ALL-IN-META-BCG-CORONA Newsletter

#1, October 2020

> "*ALL-IN meta-analysis:*
>
> *Anytime Live and Leading INterim*
>
> *meta-analysis*"

Your action list

1. Data transfer agreement
2. Data upload
3. Protocols and governance structure
4. Webinar

Dear BCG-CORONA researchers,

Last June, you received our invitation to join a unique collaboration for *live* meta-analyis of data from trials studying the effects of the BCG vaccine in healthcare workers.

Our invitation contained our proposed statistical analysis plan (SAP), and our proposed working instruction for data uploading. Since we have not received any reservations to make the SAP public, it has been submitted to PROSPERO and will soon be available.

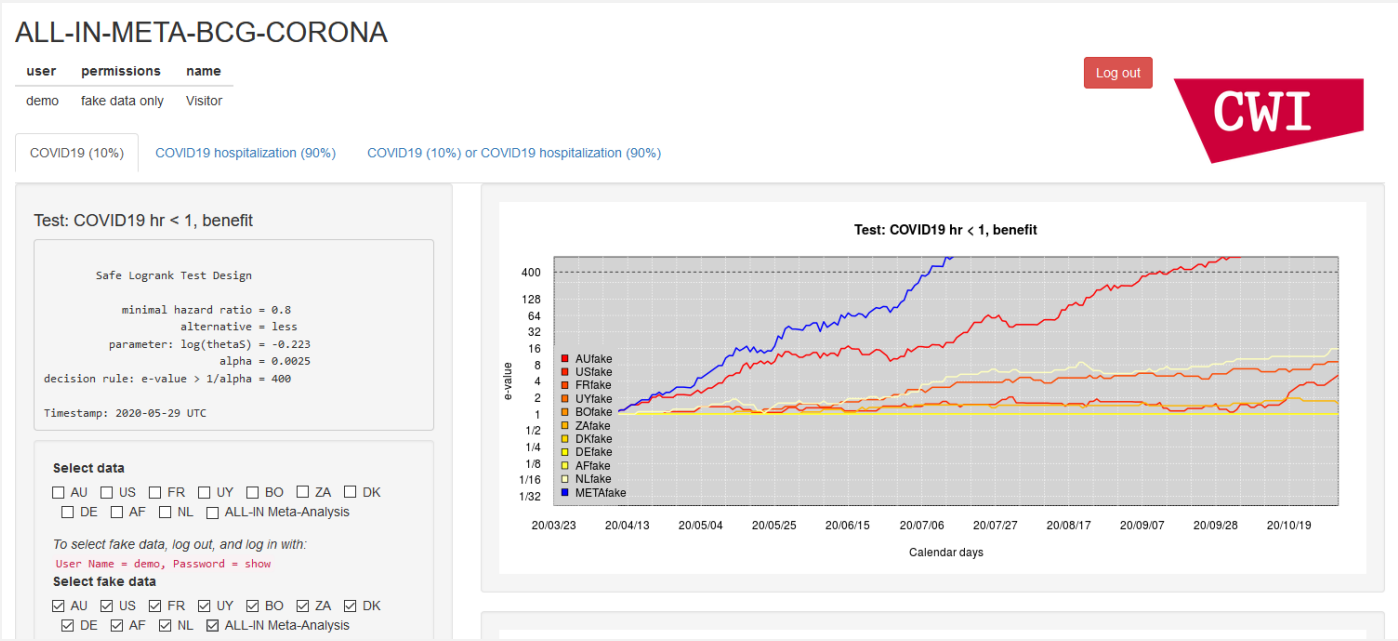
Thanks for your interest!

We want to thank you for your kind response to our initiative. Some of you already shared their protocol and received the login details to access the data upload and the live dashboard (demo screenshot below). Others are first waiting for a data transfer agreement.

In our newsletters, we wish to keep you updated and clarify the next steps of this unique collaboration.

Best wishes,

Henri van Werkhoven en Judith ter Schure
Mihai Netea, Marc Bonten en Peter Grünwald



Our ALL-IN meta-analysis will potentially include the data of 15 trials. The Dutch trial (NL), the Danish trial (*BCG-DENMARK-COVID,* DK), African trial (Guinea-Bissau, Mozambique and Cape Verde, AF), the South-African trial (ZA), the Hungarian trial (*BACH,* HU), the Australian trail (*BRACE*, AU), the Uruguay trial (UY), the American trial (*BADAS*, US), the Boston, USA trial (BO), the French trial (FR), the German trial (DE) have already expressed interest to participate. Four other trials will be approached.

Three trials have shared their protocols (NL, DK, HU), four have received their login details for data upload and dashboard (NL, DK, AF, US).

The 'Leading' in Anytime Live and Leading INterim meta-analysis

Each trial might have its own stopping rules to declare efficacy or futility. The ALL-IN meta-analysis, however, is stopping rule independent. This means that the validity of the meta-analysis is unaffected by stopping rules that drive the sample size of the studies as well as independent from results that drive the number of studies to start recruitment. Moreover, any data that is part of the meta-analysis (including the meta-analysis synthesis itself) can guide decisions to stop or expand trials. No prespecified (alpha-spending) boundaries restrict these possiblities; the meta-analysis is allowed to lead decisions in any possible way.

