34	26 (76.5%)	34	9 (26.5%)	19	4 (21.1%)	3	1 (33.3%)	34	24 (70.6%)
Switzerland	29	28 (96.6%)	29	25 (86.2%)	27	19 (70.4%)	0	N/A	29	19 (65.5%)
Denmark	22	16 (72.7%)	22	14 (63.6%)	16	4 (25.0%)	1	0	22	12 (54.5%)
Belgium	21	15 (71.4%)	21	10 (47.6%)	14	7 (50.0%)	0	N/A	21	12 (57.1%)
Sweden	21	14 (66.7%)	21	11 (52.4%)	16	6 (37.5%)	0	N/A	21	10 (47.6%)
Austria	17	15 (88.2%)	17	7 (41.2%)	10	5 (50.0%)	2	N/A	17	14 (83.4%)

6.7 Discussion

6.7.1 Summary of Findings

This chapter comprehensively examined how the EUCTR functions as a source of information about clinical trials. The first analysis examined macro-level performance of the registry and found notable gaps in some country's data quality and availability on the EUCTR that have persisted over time. Numerous major European research hubs like Spain, France, and The Netherlands have failed to maintain appropriate data for trials conducted under their regulatory purview. Additionally, the reporting of single-country trials to the registry has essentially been universally poor highlighting a lack of attention to compliance with EU reporting laws.

While an overview of systematic issues is useful, additional context improves understanding of the role the EUCTR plays in results dissemination. The second analysis examined a random sample of 500 completed trials on the EUCTR to quantify how dissemination on the registry compared to other routes. Results availability on the EUCTR (52.8%, 95% CI: 48.4-57.2) was similar to the peer-reviewed literature (58.4%, 54.1-62.7) and exceeded the proportion of results available on other registries with cross-registrations. Of the results on the EUCTR, 15% were unique to the registry and trials appeared first on the EUCTR (43.5%, 36.4-50.5) at nearly identical rates to the literature (46.6%, 39.5-53.7), and substantially more than on ClinicalTrials.gov (10.0%, 5.7-14.2). However, gaps remained as 116 trials (23.2%, 19.5-26.9) had results elsewhere but failed to submit results to the registry, and no results were located for 120 trials (24.0%, 20.26-27.74).

6.7.2 Results in Context

Prior work examining clinical trial applications to EU national authorities lends context to the protocol availability analysis.[479–481] Data on applications sourced directly from national authorities shows more consistent trends in new applications over time. While some trends are

mirrored in the EUCTR data, major deviations did not match. Dombernowsky and colleagues reported >800 trial applications per year to the French regulator in 2013 and 2014, while the EUCTR only contained 215 French protocols across both years.[480] Another analysis shows Sweden and Denmark broadly matched the EUCTR in the quantity of new applications (~200-300 applications/year), however, between 400 and 500 applications were reported in Norway from 2004-2006, yet only 76 Norwegian protocols exist on the EUCTR for those years. It is unlikely that these large discrepancies are the result of either large numbers of Phase 1 trial applications that are not public on the EUCTR or the vast majority of studies being rejected by regulators. This validates that these findings represent a genuine issue.

Issues with trial status align with prior work comparing the EUCTR and ClinicalTrials.gov. One prior study found that 16.2% of trials available on both registries had a discrepant status, the vast majority of which had an “Ongoing” status on the EUCTR but a “Completed” status on ClinicalTrials.gov.[298] This suggests a lower standard for data accuracy on completion in the EUCTR. These results show some countries have unreasonably high numbers of currently “ongoing” trials that started long ago, including the major trial hubs of Spain and the Netherlands. The registration quality results from Viergever and colleagues suggest additional issues may exist with the content of data on the EUCTR and further checks may be warranted to better describe its accuracy and completeness.[272]

As of November 2021, the EU TrialsTracker showed 76.5% of verifiably completed trials had results. However, the conservative methodology for identifying due trials will exclude trials with completion status and date issues. Transparency advocates have been similarly frustrated by these issues in their efforts to improve trial reporting throughout the EU.[482] Assessing reporting naive to any completion criteria suggests that the overall reporting percentage would be lower with more accurate data. Single-protocol trials make up 63% of all registered trials but just 43%

of all results on the registry and many of these lack required completion information. The interpretation is further supported by the search study results. Using methods to infer completion dates for trials listed as ongoing decreased the reporting rate to ~53% closer to the estimates of non-reporting of registered trials found in the most recent meta-analysis on the topic.[73]

In the only assessment of EU transparency requirements I could locate, outside of the work of myself and my advisors, Hwang and colleagues assessed reporting of trials registered on the EUCTR under the paediatric clinical trial regulations and found that among 124 completed paediatric studies assessed, “results for 63 (51%) trials were published both in a trial registry and a journal, the results for 31 (25%) trials were posted only in a trial registry, and the results for 11 (9%) trials were published in a journal but not available in a trial registry.”[299] This suggests more complete reporting to the EUCTR for the subset of completed trials taking place under an EU paediatric investigation plan.

The pooled raw data from the IntoValue studies of German academic trials registered on ClinicalTrials.gov or the German Clinical Trial Registry included 3,534 unique trials that ended between 2009 and 2017, 70.6% of which had a publication, 11.2% that reported on a registry and 72.6% reported on either source.[262,455,483] A similar study in Poland tracked 305 trials registered on ClinicalTrials.gov completed between 2009 and 2013 finding 71.5% reported in the literature, 39.3% on the registry, and 79.7% in either.[454] Even though these studies were restricted to academic sponsors and did not source trials from the EUCTR, they ended up with overall reporting rates very close to the 76% rate found in this study. Journal publications were more common in the German and Polish cohorts while registry reporting was more common in this study. When limiting this study to only those trials with a ClinicalTrials.gov registration

38.8% reported results to that registry, similar to the Polish findings and over double the rate of German sponsors.

Lastly, while the exploratory analyses in the results search were not designed to provide definitive assessments, their results are consistent with other findings. Commercial sponsorship was the only significant predictor of results availability on the EUCTR which matches the strong association between commercial sponsorship and compliance identified in the 2018 EU TrialsTracker analysis and in Chapter 5.[19] The results findings from the data quality analysis also support this finding as a persistent reporting gap between single-protocol and multi-protocol studies may be accounted for by the frequency of multinational industry-funded trials. Additionally, very low reporting by sponsors in Italy and Spain is supported by my prior work on the reporting of major non-commercial sponsors throughout Europe.[39]

6.7.3 Strengths and Limitations

The two analyses presented in this chapter both contain individual weaknesses; however, taken together they provide the most comprehensive examination of the EUCTR to date and inform the interpretation of the other. The macro-level view of the data quality analysis can identify and describe major systemic trends and variations in the operation of the registry but cannot explain how and why these variations occur, nor does it consider context outside of the EUCTR. Some of this variation will be due to trial-level idiosyncrasies (e.g., trials with very long follow-up) that could not be systematically identified from registry data alone, however the extent of between country variation is unlikely to be explained by characteristics of individual trials. Additionally, interpretations of these data must be made holistically. For instance, Romania has the highest percent of single-protocol trials reported, however it appears that many Romanian trials are simply missing from the registry and cannot be checked for results.

Examining individual trials and considering the broader context of these trials outside the EUCTR brings the use of the registry into sharper focus. Conducting manual searches for individual trials provides the micro-level detail about the fate of individual trials that could not be examined at scale. The search strategy extensively cross-referenced other registries leading to comprehensive coverage of potential results publications and more thorough and efficient matching of publications to registrations than could easily be accomplished using just the EUCTR.

Specific methods and analyses were limited by the availability of data on the EUCTR. For instance, the analysis of missing protocols was limited to only trials with tabular results and a public record. This likely included those trial sponsors most attentive to their registry entries. If single-protocol registrations, or multiple-protocol registrations without results, are missing at a higher rate than reported trials this analysis may underestimate the true extent of the issue.

The extent of missing completion date data had complex considerations for the design of the results search study. The choice to include trials with both explicit and inferred completion dates has strengths and weaknesses. Given the results from the data quality analysis concerning completion information, I felt this step was sufficiently justified to gain a more complete view of the registry. It also provides additional context in which to consider how to interpret the findings of the EU TrialsTracker. While there is certainly the possibility that this method introduced error in the analysis, mainly by including ongoing or withdrawn trials that could not be identified as such, this did not appear to be a major concern given the conservative method for deriving completion dates and inclusion criteria.

While none of the trials with inferred dates (n=147) had results available on the EUCTR, 101 (69%) either had a cross-registration supporting the trial's existence or had results available in

the literature. Ideally, if a trial withdrew and never occurred, or was still ongoing, this would be clear from the trial registration. If the comprehensive search strategy used in this analysis could not identify the status of these trials, it is unlikely a search strategy for a systematic review could have done so short of successfully contacting the authors. Uncertainty about the current status or ultimate fate of a trial could lead to wasted effort and time by reviewers in trying to locate expected results that do not exist.[484] The methods used here to infer trial completion would far exceed those expected of a typical literature search.

Additionally, this method avoids the potential selection bias of the protocol availability analysis. Restricting the population to only those with exact end dates includes only trials with the best managed data, and therefore possibly the most likely to report. The lower reporting rates among trials with inferred end dates could be indicative of this disparity in overall reporting behaviour. However, inferring end dates also makes assessing metrics like time to publication, as in Chapters 4 and 5, difficult. While these results provide confidence that these methods make reliable binary determinations as to whether results should be expected, they lacked sufficient precision for further analysis (i.e., days from completion to publication). Furthermore, since the EUCTR only added results reporting capabilities in 2014, and experienced major technical issues during the first 18 months,[485] there was limited scope to examine the EUCTR's place in the timeliness of dissemination in this study.

Resourcing was also an issue as I have not yet been able to meet my pre-specified goal of dual-searching at least 50% of the sample. I am working to address this prior to journal submission. However, it is promising that among the 20% of trials that were dual-searched, discrepancies were minimal. Given these resource limitations, and the lack of reliable contact information provided on the EUCTR, I also chose not to conduct any outreach to study teams about results as is sometimes done in similar studies.

6.7.4 Implications for Policy and Practice

EU countries are a major source of medical research globally and their registration scheme is tied directly to national and EU regulations.[158] Documenting basic trial details should be ensured through routine regulatory processes.[175,182,185] Providing accurate data to the EUCTR fulfils both ethical and legal obligations. As a primary member of the WHO International Clinical Trial Registration Platform, the EUCTR commits to "make all reasonable efforts to ensure that the data registered is complete, meaningful, and accurate."[58] The issues found in this analysis ultimately frustrate efforts to use the EUCTR as a canonical data source for trial information in Europe, despite its considerable promise.

Conflicting information on trial completion and missing results creates additional burden for users in analysing, interpreting, and acting on data from the registry. Missing public registrations may also complicate publication for researchers who rely on the EUCTR to satisfy journal requirements for prospective registration, further undermining confidence in its use.[486] Transparency issues do not end at the EUCTR as the EMA has also failed to meet deadlines for making trial information supporting marketing authorisations available under Policy 0070.[487] When regulators cannot ensure basic record-keeping requirements are fulfilled, it undermines trust in their other capacities.

The information pipeline between trial sponsors, national regulators, and the EUCTR appears to have been disrupted across multiple countries including the Netherlands, which is now home to the EMA. It is unclear whether these issues originate with the regulators, sponsors, or some combination of both. As described above, data on trends in clinical trial applications to various national regulators does not support the year-over-year fluctuations in new trials on the EUCTR seen in some countries. Other anomalies exist, for instance, it would appear impossible that

Romania - the 6th most populous country in the EU - only approved 239 clinical trials since entering the Union in 2007. A search of ClinicalTrials.gov for interventional drug trials in Romania first registered over the same period returns >1900 records as of March 2022.[aa] In the UK, delays in public protocol availability were caused by lack of administrative staff for data entry. Once these staffing issues were resolved, protocol availability improved as did updates to completion information.[488–490] It appears protocol availability issues largely originate at the regulator when they fail to act on required information provided by sponsors.

Issues with the provision of completion information are more complicated to understand from afar. End of trial documentation is required as part of the EU regulatory process, but it is difficult to know whether the gaps originate with sponsors failing to submit the necessary paperwork or regulators failing to act on paperwork after it is provided – either would be concerning. In the best-case scenario, the proper paperwork is archived with regulators but has simply not been acted upon. Addressing these issues could be rectified through improved record-keeping efforts. Regular audit cycles from both national regulators and the EMA, like the analyses presented here, would allow for timelier follow-up of missing information from either sponsors or national regulators.

While failure to provide results information ultimately falls to trial sponsor, since they upload results directly to the EUCTR, regulators can play a more active role in promoting and following-up on reporting as envisioned by the guidelines.[182] Extrapolating the rates of non-compliance found through manual searches to the entire population of trials that either are, or are very likely to be, completed suggests thousands of additional trials may be unreported beyond those

[aa] The current count of all interventional drug trials on ClinicalTrials.gov with a Romanian location first registered between 1 January 2007 and 1 December 2020 is available at https://tinyurl.com/2p8jzy3s

already documented on the EU TrialsTracker. For many of these the EUCTR would represent the first, and often only, place that results would appear.

While the EMA has conducted some outreach on reporting, national regulators may be better positioned to act within the local regulatory context.[491] The Heads of Medicines Agencies (HMA) organisation, a network of EU regulatory leadership, may be an effective partner for coordinating improvement and sharing of best practices between regulators. The HMA has recently announced plans to further encourage reporting to the EUCTR in response to external pressure.[492,493] The Austrian regulator conducted sponsor outreach concerning the results reporting requirements and has seen subsequent increases in results submissions.[494] The MHRA's work to address issues has been documented and could aid other national authorities in understanding how their processes could be improved.[495] Ultimately, flexibility in working with sponsors outside rigid bureaucratic rules, especially in rectifying data from very old trials, may be warranted to improve data quality on the EUCTR.

The current EU reporting guidelines operate under a "soft requirement" approach in which reporting is "mandatory" but relies on voluntary compliance without ramifications for non-reporting.[189] To date, the pre-Brexit UK parliament has been the only government to directly pressure sponsors to report results under these guidelines with notable success.[39,496] This may change as new EU regulations are phased into effect through 2025. The new regulations include provisions that specifically empower EU member states to implement sanctions for non-compliance.[185] Denmark and Belgium have already implemented policies targeting non-reporting sponsors under these provisions.[190,497] Recent actions for non-reporting by the US Food and Drug Administration provides further evidence for the effectiveness of enforcement activities.[349] Institutions should take proactive steps to ensure they are able to monitor and access the results of sponsored research and that compliance with reporting requirements is

built into standard procedure. In just this sample of 500 trials, there were two trials in which a sponsor, in lieu of a results submission, declared they could not locate any record of results.[bb]

The new EU CTIS trial portal launched in January 2022, but the EUCTR should not be neglected as an important source of clinical trial information. The corpus of registered trials from 2004 through the phasing out of new EUCTR registrations in 2023 contains information on thousands of trials of treatments in wide use today.[498] While the new portal promises more streamlined registration and approval processes across EU locations, national regulators will still play an important oversight role.[29,499] Individual countries will be empowered to sanction non-compliant sponsors.[185] Key learnings from the implementation of the current clinical trial regulations should inform internal stakeholder processes moving forward and ensure adequate resourcing for monitoring of data quality and results reporting for regulated trials.

However, even within the context of this limited compliance environment and concerning data quality issues the EUCTR may be useful as a source of trial information for metaresearch and evidence synthesis. Overall reporting, and first results availability, matched the literature and of 380 trials with results, 14% were only available on the EUCTR. Searching of registries is considered best practice when compiling systematic reviews[244] and has been shown to aid in identifying additional trials compared to the literature.[66] While the size and functionality of ClinicalTrials.gov makes it indispensable for metaresearch, the EUCTR should not be overlooked, especially for studies originating in Europe. Reliably having timely results available in a single open access database would be valuable to various stakeholders.

[bb] Trial IDs 2007-001377-28 & 2006-000945-20

In one recent example, two controversial Phase 3 trials for the Alzheimer's treatment aducanumab did not have to be reported under the FDAAA 2007 until after they received their approval in June 2021. The drug's maker, Biogen, submitted results to ClinicalTrials.gov that month but they did not become public until September 2021. [cc] Results were published in the literature in March 2022.[500] However, both trials had detailed results available on the EUCTR (2015-000966-72, 2015-000967-15) by November 2020 since no delays for results of unapproved therapies exist under EU regulations.[dd]

Lastly, one key methodological takeaway from the results search is the value of including Google Scholar as a method to connect trial registration to publications via trial ID searches. Recent studies assessing the publication of registered trials were mixed as to whether they used MedLine via PubMed alone[264,297,464,501], or in addition to Google Scholar.[459,502,503] However, the PubMed search functionality is limited to the metadata held in the database which does not include the full text. Google Scholar, however, has more complete full-text parsing available. Since trial IDs are often not attached to a PubMed record,[504,505] especially for older trials, but may be included in the publication, Google Scholar offers more efficient results searches. While not formally assessed in this analysis, in our final dataset 90 of the 292 (30.1%) published results were found via Google Scholar, second to only those linked directly from their ClinicalTrials.gov record (40.4%) which is usually derived from automated links to PubMed.[506] Direct searches on PubMed for trials not linked through ClinicalTrials.gov yielded 47 (16.1%) additional results. Based on this, and my work detailed in Chapter 4, I highly recommend future studies linking registrations to the published literature include Google Scholar in their search strategy.

[cc] Trial IDs NCT02477800 & NCT02484547
[dd] Trial IDs 2015-000966-72 & 2015-000967-15

6.7.5 Implications for Future Research

Understanding how the content of registrations and results on the EUCTR compares to other sources would provide further evidence as to its utility. Analyses comparing ClinicalTrials.gov results to the published literature have found improved reporting quality on the registry, especially for adverse events.[251,252,254,255] Similarly assessing EUCTR's tabular results format would provide valuable context for reviewers and timely feedback to the EMA as they consider the results format of the new Clinical Trials Information System (CTIS) registry. This would all be a natural expansion of my existing TrialsTracker work.

Many of the issues detailed in this chapter originate from poor practice by EU member state regulators and the EMA. This underscores the need for a robust system of regulatory sciences in the EU. The US FDA defines regulatory science as research that develops "new tools, standards and approaches to assess the safety, efficacy, quality and performance" of regulated products.[507] The complex regulatory environment of the EU, in which power is held by both centralised and decentralised actors, could benefit greatly from further research that aims to gather, test, and disseminate best practices for regulators and institutions throughout the continent. Investment in practical research that monitors and informs regulatory practice could help to avoid many of the issues highlighted in this chapter. The EMA has dedicated substantial resources to training and educating stakeholders about the technical aspects of the new CTIS registry.[508] Academic and civil society colleagues have led efforts to educate and share best practices among sponsors.[509–511] The next step is to invest in generating evidence on how best to implement and manage these systems across member states. Chapter 7 of this analysis represents one effort to understand how transparency of clinical trials occurs at the institutional level and disseminate key learnings to improve practice.

If public oversight of clinical trial reporting fails to take hold under the new EU regulations, then it will be essential to once again develop public accountability measures to audit and provide feedback to sponsors, regulators, and the public. I am well positioned to lead the creation of a new version of the EU TrialsTracker that ensures ongoing public assessments of compliance in the new CTIS system. As with the current EU TrialsTracker, this will allow for ongoing monitoring and facilitate opportunities for further analysis of the EU clinical trials landscape. The exploratory analyses in this chapter provide immediate starting points for more extensive analyses in the new system around country-specific reporting practices.

6.8 Reflection

A common anxiety for an early career researcher is the need to come up with new and interesting research questions. Building on my prior EU TrialsTracker work to develop two additional research questions has helped to build confidence that I can sustain an ongoing and comprehensive research programme. The studies in this chapter also helped me to develop core skills as a researcher. The data quality study involved thinking deeply about how to visualise variation across location and time without overburdening readers with figures that are either too busy or too abstract. This involved self-teaching, research, and iteration. In my publication search study, I had to think comprehensively about all aspects of a project from creating the study protocol and search strategy, to how the data was extracted, to managing the time of my colleagues who volunteered to help.

I also believe there is an inherent value to conducting hundreds of publication searches between this Chapter and Chapter 4 of my thesis, especially relatively early in my career. While this could be tedious at times, the sheer amount of exposure to the ways trials are published in the literature, and how that relates to registration, is invaluable for building intuition and expertise within the area. I was able to file away examples of best and worst practice and begin

to think about future research questions. Transparency issues and research integrity issues are often discussed in abstract or summary terms and being able to point out how they occur in practice is incredibly valuable both individually as a researcher and in the communication of these concepts to others.

6.9 Conclusion

Chapters 5 and 6 have provided a close examination of transparency practice in the US and EU. Requirements such as these are increasingly raising the profile of registries as a dissemination route for trial results. However, gaps in data quality and reporting on both registries leaves room for improvement, specifically around how regulators monitor compliance and feed information back to sponsors. Sponsors of clinical research also share in the responsibility of educating themselves and their investigators about transparency requirements. Chapter 7 will examine how one group of sponsors, public research institutions, have functioned within the regulatory framework of the UK.

6.10 Chapter Summary

- Issues in the routine management of the regulatory process in some EU countries have impacted the quality and availability of public clinical trial data on the EUCTR, compromising its use as a tool for transparency and accountability.
- Despite these issues, the EUCTR may still hold value as a source of results compared to the literature and other registries. Results appeared as frequently on the EUCTR as they did in the literature and around one-fifth of the results on the registry were unique across the dissemination routes examined.
- There will be opportunities to better manage transparency under new EU trial regulations, however the EUCTR should not be neglected or discarded as it holds a

corpus of trial information covering the past 18 years of research and development on treatments from throughout the continent.

Chapter 7: Clinical Trials Transparency at UK Public Research Institutions

A qualitative interview study

This study was preregistered on the *Open Science Framework:*

- DeVito NJ. Trials Transparency at UK Public Research Institutions. *Open Science Framework* 2020; published online November 25. https://osf.io/3r296

7.1 Chapter Rationale and Overview

As established in Chapters 5, 6, and prior work,[19,39] non-commercial sponsors fare worse at reporting under regulatory requirements than their industry counterparts; however there is sparse evidence attempting to further understand why this occurs. This study aims to use qualitative methods, specifically semi-structured interviews, to examine the transparency practices of public clinical research sponsors in the UK. This addresses the final research question of my thesis examining how institutions manage their trial transparency responsibilities.

Conducting semi-structured interviews with research governance and trial management professionals provided an opportunity for close examination of institutional policy and practice. The experiences, perspectives, and opinions of these key stakeholders offer insights into many of the issues documented throughout this thesis and my career in transparency research. Focusing on UK institutions offered practical benefits for recruitment; however, it was also a compelling setting in which to explore these issues. The UK is a leader in global clinical research and, until recently, a member of the EU leading to interactions with the major global clinical regulatory regimes.

Particular attention has been paid to issues in clinical transparency by political and civil society stakeholders within the country in recent years leading to robust reporting behaviour by UK non-commercial sponsors compared to their peers in Europe.[39] Understanding the steps taken to

accomplish this, and how things stand to change under a newly independent regulatory regime, is a worthy topic of exploration and a fitting capstone to my thesis. This study provides valuable perspective for a country working to define a new, independent clinical research environment.

7.2 Introduction and Background

7.2.1 Introduction

When assessing registrations on the EU Clinical Trials Register in Chapter 6, the UK led the EU with nearly 11,000 registered protocols and matches it's major European peers, France and Germany, with over 20,000 registrations on ClinicalTrials.gov as of early 2022.[156] An estimated £4.8 billion was spent on health research in the UK in 2018 and improving investment in life science research and development is a key aspect of the country's industrial strategy.[512,513] It is essential that this crucial sector operates within a robust and transparent regulatory environment.

