OpenSAFELY Protocol: Effectiveness of paxlovid use vs non-use

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Version	***Notes***
1.0	*Descriptive analysis to inform details surrounding sequential trials analysis*
2.0	*More detailed description of sequential trials approach informed by descriptive analyses. Details of subgroup analyses, sensitivity analysis and supplementary analyses (QBA) to be discussed with the wider study team.*
3.0	*Final description of sequential trials approach, subgroup analyses, sensitivity analyses and supplementary analyses (QBA). These analyses were informed by the results of the descriptive analyses described in earlier versions of the protocol.*

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Background

- In December 2021, COVID-19 medicine delivery units (CMDUs) were launched across England to offer antiviral medicines and neutralising monoclonal antibodies (nMABs) to nonhospitalised COVID-19 patients thought to be at high risk of severe outcomes.[1,2]
- On 10 February 2022, paxlovid (nirmatrelvir plus ritonavir, an oral antiviral) was introduced as first line medication in England. The approval and adaptation was largely driven by evidence from randomised trials in unvaccinated populations before the Omicron wave.[3]
- Amid understandable concerns surrounding early regulatory authorisations,[4] changes in population level immunity, and the emergence of new SARS-CoV-2 variants, noninterventional evidence surrounding the effectiveness of these medications is needed to guide policy surrounding the use of these medications in routine clinical practice.
- Using the target trial framework,[5] we aim to emulate a randomised trial using observational data to estimate the effectiveness of paxlovid versus no-treatment, amongst nonhospitalised COVID-19 patients in the high-risk groups where consideration of treatment was recommended in the United Kingdom.

Objectives

Primary Objectives

1. To estimate the risk of COVID-19 related hospitalisation or death within 28 days associated with use of paxlovid versus no-treatment in non-hospitalised high-risk COVID-19 patients.
2. To estimate the difference in 28-day survival in people treated with paxlovid versus no-treatment in non-hospitalised high-risk COVID-19 patients.

Methods

Data Source

Primary care records managed by the GP software provider TPP SystmOne in England were accessed through the OpenSAFELY platform, where all data were linked, stored and analysed securely (https://opensafely.org/). Data include pseudonymised data such as coded diagnoses, medications and physiological parameters. No free text data are included. The following linked data were also used for this study: patient-level vaccination status is available via the National Immunisation Management System (NIMS); accident and emergency (A&E) attendance and in-patient hospital spell records via NHS Digital's Hospital Episode Statistics (HES) provided to OpenSAFELY via NHS Digital's Secondary Use Service (SUS); national coronavirus testing records via the Second Generation Surveillance System (SGSS); and the "COVID-19

therapeutics dataset", a patient-level dataset on antiviral and nMAbs treatments, sourced from NHS England and derived from Blueteq software that CMDUs use to notify NHS England of COVID-19 treatments. Detailed pseudonymised patient data is potentially re-identifiable and therefore not shared.

Study Design and Patient Selection

The target trial specification observational emulation and challenges surrounding data for observational emulation are outlined below (summarised in Table 1).

We will conduct a population-based cohort study with all adults (≥ 18 years old) registered at a TPP practice within OpenSAFELY between 10th February 2022 and 9th February 2023 who:

a) Tested positive with SARS-CoV-2 infection (PCR or lateral flow test) [only first positive spell of all individuals will be used]

b) ≥ 1 risk factor for disease progression at time of positive test. Defined as member of high-risk cohort (see Figure 1 as described by Green et al)[6]. Operationally, this will be defined using EHR-derived data only (instead of CMDU).

c) Complete data on age, sex, STP or IMD.

