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Peer Review File

Uptake and safety of Sotrovimab for prevention of severe COVID-19 and its safety in the community in England: cohort and self-controlled case series study

Corresponding Author: Professor Julia Hippisley-Cox

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
This is a very interesting study investigating the uptake of sotrovimab in the community using a cohort study design and the safety of Sotrovimab using SCCS study design in England. The study was well designed and showed important clinical significance.
There are some points for authors to consider:
1. The authors mentioned that SARS-CoV-2 positive tests was used as a time-varying confounding, but I'm not quite sure why. Could it be an instrumental variable instead?
2. I found Table 1 difficult to follow. I am not familiar with the current guideline of how a patient is eligible for receiving sotrovimab. According to the introduction section, confirmed SARS-CoV-2 infection by either reverse transcription-polymerase chain reaction (RT-PCR) testing or a lateral flow test was needed to be eligible for receiving sotrovimab. However, in Table 1, it shows 1,245,853 patients are eligible for receiving sotrovimab in the second column, but in the third column showed 172,860 people were also with SARS-CoV-2 positive test. However, I suppose 1,245,853 people also had a SARS-CoV-2 positive test to be eligible? I wondered if it's because of the records of SARS-CoV-2 positive test not being completed in the database for example missing records for lateral flow test in the community? In that case, why did authors separate into different groups based on people with SARS-CoV-2 positive test? A footnote would be helpful and how to determine whether they were eligible in this study/database with more explanations would be useful. I'd suggest a flowchart to show how many people were eligible, and of them how many of them were extremely clinical vulnerable, and of them how many were treated would be useful with other information who did/did not have positive test/non-treated etc.
3. Authors mentioned that first occurrence of event was defined as outcome for SCCS during the study period. As people who had admitted to hospital for the outcome in the two years prior the study start were excluded from the analysis, I wondered if people who had an outcome before study period that also occurred within 2 years before the first outcome identified during study period were also excluded. For some outcomes e.g. rheumatoid arthritis and systemic lupus erythematosus or other long-term disease, it could have been better to use all the hospital records before study period to exclude people with prevalent diseases rather than 2 years screening window. That makes me wonder without the data on primary care in this study, a lot of prevalent cases
would remain, possibly explaining the results of elevated risks on day 0 and day 1 which could be due to recording of history event only.
4. It would be better if authors can justify why 28 days was defined as risk periods – would another risk period shortly after 28 days be also considered as sensitivity analysis?
5. In line 168-170, the authors mentioned that "The baseline period comprised the remaining observation time from December 11, 2021 until 29 days before the date of Sotrovimab exposure and from 29 days after the exposure date until May 24, 2022 or the censored date, if earlier."; it would be better to specify what the censor date is – is it only the death date?
6. I wondered if the authors also need to comment on how low the proportion of people were treated even they were eligible for treatment. I'd also say it would be better to have formal statistical testing to show ethnicity was associated with lower uptake of treatment

Reviewer #2

(Remarks to the Author)
Thank you for inviting me to review this manuscript.

I would like to express my appreciation to the authors for their manuscript on the safety of sotrovimab in COVID-19, which

provides valuable new information. The manuscript is well-organized and thoroughly written, with the authors addressing all aspects effectively.

I have a few questions for clarification:

1. Was there any reported evidence of drug-drug interactions in patients receiving sotrovimab, considering the limited available information on this topic?
2. Given that the study period was between December 11, 2021, and April 28, 2022, has the safety of sotrovimab been impacted by new SARS-CoV-2 variants?

Reviewer #3

(Remarks to the Author)
Thanks for asking me to review this manuscript. This is a well-written paper describing a highly technical study designed to seek out important side effects of sotrovimab treatments. This reviewer does not claim detailed technical knowledge of the statistical approach adopted, but the use of different data sources and the logic behind the analyses is explained. I suggest a more detailed description of the statistical methodology be placed in an appendix- many readers will not be familiar with the self-controlled case series approach- including me.
The authors also sought data on treatment inequalities.
The MS is persuasively written and has achieved what the authors set out to do.
The authors found a number of patients who had been treated with sotrovimab without obvious high-risk criteria. We also found this in a previous study and found patients had a shielding SNOMED code (1300561000000107; high-risk category for developing complication from coronavirus disease 19 caused by severe acute respiratory syndrome coronavirus 2 infection). Many such patients had clinic appointments with services who normally cared for patients with high risk. So this maybe a coding idiosyncrasy.
The observation of inequality by ethnic group is very clear, and should inform future policy.
I suggest the authors explain a little clearer how deaths in the community would have been captured in their analysis.
The authors have provided the reader with a thorough reflection on strengths and limitations of their work.
Otherwise, to me, this is an impressive use of routinely collected data to answer important clinical questions.