7.2.2 Trials Transparency in the UK

During an inquiry on research integrity in 2017 and 2018, the House of Commons Science and Technology committee (SciTech Committee) took evidence on trials transparency and produced a stand-alone report.[192,514] The launch of the EU TrialsTracker in Autumn 2018 put a spotlight on UK institution's performance on EU trial reporting requirements. While the UK fared better than their peers, substantial gaps remained: only four major non-commercial sponsors in the EU reported at least 50% of their due trials, three being UK universities (i.e., Oxford, Dundee, & Leeds); 11 UK universities and NHS Trusts were among the worst performing large institutions.[19] These findings drew even more attention from the SciTech Committee and throughout late 2018 and early 2019, Chair Norman Lamb, MP, would send letters to each UK public University and NHS Trust reminding them of their responsibilities under EU guidelines.[496,515]

The Committee held follow-up hearings in which leadership from both high and low performing institutions on the EU TrialsTracker, along with representative from the MHRA, HRA, and AllTrials Campaign were called to testify.[489] Prior to the follow-up session, I co-wrote an evidentiary submission with my colleagues from Sense About Science and AllTrials tracking the substantial progress made by UK institutions in the months following the letters (Box 7.1).[446,516,517]

Box 7.1: Except from Written Evidence to Science and Technology Committee by Sense About Science on Behalf of the AllTrials Campaign.

> Reporting rates for both UK university-sponsored and NHS trust-sponsored clinical trials increased between January and October 2019. In January 59.7% of trials sponsored by UK universities that were due to have results on the EU clinical trial register had reported. In October 2019 72.1% of UK university-sponsored due trials had reported. In February 2019 only 35.4% of NHS trust-sponsored due trials had reported results onto the register and in October 56.3% had. The overall reporting rate for all due UK university- and NHS trust-sponsored trials rose from 48.1% in January to 63.9% in October 2019. This of course means that over a third of these trials (36.1%) are still going unreported.
>
> For comparison, across all trials with at least one UK sponsor the current reporting rate is 70.8%. Across all non-commercial sponsors on the EU Clinical Trial Register reporting currently stands at just 30.5%. This rate is bolstered considerably by the increase in reporting for UK non-commercial sponsors. If only non-commercial trials without a UK sponsor are considered, reporting throughout the rest of the EU is at just 12.7%.

A later audit study I conducted with colleagues in Spain showed that the UK continued to stand out in compliance with EU guidelines compared to their European peers as the British institutions assessed had a reporting rate of 94%.[39] Sponsors from the next best performing country, Belgium, reported just 69% of due trials. The UK also had very low rates of issues with registry data, consistent with findings from Chapter 6. Data quality issues were also raised by the SciTech Committee and were promptly addressed by the MHRA.[518] Table 7.1 shows major sponsors (>=50 registered trials) in the EU TrialsTracker reported in January 2018 and February

2022; all UK sponsors exceeded 80% reporting rates and five institutions had perfect compliance.

The Government released their official response to the Committee's transparency report in February 2019. Appendix 7.1 summarises the recommendations of the committee and the responses from the Government.[519] In short, the Committee recommended an increased commitment from the Government to transparency in clinical research with an emphasis on using the HRA to drive improvements in the space. The recommendations would prove influential as named organisations like Universities UK and the HRA acted.[520] The HRA's primary response was the "Make it Public" strategy addressing many of the committee's recommendations. The strategy was finalised following public consultation and adopted in February 2020. Box 7.2 reproduces the headlines of the ten point strategy.[193]

In January 2021, the UK fully separated from the European regulatory infrastructure and the MHRA became the country's sole independent medicines and device regulator. Trials that were formally regulated, submitted, and registered, under the EU system would now be submitted directly to the MHRA and registration, a condition of ethics approvals in the UK,[521] would no longer occur automatically via the EUCTR for CTIMPs. The Make It Public strategy has begun to come into effect including public audits of registration, combined HRA/MHRA review, and automatic registration of CTIMPs on the ISRCTN as part of the ethics process with plans to extend automatic registration to all clinical trials in the near future.[522,523]

Table 7.1: EUCTR Reporting of Major UK Sponsors under EU Guidelines

Sponsor	January 2018	February 2022
University of Dundee	82%	100%
University of Oxford	76.9%	91.9%
University of Leeds	50%	98%
University College London	45%	95.6%
The Royal Marsden NHS Foundation Trust	40%	82.8%
Newcastle upon Tyne NHS Foundation Trust	28.6%	92.9%
Imperial College London	26.3%	94%
King's College London	18.2%	98.6%
University of Birmingham	15.4%	100%
Guy's and St Thomas' NHS Foundation Trust	12.5%	94%
NHS Greater Glasgow and Clyde	7.7%	100%
Belfast Health and Social Care Trust	6.2%	82.2%
University of Nottingham	5.9%	100%
Manchester University NHS Foundation Trust	0%	100%

Data taken from the EU TrialsTracker.

Box 7.2: UK Health Research Authority Make It Public Strategy

Make transparency easy by:

1. Being clear about what we expect of sponsors and researchers and what they can expect of us
2. Supporting good practice through guidance, support and clear communication
3. Having a high-quality, interconnected research approvals system
4. Reminding researchers and sponsors when reporting is due.

Make transparency the norm by:

5. Working with research funding bodies and other regulators to make sure that expectations around research transparency are consistent and aligned
6. Rewarding and celebrating good practice and highlighting poor performance
7. Taking action where researchers and sponsors do not fulfill their research transparency responsibilities.

Make information public by:

8. Ensuring that all clinical trials taking place in the UK are registered, unless the sponsor has permission to delay this to a later stage
9. Publishing or sharing accessible information about individual studies and their findings
10. Working with partners to ensure that information for the public is easy to understand.

In early 2022 the MHRA opened a consultation on proposals for legislative changes for clinical trials including a number of transparency provisions to guide the further development of a new, independent UK regulatory paradigm for clinical research.[524] The “research transparency” section of the consultation asks if the new legislation should explicitly require the registration of trials, the reporting of summary results within 12 months of completion, and the reporting of trial findings directly to participants.

This rapidly evolving UK regulatory environment provided the setting for this study. All interviews were conducted amid these developments from late-2020 to mid-2021 and offer a window into the way institutions have reacted to, prepared for, and changed as a result of these various new requirements, pressures, and challenges. As the UK works to further define and develop their newly independent regulatory scheme for clinical trials, including transparency issues, this study compiles valuable insights and experiences from key stakeholders at UK public research institutions.

7.2.3 Prior Research Assessing the UK Trials Transparency Environment

The transparency advocacy organisation TranspariMED has published three short case studies detailing how institutions manage the transparency of their trial portfolios.[448,525,526] These touched on how to manage reporting to the EU or US registries, including common barriers and tips to overcome them. Points raised across the case studies were reporting challenges for older trials, central governance oversight of registry access and registrations, and difficulties with the EudraCT reporting format. These case studies were very influential in planning this study. The insights from these high performing universities were interesting and useful to the broader trial community and I believed they warranted a systematic, and expanded,

examination. TranspariMED has continued to publish resources and run events to aid the community in improving their reporting behaviour.[527]

In addition to the EU TrialsTracker other audits of UK transparency policy and practice have been published in recent years. The student advocacy group Universities Allied for Essential Medicines audited the strength of transparency policies from 20 top UK universities. There was a substantial improvement in the strength of policies from 2018 to 2020 however just 6 institutions had a perfect score. The authors concluded that improvements in policy and reporting were likely in response to the attention from the SciTech Committee.[236] The same group has shown that UK universities do not routinely report results for trials registered on ClinicalTrials.gov.[528]

Simon Kolstoe at the University of Portsmouth has led two studies auditing UK transparency behaviour. The first focused on reporting of studies that completed in 2010-2011 from a single UK REC. In total, 52 (32%) of 116 studies with matched ethics applications had a results publication. The authors considered these findings indicative that ethics committees "are in a good position to detect…bias due to their unique access to original research protocols."[529] Kolstoe and colleagues also audited the registration behaviour of all clinical trials that received a favourable HRA ethics opinion in 2016. Of 1,014 trials, 397 (39%) were CTIMPs automatically registered in the European system, 18 (2%) were granted registration deferrals, and 415 (41%) had a valid registration located by the research team leaving 184 trials unregistered (18%).[303] A similar audit of trials supported by the UK NIHR through 2014 at the University of Oxford found registrations for all but 4 (1%) of 286 supported trials and results for 82 (56%) of 147 trials completed prior to January 2015.[530]

The HRA now publishes annual reports of registration behaviour.[531] The past three audits, covering trials given favourable opinions between 2017 and 2019, showed an upward trend in registration compliance: 81% of trials were registered from 2017, 84% in 2018, and 88% in 2019. These reports also attempt to understand why trials go unregistered. Among respondents the three most common reasons for non-registration were an oversight by the study team, not considering the research a clinical trial, and lack of knowledge about the registration requirements. These suggest poor communication of the registration requirement to researchers by the RECs and their institutions.[302,532,533]

Major UK funders like the NIHR, MRC, and Wellcome Trust have also begun conducting regular audits of registration and reporting practices of their supported research in response to commitments to new global funder standards from the World Health Organization.[226] Overall registration compliance among these funder's portfolios has been high in recent years, but some gaps with the completeness of information and ensuring prospective registration remain.[228,534–536]

7.3 Aim and Objectives

7.3.1 Aim

To assess how UK public research institutions manage the transparency of their research portfolios.

7.3.2 Objectives

7.3.2.1 Understand barriers and best practice to ensuring trials at UK public research institutions are registered and reported

7.3.2.2 Document how public research institutions have responded to the shifting pressures and requirements of the UK clinical research environment

7.3.2.3 Describe the structure and function of research governance and trial management at public research institutions

7.4 Methods

This study was approved by the University of Oxford Medical Sciences Interdivisional Research Ethics Committee (R67457) and reported in accordance with the Consolidated criteria for reporting qualitative research (COREQ) checklist.[537] All participants provided either written or verbal consent for participation, the use of audio recording, and the sharing of anonymised quotes and transcripts prior to the interview. Interviews were conducted between November 2020 and July 2021.

7.4.1 Research Team and Reflexivity

I conducted all interviews and have prior graduate level training in qualitative methods as well as experience in conducting and analysing qualitative research.[21] Interviews began with a generic introduction about the study's aim. I identified myself as a doctoral student and my prior work in this area was not disclosed; however, participants were generally aware of the TrialsTracker, and may have seen me or my advisor, Prof. Ben Goldacre, speak about the work at events. In addition, Freedom of Information requests were sent to UK universities and trusts in 2020 under my name as part of another project.

Some respondents did directly acknowledge a familiarity with my work, or my advisor's work, while others did not. Still, a dynamic in which some respondents may have been impacted by their background knowledge of my work and my academic affiliation cannot be ruled out. This could have manifested as reticence to be critical of the TrialsTracker project or less candid responses about gaps or shortcomings in transparency efforts. On repeated review of the manuscripts and interview recordings there did not appear to be any unusual responses that

stood out either within or between interviews nor any reluctance on the part of participants to disclose or discuss certain information. Respondents appeared comfortable in frankly discussing barriers they faced and any recognised connections to my past work. Assurances of anonymity in quotes and transcripts may have also aided in allowing respondents to speak freely.

7.4.2 Participant Selection

For this study, I aimed to enrol staff involved in the governance and management of clinical trials. I purposefully did not approach principal investigators, other than those who might hold relevant leadership positions, as I was interested in the institutional perspective on creating policy and managing processes. The experiences of investigators have been the focus of past research on transparency issues.[96] Participants were recruited through various avenues. First, short invitations to participate in the study were shared with the membership of the UK Clinical Research Collaboration, the UK Trial Managers Network, and a network of Russell Group clinical research governance staff via mailing lists; seven participants were enrolled through these invites.

Additional recruitment was conducted through referral by existing participants (n=1) or direct outreach via e-mail (n=6). Direct outreach was purposeful and aimed to increase institutional and geographic diversity of the sample. The response rate of my direct outreach was 55%. No participants who consented to participate subsequently dropped out while two respondents to the mailing list invites who expressed interest did not proceed to scheduling due to a lack of time. Participants were assigned an ID related to their institution type (i.e., NHS Trust or “NT”; University or “Uni”) and included quotes below use these identifiers for reference. Respondent Uni006 was assigned a “Uni” ID but works across both university and NHS trust contexts.

7.4.3 Setting

All interviews were conducted via online video conference software. The original intent of the study was to conduct interviews in-person wherever possible, however restrictions and practical barriers related to the Covid-19 pandemic made this impossible. Prior consideration of the impact of conducting interviews over video calls suggests some broad potential limitations like lower response density, compromised ability to observe non-verbal cues and body language, and the need for reliable technology.[538–541] Overall, however, I felt that the impact on the quality of my interviews was negligible when considering the context specific to this project.

From a technological perspective, very brief connectivity issues only occurred during two interviews and were quickly resolved without any negative impact. Furthermore, as all respondents were administrative and management professionals in the UK, selection related to reliable internet access or comfort with online calling, would not be an issue. Additionally, while the Covid-19 pandemic necessitated this approach, it also may have mitigated its impact. Most of my interviews were conducted six months or more into the pandemic and respondents would have had significant experience in remote communication due to lockdowns. While I do not have any in-person interviews to compare to when analysing my data, I felt that respondents were able to consistently provide both robust and lengthy responses that appeared both natural and conversational.

While in-person interviews may have allowed for increased richness of data through building rapport, additional observations of respondent characteristics, and the potential for more spontaneous elaborations that come with being in the same physical space, I believe this population, especially as they were being engaged in their professional capacities, was not greatly affected. Krouwel and colleagues concluded that in-person interviews with patients

"were marginally superior" but that this difference was "modest" and this aligns with my experiences.[540]

I was the only person other than the participants on each call. For two of the interviews an invited participant asked to include a relevant colleague, and both were interviewed in a single session. Overall, the study included 14 individual participants participating in 12 interview sessions from 11 different institutions in England, Scotland, and Wales. Participants worked in a research governance, NHS R&D, or sponsor's office role (n=9), as trial managers at a CTU (n=2), or within leadership of a CTU (n=3). The institutions represented were NHS trusts (n=3), clinically affiliated universities (n=7), a non-clinically affiliated university (n=1), and a joint research sponsorship office covering university and NHS trust activities (n=1). Most participants had over ten years of experience in positions related to clinical research and presented as female (n=11).

7.4.4 Data Collection

This study used a semi-structured interview format. Brinkmann, in *The Oxford Handbook of Qualitative Methods,* provides a particularly useful breakdown of semi-structured interview methods noting that: "It is defined as an interview with the purpose of obtaining descriptions of the life world of the interviewee in order to interpret the meaning of the described phenomena."[542] There were a number of advantages to using semi-structured interviews to address the aims and research question of this chapter.[543,544] First, my experience and expertise within the UK transparency environment naturally allowed for a more constructive and in-depth dialogue with respondents working in a niche professional space. Less time was required to follow-up on the meaning of key events and domain-specific lingo. This time could instead be used to explore areas of interest more deeply.

Compared to a more structured interview or survey methodology, a semi-structured format also allowed for more context and colour in responses. Rather than simply describing the basic mechanics of institutional policies and procedures respondents were able to provide their own personal experiences in how these were developed and implemented. Anecdotes and personal opinions were important to this analysis and the methodology allowed these to naturally emerge. Broadly examining compliance strategies for transparency would likely yield similar responses, however the variations in specifics between institutions, the motivations for change and internal pressures, and the unique barriers and approaches provided valuable insights.

The interview guide (Appendix 7.2) was developed with input from my advisors and colleagues working in transparency and qualitative research (TB, JM).[544] I piloted the guide with a colleague working in trial management at a clinical trials unit within the University of Oxford. This interview was solely for piloting and not included in the analysis. Minor changes to language and structure were made to the guide based on this feedback and piloting. Interviews were audio recorded with all sessions lasting approximately 60 minutes without field notes. Participants were asked, as a courtesy as this was not required by ethics, if they would like to review the transcripts following anonymisation to request further redaction or elaboration on any responses; of the 11 participants who requested to review their transcripts, 2 requested minor changes and 4 acknowledged no need for further changes. All participants consented to re-contact if necessary, but no repeat interviews nor clarifications were needed. No payment or incentive was offered for participation. The study aimed to recruit between 10 and 30 participants with the 14 participants enrolled falling within this pre-specified range.

The decision to end enrollment and begin analysis was decided in conversation with my advisors. They agree that I had reached a sufficient diversity in enrollment, based on factors like geography, institution size and type (i.e., universities, trusts, CTUs), and participant roles across

the organisations. I also felt that common elements and experiences were clearly emerging between participants and given the time and resources available to me to conduct my analysis, there would be diminishing returns of future interviews. Further discussion of data saturation is included below.

7.4.5 Theoretical Framework and Data Analysis

This work was conducted favouring an objectivist frame focusing on the institutional policies, procedures, experiences, and stated opinions of the respondents. An inductive thematic approach, broadly following Braun and Clarke, was used with analysis guided by the framework approach as described by Ritchie and Spencer.[545–547] Braun and Clarke emphasise the flexibility of thematic analysis across research paradigms and aims as well as its freedom from a focus on theoretical development that comes with approaches like grounded theory. Braun and Clarke's six phases of thematic analysis map well onto the steps of the framework method which provides the added benefits of clear auditable linkages between data, codes, and themes. While Braun and Clarke focus on the application of thematic analysis in psychology their piece offers a broad, and in my opinion extremely well-written and approachable, overview of the methodology.

As all interviews were transcribed by a third-party, review of the transcriptions and anonymisation provided a chance for initial familiarisation with the data.[548] Raw transcripts were stored securely in a digital format. Anonymised transcripts were then uploaded into NVIVO 1.0 (QRS International, 2020) and familiarisation continued with the development of broad open codes to group areas of interest like barriers, facilitators, and opinions on transparency.

While dual coding, as originally planned, was not deemed feasible given resource and time constraints, I shared a sample of transcripts with a colleague (JM) to discuss emergent themes,

theoretical background, and the overall thematic framework. The output from these processes was then reviewed and codes further refined into a general schema covering emergent areas of interest for indexing. This incorporated both deductive elements that naturally arose from the interview guide and emergent inductive elements from the interviews. Following indexing, I began the charting process which includes the development of respondent/code matrices to aid in comparative analysis and development of final themes.

7.4.5.1 Data Saturation

During analysis, after the final interview was conducted, my reflections on saturation were informed by Hennink and colleague's distinction between "code saturation" and "meaning saturation." [549] During codebook development, I was confident I had reached code saturation defined as "the point when no additional issues are identified, and the codebook begins to stabilize." The codebook refined from my initial broad coding schema very quickly stabilised during the indexing process. I believe this is likely influenced by the relative homogeneity of my target population (e.g., people with similar roles, backgrounds, and networks) and the semi-structured interview format guiding discussion.[550] Hennink and colleagues also defined meaning saturation as "the point when we fully understand issues, and when no further dimensions, nuances, or insights of issues can be found." Once again, in my analysis, I felt confident that a nuanced understanding of the emergent themes had adequately emerged with many themes even presenting interesting counter examples or nuanced variations of the common responses.

Hennink et al. summarised several study factors that influence how quickly meaning saturation is achieved in a given sample. Many of the factors that lean towards more rapid development of saturation were relevant to this analysis. Most importantly the study purpose was focused on providing a broad descriptive overview of transparency practice, not to develop "complex phenomena or develop theory" which led to a coding schema mostly focused on identifying

"explicit, concrete issues" about institutional practice and culture compared to analyses focused on "more subtle or conceptual issues". Characteristics of my study population, such as their homogeneity and willingness to speak in-depth about their experiences and institutional practice, led to a more rapid consolidation of meaning than might be seen in trials with a broader population or respondents providing "thinner" research data. That said, the exact institution-level idiosyncrasies in implementation provided nuance to the broad patterns of behaviour. This is the main value that I believe more interviews would have added to these data.

7.5 Results

Themes and sub-themes identified are summarised in Box 7.3 and discussed below with indicative supporting quotes. Key passages within quotes are bolded for emphasis.

Box 7.3: Major Themes and Sub-themes

Motivations for managing transparency practices as an institutional priority
- The value of transparency
- Creating a culture of transparency
- Causes of action

Institutional Strategies for Transparency
- Communicating with investigators
- Centralised stakeholder engagement
- Oversight and record keeping
- Networks of best practice

Barriers to Improving Institutional Transparency
- Resourcing and competing priorities
- Experiences with clinical trial registries
- Investigator awareness and capacity

7.5.1 Motivations for managing transparency as an institutional priority

7.5.1.1 The value of transparency

In each interview participants were asked to reflect on why transparency practices like registration and reporting are important to clinical research. Respondents most commonly cited the pragmatic informational value of registries used to avoid duplication and research waste while informing future research. Sharing results was important as it impacted future clinical practice. More abstractly, however, participants also stated that transparency activities created trust and meaning for research participants and the broader public.

…it's the principal of kind of ***good clinical practice and good governance around having robust records and reports of studies*** *and that that is transparent and available…even if the individual detail on a study isn't necessarily relevant or important or anybody's really looking at it,* ***it's more of a principal around we conduct everything that we do according to this really high standard****…participant's sign up to research understanding that that is the framework that we're working in so there is an understanding and awareness of the contribution that they're making and it's not something that's going into a black hole...I think it's also really* ***useful from a sort of UK sort of research base point of view to have somewhere where we know what's actually going on in terms of the amount of research and the nature of the research that we do****.* [NT001]

Publication bias was also specifically, but less commonly, noted as a reason for implementing transparency requirements; however, this was usually framed as having more to do with industry. In one respondent's experience, trials that went unreported in academia were those that the investigator "made a judgement that clinically it really isn't going to make much difference to anybody, even if that was out there in the world" most often taking the form of small feasibility or PhD projects with a specific interest in how the latter were managed *vis a vis* transparency requirements.

Well, I think the ***effect of publication bias is fairly evident*** *when you look at the data and the number of trials that are missing from the evidence base and I think there's been a very good job by AllTrials to make people aware of that, to publicise it. I think that it's* ***probably a bigger issue in many ways for Industry because I think the trials that don't publish in the public sector mostly, not exclusively, but mostly are trials that don't matter****…* [Uni007]

7.5.1.2 Creating a culture of transparency

Respondents were interested in creating a culture of transparency at their institutions. Research offices manifested this through clear policies and procedures that communicated expectations to investigators and increased buy-in from leadership. Respondents felt that research offices should be seen as a resource in aiding to fulfil transparency responsibilities. How these practices were implemented will be detailed in the next section on institutional strategies, but the general sentiment was consistent. This process was aspirational or in progress at some institutions while others had already seen an impact.

And on the academic side of things obviously there's always an almost instinctive resistance to bureaucracy and administrative process but in truth on this particular subject, I haven't met any significant resistance. There is an understanding that this is important. ***There's an understanding that this ultimately kind of backs up the validity of not just our data but clinical research data generally*** *and it supports people in decision making and in the design of future research. So there is support at an academic level in that sense that where they are able to,* ***where they have the appropriate administrative support, they will take their time and they will do what's required of them*** *to make sure that this is managed appropriately.* [Uni002]

Training for students, junior researchers, and staff in transparency issues, either explicitly or implicitly, was seen as important to professional development and worthy of investment from the research office. Training courses for research staff, like trial managers and research nurses, often included components that touched on responsibilities like registration as a routine responsibility even if it was not a primary focus. Modalities for training or providing support to research staff varied within and between institutions including both explicit materials and courses to more *ad hoc* individualised support.

