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*

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Disclaimer

This document describes a draft protocol that is still subject to change. After a thorough discussion of this draft protocol with the research team, a plan was made to first perform a couple of descriptive analyses to gain better insight in how Paxlovid was used in practice. In short, with the planned descriptive analyses we want to gain insight into who was treated with Paxlovid, sotrovimab or molnupiravir in our study population and who was not; have a better understanding of how well our baseline covariates predict treatment in our high risk population; the distribution of days between positive test and treatment initiation and how often outcomes occurred in the first 5 days (the treatment window). These descriptive statistics will provide input on how to best model the planned sequence of 5 trials and the feasibility of predicting treatment initiation in our study population using baseline covariates. The planned descriptive analyses are explained in further detail in the 'descriptive analyses' section below.

In light of transparency, this draft protocol is time stamped on 3 July 2023 and was written before any queries were run on the OpenSAFELY-TPP database. A final protocol will be shared in due course.

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 hazard 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)

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) 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)

c) Treatment history antivirals or nMABs for COVID-19 in a community setting up to 90 days before the current test-positive spell.

d) Start treatment other than Paxlovid (sotrovimab, molnupiravir) on date of entry

e) Hospitalised at the date of entry or admitted to hospital on date of entry.

f) Contraindicated for treatment: advanced decompensated liver cirrhosis; regular ascitic drainage; stage 3-5 chronic kidney disease; dialysis; renal replacement therapy; solid organ (including kidney) or Islet transplant recipient; or taking medications with potential drug-drug interactions as listed in the NHS England guideline in the previous 180 days on date of positive test.[7,8]

*Criterium a) will exclude a group of approximately 100 patients treated with remdesivir in CMDUs. This is a pragmatic choice to avoid complexities around censoring patients who initiate remdesivir during follow-up.

Cohort entry will be defined as the date of start of the sequence of trials (see for more details 'statistical analysis'). Contraindications will be ascertained via diagnosis codes (advanced decompensated liver cirrhosis, regular ascitic drainage, stage 3-5 chronic kidney disease, dialysis, renal replacement therapy, transplant recipients), clinical tests for renal impairment (eGFR/creatinine) and codelists (medications with potential drug-drug interactions [9,10]).

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 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 (or any other COVID-19 therapeutic treatment) 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 index date:

- 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

Testing behaviour

Our previous analysis surrounding 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.

Distribution of propensity scores

No information on time-varying covariates (e.g. disease severity or symptom onset) is available in our data. In a descriptive analysis, we will compare the distribution of propensity scores in the untreated (not treated with Paxlovid within 5 days) and treated (treated with Paxlovid within 5 days). As an initial step, the predictors of treatment listed under ‘covariates’ will be used in the propensity score models. Additional covariates such as whether a positive test was on a weekday or occurred in a weekend may be used to optimise model performance.

Distribution of outcomes during treatment window

In our molnupiravir and sotrovimab effectiveness study, we observed a high number of outcomes in the first 5 days in our study population (treatment window). The occurrence of outcomes during the first five days can potentially affect our choice of statistical analysis (clone-censoring-weighting versus sequential trial). In a descriptive analysis we will describe

the number of outcomes in the first 5 days and the extended 7 days after positive SARS-CoV-2 test (irrespective of treatment).

Statistical Analysis

Sequential trials

Following Hernán et al.[11], we describe the construction of a sequence of five trials with respect to our research question. Unlike traditional sequential trials, where individuals are aligned on calendar time, here individuals will be aligned on their time between treatment initiation and positive test.

In the first trial all individuals who are treated with Paxlovid on day 0 (day of positive test) will be included in the treated group and all individuals who have not started treatment on day 0 will be included in the untreated group. Individuals who start treatment after day 0 (Paxlovid, sotrovimab or molnupiravir) will be artificially censored at the day at which they switch from their treatment group at the start of a given trial.
In the second trial, all individuals who start treatment on day 1 (1 day after positive test) will be included in the treated group and all individuals not having started treatment by day 1 will be included in the untreated group. Individuals who start treatment after day 1 (Paxlovid, sotrovimab or molnupiravir) will be artificially censored at the day at which they switch from their treatment group at the start of a given trial. Individuals who started treatment on day 0 are excluded.
Same applies for trials 3, 4, and 5 starting at day 2, 3, 4 after positive test, respectively.