On the one hand, this means that the meta-analysis will not force stopping rules on participating studies; merely that it provides external guidance for these decisions. On the other hand, the ALL-IN meta-analysis does provide a way out of (alpha-spending) boundaries that seem too restrictive in the light of the meta-analysis. If a trial reaches an efficacy boundary, but its results seem not convincing compared to all other studies, the trial is allowed to continue recruitment, monitor participants and extend its contribution to the meta-analysis.

Webinar statistical methodology

We will share with you a prerecorded webinar in which we explain the meta-analysis. There will probably be two parts of half an hour; one general part (no statistical background required), and one more statistical part. Following this webinar, we would like to invite you to share your ideas, and ask questions, on three possible occasions out of the following:

Los Angeles	***New York***	***Amsterdam***	***Melbourne***
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11-18-20 9:00 AM	**11-18-20 12:00 PM**	**11-18-20 6:00 PM**	11-19-20 4:00 AM

Please let us know your interest in such a Q&A session by providing your availability through this Doodle.

More information about the statistical methodology will soon be published on: https://projects.cwi.nl/safestats/

Data transfer agreement

We wish you to sign a data transfer agreement (DTA) so that all parties are ensured that uploaded data will be processed under GDPR (EU trials) and potentially other regulations (non-EU trials). Please find attached a proposal DTA for review by your institution. For any required modifications or to submit the signed DTA, please communicate with Henri van Werkhoven (c.h.vanwerkhoven@umcutrecht.nl).
If your legal office is of the opinion that no DTA is required, please inform Henri as well. After all, as indicated in the working instructions, our meta-analysis only requires dates of randomization and events, and no identifying information.

What's next

After signing the DTA, one person per trial should be able to upload a data set of event times for the meta-analysis. We hope to contact the 'data uploaders' separately to provide them with login details to upload data and to consult the dashboard with interim meta-analysis results. Please provide us with the full name and e-mail address of the data uploader of your study and share our working instructions for data uploading with this person. If you already did so, let's start your contribution to our collaborative meta-analysis by uploading data!

Governance structure

There are differences between the trials that we potentially wish to include. Some use placebos, some don't. Some have regular testing of healthcare workers, some don't.

For this reason, we have asked Cochrane Netherlands to perform an independent assessment of the study protocols of the BCG in healthcare workers trials, and advice on the trials to include in the primary and secondary analysis. Our proposal for the governance structure is the following:

Steering Committee: Professor Peter Grünwald (CWI), Professor Marc Bonten (UMC Utrecht), Professor Mihai Netea (Radboud UMC)
Blinded for interim results

- Decide which trials to include in the primary and secondary analysis based on advice *Advisory committee* and *Cochrane Netherlands*.
- Decide when to make the meta-analysis results public in the dashboard and in a scientific publication based on advice *Advisory committee*.

Advisory committee: One representative from each trial will be offered a seat in the committee:
we will consider the PI, unless indicated otherwise

- Provide Cochrane Netherlands with detailed protocol information to perform the systematic review
- Advice on trial inclusion criteria for the primary analysis
- Advice on when to make the meta-analysis results public
- We consider those actively involved and sharing the data to meet the ICMJE authorship criteria

Operational team: Judith ter Schure (meta-trial statistician, CWI), Alexander Ly (back-up statistician, CWI), Henri van Werkhoven (meta-analysis principal investigator, UMC Utrecht)

- Coordinate data collection
- Analyze data and update dashboard
- Write news updates
- Prepare publications

Independent advice: *Cochrane Netherlands (to be confirmed)*

- Advice on which trials to include in the primary analysis

News coverage

summer

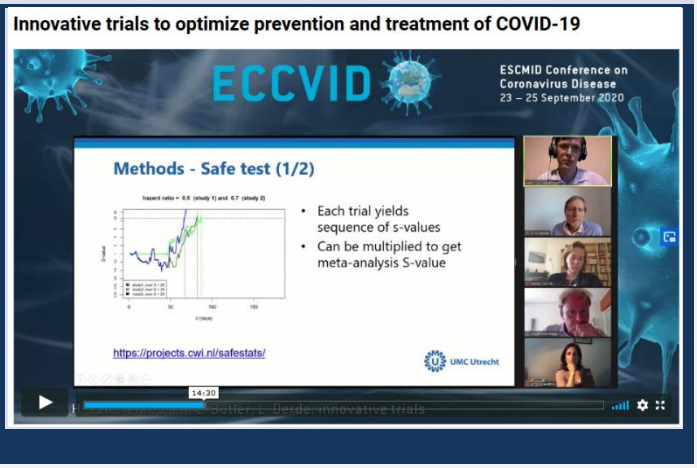

wetenschap

Gokken met data voor het beste resultaat

Amsterdam Data Science published a blogpost by Professor Peter Grünwald about the use of his work on *Safe Testing* in this meta-analysis [English].

The newspaper Het Parool and the website New Scientist published an interview about the use of ALL-IN meta-analysis in comparison to conventional meta-analysis [Dutch].

The BCG ALL-IN meta-analysis was presented at ECCVID Conference on Coronavirus Disease. The presentation can still be watched by those registered for this virtual conference [English].



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 for questions about the data upload procedure, the dashboard and statistical methodology of Safe testing and Safe confidence sequences: j.a.ter.schure@cwi.nl