If they're a newbie, we do quite a bit of hand holding in in the process so we advise and we tell them what they should be doing etc and we see that as if they're a new person we want to develop them along the right lines so they think the right way and understand our expectations as sponsor because we find ***if we do a lot of work on that first trial that they do, it saves us a lot of subsequent work*** *than all the others so it's learning process I'd say.* [NT002]

7.5.3.1 Causes of action

While the value of transparency was broadly recognised, the impetus for action and improvement was largely driven by discrete events like the SciTech Committee inquiry which focused attention on the EU reporting guidelines. MHRA inspection findings were also cited as a driver for internal changes that had positive impacts on transparency practice:

…so actually that information's being fed up to senior individuals at the University rather than previously not that long ago, it was really kind of just dealt with on a one to one basis between us and the research team so that's definitely of benefit and that's, you know, that's one of the good things I think also about ***the Science and Technology Committee focusing on this particular area, actually it focuses minds at the senior level within the University*** *and suddenly they become interested and say, "Oh what's going on in this area, what's happening?" and that pressure can come from down as well as us, from kind of up and across.* [Uni009]

We're trying to hit this target of getting 100 percent transparency so we will throw whatever we can at it to make sure we do it ***but we did that as a reaction to, you know, the Parliamentary issues*** *and all of those sorts of things* ***but it shouldn't ever get to that point*** *where it's just, oh someone's given us a kick up the backside so we're gonna, we're gonna spend six months on this.* ***It should be a continuous process,*** *so I think that's part of what we've learnt*. [NT003]

The SciTech Committee was often mentioned in an overall positive light. Even if their letters caused acute frustrations and complications as efforts to improve were rapidly prioritised, it also raised the profile of transparency issues within institutions and was an impetus for process improvements. Some, however, were sceptical of the real benefit of this attention and the ability for it to create lasting change and investment.

Ben Goldacre published his paper and it basically highjacked the entire agenda and suddenly the Clinical Trial regulation was about transparency and not about proportionate regulation and that actually was quite frankly damaging because, you know, the MEPs started to think about transparency which was important but started to lose the point that the whole idea of the clinical trial regulation was to reduce the level, make the regulation more proportionate particularly for non-commercial studies that weren't doing first-in-man studies and so in the end, you know, the rest is history, ***we ended up with these mandates [to] upload all this data onto the EudraCT…didn't achieve the purpose it was intended to do and that was to put data in the public domain.*** [Uni005]

It was a high level kind of enquiry and..it did give us the momentum to make some things happen…but, you know, now that's gone I feel like it was like, oh this is like the worst thing, we need to fix this right now. We're gonna send high level letters…now there isn't any of that pressure anymore but surely, it's

just as bad as it was probably. So yeah sort of take these things with a slight pinch of salt because it does seem it's a flavour of the month…but ***it hasn't changed the culture in that we're now going forward, going to have perfect records.*** [NT001]

External advocacy and audit efforts were also commonly cited as influential in promoting or informing transparency practice within institutions. Many respondents referred to their "percent" meaning the proportion of their CTIMPs reported on the EU TrialsTracker. Respondents saw the TrialsTracker as both a tool to aid in addressing their reporting backlog and a metric they could use to measure, report, and compare their reporting performance. As the letters and comments from the SciTech Committee directly referenced reporting to the EU system as a proxy for overall good reporting behaviour, addressing performance on the Tracker became a priority.

[Leadership is] obviously very much engaged…we have [a committee on research governance] so it's a question, it's something that we, that meets quarterly and we'll regularly put where we are with the sort of trials transparency, you know, that we're obviously when we got to [high performance] on EudraCT and as part of that we also worked on ClinicalTrials.gov etc trying to move get closer, you know, to [high performance] on those so it's something that we are expected to report on. [NT002]

In addition to registration and summary results reporting, some respondents discussed developing new processes to handle the sharing of underlying data from trials. This was seen as an emerging area of transparency practice requiring attention to ensure the proper sharing of sensitive data and satisfy requirements from funders and journals.

I think the place we're getting stuck now is obviously we, we report but then it's that if somebody requested your data how do you do that with it, with all GDPR issues and everything like that. I think that's where sponsors are getting a bit stuck at the moment with actually sharing it, you know, we have to put in your publication to say, you can share this data and but how that actually happens I think that's the next tricky part really. [Uni008]

7.5.2 Institutional Strategies for Transparency Practice

7.5.2.1 Communication with investigators

Respondents often offered particularly detailed thoughts on developing relationships between the research office and study teams and the role this played in improving practice. Clear and

early expectation setting, strong policies and standard operating procedures, and support systems for investigators were all commonly cited as keys to improvement.

*Within the University, **we have a quality manual** and within the quality manual **there are standard operating procedures** and as this has become more and more of an issue, we've fed more and more things into the standard operating procedures and at the time when they get reviewed, we'll just make sure it's up to date from that point of view… **I suppose the function I have is…mostly helping researchers to understand what it is they need to do and if they're struggling with the systems to provide the right support**…* [Uni005]

Various types and amounts of staff were used to manage these relationships. Research offices often had staff with responsibilities that included tracking the status of trials and reminding investigators when action was needed, or deadlines approached. Quality assurance (QA) teams and trial managers or coordinators were also seen, either individually or in tandem, as key aspects of meeting and managing transparency obligations with investigators when available.

I have a spreadsheet that has all our live studies on. Once they get completed, they move onto a new tab and I have a column for CSR deadline and then once we hit that month of when it's due, they move to a separate tab for basically uploads and that's how I track it. So I would go in there every month see what's due or due to be due soon and keep on top of it that way and at the same time all of our trials have a dedicated [trial monitor] on them and they'd be the ones who'd be emailing the investigators and chasing the data so I would just tell them, "Oh, this is when the CSRs due, please can you put a calendar reminder in your diary to chase them every month," for example and that's, that's how it's managed. [Uni006]

On occasions where the routine follow-up failed, many respondents referenced specific escalation pathways through which they, or their staff, could raise issues. Being able to escalate to a clinical or academic colleague was seen as particularly valuable for governance staff as receiving communications from a peer in leadership was considered more persuasive.

Well if they're, you know, if the Head of Research for the organisation, Professor whoever contacts them saying, "You know, we have been informed, you, we're a bit-," and it's usually phrased nicely "bit concerned about this one, apparently it's been hanging around for a while, what's going on?" then, you know, that makes you sit. [Uni007]

Sanctions for poor transparency performance were mentioned by three participants with differing appetites of support ranging from local implementation, to hesitant consideration, to strong opposition (Box 7.4).

Box 7.4: Differing Views on Sanctions

Local Implementation:
…in fact something with well we're mid-instigation at the moment is to make sure that shall we say there's potential penalties for those researchers that don't comply with our expectations and obviously the general HRA expectations. So, in other words if they don't complete appropriate transparency on a study then we'll consider not sponsoring future studies that they're leading on and that sort of thing, so we have tightened up on that. [NT002]

Hesitant Consideration:
Yeah so, we talked about the seriousness in terms of should we implement any sanctions as a sponsor. So, you know, again we do, we're not a sponsor that, we're an academic sponsor or an NHS sponsor, we don't really have the power to sort of say, we're going to cut your funding off or we're not going to do this. It's not in our best interest to some degree but, you know, there are things that we could do that might help smooth that path but we always use that as a last resort. You know, I don't, I don't really want to be in position to say we're not gonna sponsor any more of your work. We're not gonna do this and this because actually weighing it up that could be even more detrimental. [NT003]

Strong Opposition:
I'm not a heavy handed compliance person so for me I lobbied heavy against fine and heavy against heavy handed. I think it's completely the wrong approach. We have a very stressed research community out there anyway who have to deliver so many things in a tight timeframe that the last thing I wanted would put pressure into that community so I have only ever taken a very supportive route through this, and I would fight madly against any regulation, heavy-handed regulation. [Uni005]

7.5.2.2 Centralised Stakeholder Engagement

A number of respondents referenced the creation of specific committees or bodies with broad oversight of clinical research including transparency practice. These were consistently praised for their ability to bring together stakeholders from across the institution to manage improvements.

[Uni 005 CTU Leadership]: …*we've got this* ***clinical trials oversight committee which is kind of an independently chaired for research governance*** *or the trials units although we're all represented on it and it's an agenda item on that meeting so, you know, we talk about it, so we know where we're up to. [Research Governance] reports what our percentage is and it highlights any issues so it kind of closes the loop.*

[Uni005 Research Governance]: *Absolutely and it's really nice because the teams, well the oversight committee members are just supportive of the whole process of doing it. T**hey understand the hurdles, they understand that it needs to be done.** Yeah, no I think it works really, really well.*

Clinical Trial Units were also often presented, both by those within and outside of CTUs, as centralised sources of transparency information and best practice within their institutions. Some mentioned requirements that CTIMPs be conducted within a CTU as these have the knowledge, expertise, and staff resources available to manage the complexities, including the regulatory requirements, of "high risk" research.

…through our Trials Unit, they've got SOPs related to what to do and which process. So, if someone's from outside the Trials Unit we share that SOP with them and, you know, if it's the Trials Unit more than happy for us to do that. [Uni009]

7.5.2.3 Oversight and Record Keeping

Improved oversight of trial portfolios through more robust record keeping and increased contact with study teams were frequently discussed. Not previously having these procedures in place led to complications in addressing older trials. Incorrect assignment of sponsorship, loss of data, and researchers leaving the institution were all barriers that were highlighted during the EudraCT reporting push and led to new and improved processes.

So, we will see that a CTIMP has closed set a date that we then know this is the date in which that needs to be published and will arrange checks in advance of that date to individually go to those teams so that would be scheduled into the individual whose role that is, [they] would schedule that into [their] diary and make sure [they go] to those teams individually and checks those and [they] also [have] regular checks on EudraCT itself so as well as checking with individual studies also checking that where when we've sent corrections to EudraCT, where we've asked for things to be amended [they'll] have kind of regular check-ins to that to make sure that that's the case. [Uni002]

Notably, however, research offices explicitly did not own the process of interacting with registry entries and uploading results. The research office may manage the institutional registry account and access to the registry backend however only one institution indicated that they have processes in place for research governance staff to handle results reporting to a registry.

Outside of rare instances with older or otherwise problematic trials, respondents felt that this responsibility should sit with the research teams as they have direct access to the data, understanding of the technical study details, and ownership of responsibility for the trial. The research office role was limited to providing support and oversight.

Yeah, no like I say I was just trying to minimise it and I still think it'd be daft to have, I mean I already know some organisations are employing, you know, staff just to [put] data on the registries but ***the moment you do that you detach it from the actual academics doing it and then they'll just do it wrong*****.** [Uni007]

We exist in an ongoing way to oversee the process and to make sure that things are being submitted appropriately to make sure that things are being updated and published but obviously as sponsor is not appropriate that we necessarily have direct access to, you know, certainly not any identifiable data but ***it's not our role to have access to the direct data and to publish in that way.*** [Uni002]

There was also variation in how much sponsor offices were involved in journal publication. Reporting to the EUCTR fell under a regulatory requirement and so had a much clearer connection to the governance office. A common sentiment was that the responsibility of governance staff representing the sponsor ended at ensuring these regulatory requirements have been met. As journal articles are valuable to researchers for career advancement and institutional recognition, the feeling was that responsibility to publish should fall to the study teams. Respondents also felt like they didn't necessarily have control over an investigator's decisions about when and where to publish.

Then when it's just purely an academic trial that has been then pushed back from the CI and obviously it's their grant and it's their trial but they have delegated the running of to the CTU but ***when it actually gets to publication that can, you know, there has been where results haven't got out for, you know, for based on the CIs decision and it's very hard for a CTU to overturn that. You can have all the discussions and you've got the data but it's very hard to overturn that*** *and similarly it's very hard for the CTU to get recognition on those papers as well even if you're all collaborating it will be the CI you know, the researcher which will write that paper with your, with your data you've helped collect.* [Uni008]

While less common, some respondents discussed having a more active role in the journal publication process including contributing to the writing and quality control of journal articles and proactively following-up with investigators and encouraging publication.

[NT002 Sponsor Lead:] *it's still 90 per cent with the investigators but that 10 per cent, that quality control process of getting a draft manuscript, making sure that actually they, their methodology, you know, a classic example is that their methodology is as it was in their protocol and as per ethics, they haven't deviated.] Is it the correct sample size? Have they mentioned the Trust in in and the proper funding as, as per contract etc etc so it's a,* ***it's not a rigorous scientific critique of the paper but it's a quality control governance check if you like that we do and we get, we get the R&D Director to sign that off*** *don't we as well?*

[NT002 QA Lead]: *We do, and we get an independent statistician to look at the stats section to make sure that they sort of followed what they said they were going to do. I mean it doesn't go hugely in depth, but he will make, you know, reassure us that it's as it should be.*

7.5.2.4 Networks of best practice

Professional networks were seen as valuable sources of information and best practice within the governance community. Respondents referenced national membership organisations and committees (Table 7.2), local networks of peer institutions, and individual contacts with colleagues as influencing their actions and understanding around transparency issues.

I think the other side is because we want to link in with this then anything that HRA R&D forum have done around transparency, there's been a couple of workshops then some of my sponsor team have sort of gone to those and we've learnt and for example…and ***I think because we've got quite good contacts with other R&D officers, you know, that's quite useful so when we were having such difficulties around the EudraCT****, you know, we were talking to somebody at [another Trust] who who'd managed to do it and got a few tips off them and it's, so there is that sort of interaction about what, what is required and what what's changing and because it's such a hot topic then I think there is, there is sufficient information.*[nt002]

So I started sort of, and I think Twitter was a big help so I started following some Clinical Trial Managers and there is one University's doing it really well, I think Nottingham, Nottingham University. You know the UKTMN…I followed a few people as part of the UK, the Trial Manager Network and it's just really interesting to learn about sort of the whole Trial Manager, you know, this whole career development pathway that they're trying to set up and they're trying to make it like a valid career pathway for clinical trials. [Uni003]

Table 7.2: Organisations Mentioned for Networking and Support

Organisation	Website
NHS Research & Development Forum	https://rdforum.nhs.uk/
University Hospitals Association (UHA)	https://www.universityhospitals.org.uk/
Research Quality Association (RQA)	https://www.therqa.com/
UK Trial Manager Network (UKTMN)	https://www.tmn.ac.uk/
Russell Group Integrity Forum	https://russellgroup.ac.uk/
UK Clinical Research Collaboration (UKCRC)	https://www.ukcrc.org/research-infrastructure/clinical-trials-units/registered-clinical-trials-units/
UK Research Integrity Office (UKRIO)	https://ukrio.org/
Association of Research Managers and Administrators (ARMA)	https://arma.ac.uk/
HRA Research Champions	https://www.hra.nhs.uk/

Notably, the only participant from a non-clinically affiliated University referenced difficulties in receiving updates and communicating with colleagues within the clinical research governance space. In this instance, personal connections from a previous job at a major clinical research institution filled this gap.

I personally think that ***because we're not a medically affiliated university, we miss out on a lot of key updates particularly key updates from [the government]****...I'm very lucky, I'm still very closely linked to [my prior job] so they do send on that information to me. I imagine it's not the same at all for other Universities like [mine] that are in the same position but also do clinical research…I think there is a real disconnect between the overarching NHS [research organisation] information flow to non-affiliated, non-medically affiliated schools.* [Uni001]

7.5.3 Barriers to Building Institutional Transparency

7.5.3.1 Limited resources across competing priorities

Respondents commonly cited resourcing as a barrier to managing institutional compliance. Research and sponsorship offices often run ethics, finance, risk assessment, and other trial set-up and management processes on top of transparency responsibilities. The funding for governance duties was difficult to expand as it could not necessarily be costed into grants.

…if you look at sponsorship then you can't put sponsorship costs in a lot of the grants that we have and yet the expectation is that you do need staff to do the sponsorship responsibilities and so that is, you know, ***part of what we're trying to get right at the moment, making sure that actually people appreciate what sponsor is responsible for, appreciate that actually there's a cost to that so if we, we need as we want to do it because we want to sponsor studies for our researchers, we need to think how we get some money back to do that****. Obviously, we can do it through, we get some through RCF [NIHR Research Capability Funding] etc but that it's how much can you use for that sort of resource. Because not everything's NIHR.* [NT002]

One respondent expressed concern about whether increases in national requirements and attention to transparency issues will be matched by increased investment in already strained research offices.

I'm worried, ***I am worried about the investment in the HRA not being replicated in the investment in R&D or in delivery*** *because I think what we've seen during Covid is it's amazing we could approve projects so quickly and get them through ethical committee so quickly but that hasn't always meant that it's the most robust of processes and my feeling is that the ones that have picked up the mess, well not the mess but the problems are the sites and actually that's, there isn't investment into R&D. It doesn't really come through the Clinical Research Networks. It doesn't come through central resources, infrastructure funds have all basically gone away. There's no funding for that anymore but yet the amount of reporting and the amount of kind of responsibility at that level seems to get more*. [NT001]

These resource limitations extended from the research offices to the study teams themselves as clinical academics were noted as being pressed for time especially as funding often did not extend past trial completion. This means key staff like trial managers are not available to aid in ensuring trials are reported and further placing burdens on individual investigators to comply with requirements.

Yeah, so with my Trial Manager hat on for the [disease area] we're just in the middle I think we're, I'm just waiting for as I say, the final draft report, you know, publication any time hopefully in the next week or two. We've not actually properly published yet so in terms of putting the report together I kind of left that with the research team because I'm kind of like, I'm off the contract. That's kind of like, ***so that's part of the problem with Trial Managers because our contract kind is not until say the, you know, writing in the publication type of things. So, we don't really get involved in that.*** *For me anyway, you know, it's, not in my case.* [Uni004]

One clear throughline across interviews was that resource and attention of the research office will naturally be directed towards those trials that are most closely regulated and tracked. In the case of the UK regulations this meant CTIMPs. Some mentioned also grouping other types of "high risk" interventional research in with CTIMPs, but since CTIMPs had unique regulatory demands around transparency, and the attention of leadership, effort was focused on these trials.

It's all about the regulator trials, the regulators, the regulators and we're just a voice in the wilderness screaming, "But what about good science, what about good science, what about good science?" *and of course there's no penalty for bad science. So as long as they're getting grants and they're getting publications and REF is looking okay, where's the incentive to chase the grotty little trials that didn't publish. There isn't an actual incentive, and nobody is driven particularly organisationally but it's a good thing to do.* [Uni007]

This left respondents less confident that best practice around registration and reporting was being followed for non-CTIMPs trials. This was sometimes seen as a priority for improvement moving forward.

So CTIMPs 100 per cent I'm, I'm confident, you know, that that we have processes in place. Where I want to see us improve and that will be probably part of our joint research office discussions is that kind of range of projects which are interventional clinical trials which don't necessarily have all of the exact same processes. Most of them do apply but I wouldn't be as confident with those ones than the CTIMPs. [Uni009]

7.5.3.2 Experiences with clinical trial registries

Participants pointed out technical difficulties they encountered when addressing their reporting to the European registry. Accessing the EudraCT system, requesting updates be made via the

MHRA, and the inflexible tabular results reporting format were all cited as creating reporting barriers. There were also mixed feelings among those who had experience using ClinicalTrials.gov, the US government's trial registry. The ISRCTN, the UK's primary, privately operated registry, received consistently positive reviews for its ease of use and "human" customer support with only the cost to register being mentioned as a negative. Single trials registered across multiple registries, sometimes unavoidable due to regulations, was also cited as complicating oversight activities. Box 7.5 details experiences with these three registries.

Box 7.5: Descriptions of Experiences with Clinical Trial Registries

EudraCT/EUCTR:
EudraCT is not very user-friendly and it, it's just not very nice so we have made a word template of basically all the information that needs to go in there. So I send that off the investigators and say this is the format I need the data in to like the adverse events for example, it's a very specific format…I need time to upload it as well, especially if it's a big multi-centre study because you can't just attach something to you that you have to physically type in every single entry.[Uni006]

my staff were going round in circles with the EudraCT trying to get things uploaded and we just couldn't get access to some of the systems you know, we couldn't, and it was, we'd go from, you know, one, we'd get, we'd get somebody'd respond to an email and they'd say, "Go to such and such," and we'd go to them and you'd just go round in a circle just and even when we did manage to get access sometimes because it was a set field that you had to respond to and complete again, it didn't always quite match [NT002]

ClinicalTrials.gov:
I think it's quite a, a particularly ClinicalTrials.gov I personally think it's quite a clunky system. Mistakes are quite easily made on that system as well which is one of the reasons I have to go in and check and approve everything. [Uni001]

We find people have more trouble with trials.gov than…ISRCTN just because I don't know, ISRCTN they're a bit more human, you can actually speak to people.Trials.gov, from what I gather they send communications out to people and literally they can't interpret the words that are being said, they don't know what they're being asked to do and they just get, really sent up a roadblock so I prefer to send people to ISRCTN…[Uni007]

ISRCTN:
It was really straight forward. I found it very human if that makes any sense. I think my first sort of training when I had no idea what they meant. I thought 'okay this sounds like it's gonna be a bit more complex. It's gonna be a bit sort of mechanic, but it's, I think I did run into an issue when I was doing the CPMS [Central Portfolio Management System of the NIHR] registration to apply for ISRCTN and I immediately just contacted my network CRN lead. Got an immediate reply from her to say, "It's just this that and the other." There are two emails waiting in my inbox at the moment to say thanks for filling out the form. We just need a few more details on question 6 whatever and it just feels very human if that makes any sense. [Uni003]

Our recommendation for non-CTIMPs is always ISRCTN…because of the, the way in which ISRCTN can be managed that again we're able to have a university account and actually track things more appropriately. It's not an absolute rule so there are studies where for whatever reasons of visibility requirements of funders is also sometimes an issue. There are some studies who will say we particularly also need to be on ClinicalTrials.gov. We're less able to directly manage ClinicalTrials.gov and so we agree with very clear caveats to the research team that it's their responsibility to maintain those records. [Uni002]

Leaving the EU system, due to Brexit, would require the creation of new processes for ensuring registration and reporting of CTIMPs although at the time of these interviews respondents had limited experience with setting up trials within the post-Brexit UK regulatory system. Respondents in one interview were particularly critical of the focus on reporting to the EudraCT database and how this was not "fit for purpose" in delivering meaningful results information to colleagues and the public. While they were successfully able to address the issue at their institution there were hopes of an improved system moving forward that better accomplished the goals of advancing knowledge and informing the public. There was particular emphasis put on the negative impact the increased bureaucracy and effort had on investigators.

…we ended up with these, with these mandates [to] upload all this data onto the EudraCT…It might be useful to other people who want to do research and I genuinely don't know how much it's been used for that, but ***the actual system wasn't fit for purpose. It's really, really difficult to do it so it had a huge amount of bureaucracy and resource and there are so many elements of it that actually make it almost impossible to do.*** *You know, the head of our clinical trials oversight committee I think was just about having a heart attack trying to put his own work onto it and he's somebody where compliance is everything and he was really frustrated by it…I mean* ***I have honestly first-hand seen how it, just me encouraging and cajoling researchers to put results up has stopped them doing their research. It stopped them actually doing research they should be doing rather than fiddling round with the system that wasn't fit for purpose and that's really sad and I don't really want that.*** *I want them much more in the space where, you know, you do a study, you do a trial and you, you then look at what was the outcome and where's the next step, where's the next gap, how can I collaborate with other people? How can we pool results and…share the data in the right places? All of that matters and all of that will move us on as a society but* ***I'm yeah not convinced that being compliant with having it on the whatever registry is gonna do anything*** *in that direction.* [Uni005]

7.5.3.3 Investigator awareness and capacity

Another barrier to compliance was addressing awareness of transparency requirements among investigators and ensuring they had the time and support to fulfil these responsibilities. As described above, this was often proactively addressed through concerted efforts for culture change and relationship building within the institution.

I think even from when you get your funding, you know, if you knew within x, you know, months we expect to see this on a registry something to just plant the seed because obviously if they're not using a CTU, they might not be aware and it's usually when somebody says, 'Why do you need to get it registered or-?"