Professor Stephen Brett
Imperial College London

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
Thanks for explaining why COVID-19 positive tests was included as time-varying confounder in SCCS - it would be useful to further explain (perhaps in the appendix) how you would implement that - how long would be the "risk window" for positive tests and so as the COVID-19 vaccination when you did the adjustment.

About another comment: in Table 1, it shows 1,245,853 patients are eligible for receiving Sotrovimab in the second column, but in the third column showed 172,860 people were also with SARS-CoV-2 positive test. It seems that it suggested that the SARS-CoV-2 positive test was not complete in the database, if you assume 1,245,853 should have positive tests. I think it would be important as it shows possible misclassification bias - it would be useful to address them in the limitation

Reviewer #2

(Remarks to the Author)
I would like to thank the authors for addressing my concerns. The authors have thoroughly addressed my concerns regarding the manuscript.

Reviewer #3

(Remarks to the Author)
My suggestions and comments have been adequately addressed.

I think this MS contains useful information.

Version 2:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
I don't have any further questions or comments

Response to Referees

Reviewer 1:

This is a very interesting study investigating the uptake of Sotrovimab in the community using a cohort study design and the safety of Sotrovimab using SCCS study design in England. The study was well designed and showed important clinical significance.

There are some points for authors to consider:

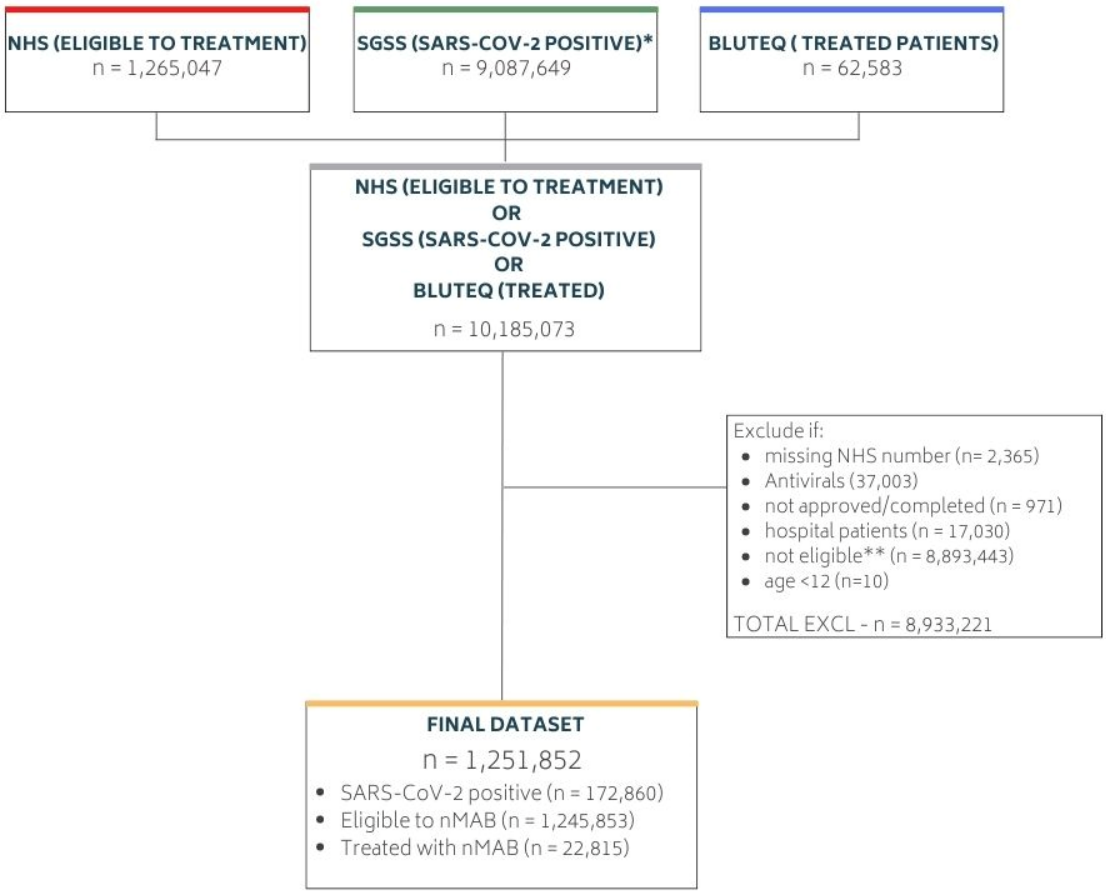
1. The authors mentioned that SARS-CoV-2 positive tests was used as a time-varying confounding, but I'm not quite sure why. Could it be an instrumental variable instead?