The following exclusion criteria will be applied:

a) Treated with remdesivir in a community setting in the 28 days after positive test*.

b) Treatment history in the previous 90 days of any antivirals or nMABs in a community setting for COVID-19 prior to positive test

c) Hospitalised at the date of entry; admitted to hospital or experiencing death at date of positive test.

d) Evidence of COVID-19 infection up to 90 days before current test-positive spell (i.e. evidence of previous COVID-19 spell evident by positive test or hospitalisation)

e) Contraindicated for treatment: advanced decompensated liver cirrhosis; regular ascitic drainage; admitted to hospital with liver disease; stage 4-5 chronic kidney disease; dialysis; renal replacement therapy; solid organ or Islet transplant recipient; or taking medications with potential drug-drug interactions in the previous 180 days on date of positive test**.[7,8]

*Criterium a) will exclude a group of approximately 70 patients treated with remdesivir in CMDUs. This is a pragmatic choice to avoid complexities around censoring patients who initiate remdesivir during follow-up.

**The codelist used to identify patients taking medications with potential drug-drug interactions will be created using the University of Liverpool COVID-19 Drug Interaction checker.

Cohort entry will be defined as the date of start of the sequential trial (see for more details 'statistical analysis'). Contraindications will be ascertained based on clinical events in

primary care and hospital admission data (advanced decompensated liver cirrhosis, regular ascitic drainage, stage 4-5 chronic kidney disease, dialysis, renal replacement therapy, solid organ transplant recipients), clinical tests for renal impairment (eGFR/creatinine) and medication data (medications with potential drug-drug interactions).

Outcome and follow-up

The outcome will be a composite of COVID-19-related hospitalisation (based on primary diagnosis ascertained from SUS) or COVID-19-related death (based on underlying/contributing causes) within 28-days of SARS-CoV-2 infection. Patients will be followed up until the earliest of the outcome (COVID-19 related hospitalisation or death), death date (death other than COVID-19-related death), deregistration or 28 days post-index date. Hospital admissions recorded as elective day case admissions or regular admissions in SUS will not be counted.

Since individuals can start treatment with sotrovimab during follow-up, and sotrovimab initiation can be registered as day case hospital admissions for infusions, these events will not be counted as outcome events. Day case admissions in patients treated with sotrovimab will be detected by hospital admissions associated with a MABs procedure or an admission on the same day, one day or two days after sotrovimab prescription with an associated discharge on the same day or the day after.

Treatment Strategies

We will look at an intention to treat effect and a per protocol effect were we look to compare the following treatment strategies:

1) Initiation of paxlovid within 5 days of SARS-CoV-2 positive test (initiation on day 0 (positive test), 1, 2, 3, or 4)
2) No initiation of paxlovid within 5 days of SARS-CoV-2 positive test

Treatment status and date will be ascertained from the COVID-19 therapeutics dataset.

Covariates

The following potential confounders available in OpenSAFELY will be extracted at date of positive test:

- Age
- Sex
- Ethnicity (in 6 categories: Black, Mixed, South Asian, White, Other, Unknown)
- Deprivation: defined using quintiles of the English Index of Multiple Deprivation, and based on postcode of residence
- Rurality (potentially influencing vaccine/treatment access)
- Region
- Smoking status

- High risk group (Down's syndrome; solid cancer; haematological disease and stem cell transplant recipients; renal disease; liver disease; immune-mediated inflammatory disorders; primary immune deficiencies; HIV/AIDS; solid organ transplant recipients; rare neurological conditions)
- Other comorbidities / clinical characteristics: chronic cardiac disease; chronic obstructive pulmonary disease (COPD); obesity (most recent adult body mass index (BMI) ≥30); diabetes; hypertension; severe mental illness (psychosis, schizophrenia and bipolar disorder); learning disabilities; dementia; autism; care home; housebound status
- Brand of most recent vaccine
- Number of vaccines
- Time since most recent vaccination date
- Calendar time

Descriptive Analysis

Descriptive analyses were done to aid the development of the protocol. These descriptive analyses are listed below.