And then you're saying, "Because-," and you're explaining it, then they understand it, but I don't think there is knowledge like that out there. ***I think CTUs are aware and do that but then the CI [Chief Investigator[, I don't think does think so much about transparency.*** *They're just thinking more of, 'We've got to get going and we've got get the data and I want a publication but they're not you know, not thinking so much about the detail.* [Uni008]

At times, this lack of awareness led directly to consequences for investigators and their studies such as delays to enrollment and complications with publication. Box 7.6 summarises a notable anecdote from a trial manager participant exemplifying a number of the themes that emerged throughout this analysis including issues with registration requirements. Notably, the idea that prospective registration was only seen as a "recommendation" from the institution created confusion leading to negative consequences for the study. Many institutions solved this problem by tying the green light for trial enrollment directly to the provision of proof of prospective registration. Some flexibility in these requirements were noted as well as suggestions that these processes were less robust for non-CTIMPs.

*I think where we're going with this is that for the CTIMPs it's an automated process, for non-CTIMPs it's not, so our safety net that we rely on is the ethics process to basically remind the applicant and I think it's fair to say that there's a mixed response and we don't necessarily police that from a resourcing point of view, we don't necessarily have the res- we haven't directed resource to that yet for non-CTIMPs. CTIMPs certainly, non-CTIMPs less so…****what we haven't necessarily got I don't think for non-CTIMPs is that joined up approach where it triggers it so even as we're talking now, I'm thinking, you know, that's just something we would potentially add to the sponsorship request.*** [NT003]

Box 7.6: Case Study on Retrospective Registration [Uni004]

This participant is a trial manager at a clinically affiliated research university CTU with prior experience working in NHS R&D. Their first trial management role saw them joining a study six months after it began. They raised that the study should have been registered but this was not a priority.

so it's sponsor recommendation, it's an ethics recommendation so, you know, as a researcher what do you do? I mean you choose, you know, what is mandatory and you get on with the mandatory and then leave the recommendation at a later date.

A lack of clarity from the sponsor around registration of non-CTIMPs and the study team's lack of awareness around the ICMJE requirements led to the rejection at a prominent journal.

[The journal] informed us that we have to be, you know, the registry has to be done before recruitment.…you know, we were really hoping for a high impact because we want to contribute to this the changes in the standard of care, you know, and more information about this, you know, so yeah really disappointed, really but at the same time, you know, what can we do?

This led the participant to change their own behaviour and inform colleagues about the ramifications of retrospective registration of non-CTIMPs for publication. This has led to some improvements, but confusion around registration practices for non-CTIMPs and ethics requirements, appears to remain.

So yes, we're in this conundrum now hence with the new study that I've got I registered before, you know, straight after as soon as I can, with that lesson learned, very hard lesson learned.

Yes so when this happened to me I immediately informed all my colleagues in the CTU that even though for non-CTIMP, you know, studies I basically says for all studies that we're doing it has to be registered in a public register, i.e. ISRCTN or ClinicalTrials.gov, you know, depending obviously on funding. But yeah so that was, as soon as that basically happened to me, I shared that information to all and now as far as I know, you know, that is part of all studies in that CTU.

…although it's a investigational clinical trials it's still considered as a non-CTIMP so for all CTIMP, all our studies are registered under obviously the EudraCT…whereas non-CTIMP even up to now, I know there's still a lot of non-CTIMP that has not been registered.

7.6 Discussion

7.6.1 Summary of Findings

This analysis examined how public research institutions in the UK manage their ethical and regulatory transparency responsibilities for clinical research. Significant resources have been devoted in recent years to improving transparency practices among these institutions mainly in response to attention from the UK Parliament. Working with constrained resources, research governance and trial management staff have created new policies and procedures to ensure investigators are aware of, and supported in fulfilling, their transparency commitments. Trials of medicinal products, as the most closely regulated sub-category of research, consequently received the most attention from research offices. While technical, practical, and cultural barriers to improved transparency practice remain, the UK contains substantial national and local professional networks around the governance and administration of clinical research where knowledge and best practice are shared.

7.6.2 Results in Context

This work builds on findings related to transparency in the UK clinical trial research environment. The substantial increases in UK trial reporting observed since 2018 are supported by the many descriptions of investments in improving reporting to the EU registry. This provided evidence to support the hypothesis, as advanced by Keestra and colleagues, that political pressure in this area can drive changes in behaviour.[19,39,236] Descriptions of updates and changes to transparency policies match the improvements noted by Keestra and colleagues and provides additional context to the motivations and implementation of these changes.

These findings are also consistent with the TranspariMED case studies of best practice in trial reporting as the descriptions of centralised and improved trial portfolio management, technical difficulties with EudraCT reporting, and increased overall attentiveness to transparency issues

were also identified as well-supported themes in this more comprehensive sample of institutions.[448,525,526]

Many of the difficulties of managing a clinical trial research portfolio align with broader metaresearch on transparency issues. For instance, a number of studies have found issues with the reliability of data for trials registered across multiple registries supporting the complaint that this causes particular record keeping complications.[298,551] Respondents also touched on difficulties in how to report older trials that never began or terminated early. This aligns with recent qualitative work showing that investigators who had to halt trials early often failed to notify relevant stakeholders or publish results.[97] Lastly, the identification of data sharing as a activity that is starting to receive more attention from governance staff aligns with survey research of UK CTU directors that found general support of these practices but barriers to implementation around topics like confidentiality, resource, and lack of clear guidance around data sharing.[552]

The US context offers an interesting point of comparison to the UK as a country with clinical research transparency regulations. Mayo-Wilson and colleagues surveyed 366 ClinicalTrials.gov account holders at US universities and academic medical centres in late 2016/early 2017 just as the Final Rule of the FDA Amendments Act 2007 came into effect. Their findings showed substantial variation in the policies and procedures of respondents. For instance, less than half of account holders surveyed indicated that their organisation has a registration policy (43%) or a results reporting policy (35%). Responsibility for registration and reporting practice was also highly variable and predominantly split between the administrators of the ClinicalTrials.gov account and individual investigators. Most respondents indicated no internal sanctions for failures to register or report. Dedicated staff focused on supporting registration and reporting practice were rare. The authors concluded that “some organizations

were prepared to meet trial registration and reporting requirements before The Final Rule took effect, but there is wide variation in practice."[304]

These findings mirror many of the experiences described in this analysis as improvements to policies and procedures were generally not implemented proactively, but rather reactively to attention from politicians. Hesitancy around imposing sanctions, the transparency responsibilities of staff, and the division of labour between the research office and investigators were all also seen within the UK context.

Networks of best practice also exist within the US including the Clinical Trials Transformation Initiative and the Clinical Trials Registration and Results Reporting Taskforce.[437,553] Two major US academic institutions have also published overviews of their trial registration and reporting procedures in order to ensure sharing of best practice in compliance with FDAAA 2007 requirements. Both institutions describe similar transformations as those described by their UK peers including centralisation of oversight within the larger institution, re-evaluation of policies and procedures, improving communication and relationships with researchers, and the implementation of ongoing monitoring of their trial portfolio, and targeted actions to improve compliance with FDAAA requirements.[305,306,422,441]

7.6.3 Strengths and Limitations

In-depth interviews with research governance personnel allows for a level of detail and context about the UK clinical trial transparency environment that has not previously been explored. Together these findings offer a clearer view of how the governance and management of UK clinical research at public institutions has evolved and responded to new pressures in the transparency space.

While the sample was relatively small, there was a diversity of institutions represented offering perspectives on how best practices manifest throughout the space. Consistency of these findings with prior work further supports that the sample was sufficient to meaningly address the research question. However, it cannot be ruled out that those who responded to the invitations to participate were more likely to be among those with the best transparency practice. If this was the case, the best practices shared among these institutions provide a valuable resource to peers even if the extent of certain remaining barriers were understated. While the sample was limited to the UK environment there were notable similarities to prior descriptions of US governance practice suggesting some applicability within the broader trial governance landscape.

Lastly, all respondents were granted anonymity that allowed them to speak more freely about their roles and institutions. However, anonymity also limits the potential scope of the analysis to match responses to existing identifiable datasets on trial reporting or policies to provide deeper insights. For this analysis, the decision was made that anonymity would offer more frank discussions of barriers and best practice and therefore, on balance, allow me to better address the research question and aid in enrollment.

7.6.4 Implications for Policy and Practice

Efforts to reduce transparency issues, most frequently focused on publication bias, have included recommendations aimed at institutions. The Overcome failure to Publish nEgative fiNdings (OPEN) project created evidence-based recommendations focused on various research stakeholders. Their recommendations for institutions included increasing guidance and training for investigators and mandating the dissemination of results by policy as best practice.[100] Two qualitative assessment of attitudes towards publication bias also suggested increased institutional investment in training and policy changes as avenues for

improvement.[98,300] These were both identified as clear priorities driving improvements in transparency within this analysis. Many of the best practices identified within this study, such as centralised record keeping, scheduled follow-ups, and stakeholder committees offer specific examples of how to operationalise these recommendations.

Neo-institutional theory presents a useful framework to understand various mechanisms that influenced changs at these institutions. Within this paradigm, institutions are influenced and subsequently affect change through regulatory, normative, and cultural processes due to the legitimacy they confer.[554,555] Macfarlane and colleagues describe these mechanisms as "analytically separable" while tending to be "intertwined" at the empirical level and this study is no exception.[556] Respondents clearly articulated the normative arguments in favour of transparency but this was not itself enough to drive change and improvement. EU results reporting guidelines imposed clear regulatory requirements on sponsors but they did not become a threat to institutional legitimacy until the SciTech Committee emphasised their importance.

While the Committee did not institute specific coercive action, they called attention to the existing regulations and established expectations for compliance while endorsing further action if necessary. The EU TrialsTracker also appears to have influenced these changes through the cultural influences of public audit and feedback. Institutions could now be easily compared on a specific transparency indicator and reputational concerns informed leadership's response to these pressures.[433] As the norms were set, professional networks within the research governance space quickly became ways for best practice in reporting to proliferate through the community (i.e., mimetic change). While the specifics of these processes were acutely frustrating to many respondents it also appears to have improved the overall management of clinical trials and ensured that public sponsors have increased visibility into research. This

decreases the chance that results go missing in the future. Some variation in the implementation of these policies exist within institutions, but there were substantial similarities between sponsors in their structure and methods for improvement. This level of homogenisation is not unusual as organisations respond to each other while operating under the same broad environmental context.[554]

The actions of the SciTech Committee appear to be what sets the UK apart from its EU peers in addressing transparency requirements. Germany has seen similar appeals to international ethical norms and institutional reputations,[557,558] research on institutional reporting practice,[262,455] and efforts to disseminate best practice[510,511,527] but no similar political or regulatory attention. While these other forms of pressure are clearly having an effect – there have been notable increases in reporting performance in Germany – overall public sponsors collectively fall far short of the level achieved in the UK.[39] While no longer applicable to the UK context, new EU regulations will offer additional opportunities to examine how variation in regulatory attention impacts reporting performance. Belgium recently became the first country to implement the threat of sanctions for non-reporting under the new system.[190] If additional countries follow suit, there will be natural opportunities for better understanding how variation in regulatory environments impacts transparency behaviour.

Reporting of CTIMPs under EU law became a norm within the UK, however, without the attendant political and public pressures non-CTIMPs have not yet reached this status and therefore lag behind in institutional attention. In Denney and colleagues's audit of registration behaviour in the UK, of 1,014 clinical trials, as defined by the HRA, receiving favourable ethics opinions in the first 6 months of 2016, just 39% were classified as CTIMPs. A paradigm that focuses transparency compliance activities solely on CTIMPs leaves a substantial gap in how the majority of clinical research in the UK is managed including for other high risk clinical trials

like those on medical devices. With the recent steps towards universal automatic registration of all UK clinical trials, the HRA has taken the first steps in addressing this disparity. Though the initial phase of implementation will only register CTIMPs there are clear plans to extend this process to all clinical trials in the near future.[559] Choosing to more fully integrate the ISRCTN into required processes is likely to be met favourably by the UK trial community based on the preferences and positive feedback around use of the registry articulated in this analysis.

Whether or not the HRA eventually plans to implement results reporting requirements, and how this will factor into the upcoming legislative efforts around clinical research[524] remains to be seen but there is substantial opportunity to continue to further build the UK's reputation as a leader in research transparency. Additional requirements, however, need to be matched with opportunities for public institutions to access funds to further invest in governance and sponsorship activities or else they will be unlikely to meet this responsibility without sacrificing resource and quality elsewhere.

7.6.5 Implications for Future Research

The UK offers a fascinating context for evaluation of clinical research governance given the recent focus on transparency issues and the transition between regulatory regimes. The efforts that led to the country becoming a leader in CTIMP reporting metrics are valuable to investigate and document. There are considerable opportunities to build on this initial investigation and examine specific transparency practices, their diffusion within the governance community, and test the best ways to implement them. Institutional behaviours are complex and worthy of additional investigation using both quantitative and qualitative methods. For instance, the work of Keestra and colleagues examining UK institutional policy offers a starting point from which to delve deeper into how transparency requirements are operationalised and communicated and how this connects to reporting performance. Since 2020 I have collected a dataset of

institutional policies and procedures and will further examine their details including specific language, variations in implementation, and mechanisms of action.

Given that the UK has been a transparency outlier among European non-commercial sponsors, similar work should be conducted to understand and compare the behaviour of sponsors in other countries. Probing the variation in how major research institutions address their reporting backlogs in Germany and Belgium, or the reasons sponsors in France, Spain, and the Netherlands have almost completely ignored their responsibilities can offer insights into the different cultural contexts around clinical research governance, transparency, and regulatory regimes and hold key insights as sponsors prepare to implement the new EU regulations.[39]

7.7 Reflection

I consider this analysis an indispensable part of my DPhil experience. I have conducted pieces of qualitative research projects before, but never had I designed, implemented, and analysed an entire study myself. While most other parts of my DPhil shifted or changed throughout the past four years, my plans to conduct this specific analysis remained unchanged from the very first meetings with my advisors.

From a professional development standpoint, improving my experience as an interviewer and utilising framework analysis for the first time as an analytic technique were both incredibly valuable. I found that time spent reviewing the qualitative methods literature to inform how I implemented the study and my analysis to be especially rewarding.

From the time I took a course in medical anthropology as an undergraduate I have always been fascinated in the ability of mixed methods approaches to offer comprehensive assessments of complex issues. Working primarily in policy research, I strongly value having the ability to lend

context, richness, and deeper understanding to my quantitative findings through the application of qualitative analysis. Successfully designing and implementing this study allows me more confidence to employ and adapt these methods to answer new research questions in the future.

Designing my own qualitative analysis also forced me to be more reflexive about my research. Earlier, I reflected on how my research background, and that of my advisors, may have had the potential to impact responses. This was not simply a *post hoc* observation but something I grappled with throughout the entire project from designing my interview guide, to conducting the interviews, to analysing the data. It's difficult to truly know how much my unconscious biases and deeply held opinions influenced the analysis in one way or another but I gained a strong appreciation of the work that goes into being aware of this risk and reflecting on ways to try and control its impact throughout a project.

Much of the work in this thesis was built around being able to precisely identify and quantify various aspects of clinical trial registration and reporting. This chapter offers a change of pace both methodologically and conceptually. With the problems well established, my natural next steps were to ask how and why these issues tend to occur and what steps might be taken to improve them in the future. Throughout the course of my work in the trials transparency space I've heard anecdotes, opinions and complaints from various stakeholders which informed assumptions and raised questions about how institutions manage these issues. While most past studies examining the causes of transparency issues tend to focus on the investigators,[96] I felt that collecting data on the institutional perspective would offer a unique viewpoint both personally and to the broader literature. Collecting primary data and speaking systematically and comprehensively with people on the front lines of transparency practice proved an incredibly valuable experience and will no doubt inform my thinking as I move beyond my DPhil and into the next stage of my career examining transparency in clinical research.

7.8 Conclusion

Investment in the institutional governance of transparency is essential to achieving more optimal transparency practice, including the use of registries. Universities and hospitals create the environment and culture in which research occurs and share responsibility for ensuring it is performed and reported to regulatory standards. This thesis has shown various issues with reporting among non-commercial sponsors, however, facing political pressure, public research institutions in the UK have made concerted efforts to improve their transparency practice. Changes have ranged from better oversight and management of research, improved communication with researchers, and innovative strategies for ensuring compliance and best practice. The lessons earned from UK sponsors provide a template that can be adapted to aid in improving the transparency of non-commercial sponsors in other contexts.

7.9 Chapter Summary

- UK public research institutions have reacted to political attention to transparency issues by improving the way they manage the transparency of their clinical trial portfolios through a variety of strategies.
- Barriers to transparency practice at these institutions are focused on three main areas: a lack of resources to match responsibilities; technical complications with the use and management of registries; and the constraints of the ability and knowledge possessed by investigators to own transparency processes.
- Change in transparency behaviour can be instigated through both top-down political pressure along with the diffusion of norms and best practices within the professional governance community.

Chapter 8: The Current Status and Future Direction of Clinical Trial Registries

8.1 Discussion

This thesis examines whether clinical trial registries are fulfilling their promise as tools for transparency and accountability in clinical research. While the full answer is complex, the results from this thesis show that clear gaps in the quality and availability of information on registries remain and prevent them from reaching their full potential. The current global registry system is the result of substantial effort and advocacy from a wide range of stakeholders. These efforts were predicated on the idea that prospective public registration of clinical trials would have benefits for the rigour, review, and reporting of the evidence for health interventions. Taking stock of the current state of the registry system, through descriptive and applied research, demonstrates that promise exists to aid accountability and transparency. However, additional action is needed to ensure gaps in the use, management, and regulation of registries are addressed.

8.2 Summary of Methods

Within this thesis, I drew on methods and techniques from a wide array of disciplines. A guiding principle of my work has been to conduct studies that fulfil a public audit function and feed results back to the relevant stakeholders. Audit is used in various areas of medicine to improve performance by measuring current practice against clear standards.[560] Creating baselines of performance and understanding the variation in that performance between stakeholders informs future work aiming to track progress, understand why laggards exist, and how best practices can best be implemented.

Resources like the TrialsTrackers are often described as fulfilling a “naming and shaming” function, however, that was never viewed by my colleagues and I as their primary purpose.

While there are certainly public accountability benefits to these resources[433], these were primarily seen as tools to drive improvement by compiling and publicising transparency measures not available by other means. For instance, when we were designing the EU TrialsTracker, our manual grouping and curation of trials by sponsor was something most individual institutions themselves did not have available. Studies throughout this thesis serve explicit audit functions on both the micro (Chapter 3) and macro (Chapters 5, 6) level.

Collecting, analysing, and communicating my findings has drawn from a cross-disciplinary toolbox to fulfil the mixed methods approach I envisioned when starting my thesis. My prior training in epidemiology provided a framework for analysing the clinical trial registration and reporting. Survival analysis was a particularly useful tool to analyse trial reporting as time-to-event data and descriptive risk factor analysis helped explore associations that can inform future research questions.[561] Additionally, building search strategies to find trial reports, essential to Chapters 3, 4, and 6, draws from methods used in both evidence synthesis and bibliographic research.[261,562–566] Learning Python was transformational for my research as it allowed for more reproducible, efficient, and sophisticated data collection and analysis than would have otherwise been possible. Lastly, I used qualitative analysis of semi-structured interview data, drawing on thematic analysis and the framework method, to gain insights into institutional transparency behaviour.[545–547]

8.3 Summary of Findings

This chapter synthesises my thesis research to inform key recommendations to improve the global registry system so that it can better serve its transparency and accountability goals. Chapter 1 outlined the overarching goals of the thesis and details on my experiences as a researcher and Chapter 2 provided technical and historical background on the development of the global registry system and its place in the broader research landscape.

My original research spanning Chapters 3-7 covers seven individual studies. In Chapter 3, I used Juul Labs, Inc., a major e-cigarette producer, as a case study to demonstrate how registries can act as references for comparison of prespecification to published work. The results of the studies examined were not made available on ClinicalTrials.gov and other dissemination routes were found to contain incomplete disclosures of key outcomes and data. This analysis also allowed for deeper considerations of the place of e-cigarette trials within the regulatory transparency framework in the US.

Chapter 4 details my work on the DIRECCT project examining the reporting of Covid-19 clinical trials. Preliminary findings showed that among trials completed during the first six months of the pandemic the overall rate of rapid reporting was low, however, reporting was likely expedited compared to standard practice. Registries were not commonly used for rapid results dissemination. The variable quality of registry data potentially limits the precision and completeness of our analyses. The final analysis of the DIRECCT project will significantly expand the scope of these findings with a broader population of trials, longer follow-up time, and the analysis of additional trial characteristics. Together Chapters 3 and 4 show the power of the global registry system in providing access to evidence and detection of bias, but also highlights shortcomings around data quality and the clarity of regulations that govern their use.

Chapters 5 and 6 build on prior work from the TrialsTracker project focusing on the US and EU regulatory landscape. In Chapter 5 I found that reporting to ClinicalTrials.gov under the FDA Amendments Act has increased over time however sponsors are not meeting their statutory reporting deadlines. Assessing additional requirements showed higher compliance but notable variation in sponsor's ability to meet logistical and data management standards. Industry and

larger sponsors were consistently better at compliance than their academic, non-profit, and government counterparts.

Chapter 6 assessed how the EUCTR, the regulatory registry of the EU, has performed as a source of reliable information on the results of clinical trials in line with legal guidelines and requirements. Assessing data quality across the entire registry showed missing protocols and completion information was concentrated amongst a few countries however this included many of the largest research hubs in the EU. Results availability issues, however, were more widespread. A close examination of results availability reveals that, despite notable gaps, the EUCTR may function as a source of registered trial's results at least on par with the literature. However, there is significant scope to increase the utility of EUCTR through continued promotion of routine reporting to ensure the results of trials enter the public domain.

Lastly, Chapter 7 assesses how UK public research institutions have approached and improved the transparency of their clinical trial portfolios. The UK has stood out as a leader in ensuring compliance with EU reporting guidelines despite overall poor performance throughout Europe. This study showed that this is a function of political attention leading to discrete changes in policy and practice at these institutions. UK universities and NHS trusts have initiated various improvements, including centralised stakeholder committees, more direct sponsor office oversight of trial responsibilities, and increasing awareness of reporting requirements among investigators. Taken together, these three chapters present a broad view of clinical transparency regulation and practice within some of the highest research output countries in the world. The qualitative findings of Chapter 7 add much valuable context from institutions who are directly dealing with the requirements assessed in Chapters 5 and 6.

The overall aim of this thesis was to assess the current structure and function of the global registry system. Chapters 3 and 4 clearly demonstrate the power of registries in the assessment of evidence and reiterate their value, while highlighting the limitations that insufficient data quality can impose on these efforts. Chapters 5 and 6 show how regulatory regimes in the US and EU have attempted to address some of these shortcomings and ensure the results of regulated trials are reported. Their impact has been notable but incomplete as gaps remain in ensuring that regulations are clearly and consistently implemented, promoted, and actively monitored to ensure compliance. Lastly, Chapter 7 provides context to these shortcomings and offers evidence from the UK public research sector on how issues in the implementation of transparency policies manifest and the best practices for overcoming them.

8.4 Implications for Policy and Practice

The data presented within this thesis highlight the current registry landscape and provide insights into where action is needed. Revisiting each of the major research questions of my thesis, detailed at the end of Chapter 2, provides a framework in which to consider what improvements are needed and which stakeholders should act.

8.4.1 How do registries function as tools for transparency and accountability?

The advocates for a global system of clinical trial registration saw the potential for clinical trial registries to serve a myriad of roles within the research landscape including reducing and better recognising biases. In many ways this vision is being met. Thousands of clinical trials, and other clinical research studies, are registered each year, often prior to commencement. The Covid-19 pandemic alone has seen over ten thousand studies registered within just a two year period as captured by the ICTRP.[147] Applying even limited amounts of standardisation and curation to this magnitude of data offers a tremendous resource for researchers. It allows quick and transparent access to existing evidence and raw data that can be examined to answer and inform various

research questions. Their use for accountability is also essential as a registration publicly notes the existence and details of a trial. This allows for assessments of individual studies for *post hoc* changes (like in Chapter 3) and audits of entire classes of trials (as in Chapters 4, 5 and 6). When registries offer the ability to host detailed results, they can also serve as a method for rapid dissemination independent of the journal publication process. Unfortunately, Chapters 3 and 4 do not support that this is currently the norm.

