ALL-IN-META-BCG-CORONA Newsletter

#4, September 2022

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

Your action list

Keep your data updated to keep our meta-analysis *alive!*

Or start to join us now:

1. Data transfer agreement
2. Share protocol for review
3. Upload data

Dear BCG-CORONA researchers,

We are approaching a conclusion! The current results of our ALL-IN meta-analysis can be consulted in the dashboard by all data-uploaders involved. The permissions are updated: each data uploader has a login that provides access to a plot of the ALL-IN meta-analysis and all individual trial contributions.

In this newsletter we discuss some details of the process so far and the steps ahead. We again include a section that we call '**A few words about statistics**'.

A preregistration of the meta-analysis can be consulted on PROSPERO. All earlier documents are still available on our project website, including the recorded webinars that stay accessible in our Youtube playlist.

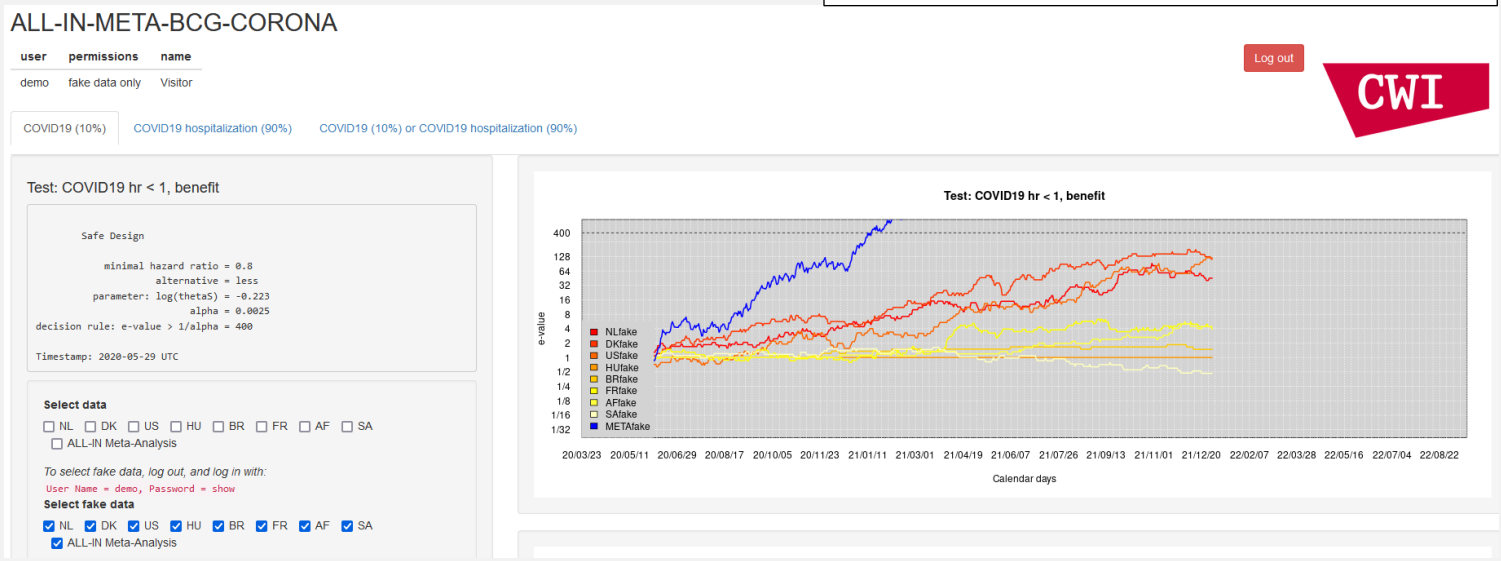
Thanks for your effort!

We have a very active collaboration with many trials involved. It was great to see many of you during the Advisory Committee meeting of July 9th 2021 that discussed the first results. We hope to see you again in a concluding meeting on October 3rd 19:00 (Amsterdam time).