Testing behaviour

Our previous analysis into the effectiveness of sotrovimab and molnupiravir vs no treatment covered a period during 2021 and 2022 where LFT/PCR testing was routine. Mass testing ended on 1 April 2022 in England for the general population, while free tests were still available for people at high risk of severe COVID-19 outcomes (our study population). However, it is uncertain how testing behaviour has changed since and this has potential consequences for this analysis, especially surrounding the untreated comparator group. Three issues are as follows: 1) a reduction in the number of people recording tests might limit the power; 2) we might hypothesise that presence of test positive LFT/PCR test is related to health-seeking behaviour and this could therefore reasonably be related to whether a patient seeks treatment and their risk of the outcome and 3) on the contrary, after 1 April 2022, people may be more likely to only perform tests when they experience symptoms, making it more likely that the untreated comparator group experienced symptoms after 1 April 2022.

Currently, the potential for changes in testing behaviour across our study period has not been quantified. Therefore, an initial step will be to extract descriptive statistics on patients recording a positive test in this cohort at intervals across our study period. Additionally, we will quantify and extract descriptive statistics of patients treated with Paxlovid without a recorded positive test. These patients will not be included in our study population but have the potential of describing ascertainment biases in routine testing data.

Based on this, we might have to redefine our proposed study period of 10th February 2022 and 9th February 2023.

Contraindications for Paxlovid

As a consequence of the ongoing debate of the effectiveness of sotrovimab for SARS-CoV-2 Omicron BA.2 infections, the threshold for treatment with Paxlovid changed over time. For example, effective from 13 June 2022, the updated policy confirms that nirmatrelvir/ritonavir (Paxlovid) may be considered as a treatment choice for patients with stage 3 chronic kidney disease (CKD 3), subject to adequate arrangements for dose adjustment. The exclusion criteria for our study population (page 4, under e)) might be too narrow and not reflect 'real world' use of Paxlovid, in particular at the end of our study period. In a descriptive analysis, we aim to describe over time those who were treated with Paxlovid despite evidence of contraindications in their electronic health records.

Distribution of initiation of Paxlovid

In our analysis, we will compare treatment within 5 days of a positive test versus no treatment. According to the [Interim Clinical Commissioning Policy]: "Treatment commencement may be extended up to a maximum of 7 days from symptom onset if clinically indicated (treatment commencement beyond 5 days from symptom onset is off-label)." We will study the occurrence of off-label use of Paxlovid beyond 5 days by exploring the distribution of the number of days between initiation of Paxlovid and positive test.

Statistical Analysis

Sequential trials

Following Hernán et al.[9] and Keogh et al.[10], we describe the construction of five sequential trials with respect to our research question.

For our analysis, twelve subsets will be created, with subset 1 including all individuals having tested SARS-CoV-2 positive between 10 February 2022 - 9 March 2022, subset 2 between 10 March 2022 - 9 April 2022, …., and subset 12 between 10 January 2023 - 9 February 2023. In other words, individuals were subdivided into 12 cohorts based on the month of their positive test. This was done to take into account differences over time in drug availability at CMDUs; policy changes in drug prescription guidelines and emerging SARS-CoV-2 variants. Individuals are followed up for 28 days from their positive test date.

Within each subset, five trials will be designed by comparing individuals having started treatment on day k since positive test vs individuals not having started treatment on day k (k \in {0, 1, 2, 3, 4}). In trial k, individuals having started treatment on day k will be included in the treated arm and individuals not having started treatment on day k in the untreated arm; individuals having started treatment other than Paxlovid (sotrovimab or molnupiravir) on day k will be excluded from trial k (note that individuals starting sotrovimab or molnupiravir on day l (l > k, l \in {1, 2, 3, 4}) will be included in the untreated arm); individuals experiencing an outcome event on day k will be excluded from trial k (COVID-19-related hospitalisation or death). In trial

k+1, individuals having started treatment on day k or having experienced an outcome event or censoring event on day k will be excluded. In the untreated arm of trial k, untreated individuals can initiate treatment (Paxlovid, sotrovimab or molnupiravir) on day l (l > k, l \in {1, 2, 3, 4}).