However, some of these functions would be best implemented and administered at the systems level rather than as independent research projects. Much of the research in this thesis is filling gaps that should be filled by other actors in the space. Regulators should better manage compliance with laws and requirements when they exist. As the ICTRP currently guides the development and direction of national registries, there should be ample opportunity for other countries to consider how to more deeply integrate trial registries into their regulatory landscape and ensure trials are registered and reported in a timely manner.

Research institutions, like universities, funders, and companies, should be managing transparency of their clinical research portfolios to align with both ethical and legal standards. Furthermore, individual researchers need to take their transparency responsibilities as vital to the rigour of their research. Lack of attention at any of these levels is likely to lead to the continuation of issues identified in this thesis such as poor reporting compliance and insufficient data quality. Findings from Chapter 5 and 6 both show that regulation alone cannot ensure that the registry data are kept complete and accurate over time. Journals also need to improve their consideration and methods for dissemination of null findings.[567–569]

Neglecting these issues has broader knock-on effects. If registrations are not properly maintained, they become easier to dismiss and disregard and less essential to maintain, which

leads to a negative feedback loop that undermines the entire system. The COMpare project documented this first hand. This project involved sending letters to top journals about undeclared outcome reporting deviations in published trials reports. The team often relied on registry data to check prespecified outcomes if a pre-study protocol was not publicly available. While all five journals assessed support CONSORT and ICMJE guidelines around the registration and reporting of clinical trials, some pushed back considerably on the methods of the project including criticisms of using registries as tools for accountability. Editors at *Annals of Internal Medicine* dismissed registry data because registries "...do not routinely monitor whether the data in the registry match the protocol, and may not be updated when the protocol changes" and that "registry information can be incomplete or lack sufficient detail" while including "vague and erroneous entries." An editor at *JAMA* stated that "inaccuracies in the trial registration documents are more of an issue for the individuals overseeing the trial registries."[6]

Both journals are ICMJE board members giving them the significant power and influence to ensure registry entries are kept up to date, checked for deviations, and properly declared as a condition of publication. Instead, they have chosen to deprioritise registration as a tool to inform editorial decision-making. This sends a powerful signal to trialists and institutions about how much they should prioritise registration. The ICMJE's decision to require prospective registration was hugely influential but may ultimately end up a half-measure if ignored in practice.[301] Transparency responsibility does not end simply with registration. A registry entry should be seen as a canonical overview of how the details of a trial evolved over time. Concerted systematic efforts are needed to raise registration from a check-box activity to an ongoing routine responsibility. Writing in response to my piece in *JAMA Internal Medicine* assessing FDAAA compliance, Drs. Deborah Zarin, former head of ClinicalTrials.gov, and Robert Califf, former (and now current) FDA commissioner noted that:[426]

…out-of-date, incomplete, or inaccurate trial information can distort understanding of the evidence base and the research landscape…As a public resource, the trial registration and results information in ClinicalTrials.gov is only as good as the quality, accuracy, and timeliness of the data submitted by researchers and trial sponsors.

8.4.2 How are regulatory systems that require registration and reporting of clinical trials functioning?

The use of registries as regulatory tools has been most complete in the US and EU. Under both regulatory regimes certain types of interventional medical trials are required to register and report the results of their clinical trials. These requirements have led to more consistent registration and reporting practice. Prior work has shown increased reporting under FDAAA, even prior to the Final Rule and large commercial sponsors are excellent at compliance, as demonstrated in Chapters 5 and 6 and in prior work, increasing transparency into their research portfolios.[19,39,296,297,419] The presence of regulations has a demonstrable effect on stakeholder behaviour. Under the FDAAA the one-year reporting deadline led to a sharp spike in reporting behaviour around the deadline (Figure 5.3a). In the EU, even with various issues in the implementation, the very existence of reporting guidelines provided the fuel for the UK SciTech Committee to pressure sponsors to improve reporting. However, for either system to fully meet their transparency goals non-compliance must come with at least the potential for real, but fair and proportional, consequences.

The FDA has stated multiple times that they value voluntary over coercive compliance with the FDAAA. The political environment and limited resources may indeed make this the most viable regulatory option. However, enforcement cannot become so lax that it undermines the credibility of the entire system. It took 17 years for the FDA to send their first official public notice of noncompliance to a sponsor under the FDAAA.[349] It has yet to be seen if this signals the beginning of more active enforcement activities. The re-appointment of Dr. Robert Califf, a vocal

proponent of transparency, as FDA Commissioner may have real ramifications for how FDAAA is implemented at the agency.[426,570] Yet the slow pace of enforcement has likely already led to low awareness of requirements and atrophy of the resources needed to address reporting requirements where they did exist. The disappointing reporting rates of non-commercial and small sponsors shows that in relatively low resource settings, compliance will not be prioritised if there is no risk of consequences. Furthermore, the FDA should consider casting a wider net in promoting compliance. The current enforcement regime appears random and *ad hoc.* While imposing fines can remain a measure of last resort, the FDA could consider implementing more proactive and widespread early warnings to out-of-compliance sponsors. This would serve as the first step on an escalation pathway to pre-notice letters, official notices of non-compliance, and finally sanctions.

The FDAAA TrialsTracker shows that trials covered under the law can reasonably be identified and tracked at scale through automated methods. In mandatory reporting to Congress under the 21st Century Cures Act, the US Department of Health and Human Services reported the number of newly registered applicable clinical trials using a nearly identical logic to the FDAAA TrialsTracker, confirming this capacity exists within the relevant agencies.[ee] While the back-end ClinicalTrials.gov system does give some warning to sponsors about failures to report,[326] more proactive outreach could more fully ensure sponsors are aware of their responsibilities. If continued non-compliance requires further escalation, then the FDA can do the more complex work of considering additional non-public information about a trial's status under the FDAAA.

[ee] From the *21st Century Cures Act, Section 2052 Second Report on Clinical Trials*, shared via personal communication with Christopher Morten and Dr. Reshma Ramachandran.

A similar lack of attention to enforcement and compliance has also led to issues in the EU. A lack of monitoring, attention, and any penalties for poor performance has compromised the transparency goals of the EU regulations. Chapter 6 clearly shows that various aspects of the regulatory process were unevenly implemented and maintained in member states. It is inexcusable that the EMA would allow national authorities to seemingly ignore their basic regulatory transparency responsibilities without any public comment or acknowledgement. Similarly, while public pressure based on my group's independent tools has impacted reporting expectations to some extent, it was short-sighted and insufficient for European decision-makers to implement requirements with no formal enforcement mechanisms. One news report summarised the EMA's position:[189]

The current rules stem from 2001 European guidelines that Fergus Sweeney, head of the EMA clinical studies and manufacturing task force, calls 'soft legislation.' Whether they represent a legal obligation or merely a recommendation is 'splitting hairs,' he says.

However, this distinction seems to have been critical in practice. In that same article a representative of the Amsterdam University Medical Centre (AUMC), one of the largest trial sponsors in Europe, said they saw "no advantage in double registrations or in doubling researchers' administrative burden" and would not address their poor reporting practice. Another one of Europe's largest sponsors, Public Assistance Hospitals of Paris (AP-HP), when confronted about their poor reporting, simply dodged the question with reference to their efforts to "strengthen transparency of studies in progress and promote scientific integrity" which apparently did not include meeting EU guidelines. As of February 2022, just 4 due trials from AP-HP have results and AUMC has just 6 reported on the EU TrialsTracker. This is in addition to dozens of trials incorrectly listed as "Ongoing" which was shown to be a major problem in Chapter 6.[189,571]

When regulators and sponsors in Norway were confronted by advocates about poor reporting they acknowledged the issues but either gave excuses with no concrete plans for further action or cited the coming new regulations as a reason to wash their hands of the former requirements.[572] While it would be a massive oversight to ignore the continued development of the EUCTR as a comprehensive source of nearly 20 years of clinical trial data, the new EU regulations could present an opportunity to address this poor behaviour moving forward. This, however, will take concerted efforts from a range of stakeholders to promote this behaviour. As I detailed in a *BMJ* editorial:[29]

The new EU regulation empowers member states to create and enforce sanctions and penalties for non-compliance, and this work should begin immediately…ethics committees and funders should also consider their responsibilities...Academic institutions should educate researchers about their statutory responsibilities. Actively managing research portfolios to ensure robust record keeping and oversight can help, and globally there is a growing profession of specialised staff charged with improving compliance. Any institution choosing to sponsor a trial should engage with this basic housekeeping now to avoid future issues.

8.4.3 How Do Institutions Manage Their Trial Transparency Responsibilities?

The behaviour of institutions emerged as a particularly important theme throughout my thesis. Sponsors of clinical trials are the organisations that take on responsibility for the conduct of a trial and ensuring regulatory responsibilities are met. Major commercial sponsors are excellent at meeting regulatory transparency responsibilities (Chapters 5 & 6) however academic institutions lag behind their peers. Chapter 7 examined this topic in-depth through interviews with research governance and management personnel at UK public research institutions. UK non-commercial sponsors have been leaders in meeting regulatory transparency responsibilities, and it appears that attention to the issues from politicians was no small part in this process.

Raising awareness and capacity for trial reporting responsibilities at academic institutions should be a clear priority for regulators. As the landscape shifts in the EU and UK, there needs

to be consistent lines of communication from regulators, to institutions, to their investigators. Building knowledge and skills for registration and reporting requirements among research staff was a key priority that emerged during interviews in Chapter 7. However, there also needs to be better recognition of research governance and sponsorship as a discrete investment in the good conduct of clinical trials. The disparity in resources between academic and commercial sponsors likely goes a long way in explaining the difference in compliance.[573]

Funders should also be more open to inclusion of line-items for sponsorship and governance costs in funding applications to ensure proper staffing and capacity for oversight. Otherwise, with limited resources, sponsors are incentivised to focus on the most tightly regulated classes of trials rather than their entire portfolio. Designating certain trials, like CTIMPs, as worthy of higher scrutiny arbitrarily de-emphasises the importance of rigour and transparency of research into other types of interventions. As the UK attempts to move to a new proportional but rigorous regulation of clinical trials,[524] stakeholders should consider how to improve and promote investment in sponsorship and governance as this is what will ultimately determine whether their goals are met.

8.4.4 Creating Norms Around Transparency and Accountability in Science

Taken together, the insights from examining each of these research questions demonstrate the need for a structural change to better prioritise and invest in transparency practice. Establishing this global system of clinical trials required substantial time and resources from a variety of stakeholders. The herculean task of repeatedly articulating the need for this investment over decades, and eventually turning that into real, useful research infrastructure should not be undermined by a failure to adopt and coordinate best practice between organisations within the institution of medical research. With the digital infrastructure of registries already in place, the

necessary changes require small improvements to policies and procedures that can multiply the value and utility provided by registries.

In Chapter 7, I examined how neo-institutional theory provided a framework through which to understand how transparency practice within UK public research universities and hospitals changed in response to a variety of new pressures and inputs within the environment.[554,555] This framework can be expanded to the broader global practice of transparency in science as it relates to registries. Macfarlane and colleagues summarise how, under this theoretical framework, institutions[ff] are influenced by "three broad types of social forces or 'pillars': regulative (laws and contracts which stipulate what must happen), normative (assumptions and expectations about what should happen) and cultural-cognitive (taken-for-granted scripts and mental models about what generally does happen)."[556]

Throughout this thesis are examples of how each of these pillars have impacted the current use of registries within the broader medical research environment. In the years following the paroxetine scandal, registration became compulsory through various mechanisms. The most obvious form of this is via the legal requirements examined in Chapters 5 & 6 of this thesis. However, coercive action to promote registration was also instituted by major journal editors and funders.[150,227] Trial registration became a condition of interacting with these vital academic organisations. These occurred alongside explicit normative change as, for instance, the 7th revision to the Declaration of Helsinki adopted language requiring registration and reporting of medical research in 2008.[164] While there has been mixed uptake in academic research organisations requiring registration from their sponsored research[236,304] these other

[ff] Here, defined as "social structures that have achieved a high degree of resilience."

requirements have made registration expected and routine, even if imperfectly implemented.[257,574]

While the act of registration itself has largely become an accepted part of conducting clinical trials, this is often where the obligation ends. The next step, in turning that registration into a tool to reduce bias and improve the rigour of clinical trial reporting, requires further action. Regulations that require data on registries to be maintained, and ensure results are disseminated, exist but their implementation and oversight by officials is often neglected as shown in Chapters 3, 5, and 6. At times, regulators are actively standing in the way of ensuring registration data is used effectively.[575] Most registries outside of the US and EU have relatively limited capacity to host results with many only offering links to external publications, the minimum standard per the ICTRP, as detailed in Chapter 2. These publications may or may not exist in the first place. However, even when this capacity does exist, it isn't necessarily being used to its full effect for rapid dissemination as shown in Chapter 4.

Even when reports do make it into journals, it is not a given that registrations are checked to ensure accurate and unbiased reporting, as shown in Chapter 3 and prior work.[6,154] Chapter 7 provided numerous anecdotes of investigators whose manuscripts were turned away from elite journals because of a failure to prospectively register. However, while binary assessments of prospective registration exist at some journals, there is little attention paid to ensuring what goes into a manuscript aligns with what was prospectively registered. When publication does occur with reporting issues, the occasional letter to the editor may be written in response, and that letter might be published, however this rarely leads to any substantial action and does not offer a systemic solution to biased reporting.[35,283,294,576] While some funders require registration, only recently have they begun to implement monitoring that informs ramifications for non-compliance including potentially barring investigators from future grants.[227,228,535]

As the registry infrastructure already exists, following substantial investment of resource, ensuring they are properly utilised is a matter of changing policy and norms. However, responsibility within the space is diffuse and stakeholders can point to each other as those with the real power to enact change. The journals, funders, universities, and relevant regulators that could impact this area are deeply entrenched in their positions and bureaucratic processes. It will take a concerted organised effort to recognize the important role of registries, beyond simply a signal of pre-specification, and ensure take advantage of the full capabilities of registries. Shifting institutional behaviour requires a shift in the environments in which these organisations operate. Various actors are working towards improvement in this space and are attempting to change behaviour in favour of transparent and rigorous research as a default.

Chapter 7 offers some examples of where these new positive forces for culture change originate. For instance, public audit has proven a powerful tool in the UK context. The TrialsTracker project was cited as offering sponsors access to information about gaps in their reporting and creating a clear performance metric that can be tracked by interested parties over time.[433] Users of the TrialsTracker have included trial sponsors, civil society advocates, and members of Parliament. In the UK, the SciTech Committee's attention to the issue changed organisational priorities as seen in Chapter 7. This committee's interest in good science has continued with a recent inquiry on reproducibility.[577] Civil society organisations have also played key roles in calling out bad behaviour and amplifying good behaviour.[233,578] Public audit allows third parties a tool with which to advocate for change. The work of TranspariMED is indicative of the power even a small organisation can have when provided with the necessary data.

Other organisations, like the growing number of national reproducibility networks (RNs), are committed to working with academic institutions to improve the quality and reproducibility of

their research through promotion, coordination, and education around principles or rigorous research. These networks are not limited to biomedical research, and go beyond promoting just preregistration, however they can play a key role in building momentum for normative and cultural change within a broad network of Universities that will undoubtedly reach the clinical trial community, for instance through advocating for the wider adoption of registered reports.[579] Cross disciplinary exchanges of ideas around registration, and other open science principles, can also promote new ways of working and managing improvements.[25,231] As of early 2022, the UKRN has institutional leads from 22 universities, the German RN lists 24 local initiatives and stakeholders, the Italian RN list 37 members, and at least eight other countries have either developed or are developing their own local networks.[580]

This level of incremental but widespread change across academia is difficult but not impossible with the Open Access movement providing a recent example of a successful ongoing campaign. While the idea of providing increased access to scientific outputs is not a new one, the movement of journals online at the turn of the century increased calls for a democratisation of knowledge.[581,582] These calls were compelling, especially when considering the large amount of research that originated from public grants and public research institutions.[583]

Today, open access publishing is prioritised by various stakeholders and has led to changes in infrastructure, policy, and funding models. Major funders often require the outputs of funded research to be published open access.[584–586] The Plan S initiative to promote Open Access in Europe is made up of major national and charitable funders from throughout the continent including the European Commission.[587] The Research Excellence Framework in the UK requires universities to maintain open access repositories of published work for inclusion in assessments.[588] Many publishers have “Open” titles alongside their main titles (e.g., BMJ, JAMA), others offer open routes alongside traditional routes (e.g., Nature), and some are built

entirely on an open model (e.g., PLOS, eLife, F1000). Open publication is usually accompanied by (sometimes exorbitant) upfront payments. Open access is not without its detractors[589,590] noting, for instance, significant barriers to Open Access publication for some groups and the rise of predatory open access journals. Yet adoption has been substantial and widespread driven by actions across each of the pillars of neo-institutional theory. The organisations that have embraced and promoted the open access movement are the same ones that could address the current registry landscape.

The same momentum that led to the creation of registries and proliferation of registration requirements must be reinvigorated through continued articulation and demonstration of the value of registries as essential research infrastructure that demands routine use, upkeep, and investment. It should not take another paroxetine scandal before these changes are seriously considered. Instead, proactive, positive shifts in behaviour across many of the organisations who have acted before is required to shift the role of registration in ensuring more rigorous and unbiased clinical research.

8.5 Strengths and Limitations

The recommendations and conclusions of this thesis need to be viewed in light of its strengths and limitations. Each chapter details the strengths and weaknesses of individual studies and here I examine some overarching considerations. One strength across multiple studies is the scale of the data being examined. Chapters 4, 5, and 6 are all based on the most complete and comprehensive collections of public data available with analyses implemented across the entire dataset. Being able to work at this scale is incredibly valuable for conducting comprehensive analyses and drawing more accurate and widely applicable conclusions. However, this thesis does not operate solely at the macro-level. Chapters 3 and 6 also consider trial transparency issues at the level of individual trials. Analysis populations in this study ranged from a case

series of five trials to nearly 40,000 trials across the entire EUCTR and from a sample of 500 trials to the entire Covid-19 research response. This multi-level view of transparency issues is incredibly valuable as specific examples provide context and meaning to the conclusions reached using summary data.

Additionally, the mixed methods approach of this thesis allowed a broader depth and richness of findings. Chapters 3-6 all detail specific problems with keeping registries up to date, reporting the results of clinical trials in a full and timely manner, and at times ensuring registered trials even appear on the public registry. Chapter 7 offers further depth and context by bringing the research questions raised by these studies to sponsors to see how and why they occur and can be addressed. Moving from describing the issues, to exploring ways to fix them, is a key step in ensuring my thesis offers not only a comprehensive view of the issues but begins the conversation about how to address them.

Finally, I aimed to incorporate open science practices throughout my thesis wherever possible. All of the processing and analytic code and study data are available to ensure reproducibility and allow others to inspect and build on my findings. As of submission, only my interviews from Chapter 7 have not been fully released as I would like to conduct final anonymisation checks on the full transcripts. My plan is to deposit the data using the UK Data Service ReShare program[gg] and make the interviews available alongside any potential publications that arise from that work.

My open science practice also grew and improved throughout my thesis. My final two analyses were both preregistered, and my two most recent publications were both made available as preprints ensuring widespread access and the opportunity for pre-publication review. I already

[gg] Details of the ReShare service available at https://reshare.ukdataservice.ac.uk/

have additional protocols preregistered in anticipation of future studies I will complete as part of my postdoctoral research. As my own open science practice grew, I also aimed to educate colleagues about these practices by co-running a departmental ReprodicibiliTea Journal Club introducing open science principles and holding discussions of their pros and cons. Moving forward, I aspire to be an example and a resource for colleagues who wish to learn about and use best open science practices in their research.

My thesis also had limitations. My work is primarily observational and descriptive in nature. While this was appropriate to address my specific research questions and vital to gain a deeper understanding of the global registry environment, it also clearly established a need for the development and testing of interventions to improve practice. Dr. Isabelle Boutron provides an excellent example of a researcher who is able to conduct impactful descriptive work[251,398] alongside innovative interventional research aimed at improving scientific practice including randomised assessments aiming to reduce spin and improve timely trials reporting.[435,591] Creating similar studies to assess interventions to improve the complete and timely reporting of clinical trials, and other aspects of research integrity, is a goal for the next phase of my career.

Unfortunately, another cross-cutting limitation of this thesis is also a key finding of the thesis: the data quality of registries is incredibly variable both within and between registries and impacts assessments that rely on these data. The findings in this thesis clearly demonstrate the issue. On ClinicalTrials.gov, one quarter of all trials required by law to verify data annually had failed to do so; on the EUCTR completion information, and entire protocols from some countries, were routinely missing. This issue may be even worse on other registries not governed by strict regulations. My experience closely examining the Covid-19 clinical trial landscape has reinforced that this issue remains widespread and problematic. In some instances, these were so noteworthy I felt compelled to act; I have written one letter to the editor about a Covid-19 trial

with an egregious violation of registration best practice and have another currently under review.[35] This limitation manifested throughout my thesis in a number of ways: assumptions around the FDA-coverage of Juul Labs trials could be challenged even though their own data stated they were covered; missing data on the EUCTR necessitated more complex and less precise methods for inferring trial completion; and poor registration of Covid-19 trials complicated searches for results and analyses of reporting. All of these areas had an impact on the conduct, analysis, and interpretation of my findings.

Lastly, some of the methods used in this thesis, like manual trial searches and qualitative analysis, were incredibly resource intensive. When designing the studies presented in Chapters 6 and 7, I planned for additional collaborative input that would allow for more dual searching of trials or coding of interview transcripts. I was able to institute some measure of this in both studies but not to the full extent originally planned given the commitment required and delays due to the Covid-19 pandemic. That said, examining and reflecting on both analyses did not raise any major issues that I could not adequately address in order to confidently share my findings.

8.6 Future Research

Each chapter in this thesis contains an overview of where I believe future research is needed in that area, and my own future plans in that space. In this section, I group some of these ideas, with additional related opportunities, into two potential programmes of research that I would like to pursue following my doctorate.

8.6.1 Building Better Tools for Transparency and Research Integrity

The TrialsTracker project was built on the idea that providing ongoing tracker tools increases impact beyond static academic papers. Rather than producing cross-sectional analyses where

fixed findings are produced from raw data sitting in an obscure CSV, the Tracker websites provide an ongoing live look at summary and per-trial compliance. A key goal will be finding funds to maintain, expand, and grow the TrialsTracker project. One natural future project would be building a Tracker for the new EU CTIS portal that allows rapid audits of compliance when trials start coming due over the next few years. This will provide immediate feedback about where investment and attention are needed as regulatory bodies and trial sponsors begin operating under the new regulatory regime. Additionally, sponsors can be supported in tracking their portfolios proactively rather than having to retrospectively scramble to address reporting issues as happened with the old system. New UK-specific regulations may also necessitate the creation of audit tools based around the ISRCTN and provide opportunities for interventional research to create better evidence on the best ways to promote transparency in clinical research.

The functionality of the current Trackers can also be extended, for instance a long-time ambition of the TrialsTracker project has been to create automated bespoke alerts and reports for sponsors and investigators that allow early notifications of when a trial becomes due and overviews of their entire portfolio. Prior research has shown that early alerts about due trials may aid timely reporting.[435] Tracking additional metrics and statistics, for instance grouping by locations, therapeutic areas, start and completion years, or compliance with additional requirements (e.g., those analysed in Chapter 5) would provide additional value for sponsors, researchers, and the public.