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. 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, none of the individuals experience an outcome or censoring event on the day of trial entry. In the first trial starting on the day of positive test (day 0), individuals can experience an outcome or censoring event on day 1-27. In the second trial starting one day after positive test (day 1), individuals experiencing an outcome or censoring on day 1 are excluded and as a consequence, individuals can experience an outcome or censoring event on day 2-27; etc. The length of follow-up decreases for trials starting at later visits, keeping constant at 28 days after positive test. Individuals will be censored if they are deregistered or experience non-COVID-19-related death.

To account for the informative censoring of individuals initiating treatment in the untreated group (for example, an individual starting treatment on day 2 in the first trial), inverse probability of artificially censoring weighting will be used. 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’. Stabilised weights will be used by multiplying the weights by the probability of censoring using a time-varying intercept, given the baseline values of the covariates.

A Cox model will be fitted using the time-dependent inverse probability of artificial censoring weights, conditional on the baseline covariates listed under ‘covariates’.

Subgroup analyses

TBC

Sensitivity and supplementary analyses

We will investigate the possible influence of extreme weights, truncating at the 2.5% and 97.5% percentiles of the weights distribution. Additionally, given the potential for unmeasured confounding, we will apply quantitative bias analysis (QBA) to obtain bias-adjusted HRs for unmeasured theoretical binary confounders representing symptomatic/ unresolved COVID-19 status and degree of immunosuppression.
In the main analysis, individuals with strict contraindications for Paxlovid were excluded. However, in some groups, Paxlovid was only prescribed after consideration of risks and benefits. We will repeat our analyses by excluding all individuals in our study population where use of Paxlovid was cautioned against.

Limitations

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

Table 1

	Target trial specification	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	<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 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. In hospital on positive test date or admitted to hospital on positive test date ascertained using NHS Digital's Hospital Episode Statistics (HES)	● 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 [13]; people eligible for COVID-19

	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).	6. See 4, no specific ascertainment of comorbidities applied. 7. Advanced decompensated liver cirrhosis or receiving regular ascitic drainage ascertained using primary care records 8. Dialysis; renal replacement therapy; stage 3-5 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 listed in the NHS England guideline [7]	treatment are still able to get free lateral flow tests (LFT)[14]. 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 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 [15] 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) via inverse-probability of treatment weighting methods	• We employed the clone-censor-weight approach to emulate this aspect of the target trial [12,16]. • 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 [17]; 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" [18]; 21 February 2023 NICE publishes report recommending use of sotrovimab in patients where paxlovid is contraindicated [19]) - Molnupiravir (10 February 2022 and onwards: third line treatment [17]) - Remdesivir (10 February 2022 and onwards: third line treatment [17]) 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 admissions recorded in Secondary Uses Services as elective day case admissions or regular admissions were not counted.	Misclassification of cause of death on death certificates.
Follow-up	Index date is date of positive SARS-CoV-2 test until end of 28 days, outcome (COVID-19 hospitalisation or death),	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

	administrative censoring (i.e. deregistration)		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 per-protocol	● Applying the clone-censor weighting approach we aimed to study the observational analog of a per-protocol analysis where we account for treatment strategy deviations between index date and day 4 (first five days), but not beyond this. ● Descriptive analyses have demonstrated that the number of patients initiating beyond day 4 is minimal [6].
Statistical analysis	● 28-day hazard ratios ● Difference in 28-day survival	Same as the target trial	● Same as the target trial with adjustment for baseline variables via inverse-weighting.

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.[20]
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.[21]
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.[22] This was extended in July 2022 for the NHS England OpenSAFELY COVID-19 research platform.[23] 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.[24]
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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