OpenSAFELY Protocol Amendment: Effectiveness of sotrovimab/molnupiravir vs non-use

V1.1 changes

1. **We have updated the weighting scheme described as part of Step 4 of protocol amendment v1.0 due to implementation difficulties (in the dummy data).**
2. **This has implications for Step 5 which has also been updated.**
3. **Unrelatedly, and given additional clinical input since the original protocol, we have updated the list of potential confounders to be accounted for. This was due to hypothesised differences between patients receiving treatment across the two periods.**

Summary

This is a significant amendment to the initial protocol written in April 2022. The validity of the initial proposal relied, in part, on there being a limited number of events during the treatment initiation window. However, initial analyses have demonstrated that there is a large burden of outcomes during this period, limiting the interpretability of the results obtained from the original proposal (explained in full below). This amendment specifies details of a clone, censor and weight (CCW) approach to alleviate these limitations.

Description of issues from initial analyses

The analysis described in the initial protocol excluded all people experiencing an event in the first five days from the date of positive test to overcome immortal time bias. People experiencing an event within the first five days who were untreated comply with both arms of the target trial as described in the initial protocol, they could have received treatment had they not experienced an event. In initial analyses we observed a significant number of events occurring in the first five days, resulting in the exclusion of a high number of people. The high number of events occuring in the first five days possibly indicates i) differences in the (time-varying) characteristics of people surviving to at least day five compared to baseline (and we are only able to account for the information at baseline due to data restrictions); ii) selection bias: people surviving to at least day five are more healthy affecting the risk of an outcome; iii) depletion of susceptibles: given that people have a heterologous risk of our outcome, people at greatest risk deplete preferentially among the untreated given that treatment is effective [1].

We sought to overcome these issues by looking at the treatment effect of treatment initiation within four, three and two days instead of five days. This was at the cost of including a higher number of treated patients in the untreated arm. For example, people treated on day four or

later were included in the untreated arm in the day four analysis, because they did not adhere to the protocol of being treated within four days (i.e., being treated on day 0, 1, 2, or 3). Descriptive analyses highlighted that most of the events occurred in the first few days, however, this was also when most treated patients were misclassified (since they had not been treated within 2 days). These analyses are therefore difficult to interpret.

One solution to solve the immortal time bias and to artificially include people experiencing an event within the first five days who were untreated to both arms while not excluding patients experiencing events within the first five days is the clone censor weight (CCW) approach described by Hernan [2], [3]. **This protocol amendment describes this approach for answering our research question.**

Clone, censor and weight approach

Following the steps outlined in the tutorial by Maringe et al. [3], we describe the construction of the CCW cohort with respect to our research question.

Step 1: Specification of target trial and inclusion criteria

We have described the target trial and inclusion in Table 1 of the original protocol. The primary grace period (i.e. the treatment initiation window) is treatment within 5 days of a positive test. Should resources permit, we will investigate grace periods considering treatment within 2,3,4 days.

This leads to comparison of the following 2 treatment strategies:

1. Initiation of either sotrovimab or molnupiravir within 5 days after positive SARS-CoV-2 test
2. No initiation of therapy within 5 days after positive SARS-CoV-2 test

Step 2: Cloning

We will create two clones of each patient, with one clone allocated to each of the arms/strategies described in Step 1 (only for the duration of time when allocation of treatment strategy is unknown).

Step 3(a): Defining censoring and time to censoring

Clones will be artificially censored when their treatment is no longer compatible with the treatment strategy assigned, i.e:

1. Clones assigned to the treated arm who did not receive treatment within 5 days are artificially censored at day 4
2. Clones assigned to the no treatment arm who received treatment are artificially censored at their time of treatment if treatment is within 5 days

Step 3(b): Defining outcome and survival time

For each clone, any outcome event only contributes if this clone is not artificially censored at the time of the event. When an outcome is before or on the same day as treatment, then this outcome is counted in both arms; when an outcome is after treatment, then this outcome is

only counted in the treatment arm; when an outcome is after day 4 without an individual being treated, then this outcome is only counted in the untreated arm.

Additionally, any patients experiencing hospitalisation on day 0 will be excluded from the study population since it precludes treatment. Finally, data on treatment after individuals experience an event is ignored.