RESPONSE: Thank you for your question. Evidence suggests that SARS-CoV-2 infections provide an effective but waning level of immunity/protection against future infection comparable to the nature of the immunity provided through vaccination. For this reason, both COVID-19 vaccinations and SARS-CoV-2 positive tests were treated as time-varying factors to account for the temporarily heightened immune-response. This is now explained more clearly in the revised Methods section as indicated below:

"In each model in the self-controlled case series analysis, we treated a first, second, third or fourth dose of the three main COVID-19 vaccines in use in the UK (I.e., ChAdOx1, BNT162b2 or mRNA-1273) as time-varying factors. Due to the small number of events, we did not stratify by vaccine type. We also included SARS-CoV-2 positive tests as a time-varying confounder. COVID-19 vaccinations and SARS-CoV-2 positive tests were treated as time-varying factors to account for the temporarily heightened immune-response brought on by both [13]. Age was not included in the model (I.e., was treated as a fixed variable) because the study period was short."

2. I found Table 1 difficult to follow. I am not familiar with the current guideline of how a patient is eligible for receiving sotrovimab. According to the introduction section, confirmed SARS-CoV-2 infection by either reverse transcription-polymerase chain reaction (RT-PCR) testing or a lateral flow test was needed to be eligible for receiving sotrovimab. However, in Table 1, it shows 1,245,853 patients are eligible for receiving Sotrovimab in the second column, but in the third column showed 172,860 people were also with SARS-CoV-2 positive test. However, I suppose 1,245,853 people also had a SARS-CoV-2 positive test to be eligible? I wondered if it's because of the records of SARS-CoV-2 positive test not being completed in the database for example missing records for lateral flow test in the community? In that case, why did authors separate into different groups based on people with SARS-CoV-2 positive test? A footnote would be helpful and how to determine whether they were eligible in this study/database with more explanations would be useful. I'd suggest a flowchart to show how many people were eligible, and of them how many of them were extremely clinical vulnerable, and of them how many were treated would be useful with other information who did/did not have positive test/non-treated etc.

RESPONSE: Thank you for your comments. 1,245,853 patients were potentially eligible for treatment, as they met NHS vulnerability criteria, assuming they went on to receive a positive SARS-CoV-2 test result. In total, 22,815 patients were treated and of these 5,999 patients were treated despite not being on the eligible list. A flow chart (see below) describing the data flow is available as supplementary figure 1. The Authors will include the flow diagram in the main figures as "Figure 1" so that it is more accessible to the reader.



*Between December1, 2021 and May 24, 2022; **Exclude patients not eligible to nMAB if they were not treated.

3. Authors mentioned that first occurrence of event was defined as outcome for SCCS during the study period. As people who had admitted to hospital for the outcome in the two years prior the study start were excluded from the analysis, I wondered if people who had an outcome before study period that also occurred within 2 years before the first outcome identified during study period were also excluded. For some outcomes e.g. rheumatoid arthritis and systemic lupus erythematosus or other long-term disease, it could have been better to use all the hospital records before study period to exclude people with prevalent diseases rather than 2 years screening window. That makes me wonder without the data on primary care in this study, a lot of prevalent cases would remain, possibly explaining the results of elevated risks on day 0 and day 1 which could be due to recording of history event only.

