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

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). Patients initiating treatment at day zero will not be cloned to the no treatment arm.

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 an outcome event on day 0 will be excluded from the study population. 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 1,2,3,4 throughout the grace period (this is not applied on day 0 as there is no artificial censoring).

Weighting scheme for a hypothetical trial

Following Hernán's initial paper on the CCW approach [2], we designed a hypothetical trial to motivate our weighting scheme. An overview of this hypothetical trial is given in Supplemental Table S1. Assume a trial with 36 individuals, of whom 30 are randomised to the 'treatment within 5 days' arm and 6 are randomised to the 'no treatment' arm. Of the 30 individuals in the treatment arm 6 initiated treatment on day 0; 6 on day 1; 6 on day 2; 6 on day 3; and 6 on day 4. Further, assume treatment had no effect on the outcome. That is, assume 5 of the 6 individuals in the untreated arm had an outcome on day 1, 2, 3, 4 or 28, respectively. And assume the same for the 6 individuals treated on day 0, 1, 2, 3 or 4. The risk ratio in this trial is 25/30 / 5/6 = 1.

Suppose now, in Supplemental Table S1, we do not know what arm the 36 individuals were assigned to (i.e., we do not know column 2 and 3 of Supplemental Table S1). Ten individuals of the 30 treated individuals in the trial have an outcome *on or before* treatment initiation. The biased risk ratio in the observational data would be: 15/20 / 15/16 < 1 (the ten individuals with an outcome before treatment initiation have been shifted to the untreated arm).

Now suppose we apply the CCW approach to this data following step 2-4 above using the following weights. In the *no* treatment arm, on days 0-4, we up-weight people remaining in the at-risk set by the inverse probability of remaining uncensored on that day; on days 5-28 we use a weight of 1. In the treatment arm, on days 0-3, we use a weight of 1; on day 4, we up-weight people remaining in the at-risk set by the inverse probability of remaining uncensored on day 4; on days 5-28 we use a weight of 1. An overview of the weights in the hypothetical trial in Supplemental Table S1 is given in Supplemental Table S2 and S3 for the *no* treatment arm and treatment arm, respectively. The risk ratio in the cloned-censored-weighted data in these tables is 30/36 / 25/30 = 1, as desired. We refer to [this spreadsheet](#) for more information.

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 pooled logistic regression for the outcome of COVID-19 related hospitalisation or death including an indicator for treatment strategy (initiation vs no initiation), day of follow-up (cubic spline with 1 knot) and the baseline covariates described in the 'Covariates' section of the original protocol. This model is fitted on a dataset which is constructed as one line per clone per day of follow-up (needed to allow us to specify time-varying weights). These weights are the cumulative probability of remaining uncensored (the probability of being uncensored on a specific day during follow-up is described above). The cumulative probability of remaining artificially uncensored, for example on day 2, would be the probability of being uncensored on day 1 multiplied by that probability on day 2. The cumulative probability of remaining uncensored beyond day 4 is carried forward for the rest of follow-up since this is the last point artificial censoring can occur (i.e. the probability of remaining artificially uncensored is 1 after this point). The odds ratios from this model are equivalent to the hazards ratios that would be obtained from the equivalent Cox model.

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.

Supplemental Material

Person	Assigned to initiate within 5 days	trtA	T{d0}	Y{d0}	T{d1}	Y{d1}	T{d2}	Y{d2}	T{d3}	Y{d3}	T{d4}	Y{d4}	Y{d28}
1	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	1
3	0	0	0	0	0	0	0	0	0	0	0	1	-
4	0	0	0	0	0	0	0	0	0	1	-	-	-
5	0	0	0	0	0	0	0	1	-	-	-	-	-
6	0	0	0	0	0	1	-	-	-	-	-	-	-
7	1	1	1	0	0	0	0	0	0	0	0	0	0
8	1	1	1	0	0	0	0	0	0	0	0	0	1
9	1	1	1	0	0	0	0	0	0	0	0	1	-
10	1	1	1	0	0	0	0	0	0	1	-	-	-
11	1	1	1	0	0	0	0	1	-	-	-	-	-
12	1	1	1	0	0	1	-	-	-	-	-	-	-
13	1	2	0	0	1	0	0	0	0	0	0	0	0
14	1	2	0	0	1	0	0	0	0	0	0	0	1
15	1	2	0	0	1	0	0	0	0	0	0	1	-