Of note, non-initiators in trial *k* ($k \in \{0, 1, 2, 3, 4\}$) can appear as initiators in a later trial (*k + 1,.., 4*). Individuals can therefore appear as initiators in only one trial, but as non-initiators in several trials. We assume that individuals remain on treatment once they start it and that there can only be one switch (i.e., we assume an individual starts treatment and continues taking it or does not start treatment at all). If treatment is initiated not within 5 days (on or after day 5), treatment will be ignored. If treatment is initiated on the same day an outcome is experienced, treatment will be ignored (following the reasoning that treatment can not plausible have a biological effect within one day).

As a consequence of the defined eligibility criteria (see criteria c on page 4), none of the individuals (untreated and treated) experience an outcome or censoring event at their date of positive test. Some individuals may however experience an outcome (COVID-19-related hospitalisation or death) or censoring event (non-COVID-19-related death or deregistration) on the first day of follow-up in a given trial k. For example, an untreated individual can experience an outcome 2 days after a positive test, which is the start of follow-up in trial k. These individuals will be excluded from the matched set, as defined in the above. In a sensitivity analysis we will explore the impact of this decision by adding 0.5 days of time to each individual's follow-up. The length of follow-up decreases for trials starting follow-up 1-4 days after positive test, keeping constant at 28 days after positive test. Individuals will be censored if they are deregistered or experience non-COVID-19-related death.

In the intention to treat analysis, we will not censor individuals starting treatment (Paxlovid, sotrovimab or molnupiravir) during follow-up. In the per protocol analysis, we will artificially censor individuals starting Paxlovid, or sotrovimab/molnupiravir, during follow-up. That is, in trial *k,* individuals who start one of the three treatments after day *k,* will be artificially censored at the day at which they switch from their treatment group at the start of a given trial. Individuals who start sotrovimab or molnupiravir on day *k* will be excluded from trial *k*. Inverse probability of artificial censoring weights will be used to account for the informative censoring of the treatment initiators. Ideally, time-varying covariates will be used to model these probabilities, by modelling the probabilities of censoring in a given trial given these time-varying covariates (for example using pooled logistic regression). In the absence of time-varying covariates, the probabilities of artificial censoring will be estimated using pooled logistic regression, conditional on baseline covariates listed under 'covariates' using a time-varying intercept, varying by trial number and month of positive test. We will investigate the use of different models to model the censoring mechanism (e.g. one model for Paxlovid initiation and one model for sotrovimab or molnupiravir initiation). Use of stabilised weights will be explored. Simpler models will be used if power is not sufficient.

To estimate the effect of treatment on our outcome in the intention to treat analysis, a pooled logistic regression model will be fitted, conditional on the baseline covariates listed under

‘covariates’, trial number and month of positive test. Interaction terms between trial and month of positive test and treatment will be investigated.

To estimate the effect of treatment on our outcome in the per protocol analysis, a pooled logistic regression will be fitted, using the inverse probability of artificial censoring weights, conditional on the baseline covariates listed under ‘covariates’, trial number and month of positive test. Interaction terms between trial and month of positive test and treatment will be investigated.

Confidence intervals will be obtained by bootstrapping.

In our exploratory analyses, we saw that subsets of 1 month of the data might be too granular (i.e. on day 4 there is a relatively small number of individuals initiating treatment each month). If this results in unstable models for the weights in our per-protocol analysis, we will explore the following approaches to overcome this: a) not including the subset-indicator to the models of the weights but model calendar time as a continuous variable using splines; b) treating those treated on day 4 as untreated (and not designing a fifth trial).

Sensitivity and supplementary analyses

Sotrovimab and molnupiravir initiators

In our planned intention to treat and per protocol analysis, individuals can initiate molnupirarvir or sotrovimab during follow-up. In a sensitivity analysis we plan to exclude sotrovimab and molnupiravir initiators from the study population based on future information and perform our intention to treat and per protocol analysis as described above.

Treatment effect modification

We will investigate treatment effect modification by previous treatment with a nMAB or AV in a community setting by not excluding those who are treated with a nMAB or AV in the previous 90 days and stratifying the analysis by treated in the previous 90 days yes/no.