RESPONSE: - Thank you for your comment. It is possible that some of the patients who were hospitalised may have had a history of one of more of the study outcomes, prior to or during the 2-year exclusion window, reflected in their GP records. However, for the purposes of this study, we were only interested in excluding/identifying patients with severe outcomes resulting in hospitalisation, regardless of whether the patient had been previously diagnosed with the outcome. To prevent the misclassification of ICD10 codes representing historic outcomes, which may appear in a patient's admission record, only hospitalisations with study outcomes recorded as the primary reason for admission were classified as qualifying events for the analyses. Please see the amended manuscript text below:

"The outcomes were defined as the first hospital admission due to the outcome of interest (where the primary reason for admission) or a death, with an ICD-10 code related to the outcome recorded on the death certificate, within the study period."

4. It would be better if authors can justify why 28 days was defined as risk periods – would another risk period shortly after 28 days be also considered as sensitivity analysis?

RESPONSE: 28 days is a commonly used, standardised risk period used to assess short-term health outcomes relating to clinical interventions or treatments. We determined that it was likely that any adverse health events would occur within 28 days of treatment with Sotrovimab. Therefore, analysis of adverse events occurring > 28 days after treatment was beyond the scope of this study as the focus was on assessing short term safety. 28 days was also selected to ensure that the risk periods aligned with those used in the PANORAMIC Trial. Please see reference below:

"Butler, C. C., et al. (2023). "Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial." The Lancet 401(10373): 281-293."

5. In line 168-170, the authors mentioned that "The baseline period comprised the remaining observation time from December 11, 2021 until 29 days before the date of Sotrovimab exposure and from 29 days after the exposure date until May 24, 2022 or the censored date, if earlier."; it would be better to specify what the censor date is – is it only the death date?

RESPONSE: Thank you. Yes, this is correct – we only used the date of death as the censor date. See updated text below:

"The baseline period comprised the remaining observation time from December 11, 2021 until 29 days before the date of Sotrovimab exposure and from 29 days after the exposure date until May 24, 2022 or the censored date (death), if earlier."

6. I wondered if the authors also need to comment on how low the proportion of people were treated even they were eligible for treatment. I'd also say it would be better to have formal statistical testing to show ethnicity was associated with lower uptake of treatment

RESPONSE: Thank you for your comment. Formal testing, in the form of multivariable logistic regression, has been conducted and added to the manuscript. The following text has been added to the Results section:

"Results from the multivariable analyses are reported in Table 3. Patients of Pakistani (OR 0.76; 95% CI 0.64, 0.91), Black Caribbean (OR 0.61; 95% CI 0.51, 0.72), Black African (OR 0.41; 95% CI 0.36, 0.48), "Other" (OR 0.77; 95% CI 0.69, 0.86), and those with no recorded ethnicity (OR 0.59; 95% CI 0.56, 0.63) had lower odds of uptake compared to those of White ethnicity, while those of Indian ethnicity (OR 1.18, 95% CI 1.07, 1.30) showed higher odds of uptake. Those of male sex (OR 0.88; 95% CI 0.85, 0.90) or no recorded sex (OR 0.28; 95% CI 0.19, 0.42) were less likely to be treated than females. Patients between the ages of 30-39 (OR 1.16; 95% CI 1.08, 1.25), 40-49 (OR 1.30; 95% CI 1.22, 1.40), 50-59 (OR 1.23; 95% CI 1.15, 1.31), 60-69 (OR 1.17; 95% CI 1.09, 1.26) were more likely to be treated than the baseline group (17-29), while those between 80-89 (OR 0.54; 95% CI 0.50, 0.60) and above 90 years (OR 0.28; 95% O.23, 0.35) of age were significantly less likely to be treated. Patients with at least 1 vaccination dose were significantly more likely to be treated than patients with no history of vaccination, with the greatest difference observed amongst those receiving 4 doses prior to treatment (OR 6.29; 95% CI 5.42, 7.30). Patients with a record of hospital admission relating to pre-specified blood (OR 1.77; 95% CI 1.55, 2.02), neurological (OR 1.42; 95% CI 1.33, 1.50), or cardiovascular (OR 1.59; 95% CI 1.52, 1.66) conditions in the preceding 2 years, were more likely to be treated than those with no record."

The complete results of the analyses can be found in Table 3.
Regarding the low proportion of people treated, the following text has been added to the Discussion:

"The causes behind the relatively low levels of uptake reported in this study and others are unknown and should be the subject of future research. However, it's possible but not substantiated that stockpiling of available treatments; unequal distribution; hesitancy to adopt treatments by patients or providers; or barriers to patient access to treatments requiring intravenous infusion may have been contributing factors [16]."