16	1	2	0	0	1	0	0	0	0	1	-	-	-
17	1	2	0	0	1	0	0	1	-	-	-	-	-
18	1	2	0	0	1	1	-	-	-	-	-	-	-
19	1	3	0	0	0	0	1	0	0	0	0	0	0
20	1	3	0	0	0	0	1	0	0	0	0	0	1
21	1	3	0	0	0	0	1	0	0	0	0	1	-
22	1	3	0	0	0	0	1	0	0	1	-	-	-
23	1	3	0	0	0	0	1	1	-	-	-	-	-
24	1	3	0	0	0	1	-	-	-	-	-	-	-
25	1	4	0	0	0	0	0	0	1	0	0	0	0
26	1	4	0	0	0	0	0	0	1	0	0	0	1
27	1	4	0	0	0	0	0	0	1	0	0	1	-
28	1	4	0	0	0	0	0	0	1	1	-	-	-
29	1	4	0	0	0	0	0	1	-	-	-	-	-
30	1	4	0	0	0	1	-	-	-	-	-	-	-
31	1	5	0	0	0	0	0	0	0	0	1	0	0
32	1	5	0	0	0	0	0	0	0	0	1	0	1
33	1	5	0	0	0	0	0	0	0	0	1	1	-
34	1	5	0	0	0	0	0	0	0	1	-	-	-
35	1	5	0	0	0	0	0	1	-	-	-	-	-
36	1	5	0	0	0	1	-	-	-	-	-	-	-

Table S2. Calculation of weights in the *no* treatment arm of the synthetic trial

Synthetic alloc	Trial alloc	n	c{day 0}	y{day 0}	uncens{day 0}	weight{day 0}	c{day 1}	y{day 1}	uncens{day 1}	weight{day 1}	c{day 2}	y{day 2}	uncens{day 2}	weight{day 2}	c{day 3}	y{day 3}	uncens{day 3}	weight{day 3}	c{day 4}	y{day 4}	uncens{day 4}	weight{day 4}	c{day 28}	y{day 28}	uncens{day 28}	weight{day 28}
No	No (person 1-6)	6	0	0	6	1	0	1	5	1.25	0	1.25	5	1.33333333	0	1.66666667	5	1.5	0	2.5	5	2	0	5	5	1
	Day 1 (person 13-18)	6	0	0	6	1	5	1	0	1.25	0	0	0	1.33333333	0	0	0	1.5	0	0	0	2	0	0	0	1
	Day 2 (person 19-24)	6	0	0	6	1	0	1	5	1.25	5	1.25	0	1.33333333	0	0	0	1.5	0	0	0	2	0	0	0	1
	Day 3 (person 24-30)	6	0	0	6	1	0	1	5	1.25	0	1.25	5	1.33333333	5	1.66666667	0	1.5	0	0	0	2	0	0	0	1
	Day 4 (person 30-36)	6	0	0	6	1	0	1	5	1.25	0	1.25	5	1.33333333	0	1.66666667	5	1.5	5	2.5	0	2	0	0	0	1
		30	0	0	30	probability of remaining uncensored at day 0	5	5	25	probability of remaining uncensored at day 1	5	5	20	probability of remaining uncensored at day 2	5	5	15	probability of remaining uncensored at day 3	5	5	10	probability of remaining uncensored at day 4	0	5	5	probability of remaining uncensored at day 28
				0		1		0.16666667		1.25		0.2		1.33333333		0.25		1.5		0.33333333		2		0.5		1
					30				30				25				20				15					

Table S3. Calculation of weights in the treatment arm of the synthetic trial

Synthetic alloc	Trial alloc	n	c{day 0}	y{day 0}	uncens{day 0}	weight{day 0}	c{day 1}	y{day 1}	uncens{day 1}	weight{day 1}	c{day 2}	y{day 2}	uncens{day 2}	weight{day 2}	c{day 3}	y{day 3}	uncens{day 3}	weight{day 3}	c{day 4}	y{day 4}	uncens{day 4}	weight{day 4}	c{day 28}	y{day 28}	uncens{day 28}	weight{day 28}
Within 5 days	No (person 1-6)	6	0	0	6	1	0	1	5	1	0	1	4	1	0	1	3	1	2	1	0	1.2	0	0	0	1
	Day 0 (person 7-13)	6	0	0	6	1	0	1	5	1	0	1	4	1	0	1	3	1	0	1	2	1.2	0	1.2	1.2	1
	Day 1 (person 13-18)	6	0	0	6	1	0	1	5	1	0	1	4	1	0	1	3	1	0	1	2	1.2	0	1.2	1.2	1
	Day 2 (person 19-24)	6	0	0	6	1	0	1	5	1	0	1	4	1	0	1	3	1	0	1	2	1.2	0	1.2	1.2	1
	Day 3 (person 24-30)	6	0	0	6	1	0	1	5	1	0	1	4	1	0	1	3	1	0	1	2	1.2	0	1.2	1.2	1
	Day 4 (person 30-36)	6	0	0	6	1	0	1	5	1	0	1	4	1	0	1	3	1	0	1	2	1.2	0	1.2	1.2	1
		36	0	0	36	probability of remaining uncensored at day 0	0	6	30	probability of remaining uncensored at day 1	0	6	24	probability of remaining uncensored at day 2	0	6	18	probability of remaining uncensored at day 3	2	6	12	probability of remaining uncensored at day 4	0	6	6	probability of remaining uncensored at day 4
				0		1		0.16666667		1		0.2		1		0.25		1		0.33333333		1.2		0.5		1
					36				36				30				24				18				12	