I also hope to extend my work beyond the TrialsTrackers to new tools and research that promotes transparency and open science practice. I have already begun work on the RetractoBot project which aims to send alerts to authors that cite retracted papers to reduce the spread of future citations. I will be leading the implementation of a trial testing the service's

impact over the coming years and the eventual manuscript is already accepted as a registered report. I have also worked with colleagues in the US and Australia to develop a research programme focused on building and assessing the impact of an automated conflict of interest disclosure check system during manuscript submission using the US Open Payments database that we are attempting to get funded.

Other broad areas that I am interested in pursuing include developing Python libraries and packages that aid in programmatic interaction with registries like ClinicalTrials.gov, automated methods to recognise misconduct like p-hacking in clinical trial reports and enhancing the accessibility of registry data. Each of these areas would challenge and push me to further develop and grow as a researcher building on many of the skills I gained during my doctorate.

8.6.2 Developing a Deeper Understanding of Transparency Research and Practice

As I developed my thesis research programme, there were additional projects I considered, and even started pursuing, but were not included in this final document. These ideas either required more time and resources than I had available, required additional planning and development, or were delayed due to Covid-19 and could not be completed. Overall, the breadth of the analyses in my DPhil was already ambitious and it would have been difficult to include further analyses. I have every intent of returning to and continuing pursuit of these projects in the future. There is no shortage of areas that require further examination of clinical trials transparency. One particularly exciting project to pursue would be updating the review on reporting of registered trials by Schmucker and colleagues.[73] Since this study was published in 2014, there has been considerable additional research published in this area. By my rough estimate, there are at least 40 studies to be considered in this updated review. As I did not conduct a systematic review as part of my thesis this is a target area for future professional development.

Results quality on registries is another area I would be interested to further examine. This topic has been covered extensively by other examining results on ClinicalTrials.gov.[251,252,254,255] As the reporting of results becomes a key element of registry standards, it is essential that the research community understand what quality of results information can be expected to appear on registries. Examining the quality of results on the EUCTR, and the new CTIS system, would further build on research presented in this thesis. I have conducted preliminary scoping of a study to characterise reporting practices more broadly across ICTRP primary registries.[72] The beginnings of this project were presented in Chapter 2. This work could be especially timely as the ICTRP may soon be considering more robust and unified minimum standards for trial results on registries.[hh]

There is also considerable room to build and expand on my qualitative work from Chapter 7 detailing institutional policies and procedures. I have collected documentation from top UK public research institutions on transparency management that I plan to examine using qualitative document analysis. This work will inform the creation of resources like model policies and support further harmonisation across the UK governance landscape.[592] Furthermore, there is ample opportunity to apply similar in-depth interview methods to other stakeholder groups including trial investigators, commercial sponsor representatives, regulators, and trial participants both within and outside the UK. Each of these groups can offer additional perspectives on the value of transparency, how it occurs in practice, and how the current system creates barriers or promotes best practice. This would be particularly valuable in EU member states as new regulations come into effect as it would provide insights into how current institutional and regulatory best practice occurs throughout the continent and allow cross-cultural comparisons of clinical research management and views on transparency topics.

[hh] Personal communication with ICTRP steering committee member.

8.7 Final Reflections

Undertaking this thesis work has been the most difficult, but also the most rewarding, thing I have ever done. Pursuing my doctorate was something I had long considered but was never quite sure if I would have the opportunity. As I complete my thesis, I look back at the skills I've developed and the research I've produced with great pride and excitement about what will come next. Writing this thesis has allowed me time to reflect on these accomplishments and plan out the next steps for my career. When I first came to work at Oxford in 2017, I was a junior researcher who had yet to even be co-authored on a research paper. Now, many papers, editorials, and reviews later I'm increasingly viewed as a peer by experts in my field. I've had the pleasure of meeting and exchanging ideas with many of the pioneers mentioned throughout my thesis. During my degree, I've been asked to speak to various groups, give interviews to news organisations,[45,47,593] provide advice and perspective to colleagues, and even serve as an invited lead author in pieces for *The BMJ* and *Nature*.[29,32] The transition from novice researcher to expert is a natural outcome of immersing yourself deeply in an area but deserves reflection and acknowledgement.

Still, even as I grow in confidence as an academic, I also need to humbly respect the limits of my knowledge and how much there is still left to learn and grow as a researcher. Whether that's conducting my first systematic review, building a data-driven Django app from scratch, or sitting with my copy of *Rethinking Statistics* to finally try and wrap my head around Bayesian statistics there is plenty to explore. I also hope to further pursue opportunities for teaching and mentorship as a postdoc. While I had some experience working in conducting trainings and aiding in a one-day course, more formally teaching students is something I think I could meaningfully contribute to and enjoy.

Lastly, I'm very interested in pursuing experiences that could bring a deeper perspective and understanding to my work. My research has naturally led to an interest in the ethics and function of academic journals and I've been increasingly called on to act as a reviewer. I've found the process to be interesting and insightful and believe pursuing editorial positions could be rewarding on numerous fronts including fostering better understanding of where to intervene. Another idea I've discussed with colleagues is developing ways for researchers interested in clinical trial management and oversight to gain direct experience in these areas that would otherwise not be available. If one isn't a trialist, clinician, or statistician, there are few chances to see a trial up close even though this would be an incredibly valuable opportunity. This could take the form of sitting on a Data and Safety Monitoring Board as a non-voting member or shadowing colleagues working on trial management. It's difficult to say if something like this would be possible, but these are the types of experiences I would like to pursue and develop so that I, and others, could gain valuable perspective and grow as researchers in this area.

8.8 Concluding Remarks

This thesis provides a mixed methods approach to examining the current state of clinical trial registration as a tool to improve transparency and accountability. The research presented examines how registries can better fulfil their goals, highlight where shortcomings still exist, and explore ways to address them. Clinical research is unique in academia as essentially the entire global research agenda is publicly indexed, searchable, and available for use and audit by any interested parties. The development of this global clinical trial registration system has been a 40 year process and further progress demands additional attention and investment. This thesis provides insights into how research policy and practice requires constant effort in order to progress and ensure more rigorous, transparent, and unbiased research is created to inform clinical decision making and health policy.

Appendices

Chapter 3

Appendix 3.1: Additional Design Details of Included Trials

NCT03463837

This was a parallel group trial in which 90 adult smokers were randomised to one of six arms: four arms exclusively used different flavoured Juul 5% products, an active comparator arm smoked their standard combustible cigarettes, and a control arm abstained from smoking. The primary outcome was the change in biomarkers of exposure in urine or blood over the five day study period. Secondary outcomes included changes in ten additional biomarkers, three measures of nicotine absorption, product use, smoking urges, measures of product satisfaction and future intent to use, and any adverse events (AEs) or device malfunctions.

NCT03605641

This was an open label study to examine emissions across three different environments for a Juul device, a competitor device (Vuse solo), and conventional cigarettes. According to the registry entry, 46 adult smokers were assigned one of these arms and asked to vape or smoke across residential, office, and hospitality environments. The study lists 12 primary outcomes measuring specific constituents of exhaled breath (n=4) or room air following product use (n=8).

NCT03593239

This was an open label, randomised, crossover study intended to examine the nicotine pharmacokinetics of various Juul 1.7% and 5% nicotine salt products. Overall, 24 adult smokers were to be enrolled. It is unclear from the registry entry exactly how participants flowed through the trial and were assessed. The primary outcomes were four nicotine pharmacokinetic

measures: concentration maximum (CMax), time to CMax, Cmax-baseline and Area Under the Curve (AUC), and AUC 1 hour-baseline of nicotine. The two secondary outcomes were measures of exhaled CO and user satisfaction.

NCT03596034

This was an open-label, single-arm study to assess “puff topography” (PT) in adult smokers using the “Juul 5% Electronic Nicotine Delivery Systems” product. The study enrolled 30 adult participants whose PT was evaluated on days 1 and 15. The primary outcome was various measures of PT including the duration, volume, peak flow rate, average flow rate, and inter-puff interval. There were seven secondary outcomes including self-reported use of the product and subjective measures of various smoking-related areas (e.g. nicotine dependence, smoking urges).

NCT03719391

This was an open label randomised crossover study intended to examine the nicotine pharmacokinetics of various Juul 5% nicotine salt products, Vuse Solo e-cigarettes, Nicorette 4mg nicotine gum, and standard combustible cigarettes in 67 adult smokers who were each exposed to each product. The primary outcome was vaguely specified as pharmacokinetic measurements of nicotine uptake in the plasma with details “provided in the SAP” however no statistical analysis plan could be located. Secondary measures included exhaled CO, measurements of blood pressure, heart rate, product use, safety/tolerability and various subjective scales (product evaluation, intent to use, nicotine withdrawal, direct effect, and product liking).

Chapter 5

Appendix 5.1: Description of Study Cohort by Start Year

	Year	Total	%	Trials with Any Results	% with Any Results	95% CI	Compliant Trials	% Compliant	95% CI
Start Year	1991	1	.02	1	100	..	0	0	..
	1994	1	.02	1	100	..	0	0	..
	1997	1	.02	0	0	..	0	0	..
	1998	2	.05	1	50.0	1.9-98.1	0	0	..
	1999	3	.07	2	66.7	9.6-97.4	1	33.3	2.6-90.4
	2002	4	.1	1	25.0	2.4 -82.0	0	0	..
	2003	3	.07	1	33.3	2.6-90.4	0	0	..
	2004	11	.3	9	81.8	47.4-95.7	5	45.5	19.4-74.3
	2005	17	.4	12	70.6	45.0-87.6	6	35.3	16.4-60.3
	2006	27	.6	19	70.4	50.6-84.6	7	25.9	12.7-45.7
	2007	22	.5	15	68.2	46.1-84.3	8	36.4	19.0-58.2

	2008	44	1.1	30	68.2	53.0-80.3	20	45.5	31.4-60.3
	2009	68	1.6	50	73.5	61.7-82.7	30	44.1	32.8-56.1
	2010	90	2.1	63	70.0	59.7-78.6	38	42.2	32.4-52.7
	2011	136	3.2	86	63.2	54.8-70.9	48	35.3	27.7-43.7
	2012	233	5.5	171	73.4	67.3-78.7	108	46.4	40.0-52.8
	2013	388	9.2	267	68.8	64.0-73.2	156	40.2	35.4-45.2
	2014	501	11.9	359	71.7	67.5-75.4	230	45.9	41.6-50.3
	2015	801	19.0	539	67.3	64.0-70.5	334	41.7	38.3-45.2
	2016	943	22.4	604	64.1	60.9-67.1	414	43.9	40.8-47.1
	2017	787	18.7	401	51.0	47.5-54.4	275	34.9	31.7-38.3
	2018	126	3.0	54	42.9	34.5-51.7	42	33.3	25.6-42.0

Appendix 5.2: Sensitivity Analysis - ACT Only Cohort Description

Variables		Total ACTs (% of Total)	Trials with Results	% with Results	95% CI	Compliant Trials	% Compliant	95% CI
Trials		883	440	49.8	46.5 to 53.1	306	34.7	31.6 to 37.9
Sponsor Class:	Non-Industry	400 (45.3)	174	38.7	38.7 to 48.4	102	25.5	21.5 to 30.0
	Industry	478 (54.1)	263	50.5	50.5 to 59.4	203	42.5	38.1 to 47.0
	US Gov	5 (.6)	3	16.8	16.8 to 91.7	1	20.0	2.1 to 74.4
Industry Collaborator		119 (13.5)	56	47.1	38.2 to 56.1	41	34.5	26.4 to 43.5
US Gov Collaborator		26 (2.9)	17	65.4	45.3 to 81.2	10	38.5	21.8 to 58.3
Phase:	Phase 1/2	38 (4.3)	15	39.5	25.2 to 55.8	12	31.6	18.7 to 48.0
	Phase 2	186 (21.1)	100	53.8	46.5 to 60.8	75	40.3	33.5 to 47.6
	Phase 2/3	20 (2.3)	10	50.0	28.9 to 71.1	8	40.0	21.0 to 62.6
	Phase 3	114 (12.9)	76	66.7	57.5 to 74.7	57	50.0	40.9 to 59.1
	Phase 4	147 (16.7)	70	47.6	39.6 to 55.7	46	31.3	24.3 to 39.3
	N/A	378 (42.8)	169	44.7	39.8 to 49.8	108	28.6	24.4 to 33.3
Terminated		124 (14.0)	77	62.1	53.2 to 70.2	54	43.5	35.1 to 52.4
Reached Full Completion		843 (95.5)	425	50.4	47.0 to 53.8	293	34.8	31.6 to 38.0
Trial Contains a Drug		459 (52.0)	245	53.4	48.8 to 57.9	176	38.3	34.0 to 42.9
Trial Contains a Biological/Vaccine		38 (4.3)	25	65.8	49.3 to 79.2	19	50.0	34.4 to 65.6
Trial Contains a Device		394 (44.6)	180	45.7	40.8 to 50.6	119	30.2	25.9 to 34.9
Trial Contains a Diagnostic Test		12 (1.4)	6	50.0	23.4 to 76.6	4	33.3	12.5 to 63.7
Trial Contains a Radiation Treatment		2 (.2)	1	50.0	1.9 to 98.1	0	0	--
Trial Contains a Combination Product		8 (.9)	2	25.0	5.7 to 64.9	0	0	--
Trial Contains a Genetic		0	0	0	--	0	0	--

Treatment								
Trial Location:	US Only	622 (70.4)	326	52.4	48.5 to 56.3	213	34.2	30.6 to 38.1
	US and Other County	98 (11.1)	76	77.6	68.2 to 84.8	66	67.3	57.4 to 75.9
	No US Location	143 (16.2)	37	25.9	19.3 to 33.7	27	18.9	13.3 to 26.2
	No Location Data Available	20 (2.3)	1	5.0	.7 to 29.3	0	0	-
Total No. of Trials on Register for Trial's Sponsor	First Quarter (1-12)	339 (38.4)	102	30.1	25.4 to 35.2	63	18.6	14.8 to 23.1
	Second Quarter (13-219)	275 (31.1)	131	47.6	41.8 to 53.6	86	31.3	26.1 to 37.0
	Third Quarter (221-910)	157 (17.8)	108	68.8	61.1 to 75.6	76	48.4	40.7 to 56.2
	Fourth Quarter (925-3276)	112 (23.7)	99	88.4	81.0 to 93.2	81	72.3	63.3 to 79.8
Start Year	2017	757 (85.7)	386	51.0	47.4 to 54.5	264	35.0	31.6 to 38.3
	2018	126 (14.3)	54	42.9	34.5 to 51.7	42	33.3	25.6 to 42.0

Appendix 5.3: Sensitivity Analysis - Crude and Adjusted ORs for ACT Only Cohort

Variables		Any Results Crude OR (95% CI; p value)	Any Results Adjusted OR (95% CI; p value)	Compliant Crude OR (95% CI; p value)	Compliant Adjusted OR (95% CI; p value)
Sponsor Class	Non-Industry	Ref	Ref	Ref	Ref
	Industry	1.59 (1.22-2.07; 0.001)	2.58 (1.72-3.89; <0.001)	2.16 (1.62-2.88; <0.001)	3.92 (2.49-6.19, <0.001)
	US Gov	1.95 (0.32-11.79; 0.468)	4.37 (0.67-28.42; 0.123)	0.73 (.08-6.61; 0.780)	2.13 (0.22-20.33; 0.511)
Industry Collaborator		0.88 (0.60-1.30; 0.516)	0.90 (0.56-1.45; 0.658)	0.99 (.66-1.49; 0.961)	1.22 (.74-1.98; 0.436)
US Gov Collaborator		1.94 (0.85-1.11; 0.707)	2.77 (0.95-8.10; 0.062)	1.18 (0.53-6.24; 0.679)	1.61 (0.59-4.39; 0.354)
Phase	Phase 1/2	0.33 (0.15-0.70; 0.004)	0.28 (0.12-0.72; 0.008)	0.46 (0.21-1.00; 0.051)	0.66 (0.25-1.72; 0.394)
	Phase 2	0.58 (0.36-0.94; 0.028)	0.28 (0.12-0.72; 0.008)	0.46 (0.21-1.00; 0.051)	0.66 (0.25-1.72; 0.394)
	Phase 2/3	0.50 (0.19-1.30; 0.157)	0.65 (0.20-2.10; 0.474)	0.67 (0.25-1.76; 0.411)	1.12 (0.35-3.64; 0.845)
	Phase 3	Ref	Ref	Ref	Ref
	Phase 4	0.45 (0.27-0.75; 0.002)	0.79 (0.41-1.54; 0.491)	0.46 (0.27-0.76; 0.002)	0.98 (0.50-1.91; 0.958)
	N/A	0.40 (0.26-0.63; <0.001)	0.68 (0.23-2.01; 0.481)	0.40 (0.26-0.61; <0.001)	0.42 (0.14-1.27; 0.123)
Terminated		1.79 (1.21-2.64; 0.003)	1.50 (0.94-2.39; 0.088)	1.55 (1.06-2.28; 0.026)	1.29 (0.81-2.03; 0.282)
Reached Full Completion		1.69 (0.88-3.26; 0.114)	2.59 (1.16-5.79; 0.021)	1.11 (0.56-2.18; 0.770)	1.39 (0.61-3.20; 0.431)
Trial Contains a Drug		1.34 (1.03-1.75; 0.028)	1.28 (0.48-3.44; 0.625)	1.41 (1.06-1.86; 0.017)	0.84 (0.30-2.32; 0.735)
Trial Contains a Biological/Vaccine		1.99 (1.01-3.95; 0.048)	2.10 (0.64-6.94; 0.223)	1.94 (1.01-3.73; 0.046)	1.31 (0.40-4.27; 0.657)
Trial Contains a Device		0.74 (0.57-0.97; 0.027)	1.41 (0.55-3.66; 0.477)	0.70 (0.53-0.93; 0.013)	1.85 (0.70-4.92; 0.216)
Trial Contains a Diagnostic Test		1.01 (0.32-3.15; 0.991)	1.16 (0.23-5.87; 0.855)	0.94 (0.28-3.15; 0.923)	1.65 (0.32-8.57; 0.551)

Trial Contains a Radiation Treatment		1.01 (0.06-16.15; 0.996)	0.14 (0.01-3.15; 0.214)	OFC	OFC
Trial Contains a Combination Product		0.33 (0.07-1.66; 0.179)	0.70 (0.12-4.10; 0.691)	OFC	OFC
Trial Contains a Genetic Treatment		OFC	OFC	OFC	OFC
Trial Location	US Only	Ref	Ref	Ref	Ref
	US and Other County	3.14 (1.90-5.17; <0.001)	1.97 (1.08-3.58; 0.027)	3.96 (2.52-6.23; <0.001)	2.24 (1.28-3.90; 0.005)
	No US Location	0.32 (0.21-0.48; <0.001)	0.32 (0.20-0.51; <0.001)	0.45 (0.28-0.70, <0.001)	0.51 (0.30-0.85; 0.010)
	No Location Data Available	0.05 (0.01-0.36; 0.003)	0.03 (0.00-0.22; 0.001)	PPF	PPF
Total No. of Trials on Register for Trial's Sponsor	First Quarter (1-12)	Ref	Ref	Ref	Ref
	Second Quarter (13-225)	2.11 (1.52-2.94; <0.001)	2.48 (1.71-3.61; <0.001)	1.99 (1.37-2.90; <0.001)	2.24 (1.48-3.39; <0.001)
	Third Quarter (229-874)	5.12 (3.40-7.71; <0.001)	9.20 (5.55-15.26; <0.001)	4.11 (2.71-6.23; <0.001)	9.32 (5.47-14.88; <0.001)
	Fourth Quarter (887-3254)	17.69 (9.49-32.99; <0.001)	30.26 (14.49-63.20; <0.001)	11.45 (6.97-18.80; <0.001)	19.52 (10.70-35.61; <0.001)
Start Year (Increase of one year)		0.72 (0.49-1.05; 0.092)	0.74 (0.47-1.17; 0.196)	0.93 (0.63-1.39; 0.736)	1.02 (0.64-1.62; 0.946)

OFC: Omitted for colinearity

PPF: Omitted as perfectly predicts failure

Appendix 5.4: Sensitivity Analysis - Description of ACT-only Variable

Variables	Total Trials (% of Total)	Trials with Results	% with Results	95% CI	Compliant Trials	% Compliant	95% CI
Trials	4209	2686	63.8	62.4 to 65.3	1722	40.9	39.4 to 42.4
Is an ACT	883 (20.98)	440	49.8	46.5 to 53.1	306	34.7	31.6 to 37.9

Appendix 5.5: Sensitivity Analysis - Addition of ACT Status to Regression

Variables		Any Results Crude OR (95% CI; p value)	Any Results Adjusted OR (95% CI; p value)	Compliant Crude OR (95% CI; p value)	Compliant Adjusted OR (95% CI; p value)
Sponsor Class	Non-Industry	Ref	Ref	Ref	Ref
	Industry	1.09 (0.96-1.25; 0.169)	1.64 (1.36-1.98; <0.001)	1.98 (1.74-2.25; <0.001)	3.09 (2.53-3.78; <0.001)
	US Gov	1.74 (1.25-2.43; 0.001)	0.82 (0.55-1.23; 0.345)	0.90 (0.65-1.23; 0.499)	0.48 (0.33-0.69; <0.001)
Industry Collaborator		1.21 (1.02-1.44; 0.028)	1.29 (1.06-1.58; 0.012)	1.13 (0.96-1.33; 0.145)	1.31 (1.08-1.58; 0.006)
US Gov Collaborator		1.49 (1.20-1.84; <0.001)	1.44 (1.11-1.86; 0.005)	0.92 (0.75-1.12; 0.388)	1.19 (0.94-1.50; 0.157)
Phase	Phase 1/2	0.49 (0.37-0.64; <0.001)	0.64 (0.47-0.89; 0.008)	0.45 (0.34-0.59; <0.001)	0.91 (0.66-1.24; 0.541)
	Phase 2	0.77 (0.63-0.94; 0.010)	0.98 (0.78-1.24; 0.842)	0.62 (0.51-0.74; <0.001)	1.04 (0.84-1.30; 0.700)
	Phase 2/3	0.45 (0.29-0.69; <0.001)	0.52 (0.32-0.85; 0.009)	0.55 (0.36-0.84; 0.006)	0.93 (0.58-1.51; 0.779)
	Phase 3	Ref	Ref	Ref	Ref
	Phase 4	0.65 (0.52-0.83; <0.001)	1.01 (0.75-1.35; 0.966)	0.55 (0.44-0.68; <0.001)	1.15 (0.88-1.52; 0.312)
	N/A	0.38 (0.31-0.46; <0.001)	0.64 (0.46-0.90; 0.011)	0.35 (0.29-0.42; <0.001)	0.86 (0.62-1.20; 0.379)
Terminated		1.53 (1.27-1.83; <0.001)	1.41 (1.15-1.73; 0.001)	1.24 (1.05-1.47; 0.011)	1.16 (0.96-1.40; 0.132)
Reached Full Completion		1.02 (0.83-1.27; 0.828)	1.71 (1.31-2.21; <0.001)	0.87 (0.71-1.07; 0.193)	1.30 (1.01-1.67; 0.041)