Best wishes,

Henri van Werkhoven, Judith ter Schure and Alexander Ly
Mihai Netea, Marc Bonten and Peter Grünwald

Demo version of the dashboard (with fake data)



Our ALL-IN meta-analysis is *live*! The trials in the meta-analysis all received a positive recommendation from the Advisory Committee based on Cochrane Netherlands' risk-of-bias assesment, after which our Steering Committee gave the green light to include these trials in the primary meta-analysis.

Where we are and what's next

The dashboard now includes final data from six trials: **NL, DK, US, HU, BR, AF!**

The Danish trial (**DK**) inclusion was already annnounced in the May 2021 newsletter, but the data transfer agreements had to still be arranged. The data from the Brazilian (**BR**) trial and **US** (*BADAS*) trial were updated since we presented results during the July 9th 2021 meeting. At that meeting, it was decided that also the African trial (Guinea-Bissau, Mozambique, **AF**) will be included. We have the data from the South-African trial (**SA**) ready, but are awaiting a decision on trial inclusion from the Steering Committee, following external assessment by Cochrane Netherlands and input from the Advisory Committee.

The French trial (*COVID-BCG*, **FR**) is still in preparation. We also hope to still engage the Polish trial (**PL**) and the Australian trail (*BRACE*, **AU**).

The Indian trial was not included, following the advice of the Advisory committee and decision of the Steering committee. See their statement below at the end of this newsletter.

The dashboard can be consulted by all data-uploaders using a personal login. To explore the functionality, or to explain the procedure to others, the dashboard includes a 'Select fake data' option, that can be viewed using login details: User Name = demo, Password = show.

Please check your data

The draft manuscript now contains the following definitions for Covid-19 events and participants at risk

Outcome definitions
During an advisory committee meeting on April 23rd, 2021 we expanded the definition of an event of Covid-19 infection. An event of Covid-19 infection is now defined as (1) PCR-based detection of SARS-CoV-2 in a respiratory sample, (2) detected with a lung CT, or (3) an antigen test. See our updated statistical analysis plan. Please contact us if your event definition deviates from this.

Participants at risk
Once a participant is vaccinated with a Covid-19 specific vaccine, e.g. Moderna, Pfizer/BioNtech, this participant should be viewed as censored per date at which he/she received the Covid-19 specific vaccine, i.e. that will be their date of last follow-up. Participants were considered at risk of Covid-19 infection and hospitalization from the date of randomization to the date of either a Covid-19 infection/hospitalization, the end of follow-up, loss to follow-up or date of Covid-19 specific vaccination. So some of the participants and infections after Covid-19 vaccination were not considered as events, and neither were reinfections. Please contact us if your event definition deviates from this.

Data storage

Newsletter 2 Q&A stated that all data will be deleted when Judith's contract at CWI expires. For data storage purposes this moment was postponed from January 1st 2022 to January 1st 2023. At the next Advisory committee meeting we will discuss whether and how we can make the data publicly available.

Next advisory committee meeting

Our next Advisory Committee meeting will be on October 3rd 19:00 (Amsterdam time). We will discuss results, and some of decisions of presentation in the draft manuscript that we will circulate soon after the meeting.

Decision on trial inclusion

Next advisory committee meeting, our Steering committee will make a decision to possibly add two more trials to the ALL-IN meta-analysis – **SA** and **FR** – based on an external risk-of-bias assessment by Cochrane Netherlands and advise from the Advisory committee. There are three parts to this decision:

Trial quality
The protocols of the trials will be shared and a risk-of-bias assessment will be written for each by Cochrane Netherlands. As an external party, Cochrane advises on the trial inclusion. During the meeting of October 3rd any remaining questions can be answered by the **SA** and **FR** trial representatives.

Trial homogeneity
The shared protocols and meeting with the Advisory committee need to give a good impression of the similarities and differences between the trials. Some heterogeneity is accounted for in the ALL-IN methodology, but the included trials should be homogeneous enough to answer the same research questions.