Reviewer #2 (Remarks to the Author):

Thank you for inviting me to review this manuscript.
I would like to express my appreciation to the authors for their manuscript on the safety of sotrovimab in COVID-19, which provides valuable new information. The manuscript is well-organized and thoroughly written, with the authors addressing all aspects effectively.

RESPONSE: We're very grateful for your kind comments – thank you!

I have a few questions for clarification:

1. Was there any reported evidence of drug-drug interactions in patients receiving sotrovimab, considering the limited available information on this topic?

RESPONSE: Assessing drug-drug interactions wasn't within scope of study. We have added a sentence to the discussion to highlight this as an area for future research. Please see below:

> "Assessing drug-drug Interactions (DDI) was beyond the scope of this study. However, as Sotrovimab is neither renally excreted nor metabolised by cytochrome P450 enzymes, interactions with medications which are renally excreted or are substrates, inducers, or inhibitors of CYP enzymes, are unlikely [17]. A recently published Expert Opinion by Davoutis et al. (2023) examining the evidence for the risk of DDI between COVID-19 drug therapies and antidepressants, reported a low risk of potential DDI between Sotrovimab and antidepressants [18]. However, the body of literature analysing the risk of DDI's with Sotrovimab and COVID-19 therapeutics, generally, is very small."

2. Given that the study period was between December 11, 2021, and April 28, 2022, has the safety of Sotrovimab been impacted by new SARS-CoV-2 variants?

RESPONSE: Thank you for your comment. The discussion has been amended as follows:

> "At present, the evidence suggests that the safety of Sotrovimab in COVID-19 patients does not seem to differ depending on the SARS-CoV-2 variant detected. The review by Amani & Amani (2022) (introduced above) found no significant difference in the risk of adverse events from treatment with Sotrovimab based on SARS-CoV-2 variant type (Omicron and Delta)."

Reviewer #3 Professor Stephen Brett, Imperial College London

Thanks for asking me to review this manuscript. This is a well-written paper describing a highly technical study designed to seek out important side effects of sotrovimab treatments. This reviewer does not claim detailed technical knowledge of the statistical approach adopted, but the use of different data sources and the logic behind the analyses is explained. I suggest a more detailed description of the statistical methodology be placed in an appendix- many readers will not be familiar with the self-controlled case series approach- including me.
The authors also sought data on treatment inequalities.
The MS is persuasively written and has achieved what the authors set out to do.

- Thank you for your kind remarks!

RESPONSE: Thank you for the suggestion. Readers will be directed to an appendix which will be submitted alongside the main manuscript. Please see additional text added to the "Study Design" section below:

"Further reading and resources on the SCCS method and analyses may be found in Appendix 1."

The authors found a number of patients who had been treated with sotrovimab without obvious high-risk criteria. We also found this in a previous study and found patients had a shielding SNOMED code (1300561000000107; high-risk category for developing complication from coronavirus disease 19 caused by severe acute respiratory syndrome coronavirus 2 infection). Many such patients had clinic appointments with services who normally cared for patients with high risk. So this maybe a coding idiosyncrasy.

RESPONSE: Thank you for the comment! Please see additional text below which has been added to the Discussion:

"It is also possible that these "non-eligible" patients were considered high-risk at an earlier time, but were removed from the high-risk category as they no longer met all criteria in accordance with national methodology, or were removed by their hospital consultant/GP practice [13]. Patel et al. (2022) found that most patients treated with a COVID-19 therapeutic without clear evidence of a high-risk condition had a SNOMED code (1300561000000107) used to identify high-risk patients requiring shielding present in their GP records [14]. This indicates that they were considered at high-risk of developing COVID-19-related complications at some point during the pandemic. Many such patients also had active outpatient appointments for renal, oncology, haematology, rheumatology, or gastroenterology services."

The observation of inequality by ethnic group is very clear, and should inform future policy.

RESPONSE: - Thank you.

I suggest the authors explain a little clearer how deaths in the community would have been captured in their analysis.

RESPONSE: In the UK, all deaths are recorded on the mortality register by the Office of National Statistics regardless of whether the deaths are in hospital or in the community. These data were linked to the national Blueteq database and are included in the analysis. Please find our amended manuscript text below:

"The baseline period comprised the remaining observation time from December 11, 2021 until 29 days before the date of Sotrovimab exposure and from 29 days after the exposure date until May 24,

2022 or the censored date (death), if earlier. All UK deaths (hospital or community) were captured in the ONS mortality dataset."