Preliminary analyses showed that a relatively big group of people with CKD stage 3 (as identified by their health records) were treated with Paxlovid, informing the decision to not exclude these individuals from our study population. According to the CMDU guidelines, people with CKD stage 3 were treated with half a dose of Paxlovid. We will explore treatment effect modification by stratifying the analysis by CKD stage 3 yes/no.

COVID-19 infection episodes

Every individual’s *first* COVID-19 episode in our study period is included in our analysis. In some cases, individuals may have more than one COVID-19 episode in our study period, for which they may have been treated or not. We will aim to describe the number of COVID-19 episodes for each individual that are 90 days apart, informing the added value of including these in our analysis.

Extreme weights

For relevant analyses, we will investigate the possible influence of extreme weights, truncating at the 2.5% and 97.5% percentiles of the weights distribution.

QBA

Given the potential for unmeasured confounding, we will apply quantitative bias analysis (QBA) to obtain bias-adjusted hazard ratios for unmeasured theoretical binary confounders.[11]

Scenario 1: Unresolved/symptomatic COVID-19 status
There is no data on the presence of COVID-19 symptoms at baseline (SARS-CoV-2 positive test). We hypothesise that the prevalence of unresolved or symptomatic COVID-19 is more common in treated individuals compared to untreated individuals. We will vary the prevalence of the confounder in the treated from 0.70 to 0.85 to 0.90 and keep the prevalence of the confounder in the untreated constant at 0.65. We additionally hypothesise that the presence of COVID-19 symptoms increased the likelihood of experiencing our combined outcome of COVID-19-related hospitalisation or death. We will vary the hazard ratio for the relationship between the unmeasured confounder and outcome from 1.20 to 1.50 to 2.50.

Scenario 2: Degree of immunosuppression
People identified as potentially eligible in our study might not be in the identified at-risk group because of overinclusion within the NHS Digital codelists used (e.g., immune deficiencies). The service evaluation in CMDUs showed that the most common reason for being ineligible on presentation to CMDUs was not being in an at-risk clinical group.[12] We hypothesise that the prevalence of less severe immunosuppressive conditions was more common in untreated individuals compared to treated individuals. We will vary the prevalence of the confounder in the untreated from 0.15 to 0.30 to 0.50 and kept the prevalence of the confounder in the treated constant at 0.1. We will additionally hypothesise that the presence of less severe immunosuppressive conditions decreases the likelihood of experiencing our combined outcome of COVID-19-related hospitalisation or death. We will vary the hazard ratio for the relationship between the unmeasured confounder and outcome from 0.70 to 0.50 to 0.20.

Limitations

Limitations are described in column ‘challenges in observational emulation’ in Table 1.

