

# ALL-IN-META-BCG-ELDERLY

## Instruction to participating data uploaders

V2 – 31 October 2022

### 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 is 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](#) (<https://tinyurl.com/rtcfcurp>) requires only basic statistical knowledge, [Webinar Part 2](#) (<https://tinyurl.com/bdz3zb7u>) contains more technical details.

### ALL-IN-META results

#### *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.

### *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](mailto:j.a.ter.schure@cwi.nl) and [alexander.ly@cwi.nl](mailto:alexander.ly@cwi.nl) for verification.

### **Data export**

The data required for the ALL-IN meta-analysis are the following. Please find a toy example data set in Figure 1 on page 3.

<b>Preferred variable name</b>	<b>Description</b>	<b>Preferred value levels / format</b>
intervention	Intervention randomized to	<i>control</i> or <i>BCG</i>
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	<i>no</i> or <i>yes</i>
dateCOV19	Calendar date of being COVID-19 positive	yyyy-mm-dd
COV19hosp	Status COVID-19 related hospitalization	<i>no</i> or <i>yes</i>
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 1 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.

## 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.

We elaborate on date of last follow regarding covid-specific vaccination and reinfections further.

### Covid-specific vaccination

If a participant is vaccinated 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. 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. 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 a *data-upload password*. Please do not share this password 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.

### **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](mailto: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@cw.nl](mailto:j.a.terschure@cw.nl), [alexander.ly@cw.nl](mailto:alexander.ly@cw.nl)