The authors have provided the reader with a thorough reflection on strengths and limitations of their work.

RESPONSE: - Thank you

Otherwise, to me, this is an impressive use of routinely collected data to answer important clinical questions.

RESPONSE: Thank you

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Reviewers' comments:

Reviewer #1 (Remarks to the Author):

Thanks for explaining why COVID-19 positive tests was included as time-varying confounder in SCCS - it would be useful to further explain (perhaps in the appendix) how you would implement that - how long would be the "risk window" for positive tests and so as the COVID-19 vaccination when you did the adjustment.

Thank you for the question. The following text has been added to manuscript:

"This was achieved though the creation of grouped (29 days or earlier (baseline); 28 to 1 day prior; 0 days (exposure date); 1 day post exposure; 2 to 28 days post exposure; 29 days or later (baseline)), exposure categories. These grouped variables were adjusted for in the final models for each outcome. A link to example code can be found in the "Code availability" section."

About another comment: in Table 1, it shows 1,245,853 patients are eligible for receiving Sotrovimab in the second column, but in the third column showed 172,860 people were also with SARS-CoV-2 positive test. It seems that it suggested that the SARS-CoV-2 positive test was not complete in the database, if you assume 1,245,853 should have positive tests. I think it would be important as it shows possible misclassification bias - it would be useful to address them in the limitation:

Thank you for your feedback. A total of 1,245,853 patients were considered "eligible" for treatment, as they met NHS vulnerability criteria, but only fully qualified for treatment once they received a positive SARS-CoV-2 test. Having received a positive SARS-CoV-2 test was not included in the NHS's vulnerability criteria. Further, we would not expect all potentially eligible patients to have a positive test. In total, 22,815 patients were treated and of those treated, 5,999 were not on the NHS's vulnerable list. Of the 22,815 patients treated, 21,487 received a positive SARS-CoV-2 test result of which 5,378 were not on the eligible list.

Notes have been added at the bottom of table 1. Please see below:

Table 1. Demographic characteristics of patients receiving Sotrovimab treatment in the community and patients who did not, amongst those eligible for treatment in the community in England between December 11, 2021 until May 24, 2022. Figures are counts (column %).

	Eligible for or treated with Sotrovimab [1]	**Eligible for or treated with Sotrovimab (SARS-CoV-2 positive)**	**Treated with Sotrovimab (SARS-CoV-2 positive)**	**Not treated with Sotrovimab (SARS-CoV-2 positive)**
	Counts (col %)	*Counts (col %)*	*Counts (col %)*	*Counts (col %)*
Total number of people	1,251,852	172,860	21,487 [3]	151,373
Eligible for Sotrovimab [1]	1,245,853 (99.5)	167,482 (96.9)	16,109 (75.0)	151,373 (100.0)
SARS-CoV-2 positive	172,860 (13.8)	172,860 (100.0)	21,487 [3] (100.0)	151,373 (100.0)

