ALL-IN-META-BCG-CORONA

Instruction to participating data uploaders

V2 – 31 October 2022

Introduction

ALL-IN-META-BCG-CORONA stands for "**Anytime Live and Leading INterim meta-analysis of the impact of Bacillus Calmette-Guérin vaccination in healthcare workers during the SARS-CoV-2 pandemic**". Several trials are ongoing and planned to test the hypothesis that BCG vaccination in healthcare workers decreases their risk to acquire COVID-19 and/or reduce the severity of COVID-19. The purpose of the ALL-IN meta-analysis is (1) to prevent the detrimental effects of putative false-positive interim trial results by immediately confirming or negating the result through pooling of all interim trial results, and (2) to increase the chance of identifying the putative beneficial effects of BCG by continuously pooling all interim trial results.

This instruction document has been updated in anticipation of the completion of the meta-analysis. We expect all involved trial to upload their final data set. While the V1 of this document mentioned more about blinding and interim data, this version focuses on the risk set definitions needed for the final analysis.

Statistical method 'Safe Testing' & Webinar

The statistical method is described in detail in a statistical analysis plan that is published on PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=213069). More details on the statistical method can be found on https://projects.cwi.nl/safestats/. Recorded webinars on the methodology can be found online, with the ALL-IN-META-BCG-CORONA for healthcare workers as a running example. Webinar Part 1 requires only basic statistical knowledge, Webinar Part 2 contains more technical details.

Live dashboard of ALL-IN-META results

After manual processing the results, the meta-analysis will be available to you at an online dashboard. The link to the dashboard can be found on: https://projects.cwi.nl/safestats/.

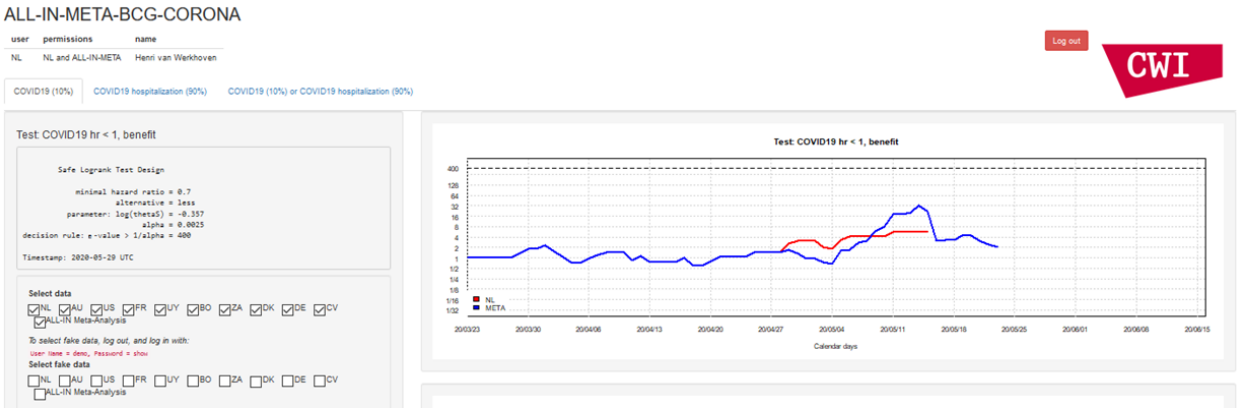

Figure 1 ALL-IN-META-BCG-CORONA dashboard (showing fake data for the purpose of this screenshot)

Blinding of the ALL-IN-META results

For each trial, the person extracting and uploading the data for the meta-analysis is considered unblinded to their own trial results, since the event-times in the data need to be characterized by intervention group for inclusion in the meta-analysis.

Therefore, for each trial, the person uploading the data will also be considered unblinded to the meta-analysis results. The 'data-uploader' receives a personal login to the dashboard that initially only showed two e-value sequences: that of the ALL-IN meta-analysis and that of their own trial. All included trial data uploaders now also have permission to inspect other trial's contribution to the meta-analysis. This was decided unanimously during the July 9th 2021 Advisory Committee meeting.

More insight into processing of data set into e-values

All uploaded data is checked for errors and processed into e-values by Judith ter Schure and Alexander Ly. To provide more insight we encourage the 'data-uploaders' to check their e-value sequences: e-values for benefit should go up on all calendar dates with an event in the control group and should go down on all calendar dates with an event in the treatment group. A complete tutorial on retrospectively recalculating e-values is available on https://projects.cwi.nl/safestats/. If you identify a discrepancy with the e-value in the dashboard, please contact us at j.a.ter.schure@cwi.nl and alexander.ly@cwi.nl for verification.

Strictly personal login and demo login

The login received by all persons uploading the data is strictly personal, and should not be shared with others involved in their own or other trials, to prevent unblinding of the results. To explain the procedure to others, the dashboard includes a 'Select fake data' option, that can be consulted using login details: User Name = demo, Password = show

Data export

The data required for the ALL-IN meta-analysis are the following. Please find a toy example data set in Figure 2.

