ALL-IN-META-BCG-ELDERLY

Instruction to participating data uploaders

V1 – 01 March 2021

Introduction

ALL-IN-META-BCG-ELDERLY stands for "**Anytime Live and Leading INterim meta-analysis of the impact of Bacillus Calmette-Guérin vaccination in elderly with or without chronic comorbidities during the SARS-CoV-2 pandemic**". Several trials are ongoing and planned to test the hypothesis that BCG vaccination in elderly or adults with chronic comorbidities 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.

Statistical method 'Safe Testing' & Webinar

The statistical method is described in detail in a statistical analysis plan that will soon be published on https://www.crd.york.ac.uk/PROSPERO/. 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

Strictly personal login and demo login
A dashboard is developed to track the evidence across trails. This dashboard can found on: https://projects.cwi.nl/safestats/, see also Figure 1 for a screenshot. To explore the functionality, or 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

For the analysis of real data each person uploading the data receives a strictly personal login that should not be shared with others involved in their own or other trials, to prevent unblinding of the results.

The uploaded data will be processed manually. After the first upload you will receive a confirmation e-mail. For subsequent uploads you will only receive an e-mail when there are potential issues with the data. After manual processing the results, the meta-analysis will be available to you at an online dashboard (link at https://projects.cwi.nl/safestats/). At a later stage we may switch to automated data processing.
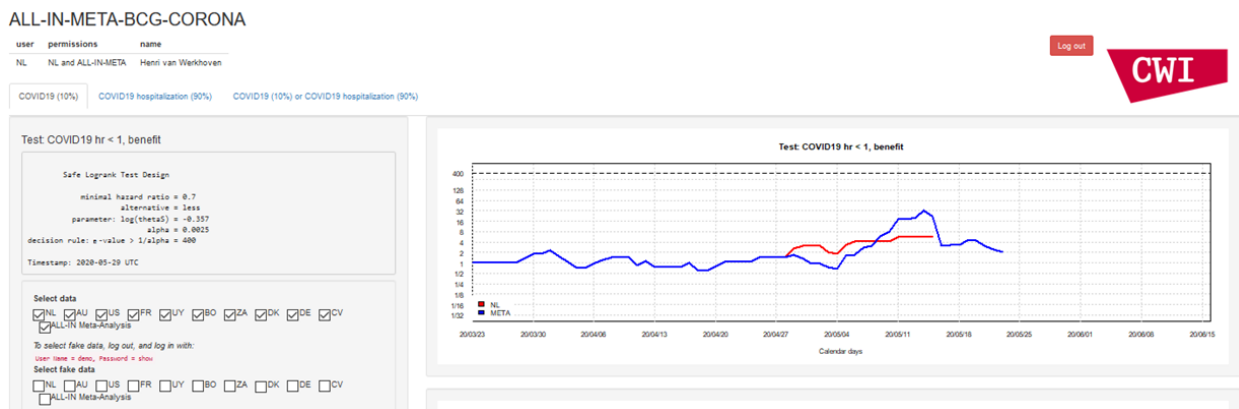

Figure 1 ALL-IN-META-BCG-ELDERLY dashboard (showing fake data for the purpose of this screenshot)

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 visualizes two e-value sequences: that of the ALL-IN meta-analysis and that of their own trial. Unless others have given permission to show this information, no contributions of other individual trials are visible (the boxes can be checked, but the e-values won't show in the plot, as shown in *Figure 1*).

Data export

Only privacy insensitive (i.e., person unidentifiable) information is needed to compute an individual trial and meta-analytic e-value. The data required for the ALL-IN meta-analysis are the following. Please find a toy example data set in Figure 2 on page 3.

Preferred variable name	Description	Preferred value levels / format
intervention	Intervention randomized to	control or BCG
dateRand	Calendar date of randomization	yyyy-mm-dd
site	Site of enrolment	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	site	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-ELDERLY 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.

When results of the meta-analysis trigger a decision to publish the results, we will ask for additional data in order to determine the secondary endpoints. We have decided to keep the regular data extractions as lean as possible to keep the workload acceptable.

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. NL1, NL2 for trials from the Netherlands. Make sure that your filename has this structure and keep it the same all the time:
BCG-ELDERLY-<study code>-<date: YYYY-MM-DD>, e.g.: *BCG-ELDERLY-NL1-2020-05-23.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* that 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.

Frequency of uploading new dataset

The statistical method used for the meta-analysis allows unlimited interim analysis. Therefore, new data can be uploaded as frequently as you like. We ask to upload new data at least once every two weeks to not delay a conclusion.

In two situations we will request to upload new data within 72 hours: (1) if one of the trials reaches a conclusion, (2) if the meta-analysis yields a conclusion. In both cases this serves to confirm or refute the result with the most complete pooled data.

Data upload out-of-date
The ALL-IN-META e-value sequence is always as up-to-date as the most recently uploaded trial data set. See the blue meta-analysis curve in *Figure 1* in comparison to the red curve of the NL trial. If you find your own trial e-value sequence out-of-date, please upload a more recent data set (procedures for data export and upload are detailed below).

Give permission to show your individual trial e-value contribution to others
It is also possible to allow all other logins to inspect your trial's contribution to the meta-analysis; please send an e-mail to j.a.ter.schure@cwi.nl. The default is that individual trial contributions are only visible to the corresponding 'data-uploader' login. Alternatively, you can share the evidence of your trail to specific collaborators. For instance, if you are in contact with the person uploading the data of a different trial and together agree to give permission to stay updated on each other's trial contribution to the meta-analysis, please explain the situation in an e-mail to j.a.ter.schure@cwi.nl so the permissions of your login details can be updated.

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.

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