Table 1

	Target trial specification, inspired by Hammond et al. [3]	Target trial emulation	Challenges in observational emulation
Eligibility criteria	<u>Inclusion criteria:</u> 1. Symptomatic (at least one sign or symptom) SARS-CoV-2 infection (non-hospitalised) and ≤5 days since onset of symptoms 2. At least one characteristic or coexisting condition associated with high risk of progression to severe COVID-19 3. Aged ≥ 18 <u>Exclusion criteria:</u> 1. Anticipated need for hospitalisation within 48 hours of randomisation 2. Pregnancy or breastfeeding 3. Prior treatment of antivirals or nMABS 4. Evidence of SARS-CoV-2 infection up to 90 days before current symptomatic SARS-CoV-2 infection spell 5. Comorbidity requiring hospitalisation and/or surgery ≤7 days prior to study entry 6. Comorbidity considered life threatening ≤30 days prior to study entry 7. History of active liver disease 8. Moderate to severe renal impairment 9. On prohibited prior or concomitant therapies, including: medications highly dependent on CYP3A4 for clearance and that may be clinically concerning at elevated plasma concentrations (during and through 4 days following treatment), or strong inducers of CYP3A4 (≤28 days prior to and during treatment).	<u>Inclusion criteria:</u> 1. We defined symptomatic SARS-CoV-2 infection as evidence of a positive test (PCR or lateral flow test) 2. Membership of a 'high risk cohort' was ascertained using primary care records 3. Aged ≥ 18 4. Only patients with complete records on age, sex, IMD and STP were included <u>Exclusion criteria:</u> 1. Anticipated need for hospitalisation within 48 hours not applied in emulation. In emulation, individuals are excluded if hospitalised on positive test date or admitted to hospital on positive test date ascertained using NHS Digital's Hospital Episode Statistics (HES) 2. Pregnancy or breastfeeding eligibility criteria not applied in emulation 3. Prior treatment history ascertained using primary care records 4. Previous SARS-CoV-2 infection defined using positive test and hospitalisation data 5. Exclusion around comorbidities not applied in emulation. These criteria were not relevant to CMDU treatment decisions. 6. Not applied in emulation. See 5. 7. Advanced decompensated liver cirrhosis or receiving regular	• Second Generation Surveillance System (SGSS) contains information surrounding symptomatic SARS-CoV-2 infection, however, the reliability of this information has not been validated (important in light of substantial missingness). • Electronic health records data will not have complete information on symptoms of COVID-19 recorded. For example, Hammond et al. defined the following symptoms and signs: cough, shortness of breath or difficulty breathing, fever, chills or shivering, fatigue, muscle or body aches, diarrhoea, nausea, vomiting, headache, sore throat, stuffy or runny nose [3]. • We chose to restrict our study population to people in 'high risk cohort' (ascertained using primary care records), to ensure comparability between users and non-users. However, this might affect generalizability. Specifically, there are people receiving treatment who are in the data but not recorded to be in the high-risk cohort (we assume this is misclassification due to data recording). If we decide NOT to require this criteria, we are essentially selecting a 'high risk' group in the exposed group but applying other criteria in the controls will lead us to have controls across the risk spectrum (with tendency towards low risk -> severe confounding by indication). Therefore we have decided to restrict to the 'high risk' inclusion even at the cost of losing some of the treated group. • Mass testing in England ended on 1 April 2022 [15]; people eligible for COVID-19 treatment are still able to get free lateral flow tests (LFT)[16]. Possibly, the likelihood of testing is associated with health behaviours and only a specific group of people keeps doing LFTs regularly (differentially affecting the untreated and treated group). On the contrary, another possibility is that people are more likely to test if they experience symptoms, making the non-initiators more comparable to the initiators. • To ensure consistent identification of 'highest' risk group information we only used information available

		ascitic drainage ascertained using primary care records 8. Dialysis; renal replacement therapy; stage 4-5 chronic kidney disease ascertained using primary care records and clinical tests for renal impairment (eGFR/creatinine) 9. Solid organ (including kidney) or Islet transplant recipient ascertained using primary care records 10. Taking medications with potential drug-drug interactions using guidance to refer to SmPC [13] and University of Liverpool COVID-19 Drug interaction tracker [14]	in primary care records (as opposed to CMDU records; only available for treated patients). Previous work showed recording of this information was reliably identifiable in primary care data alone.[6] However, the codelists used are inclusive but not specific, and as a consequence these groups do not represent strict clinical groupings. People identified as potentially eligible in our study might not be in the identified at-risk group because of overinclusion within the NHS Digital codelists used (eg, immune deficiencies). A service evaluation of CMDUs in four regions across England [12] showed that the most common reason for being ineligible on presentation to CMDUs was not being in an at-risk clinical group. ● No information on (time-varying) current health status (ie severity of COVID-19 or severity of current comorbidities) available in electronic health records (exclusion criteria 1, 5, and 6 in target trial). ● Difficult to reliably identify patients who are pregnant and current methods are likely to substantially overestimate pregnancy.
Treatment strategies	Eligible patients are then randomised on the day of diagnosis to either: I. Initiate paxlovid therapy within 5-days II. Not initiate COVID-19 therapeutic treatment (paxlovid; sotrovimab; molnupiravir; remdesivir) within 5-days	We defined the date of medication initiation to be the first date of prescription received. Otherwise, same as the target trial	● Paxlovid is given as 2 tablets twice a day for 5 days. Once prescribed, we do not have data on whether the full course of treatment is completed. ● Prescription date might not be the date a patient receives treatment which could lead to a slight lag between prescription date and date the treatment was initiated.
Treatment groups	Patient treatment groups are defined by randomisation to one of two treatment strategies defined above.	Same as the target trial	-