Sotrovimab treated patients	22,815 [2] (1.8)	21,487 [3] (12.4)	21,487 [3] (100.0)	0
COVID-19 symptomatic	66,425 (5.3)	66,425 (38.4)	8,089 [4] (37.6)	58,336 (38.5)
Sex				
Women	685,635 (54.8)	100,975 (58.4)	13,090 (60.9)	87,885 (58.1)
Men	555,369 (44.4)	70,616 (40.9)	8,369 (38.9)	62,247 (41.1)
Not recorded	10,848 (0.9)	1,269 (0.7)	28 (0.1)	1,241 (0.8)
Age				
Mean age (SD)	60.6 (17.5)	54.1 (18.1)	54.6 (16.1)	54.1 (18.3)
12-16 years	16,196 (1.3)	3,743 (2.2)	238 (1.1)	3,505 (2.3)
17-29 years	54,585 (4.4)	13,118 (7.6)	1,230 (5.7)	11,888 (7.9)
30-39 years	88,888 (7.1)	22,240 (12.9)	2,585 (12.0)	19,655 (13.0)
40-49 years	134,921 (10.8)	28,559 (16.5)	3,887 (18.1)	24,672 (16.3)
50-59 years	216,402 (17.3)	34,567 (20.0)	4,796 (22.3)	29,771 (19.7)
60-69 years	242,880 (19.4)	30,000 (17.4)	4,369 (20.3)	25,631 (16.9)
70-79 years	269,058 (21.5)	25,193 (14.6)	3,257 (15.2)	21,936 (14.5)
80-89 years	136,111 (10.9)	11,080 (6.4)	917 (4.3)	10,163 (6.7)
90+ years	19,323 (1.5)	2,236 (1.3)	97 (0.5)	2,139 (1.4)
Not recorded	73,488 (5.9)	2,124 (1.2)	111 (0.5)	2,013 (1.3)
Ethnicity				
White	979,195 (78.2)	137,892 (79.8)	18,552 (86.3)	119,340 (78.8)
Indian	24,788 (2.0)	3,184 (1.8)	479 (2.2)	2,705 (1.8)
Pakistani	16,735 (1.3)	1,689 (1.0)	144 (0.7)	1,545 (1.0)
Bangladeshi	4,240 (0.3)	473 (0.3)	54 (0.3)	419 (0.3)
Other Asian	9,138 (0.7)	1,201 (0.7)	165 (0.8)	1,036 (0.7)
Black Caribbean	17,723 (1.4)	2,064 (1.2)	132 (0.6)	1,932 (1.3)
Black African	34,216 (2.7)	4,191 (2.4)	197 (0.9)	3,994 (2.6)
Chinese	2,613 (0.2)	289 (0.2)	43 (0.2)	246 (0.2)
Other ethnic group	28,421 (2.3)	3,867 (2.2)	349 (1.6)	3,518 (2.3)
Ethnicity not recorded	134,783 (10.8)	18,010 (10.4)	1,372 (6.4)	16,638 (11.0)
Vaccine status (prior to treatment /end of the study if not treated)				
No vaccine	84,324 (6.7)	7,743 (4.5)	305 (1.4)	7,438 (4.9)
1 dose only	23,295 (1.9)	3,201 (1.9)	206 (1.0)	2,995 (2.0)
2 doses only	114,269 (9.1)	17,577 (10.2)	1,120 (5.2)	16,457 (10.9)
3 doses only	819,307 (65.4)	116,589 (67.4)	14,480 (67.4)	102,109 (67.5)
4 doses only	210,657 (16.8)	27,750 (16.1)	5,376 (25.0)	22,374 (14.8)
Hospital admission in the previous two years for				
Cardiovascular				