The ALL-IN meta-analysis is designed to reject the global null hypothesis of no effect in all trials. More trials means more observed events and will increase the power of the meta-analysis. The analysis of a BCG benefit sets a minimum effect for both COVID19 events and hospitalizations (hazard ratio 0.8 and 0.7, so 20% and 30% vaccine efficacy, respectively) meaning that any trial that shows an effect that is as large or larger will contribute to the power of the meta-analysis. Hence, heterogeneity is accounted for, as long as trials observe an effect in the same direction (e.g. benefit, not harm; we test both sides with a one-sided test each).

If trials are expected to fall in two groups that could have opposite effects they should not be combined in the same meta-analysis. Therefore, the selection of trials for the primary analysis emphasizes that all selected trials are homogeneous enough to answer a single question: whether BCG affects Covid-19 or Covid-19 hospitalization incidence in a way that can possibly be detected in all included trials.

Trial event definitions
The Statistical Analysis Plan (SAP) of June 17th 2020 stated the following: *Documented COVID-19 disease is defined as PCR-based detection of SARS-CoV-2 in a respiratory sample.* During the advisory committee meeting on April 23rd, 2021 this was expanded to lung CTs and antigen tests. An updated Statistical Analysis Plan (v2 September 19 2022) now reflects this new definition.

Dashboard permissions

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.

Update data upload

The ALL-IN-META e-value sequence is as up-to-date as the most recently uploaded trial dataset. We ask data uploaders to check the dashboard to see if their trial data is up-to-date.

We also encourage 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 our project page: 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 for verification.

Governance structure

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 of the *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 of the *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*

- Advice on which trials to include in the primary analysis

The statement from the Steering Committee about the Indian trial

We have concerns about possible biases in the data from the India trial following an assessment by Cochrane Netherlands and our operational team. Cochrane Netherlands provided us with a risk-of-bias assessment based on protocol information that raised questions about proper randomization. Our operational team arranged a description of the data structure that raised questions about proper adjudication of endpoints and data management. These reports were detailed (structured assessment, summary statistics) but did not disclosure any trial results by BCG vaccine allocation.

Unfortunately, the questions raised could not be fully answered by the India trial such that the concerns of bias were not alleviated. We therefore decide to exclude the India trial from ALL-IN-META-BCG-CORONA. We were blinded to the data of the Indian trial when making this decision.

More trials are assessed by Cochrane Netherlands and DTAs are being approved. As before, we will remain blinded to the data of these additional trials until a decision is made about their inclusion or exclusion in the meta-analysis.

July 8th, 2021
ALL-IN-META-BCG-CORONA Steering committee
Mihai Netea, Marc Bonten and Peter Grünwald

A few words about statistics: e-values below 1

Our analysis on Covid-19 events (COV19) is designed to detect a minimal effect of hazard ratio 0.8 (20% Vaccine Efficacy) and our analysis on Covid-19 hospitalization events (COV19hosp) is designed to detect a minimal effect of hazard ratio 0.7 (30% Vaccine Efficacy).

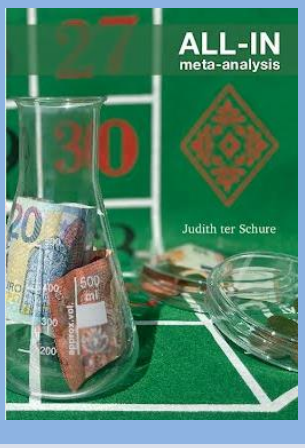
If we reach the threshold of 400 for COV19 and 44 for COV19hosp, we can reject the null hypothesis of no effect (our null hypothesis is a hazard ratio of 1, which is the same as 0% Vaccine Efficacy).

e-values of 1 provide neutral evidence.

If our e-values for benefit are below 1, that means that the null hypothesis of hazard ratio 1 or 0% Vaccine Efficacy is actually performing better than the alternative hypotheses above. The same is true of our e-values for harm, meaning that the null hypothesis is performing better than the alternative hypothesis for harm (which is 1/0.8 = 1.25 for COV19 and 1/0.7=1.43 for COV19hosp).