Trial Contains a Drug		1.88 (1.65-2.16; <0.001)	1.68 (1.18-2.40; 0.004)	1.67 (1.45-1.92; <0.001)	1.45 (1.05-2.01; 0.025)
Trial Contains a Biological/Vaccine		1.49 (1.18-1.89; 0.001)	1.62 (1.13-2.32; 0.009)	1.42 (1.15-1.76; 0.001)	1.52 (1.11-2.08; 0.010)
Trial Contains a Device		0.53 (0.46-0.61; <0.001)	1.99 (1.36-2.91; <0.001)	0.56 (0.48-0.65; <0.001)	1.38 (0.97-1.97; 0.076)
Trial Contains a Diagnostic Test		0.72 (0.33-1.59; 0.482)	1.61 (0.64-4.06; 0.317)	0.56 (0.23-1.34; 0.194)	1.18 (0.44-3.11; 0.743)
Trial Contains a Radiation Treatment		0.93 (0.62-1.39; 0.720)	0.85 (0.52-1.39; 0.524)	0.71 (0.47-1.07; 0.100)	1.02 (0.64-1.62; 0.944)
Trial Contains a Combination Product		0.66 (0.22-1.97; 0.457)	1.65 (0.48-5.67; 0.425)	0.26 (0.06-1.18; 0.081)	0.48 (0.10-2.36; 0.370)
Trial Contains a Genetic Treatment		0.47 (0.14-1.55; 0.215)	0.96 (0.26-3.57; 0.947)	0.82 (0.24-2.82; 0.759)	1.74 (0.47-6.47; 0.409)
Trial Location	US Only	Ref	Ref	Ref	Ref
	US and Other County	2.50 (2.08-2.99; <0.001)	1.81 (1.44-2.27; <0.001)	3.39 (2.90-3.97; <0.001)	1.91 (1.55-2.35; <0.001)
	No US Location	0.43 (0.33-0.57; <0.001)	0.48 (0.35-0.66; <0.001)	0.91 (0.68-1.20; 0.485)	0.80 (0.57-1.11; 0.177)
	No Location Data Available	0.59 (0.39-0.89; 0.013)	0.41 (0.25-0.68; <0.001)	1.01 (0.65-1.57; 0.953)	0.66 (0.40-1.11; 0.122)
Total No. of Trials on Register for Trial's Sponsor	First Quarter (1-12)	Ref	Ref	Ref	Ref
	Second Quarter (13-225)	1.74 (1.47-2.06; <0.001)	1.72 (1.43-2.05; <0.001)	1.76 (1.46-2.13; <0.001)	1.75 (1.43-2.15; <0.001)
	Third Quarter (229-874)	4.83 (4.00-5.83; <0.001)	6.07 (4.91-7.51; <0.001)	3.52 (2.92-4.25; <0.001)	6.14 (4.91-7.68; <0.001)
	Fourth Quarter (887-3254)	14.48 (11.30-18.54; <0.001)	17.13 (13.00-22.56; <0.001)	7.00 (5.76-8.51; <0.001)	11.78 (9.31-14.91; <0.001)
Start Year (Increase of one year)		0.91 (0.90-0.94; <0.001)	1.04 (1.00-22.56; 0.043)	1.00 (0.97-1.02; 0.747)	1.07 (1.03-1.10; <0.001)
Trial is ACT		0.48 (0.41-0.56; <0.001)	0.66 (0.54-0.81; <0.001)	0.72 (0.61-0.84; <0.001)	0.84 (0.68-1.03; 0.098)

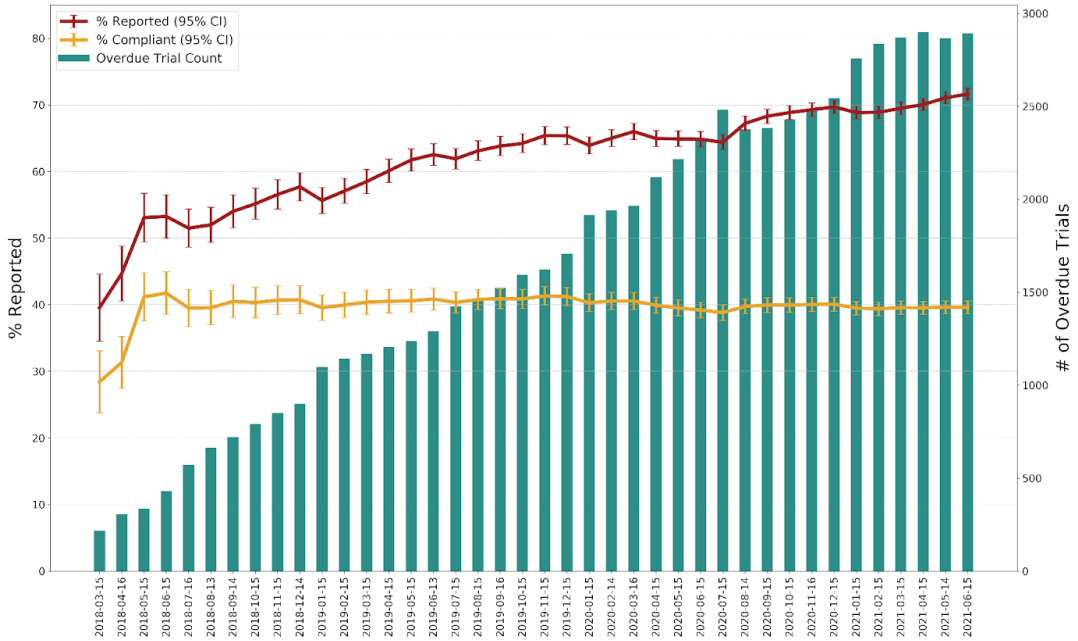
Appendix 5.6: Reporting statistics for all sponsors with ≥10 due trials

Sponsor	Trials Due	Any Reported Trials	% Reported	Compliant Trials	% Compliant
M.D. Anderson Cancer Center	85	71	83.5	43	34.1
National Cancer Institute (NCI)	79	65	82.3	38	30.4
Massachusetts General Hospital	58	46	79.3	44	55.2
Mayo Clinic	47	45	95.7	12	21.3
Novartis Pharmaceuticals	46	46	100	46	100
Gilead Sciences	45	45	100	43	95.6
GlaxoSmithKline	43	43	100	42	97.7
Pfizer	42	42	100	39	92.9
Hoffmann-La Roche	38	38	100	36	94.7
University of California, San Francisco	38	26	68.4	18	15.8
AstraZeneca	37	37	100	37	100
Memorial Sloan Kettering Cancer Center	36	34	94.4	35	91.7
University of North Carolina, Chapel Hill	32	32	100	26	81.2
Emory University	29	29	100	20	69
Washington University School of Medicine	28	28	100	25	89.3
The University of Texas Health Science Center, Houston	28	28	100	23	82.1
University of Pennsylvania	27	22	81.5	18	48.1
Duke University	26	26	100	25	96.2
University of Chicago	26	13	50	19	23.1
Eli Lilly and Company	25	25	100	22	88
Johns Hopkins University	24	24	100	21	87.5
Stanford University	24	18	75	19	54.2
National Institute of Allergy and Infectious Diseases (NIAID)	23	21	91.3	19	73.9
Bristol-Myers Squibb	23	23	100	23	100

University of Virginia	23	6	26.1	20	13
Allergan	23	23	100	23	100
Sanofi	22	22	100	22	100
University of Washington	22	17	77.3	17	54.5
Wake Forest University Health Sciences	22	19	86.4	14	50
Merck Sharp & Dohme Corp.	20	20	100	20	100
New York State Psychiatric Institute	20	12	60	10	10
Amgen	19	19	100	19	100
Celgene	19	19	100	18	94.7
Yale University	18	14	77.8	7	16.7
VA Office of Research and Development	18	16	88.9	8	33.3
Columbia University	17	17	100	7	41.2
University of Colorado, Denver	17	9	52.9	13	29.4
Bayer	16	16	100	16	100
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins	16	16	100	6	37.5
Icahn School of Medicine at Mount Sinai	16	14	87.5	6	25
Montefiore Medical Center	15	8	53.3	13	40
Novo Nordisk A/S	15	15	100	13	86.7
Boehringer Ingelheim	14	14	100	14	100
Northwestern University	14	14	100	6	42.9
University of Wisconsin, Madison	14	13	92.9	6	35.7
Dana-Farber Cancer Institute	14	6	42.9	13	35.7
University of Minnesota - Clinical and Translational Science Institute	14	11	78.6	3	0
AbbVie	14	14	100	14	100
Johnson & Johnson Vision Care, Inc.	14	14	100	14	100
Indiana University	14	14	100	9	64.3
National Heart, Lung, and Blood Institute (NHLBI)	14	12	85.7	3	7.1
Medical University of South Carolina	13	11	84.6	9	53.8
University of Michigan	13	13	100	12	92.3

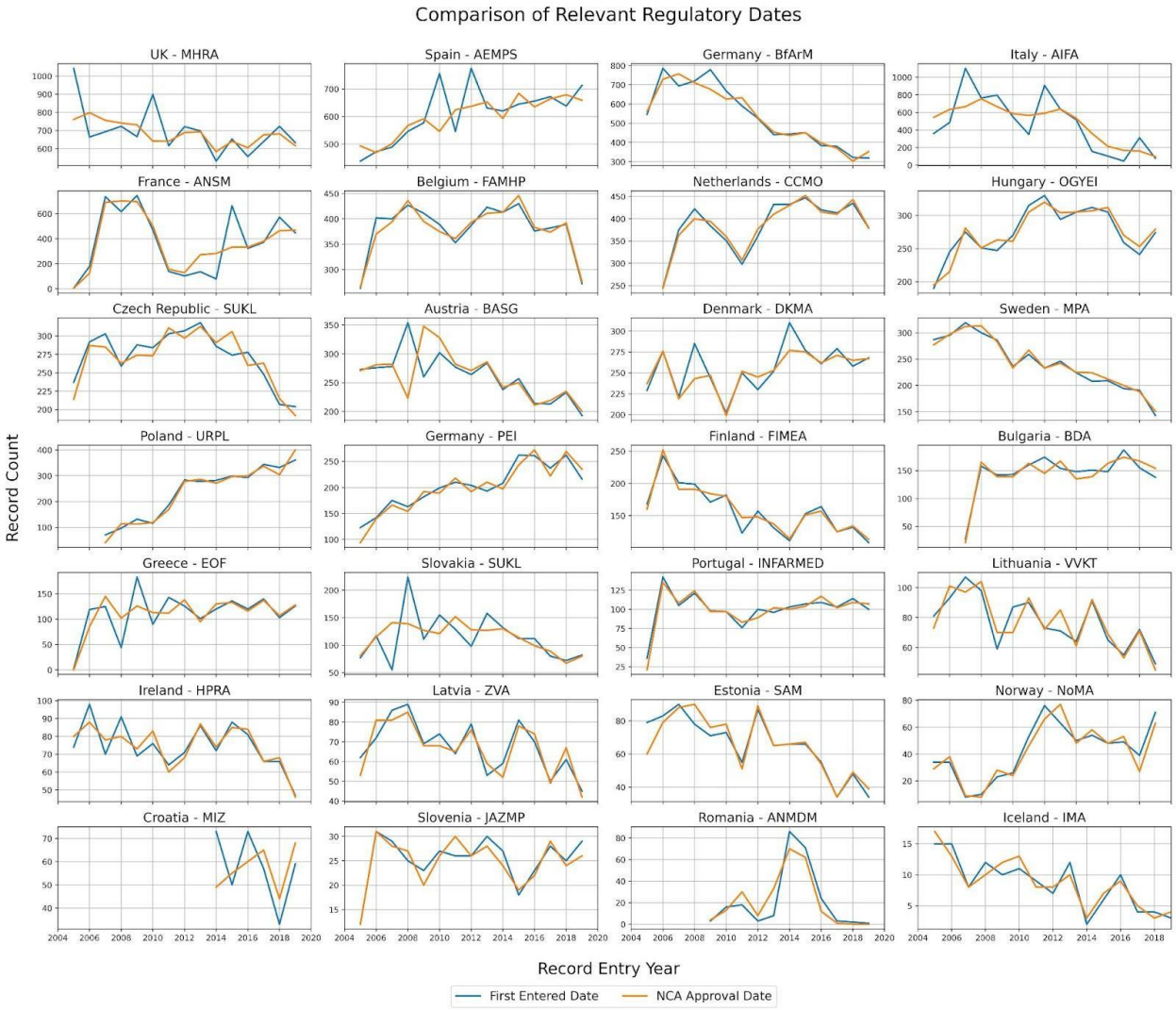
Oregon Health and Science University	13	13	100	4	30.8
University of Alabama at Birmingham	13	11	84.6	9	53.8
Alcon Research	12	12	100	12	100
University of Texas Southwestern Medical Center	12	8	66.7	7	25
Fred Hutchinson Cancer Research Center	12	12	100	10	83.3
Children's Hospital Medical Center, Cincinnati	12	2	16.7	12	16.7
NYU Langone Health	12	10	83.3	4	16.7
Abramson Cancer Center of the University of Pennsylvania	11	2	18.2	9	0
Brigham and Women's Hospital	11	9	81.8	6	36.4
Boston Scientific Corporation	11	10	90.9	5	36.4
Teva Branded Pharmaceutical Products, R&D Inc.	11	11	100	4	36.4
Vanderbilt University Medical Center	11	11	100	5	45.5
St. Jude Children's Research Hospital	11	11	100	10	90.9
Milton S. Hershey Medical Center	11	11	100	8	72.7
Southwest Oncology Group	11	11	100	5	45.5
Baylor College of Medicine	11	3	27.3	8	0
Roswell Park Cancer Institute	11	3	27.3	9	9.1
University of Southern California	11	8	72.7	3	0
The Cleveland Clinic	10	7	70	6	30
Cairo University	10	1	10	9	0
University of California, San Diego	10	9	90	3	20
Alexion Pharmaceuticals	10	10	100	9	90
Takeda	10	10	100	9	90
Case Comprehensive Cancer Center	10	3	30	7	0
Janssen Research & Development, LLC	10	10	100	10	100

Appendix 5.7: Update of Figure 5.2 Showing Reporting Trends Through June 2021



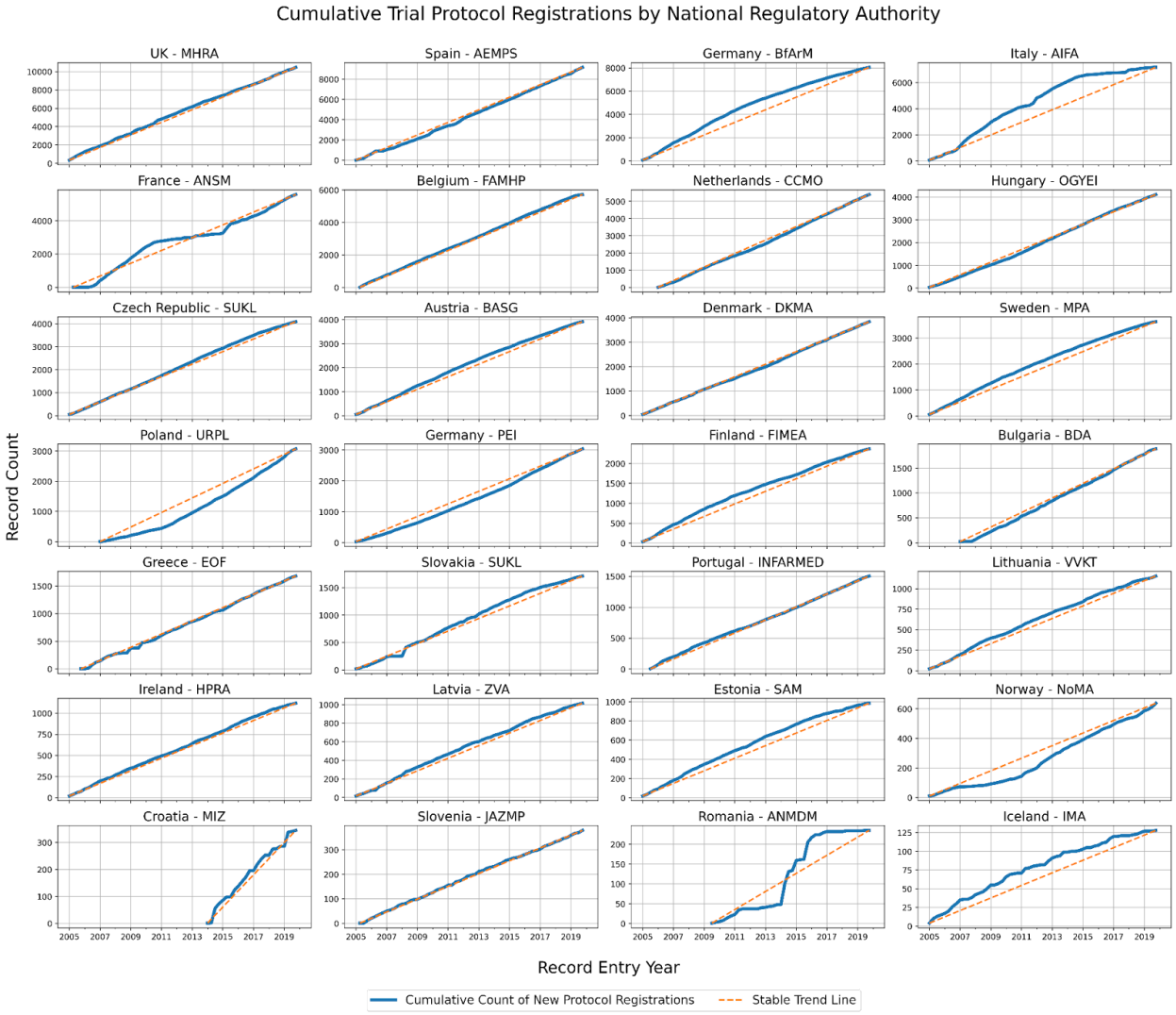
Chapter 6

Appendix 6.1: Comparison of Available Key Regulatory Dates



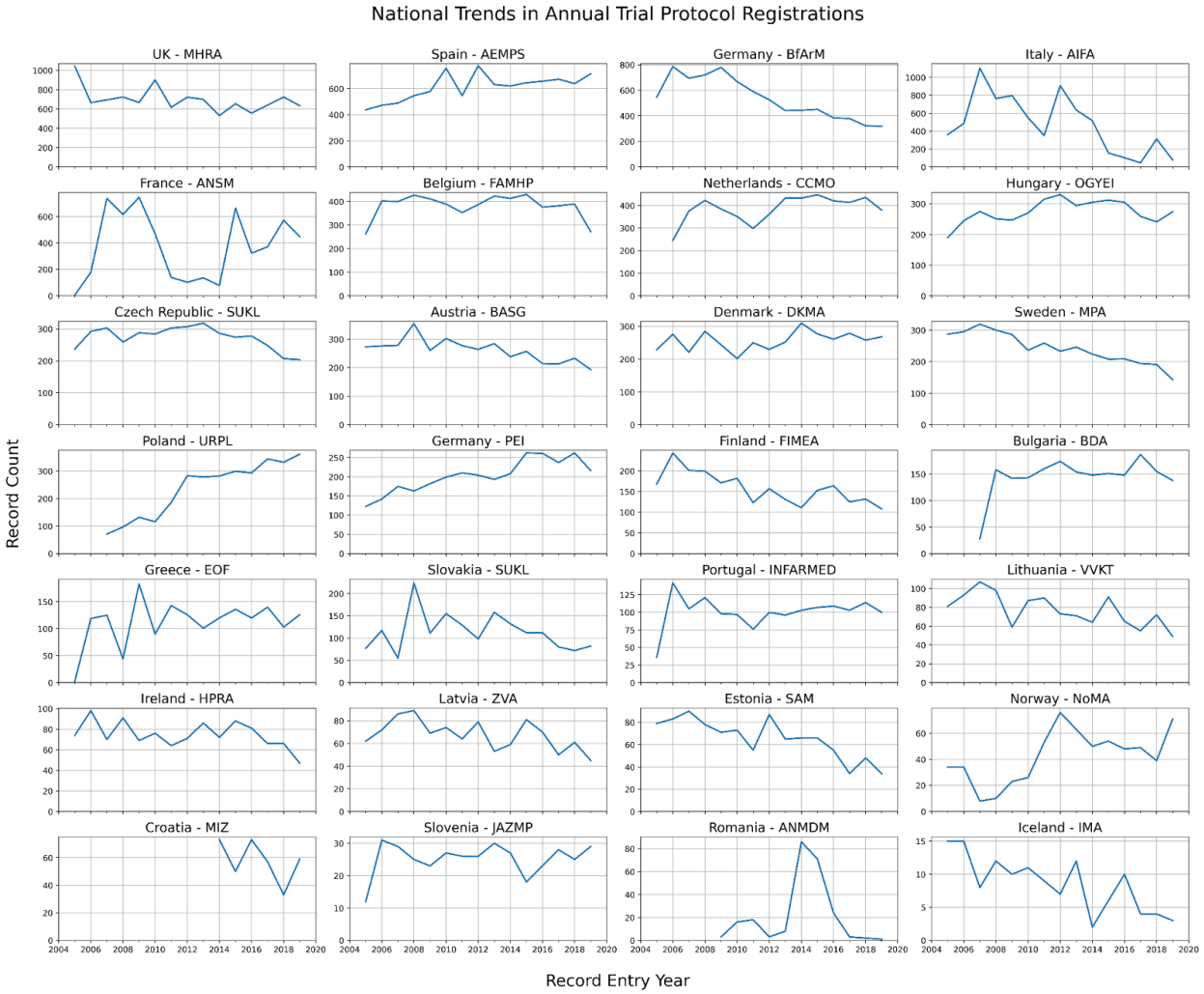
The annual trend in new protocol registrations by each regulator. Here we compare the trend using the field "Date on which this record was first entered in the EudraCT database", which was used throughout the manuscript, to the "Date of Competent Authority Decision". While regulatory approval dates generally represent a smoother trend, they match very closely over time suggesting there would be no variation in overall conclusions based on choosing one date over the other.

Appendix 6.2: Cumulative Trends in New Trials by Country



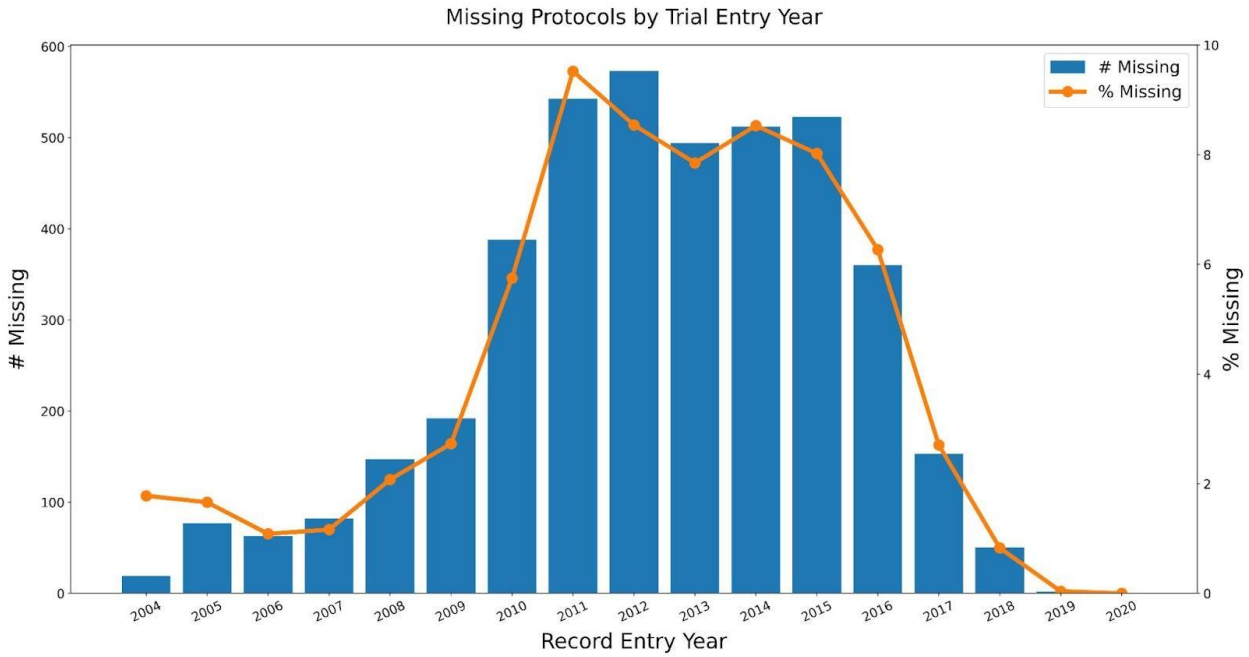
The cumulative trend in new protocol registrations by each regulator. The dotted orange line represents what a stable trend in new registrations over time would look like. Data here was aggregated by quarter for more precise visualisation of the trend over time.