Venous thromboembolism	17,695 (1.4)	1,859 (1.1)	390 (1.8)	1,469 (1.0)
Immune thrombocytopenic purpura	18,358 (1.5)	2,003 (1.2)	474 (2.2)	1,529 (1.0)
Arterial thromboembolism	63,382 (5.1)	6,017 (3.5)	882 (4.1)	5,135 (3.4)
Cerebral venous thrombosis	75 (0.0)	15 (0.0)	4 (0.0)	11 (0.0)
Other arterial thrombosis	2,955 (0.2)	242 (0.1)	41 (0.2)	201 (0.1)
Myocardial infarction	51,258 (4.1)	4,801 (2.8)	717 (3.3)	4,084 (2.7)
Ischaemic stroke	11,820 (0.9)	1,197 (0.7)	159 (0.7)	1,038 (0.7)
Myocarditis	634 (0.1)	81 (0.0)	18 (0.1)	63 (0.0)
Pericarditis	590 (0.0)	83 (0.0)	18 (0.1)	65 (0.0)
Atrial fibrillation	82,121 (6.6)	8,006 (4.6)	1,222 (5.7)	6,784 (4.5)
Heart block	32,678 (2.6)	3,223 (1.9)	483 (2.2)	2,740 (1.8)
Ventricular tachycardia	2,059 (0.2)	223 (0.1)	34 (0.2)	189 (0.1)
Ventricular fibrillation	482 (0.0)	51 (0.0)	13 (0.1)	38 (0.0)
Arrhythmia	127,781 (10.2)	13,437 (7.8)	2,154 (10.0)	11,283 (7.5)
Neurological				
Demyelinating disorders	2,658 (0.2)	454 (0.3)	83 (0.4)	371 (0.2)
Myasthenia	6,825 (0.5)	915 (0.5)	161 (0.7)	754 (0.5)
Guillain Barre syndrome	611 (0.0)	74 (0.0)	14 (0.1)	60 (0.0)
Encephalitis	1,465 (0.1)	202 (0.1)	33 (0.2)	169 (0.1)
Haemorrhagic stroke	1,345 (0.1)	142 (0.1)	19 (0.1)	123 (0.1)
Subarachnoid haemorrhage	696 (0.1)	81 (0.0)	7 (0.0)	74 (0.0)
Bell's Palsy	2,385 (0.2)	275 (0.2)	42 (0.2)	233 (0.2)
Multiple sclerosis	45,371 (3.6)	6,986 (4.0)	1,176 (5.5)	5,810 (3.8)
Optic neuritis	1,375 (0.1)	226 (0.1)	47 (0.2)	179 (0.1)
Blood conditions				
Aplastic anaemia	6,862 (0.5)	726 (0.4)	180 (0.8)	546 (0.4)
Pernicious anaemia	3,073 (0.2)	383 (0.2)	77 (0.4)	306 (0.2)
Haemolytic anaemia	1,816 (0.1)	283 (0.2)	65 (0.3)	218 (0.1)
Disseminated intravascular coagulation	82 (0.0)	11 (0.0)	<5	7 (0.0)
Other conditions				
Coeliac disease	4,265 (0.3)	694 (0.4)	133 (0.6)	561 (0.4)
Anaphylaxis	822 (0.1)	144 (0.1)	28 (0.1)	116 (0.1)
Cholangitis	4,740 (0.4)	620 (0.4)	137 (0.6)	483 (0.3)
Acute pancreatitis	4,753 (0.4)	511 (0.3)	94 (0.4)	417 (0.3)
Autoimmune hepatitis	4,674 (0.4)	777 (0.4)	191 (0.9)	586 (0.4)
Acute renal failure	75,733 (6.0)	7,286 (4.2)	1,426 (6.6)	5,860 (3.9)
Rhabdomyolysis	1,707 (0.1)	190 (0.1)	25 (0.1)	165 (0.1)
Acute liver failure	5,292 (0.4)	478 (0.3)	96 (0.4)	382 (0.3)
Jaundice	50 (0.0)	7 (0.0)	1 (0.0)	6 (0.0)
Angioedema	1,064 (0.1)	169 (0.1)	23 (0.1)	146 (0.1)

Transplant rejection	7,562 (0.6)	1,100 (0.6)	306 (1.4)	794 (0.5)
Bullous pemphigoid	2,657 (0.2)	290 (0.2)	34 (0.2)	256 (0.2)
Inflame arthropathy	33,965 (2.7)	3,691 (2.1)	642 (3.0)	3,049 (2.0)
Rheumatoid arthritis	42,621 (3.4)	5,294 (3.1)	1,191 (5.5)	4,103 (2.7)
Systemic lupus erythematosus	7,627 (0.6)	1,356 (0.8)	313 (1.5)	1,043 (0.7)
Addison's disease	6,789 (0.5)	944 (0.5)	227 (1.1)	717 (0.5)
Crohn's disease	21,584 (1.7)	4,626 (2.7)	783 (3.6)	3,843 (2.5)
Colitis	21,725 (1.7)	4,357 (2.5)	687 (3.2)	3,670 (2.4)
Thyroiditis	874 (0.1)	165 (0.1)	40 (0.2)	125 (0.1)
Vasculitis	15,566 (1.2)	1,972 (1.1)	414 (1.9)	1,558 (1.0)
Gastrointestinal bleeding	27,689 (2.2)	3,014 (1.7)	554 (2.6)	2,460 (1.6)

[1] Patients were considered “eligible” for treatment if they met NHS vulnerability criteria, but only fully qualified once they received a positive SARS-CoV-2 test.
[2] Includes 5,999 patients who were not on the NHS’s vulnerable list.
[3] Includes 5,378 patients who were not on the NHS’s vulnerable list.
[4] Includes 1,530 patients who were not on the NHS’s vulnerable list.

Reviewer #2 (Remarks to the Author):

I would like to thank the authors for addressing my concerns. The authors have thoroughly addressed my concerns regarding the manuscript.

Reviewer #3 (Remarks to the Author):

My suggestions and comments have been adequately addressed.

I think this MS contains useful information.