Treatment assignment	Eligible patients are randomly assigned to a strategy	• Patients are classified as receiving a given strategy based on information in their medical records • Although treatment assignment was based on clinical need, we attempted to emulate randomisation by adjusting for baseline variables (defined at index date)	• We employed the sequential trial approach to emulate this aspect of the target trial [9,10,17]. • Patients initiating therapy versus not are likely to be different and possible residual confounding is a key issue. Possible mechanisms include initiators being healthier than non-intiatiors due to coming forward for treatment; initiators experiencing more (severe) COVID-19 symptoms without signs of improvement than non-initiators; and initiators more likely to be correctly classified as in an at-risk group. Treatment initiation might also signify increased trust in the healthcare system. • Patients can initiate one of the other COVID-19 treatments available: - Sotrovimab (10 February 2022 - 28 November 2022: first line treatment [18]; 28 November 2022 - 21 February 2023: "sotrovimab may be considered where the available antiviral treatments are deemed unsuitable, and its use is supported following multi-disciplinary team assessment" [19]; 21 February 2023 NICE publishes report recommending use of sotrovimab in patients where paxlovid is contraindicated [20]) - Molnupiravir (10 February 2022 and onwards: third line treatment [18]) - Remdesivir (10 February 2022 and onwards: third line treatment [18]) See Figure 2a in OpenSAFELY's coverage report for an overview of the cumulative uptake of these treatment.
Outcomes	COVID-19-related hospital admission or death within 28 days	Same as the target trial • COVID-19 outcomes recorded using ICD-19 codes in hospital records or on death certificates: COVID-19 as primary diagnosis for hospital admission and COVID-19 as contributing or underlying cause of death. • To exclude events where patients were admitted to receive planned or regular treatment (eg, chemotherapy), hospital	Misclassification of cause of death on death certificates.

		admissions recorded in Secondary Uses Services as elective day case admissions or regular admissions were not counted.	
Follow-up	Index date is date of positive SARS-CoV-2 test until end of 28 days, outcome (COVID-19 hospitalisation or death), administrative censoring (i.e. deregistration)	Same as target trial	• We have assumed that when outcomes occur on the same day as treatment, the outcome preceded the treatment. The artificial censoring induced by the clone-censor-weight approach leads to this having an equal effect on both emulated arms. This seems reasonable since we would not expect an immediate causal effect of paxlovid on the outcome. • Non-COVID-19-related hospitalisations (no COVID-19 as primary diagnosis) are not censored since patients are still able to experience the outcome of interest.
Causal contrasts	Per-protocol	Observational analogue to intention to treat and per-protocol	• Only information on treatment prescription is available and we therefore assume everyone with a treatment prescription starts and continues taking their medication. We do not have information to account for treatment discontinuations in our analysis. • Applying the sequential approach we aimed to study the observational analog of an intention to treat effect where treatment strategy deviations in the untreated arm are not accounted for after the start of each of the sequential trials. Treatment discontinuation in the treated arm is not accounted for as constrained by the data available (see first point). The estimand of this analysis is the effect of initiating Paxlovid vs initiating no-treatment at baseline (irrespective of initiation of Paxlovid, Molnupiravir or Sotrovimab after baseline). • Applying the sequential approach we aimed to study the observational analog of a per-protocol effect where individuals starting treatment after day zero are artificially censored and inverse probability of artificial censoring weights are used to account for this informative censoring. Treatment discontinuations in the treated arm are not accounted for as constrained by the data available (see first point). The estimand of this analysis is the effect of initiating Paxlovid at baseline vs initiating no-treatment at baseline or during follow-up.