Preferred variable name	Description	Preferred value levels / format
intervention	Intervention randomized to	*control* or *BCG*
dateRand	Calendar date of randomization	yyyy-mm-dd
hospital	Hospital of employment/enrolment at time of randomization	Free to use site name, abbreviation or A, B, C, etc.
COV19	Status COVID-19	*no* or *yes*
dateCOV19	Calendar date of being COVID-19 positive	yyyy-mm-dd
COV19hosp	Status COVID-19 related hospitalization	*no* or *yes*
dateCOV19hosp	Calendar date of being hospitalized for COVID-19-related reason	yyyy-mm-dd
dateLastFup	Calendar date of last follow-up. For patients still in follow-up this should be the date of the data extraction.	yyyy-mm-dd

It is preferred that the variable name and formats are used as indicated in the table. If this is not possible or very cumbersome, please contact us to discuss alternative options.

intervention	dateRand	hospital	COV19	dateCOV19	COV19hosp	dateCOV19hosp	dateLastFup
control	2020-05-07	A	yes	2020-05-11	yes	2020-05-15	2020-06-23
control	2020-05-04	B	yes	2020-05-08	yes	2020-05-12	2020-06-23
BCG	2020-05-08	A	yes	2020-05-21	yes	2020-06-01	2020-06-23
control	2020-05-07	B	yes	2020-05-25	no	NA	2020-06-23
BCG	2020-05-05	A	yes	2020-05-24	no	NA	2020-06-23
BCG	2020-05-10	B	yes	2020-06-03	no	NA	2020-06-23
control	2020-05-14	A	yes	2020-06-23	no	NA	2020-06-23
control	2020-05-10	B	no	NA	no	NA	2020-06-23
BCG	2020-05-08	A	no	NA	no	NA	2020-06-23
BCG	2020-05-04	B	no	NA	no	NA	2020-06-23

Figure 2 Example data set from the Example code on how to process your BCG-CORONA data set into an e-value sequence by calendar date

Please do not include identifiable information. A subject ID is not needed. Each randomized participant should be included as one row in the dataset.

Risk set definitions

Participants are considered at risk of COVID-19 infection and hospitalization from the date of randomization to the date of either:

(1) a COVID-19 infection and possibly hospitalization,

(2) the end of follow-up,

(3) loss to follow-up, or

(4) date of COVID-19 specific vaccination (PfizerBioNtech/Moderna/J&J/OxfordAZ/Novavax).

So follow-up time is censored at the date of COVID-19 specific vaccination for some of the participants and infections after COVID-19 vaccination are not considered as events, and neither are reinfections.

Covid-specific vaccination

If a participant is vaccinated with a COVID-19 specific vaccine during the trial, then please report the participant's date of COVID-19 specific vaccination as the date of last follow-up (dateLastFup).

Please set all events after COVID-19 vaccination to COV19 = "no" and COV19hosp = "no" and dateCOV19 = NA and dateCOV19hosp = NA (or empty/missing, NA means 'Not Available'). This way the participant is censored at the date of COVID-19 vaccination, and we can't distinguish such censoring from other loss of follow-up/end of follow-up. (So make sure no cases exist with dateCOV19 > dateLastFup, since that would provide information about the COVID-19 vaccination status and the date of vaccination, that according to our Data Transfer Agreement, we should not have.)

Reinfections

Reinfections are not considered in the analysis, hence, please do not mark the participants in the data set that had a second event.

Other

The dataset should be uploaded as CSV file. If a CSV is not possible, please contact us to discuss alternatives.

You will be provided with a study code, e.g. NL, for the Netherlands, FR for France. Make sure that your filename has this structure and keep it the same all the time:
BCG-CORONA-<study code>-<date: YYYY-MM-DD>, e.g.: *BCG-CORONA-NL-2020-05-23.csv*

Data uploading

You will receive two passwords: a *data-upload password* and a *dashboard password*, connected to the user name of your personal login to the dashboard (two-letter abbreviation of the country of your trial). The data-upload password is not personal, the dashboard password is. Please do not share any of the two passwords with others.

The website where data are uploaded meets the privacy regulations as dictated by the General Data Protection Regulation (GDPR).

Go to https://surfdrive.surf.nl/files/index.php/s/tlgQuK2KS1Kzrqw

Log in using the *data-upload password* which is provided to you via e-mail.

Upload the data set.

Please keep an eye on the dashboard to check whether your data set is up-to-date and try to update the data by uploading a new data set as timely as possible. You will receive your login details for the dashboard in a separate e-mail.

Contact information

If you have any questions, please contact:

- Henri van Werkhoven for questions about operational and clinical details of the trials: c.h.vanwerkhoven@umcutrecht.nl
- Judith ter Schure or Alexander Ly for questions about the data upload procedure, the dashboard and statistical methodology of Safe testing and Safe confidence sequences: j.a.terschure@cwi.nl, alexander.ly@cwi.nl