Appendix 6.3: Annual Trend in New Trials Registrations From Each Regulator



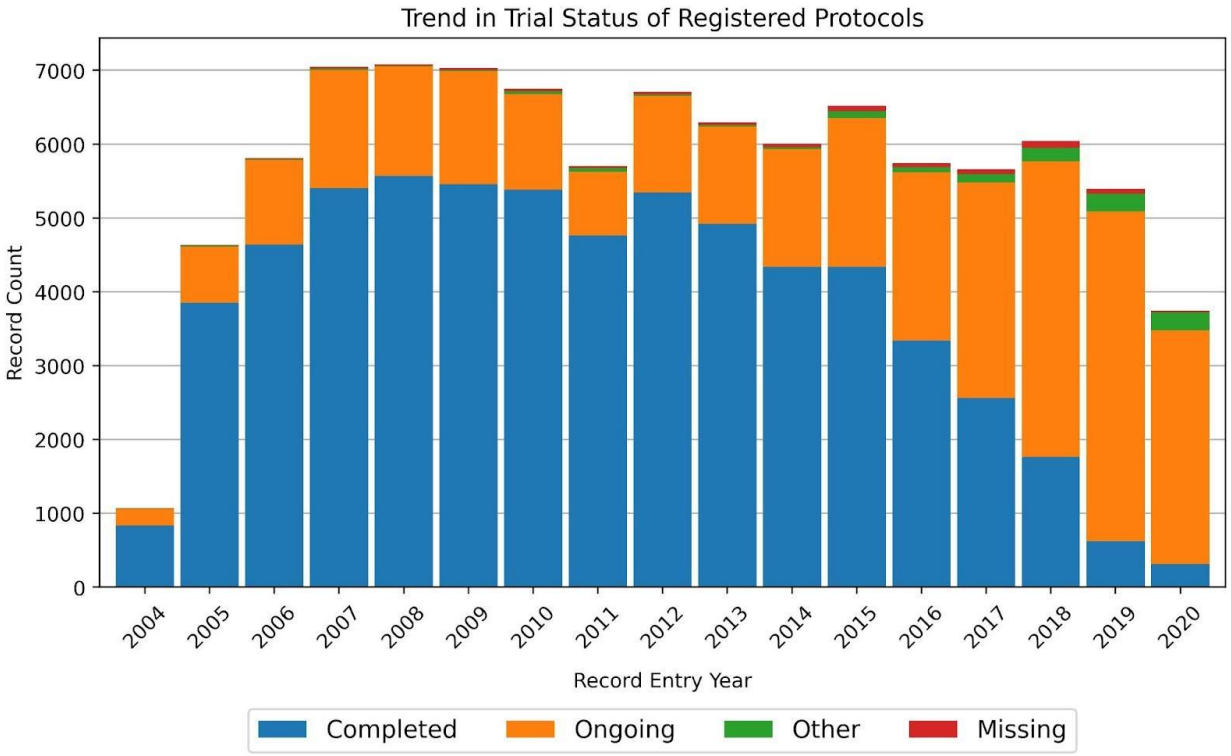
The annual trend in new protocol registrations approved by each country regulator by year. Countries with very few registration are excluded.

Appendix 6.4: Missing Protocols by Trial Entry Year



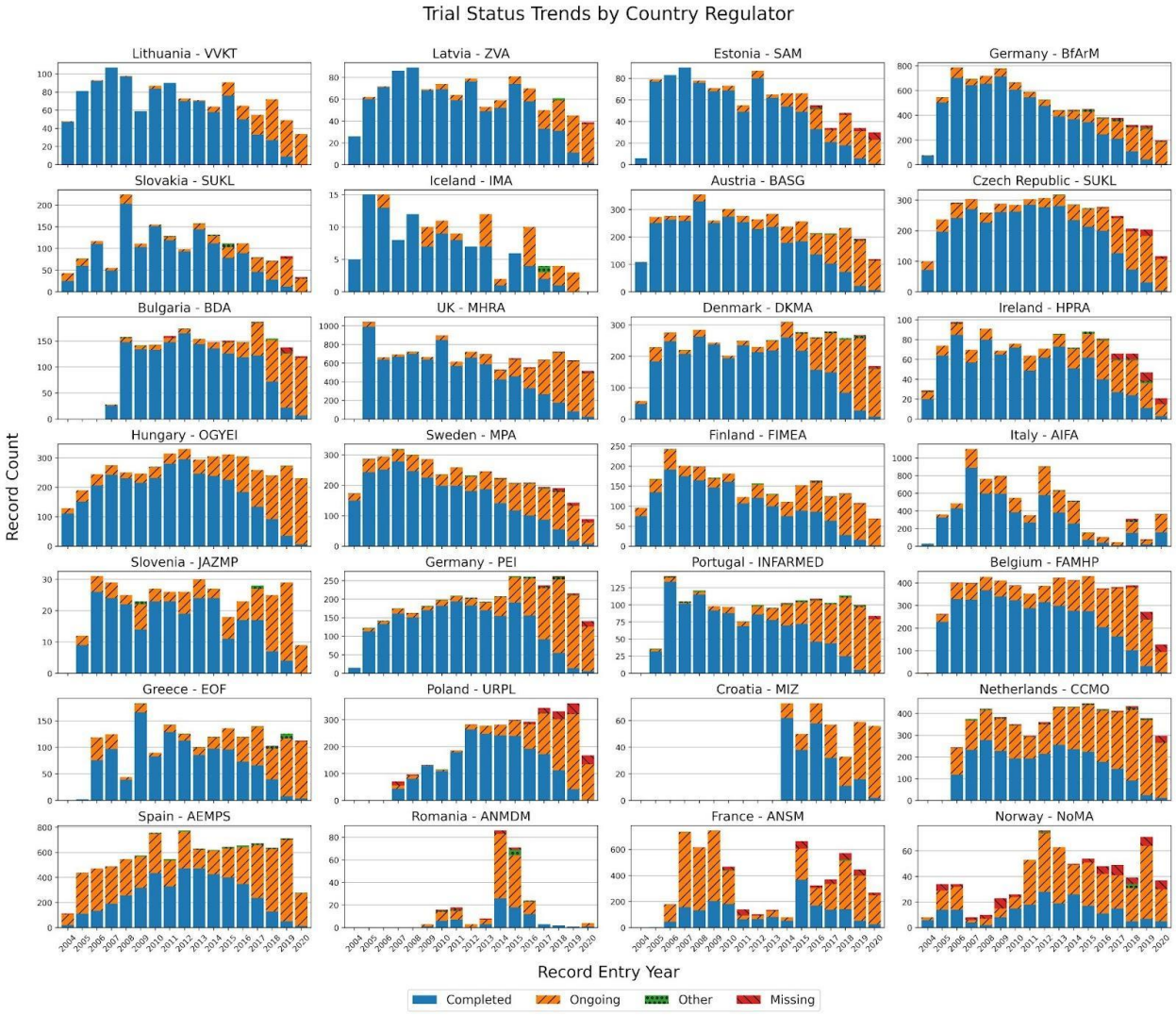
The bars represent the total number of missing protocols by the year in which the earliest public protocol was entered for the parent trial registration. The line represents the missing protocols for trials first entered in that year as a percentage of all publicly available protocols first entered in that year.

Appendix 6.5: Trial Status of Registered Protocols by Record Entry Year



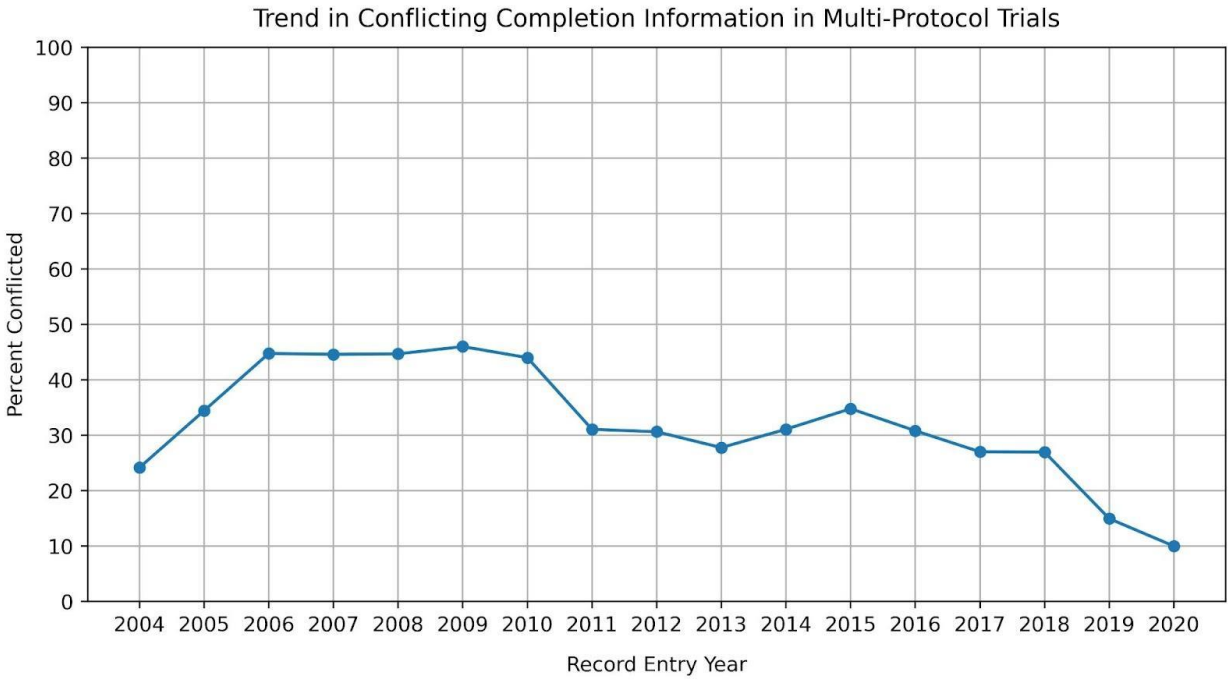
This graph shows the distribution of trial status for all protocols entered in each year. As expected the proportion of trials in a "Completed" status decreases over time as more recent trials are still ongoing.

Appendix 6.6: Trial Status by Country Regulator



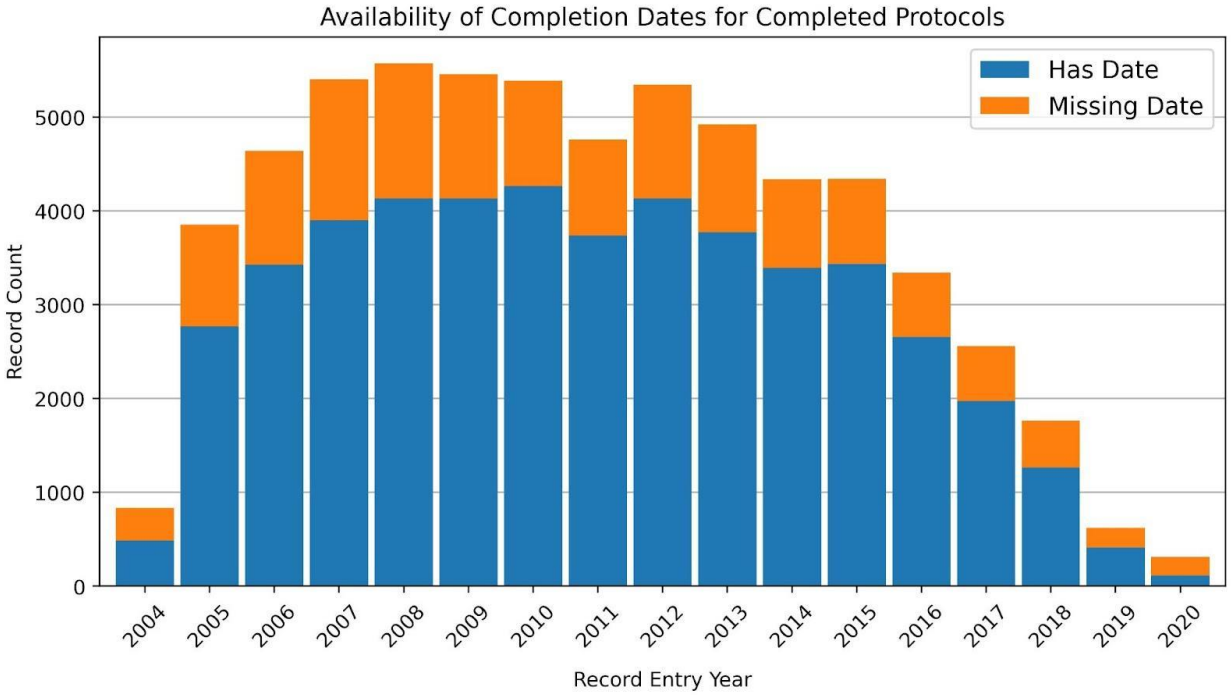
The typical trend in completion date availability can be seen across most countries.

Appendix 6.7: Trial with Conflicting Trial Status



The record entry year represents the latest record entry date across all protocols for a given trial. The percent of all trials from a given year currently have conflicting status information between protocols is shown.

Appendix 6.8: Availability of Completion Date for Completed Protocols



The overall trend in completion date availability by record entry year. Missing competition dates persist in the data beyond the "historical".

Appendix 6.9: Trends in Completion Date Availability by National Regulator

The availability of completion dates among all completed protocols is shown for each regulator with poor performance concentrated among a few sponsors.

Appendix 6.10: Dissemination Across All Sponsor Countries

	Any Result		EUCTR		ClinicalTrials.gov		ISRCTN		Journal	
Sponsor Country	Total	# Reported (%)	Total	# Reported (%)	Total	# Reported (%)	Total	# Reported (%)	Total	# Reported (%)
USA	68	57 (83.8%)	68	49 (72.1%)	65	41 (63.1%)	0	N/A	68	45 (66.2%)
UK	61	55 (90.2%)	61	46 (75.4%)	32	14 (43.8%)	21	1 (4.8%)	61	45 (73.8%)
Germany	59	44 (74.6%)	59	30 (50.8%)	41	7 (17.1%)	3	0	59	31 (52.5%)
France	49	36 (73.5%)	49	28 (57.1%)	39	11 (28.2%)	1	0	49	22 (44.9%)
Italy	46	25 (54.3%)	46	8 (17.4%)	16	3 (18.8%)	0	N/A	46	21 (45.7%)
Spain	35	18 (51.4%)	35	5 (14.3%)	20	0	0	N/A	35	17 (48.6%)
Netherlands	34	26 (76.5%)	34	9 (26.5%)	19	4 (21.1%)	3	1 (33.3%)	34	24 (70.6%)
Switzerland	29	28 (96.6%)	29	25 (86.2%)	27	19 (70.4%)	0	N/A	29	19 (65.5%)
Denmark	22	16 (72.7%)	22	14 (63.6%)	16	4 (25.0%)	1	0	22	12 (54.5%)
Belgium	21	15 (71.4%)	21	10 (47.6%)	14	7 (50.0%)	0	N/A	21	12 (57.1%)
Sweden	21	14 (66.7%)	21	11 (52.4%)	16	6 (37.5%)	0	N/A	21	10 (47.6%)
Austria	17	15 (88.2%)	17	7 (41.2%)	10	5 (50.0%)	2	N/A	17	14 (83.4%)
Multi-country	9	9 (100%)	9	9 (100%)	7	3 (42.9%)	0	N/A	9	5 (55.6%)
Finland	5	5 (100%)	5	1 (20%)	3	1 (33.3%)	0	N/A	5	4 (80%)
Australia	3	2 (66.7%)	3	2 (66.7%)	1	1 (100%)	0	N/A	3	1 (33.3%)
Ireland	3	2 (66.7%)	3	1 (33.3%)	0	N/A	0	N/A	3	2 (66.7%)

Hungary	3	3 (100%)	3	2 (66.7%)	2	0	0	N/A	3	2 (66.7%)
Japan	3	2 (66.7%)	3	2 (66.7%)	3	2 (66.7%)	0	N/A	3	2 (66.7%)
South Korea	2	2 (100%)	2	1 (50%)	2	1 (50%)	0	N/A	2	1 (50%)
Portugal	2	2 (100%)	2	2 (100%)	2	1 (50%)	0	N/A	2	0
Czechia	2	0	2	0	1	0	0	N/A	2	0
Canada	2	2 (100%)	2	1 (50%)	2	1 (50%)	1	0	2	2 (100%)
No Data Available	1	0	1	0	0	N/A	0	N/A	1	0
Noway	1	0	1	0	1	0	0	N/A	1	0
Greece	1	1 (100%)	1	1 (100%)	0	N/A	0	N/A	1	0
UAE	1	1 (100%)	1	0	1	1 (100%)	0	N/A	1	1 (100%)

Chapter 7

Appendix 7.1: Summarised Recommendations of the House of Commons Science and Technology Committee Trials Transparency Report and Government Response

	Committee Recommendation	Government Response
1	The Government should commit to introduce trial transparency provisions of the new EU regulations into UK law so they persist following Brexit.	The UK will either negotiate access to the new EU portal and implement the requirements or ensure the same information can be published on a national basis.
2	The Concordat to Support Research Integrity should include trial reporting requirements and efforts to share best practice in this space.	The Government has confirmed with Universities UK that this will be explicit in the Concordat with monitoring requirements.
3	Public Health England, and other NHS bodies, should explain its unreported trials and how this will be corrected.	Public Health England has responded to the committee and the HRA is taking steps to reach out to NHS Trusts about their reporting practices.
4	The Government should commit to trial transparency through a ministerial speech with clear timelines and consequences for non-compliance.	The Government and its bodies have taken recent action like revising the model clinical trial and strengthening policies around public trial funding.
5 & 6	The HRA should be resourced to establish a national audit programme of clinical trial transparency that tracks reporting on a per trial basis and weigh the potential costs of this against the benefits of reducing research waste.	The HRA is working on considering how best to address this in the future and will present their plans in a new transparency strategy.
7	The HRA should publish information about trials that are approved but not registered on a per trial basis.	The HRA agrees that it should publish more information and is working with the Government to determine the most effective way of achieving this including potentially expanding their current research summaries database.
8	The HRA should introduce a system of sanctions to drive improvement of transparency.	The HRA and the Government are considering the right balance of measures to put in place to improve transparency and the HRA will consult on this widely before moving forward.
9 & 10	The HRA should publish a detailed strategy on transparency with clear deadlines and milestones and the Government should clarify that it is the HRA who holds the power to address these issues and extend their remit if necessary.	The Government will address the HRA to develop this strategy and consult with the agency about how best to drive improvements in transparency.

Appendix 7.2: Interview Guide for Discussions of Trials Transparency at UK Public Research Institutions

Research Question: What are the barriers and best practices that impact the complete and timely registration and reporting of clinical trials at UK public research institutions?

Format: Semi-structured

Timeframe: 30-90 minutes

The questions in RED are core questions and can be prioritised in a time-limited situation.

Pre-Interview Reminders

1. Give short introduction to the interview (scripted, separate document)
2. Obtain oral consent if have not returned signed consent form
3. Make clear when recording starts.

Introduction

We'll be talking today about trial transparency at your organisation. We will generally focus on the registration and reporting of clinical trials but if you have other areas of trials transparency you would like to touch on, please feel free to include them in your responses. Ultimately, the aim of this research is to identify barriers and best practices to research that can be shared with the larger community to inform discussion and plans for improvement.

Part 1: Individual and Organisational Background (5-15 minutes)

In this section we will collect some basic information on research at the participant's organisation, the research support infrastructure in place, and their role within the organisation. This will allow for essential context for the rest of the interview and allow for establishment of rapport through these background questions.

Question 1: Can you tell me about your role?

- Potential follow-ups:
    - How are you involved with the registration and reporting of clinical trials?
    - How long have you worked in this area?
    - Can you talk about the responsibilities of anyone else in your organisation who works specifically in these areas?

Question 2: Tell me a bit about your organisation and the type of clinical research it undertakes?

- Potential follow-ups:
    - Probe on CTIMPS vs. non-CTIMPS as necessary based on response

Part 2: Investigating Participant's Reflections on Trials Transparency (5-10 minutes)
In this section the participants are asked to explain their understanding of trials transparency topics and reflect on their personal role in trials transparency at their organisation. This allows an overall sense of their understanding of the topic and hopefully their own underlying opinions on the value of these activities. These questions will most easily move around in the actual interview context.

Question 1: Can you explain to me, in your own words, why requirements for the registration and reporting of clinical trials are in place?

- Potential follow-ups:
    - Could there be any potential disagreements that arise from this expectation?

For senior participants:
Question S1: What has helped to inform the policies and procedures you have been involved in creating and implementing?

For junior participants:
Question J1: How do you feedback information about the registration and reporting process to those above you?

Part 3: How registration and reporting works at your organisation (20-45 minutes)
Here we get into the specifics of the policies and procedures at the institution as well as the specific role of the participant at the institution.

Question 1: Can you talk me through the process of how trials are registered at your organisation?

- Potential follow-ups:
    - How is that registration maintained throughout the trial process?
    - How is this process monitored?
    - What registries do you use?
    - Potentially ask to expand on specific examples or anecdotes from the response.

Question 2: When a trial is completed, what is the process for reporting the results of that trial?

- Potential follow-ups:
    - Are there different processes for different forms of dissemination, for example journal articles vs. putting results on a registry?
    - How is this process monitored?
    - Are you working to ensure older trials are reported? How?
    - Potentially ask to expand on specific examples or anecdotes from the response.

Question 3: How are you involved in these processes?

- Potential follow-ups:
    - Can you talk about any changes you've seen in these processes over time?
    - What was the impetus for these changes?

Question 4: What, in your opinion, has worked well about the way your organisation manages these processes?

- Potential follow-ups:
    - What could be the key aspects that allow these processes to work well?

Question 5: What has not worked well or could be improved in your experience?

- Potential follow-ups:
    - What could be biggest barriers to full compliance?
    - What could be the key aspects that allow these processes to not work well?

Question 6: Do you have any examples in which changes led to a barrier being removed or a process running more smoothly?

Question 7: Can you compare how the registration and reporting of clinical trials works at your current organisation compared to others you've worked at?

Question 8: Are you planning/aware of any impending changes to the way your organisation manages the registration and reporting of clinical trials?

Question 9: How would you describe top-level support for this work at your institution?

Question 10: Are you aware of how your organisation performs on ensuring trials are registered and reported according to legal or ethical standards? How?

Question 11: Have there been notable moments of external change or pressure in the trials transparency space that your organisation had to adapt or respond to?

- Potential follow-ups:
    - Consider prompting on external events if they have not been covered for example:
        - Brexit
        - House of Commons Letters
        - AllTrials
        - HRA Strategy

Part 4: Individual Support & Learning (10-20 minutes)

Here we will get to how knowledge, support, and best practice is shared and disseminated to the participant both by their organisation and from other entities.

Question 1: Can you talk about the level of practical support and training provided by your institution in these areas?

- Potential follow-ups:
    - What resources could support you in order to do your job successfully?
    - When does this training/support typically occur?

Question 2: When there are changes related to the processes for registering and reporting of clinical trials, how do you hear about them?

Question 3: What groups outside your organisation, if any, have been useful for you to learn about working on the registration and reporting of clinical trials?

- Potential follow-ups:
    - How could these groups external to your organisation better support you?
    - What about informal support and self-teaching?

Conclusion (5 minutes)

That is all my questions. Do you have any final thoughts or would you like to expand on anything else we talked about today? Is there anything you think I should have asked about but did not?

Thank you again for participating in this study. Do not hesitate to let me know if you have any questions related to your participation or if you would like to note any additional information related to what we talked about today. I'm also happy to share the transcript, my final analysis, or both with you for your review. Please let me know and we can arrange that.

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