Step 4: Accounting for informative censoring due to artificial censoring

Artificially censored patients in the untreated arm (i.e. who receive treatment within 5 days) are likely to be different from patients who remained in the risk set for that arm (i.e. who did not receive treatment within 5 days). In order to maintain comparability between the study strategies throughout the grace period, inverse weighting weighting will be used to up-weight patients remaining in the risk set to represent artificially censored patients.

In the absence of post-baseline variables, the weights will be computed by calculating the probability of each clone remaining uncensored at day 0,1,2,3,4 throughout the grace period.

Estimation of weights

We will use a model-based approach for estimating the weights; predicting individual probabilities of remaining uncensored at each time of event. A Cox model will be used, working with a dataset split at each time of event [3]. The variables included are described below and the probabilities are estimated separately in the emulated treatment arms to capture potential interactions between covariates and treatment. The weights are simply the inverse of these probabilities [3].

Covariates

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

- Age
- Sex
- Ethnicity (in 6 categories: Black, Mixed, South Asian, White, Other, Unknown)
- Deprivation: defines using quintiles of the English Index of Multiple Deprivation, and based on postcode of residence.
- Rurality (potentially influencing vaccine access)
- Smoking status
- Other comorbidities / clinical characteristics: chronic cardiac disease; chronic obstructive pulmonary disease (COPD); obesity (most recent adult body mass index (BMI) ≥30); dialysis; severe mental illness (psychosis, schizophrenia and bipolar disorder); learning disabilities including Down's syndrome; dementia; autism; care home; housebound status; diabetes;
- Brand of most recent vaccine/number of vaccines
- High risk group
- Time since most recent vaccination date
- STP
- Calendar time

Step 5: Statistical analysis

Beyond artificial censoring, patients are followed from day of positive SARS-CoV-2 test until the earliest of outcome (COVID-19 related hospitalisation or death), death date (death other than COVID-19 related death), registration or 28 days post-SARS-CoV-2 test. We will not censor at the occurrence of non-COVID hospitalisation. We therefore aim to study the observational analog of a per-protocol analysis where we account for deviations between index and day 4, but not beyond this. Descriptive analyses have demonstrated that the number of patients initiating beyond day 4 is minimal.

We will fit a weighted Cox regression model for the outcome of COVID-19 related hospitalisation or death including an indicator for treatment strategy (initiation vs no initiation).

In light of the uncertainty in weight estimation and inflation of the sample size, robust standard errors will be applied.

As with original analysis, Steps 1-5 will be repeated for a) initiation of any therapy b) treatment with sotrovimab and c) treatment with molnupiravir. One consideration for these subgroup analyses is how to handle treatment with the other therapy. For example, when comparing sotrovimab versus no treatment, some patients will be expected to initiate molnupiravir. We plan to exclude all patients treated with the other drug from these subgroup analyses, acknowledging the potential selection bias this induces.

All analyses will be performed separately across the BA.1 (16th December 2021 and 10th February 2022) and BA.2 (11th February 2022 and 21st May 2022) periods. These will be combined using an inverse variance-weighted fixed-effect meta-analysis of the hazard ratios for 28-day COVID-19 hospitalisation and death.

Dependent on successful implementation of these analyses, we will consider an identical approach to investigate treatment with Paxlovid.

References

[1] R. Kahn, S. J. Schrag, J. R. Verani, and M. Lipsitch, ‘Identifying and Alleviating Bias Due to Differential Depletion of Susceptible People in Postmarketing Evaluations of COVID-19 Vaccines’, *Am. J. Epidemiol.*, vol. 191, no. 5, pp. 800–811, Mar. 2022, doi: 10.1093/aje/kwac015.

[2] M. A. Hernán, ‘How to estimate the effect of treatment duration on survival outcomes using observational data’, *BMJ*, vol. 360, p. k182, Feb. 2018, doi: 10.1136/bmj.k182.

[3] C. Maringe *et al.*, ‘Reflection on modern methods: trial emulation in the presence of immortal-time bias. Assessing the benefit of major surgery for elderly lung cancer patients using observational data’, *Int. J. Epidemiol.*, vol. 49, no. 5, pp. 1719–1729, Oct. 2020, doi: 10.1093/ije/dyaa057.