			● Descriptive analyses have demonstrated that the number of patients initiating beyond day 4 is minimal [6].
Statistical analysis	● 28-day odds ratios ● Difference in 28-day survival	Same as the target trial	● Same as the target trial with adjustment for baseline variables by conditioning on baseline variables in the outcome model.

Box 1: Patient cohorts considered at higher risk from COVID-19 and to be prioritised for treatment with antivirals and nMABs, as determined by an independent advisory group commissioned by the UK Department of Health and Social Care (DHSC)[7]. For further details on these criteria and how they were applied in the present study see Supplementary Table S1.

- Patients with **down's syndrome**;
- Patients with a **solid cancer,** such as active metastatic cancer, or active solid cancers at any stage;
- Patients with a **haematological disease and stem cell transplant recipients**, such as those with sickle cell disease;
- Patients with **renal disease**, such as those with chronic kidney stage 4 or 5;
- Patients with **liver disease**, such as those on immune suppressive therapy;
- Patients with **immune-mediated inflammatory disorders,** such as those treated with rituximab or other B cell depleting therapy in the past 12 months;
- Patients with **primary immune deficiencies**, such as severe combined immunodeficiency;
- Patients with **HIV/AIDS** with high levels of immune suppression;
- **Solid organ transplant recipients**;
- Patients with **rare neurological conditions** (multiple sclerosis motor neurone disease, myasthenia gravis or huntington's disease)

Figure 1: **High risk cohort**. Copied from Green et al. (2022)[6]

Administrative

Data sharing

Access to the underlying identifiable and potentially re-identifiable pseudonymised electronic health record data is tightly governed by various legislative and regulatory frameworks, and restricted by best practice. The data in OpenSAFELY is drawn from General Practice (GP) data across England where TPP is the data processor. TPP developers initiate an automated process to create pseudonymised records in the core OpenSAFELY database, which are copies of key structured data tables in the identifiable records. These pseudonymised records are linked onto key external data resources that have also been pseudonymised via SHA-512 one-way hashing of NHS numbers using a shared salt. Bennett Institute for Applied Data Science developers and PIs holding contracts with NHS England have access to the OpenSAFELY pseudonymised data tables as needed to develop the OpenSAFELY tools. These tools in turn enable researchers with OpenSAFELY data access agreements to write and execute code for data management and data analysis without direct access to the underlying raw pseudonymised patient data, and to review the outputs of this code. All code for the full data management pipeline, from raw data to completed results for this analysis, and for the OpenSAFELY platform as a whole is available for review at github.com/OpenSAFELY.

Information governance

NHS England is the data controller for OpenSAFELY-TPP; TPP is the data processor; all study authors using OpenSAFELY have the approval of NHS England. This implementation of OpenSAFELY is hosted within the TPP environment which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant.[21]

Patient data has been pseudonymised for analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymised datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the platform is via a virtual private network (VPN) connection, restricted to a small group of researchers; the researchers hold contracts with NHS England and only access the platform to initiate database queries and statistical models; all database activity is logged; only aggregate statistical outputs leave the platform environment following best practice for anonymisation of results such as statistical disclosure control for low cell counts.[22]

The OpenSAFELY research platform adheres to the obligations of the UK General Data Protection Regulation (GDPR) and the Data Protection Act 2018. In March 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 (COPI) to require organisations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure; this sets aside the requirement for patient consent.[23] This was extended in July 2022 for the NHS England OpenSAFELY COVID-19 research platform.[24] In some cases of data sharing, the

common law duty of confidence is met using, for example, patient consent or support from the Health Research Authority Confidentiality Advisory Group.[25]
Taken together, these provide the legal bases to link patient datasets on the OpenSAFELY platform. GP practices, from which the primary care data are obtained, are required to share relevant health information to support the public health response to the pandemic, and have been informed of the OpenSAFELY analytics platform.

Software and Reproducibility

Data management was performed using Python [version 3.8.10], with analysis carried out using R [version 4.0.5]. Code for data management and analysis, as well as codelists, are archived online.

Transparency statement

The lead authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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