That does not necessarily mean that the null hypothesis is good in comparison to other hypotheses, for example those describing effects that are smaller than our minimal effect of interest but larger than our null hypothesis. Our confidence intervals in the paper (that are anytime-valid) will show which values of our hazard ratio are compatible with the data.

News coverage



Judith defended her PhD dissertation with the title ALL-IN meta-analysis, that as a chapter 2 introduces the e-values we use in this meta-analysis: the Safe logrank test.

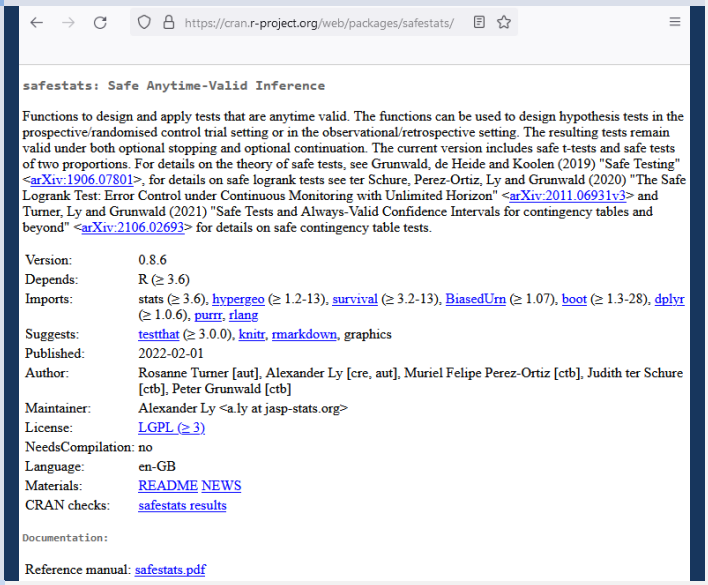
You can find her PhD dissertation here in the CWI repository.

A small article with the announcement of her defense and a mention of this collaboration for BCG-CORONA can be found here on the CWI website.

CRAN release safestats package

The packages that calculates all e-values and hazard ratios for our ALL-IN meta-analysis was released on CRAN: the Comprehensive R Archive Network.

For tutorials on how to use the package to process your own data into e-values please visit the project website https://projects.cwi.nl/safestats/


https://cran.r-project.org/web/packages/safestats/

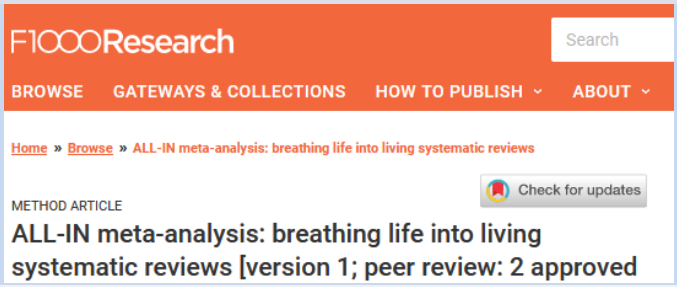
safestats: Safe Anytime-Valid Inference

Functions to design and apply tests that are anytime valid. The functions can be used to design hypothesis tests in the prospective/randomised control trial setting or in the observational/retrospective setting. The resulting tests remain valid under both optional stopping and optional continuation. The current version includes safe t-tests and safe tests of two proportions. For details on the theory of safe tests, see Grunwald, de Heide and Koolen (2019) "Safe Testing" <arXiv:1906.07801>, for details on safe logrank tests see ter Schure, Perez-Ortiz, Ly and Grunwald (2020) "The Safe Logrank Test: Error Control under Continuous Monitoring with Unlimited Horizon" <arXiv:2011.06931v3> and Turner, Ly and Grunwald (2021) "Safe Tests and Always-Valid Confidence Intervals for contingency tables and beyond" <arXiv:2106.02693> for details on safe contingency table tests.

Version:	0.8.6
Depends:	R (≥ 3.6)
Imports:	stats (≥ 3.6), hypergeo (≥ 1.2-13), survival (≥ 3.2-13), BiasedUrn (≥ 1.07), boot (≥ 1.3-28), dplyr (≥ 1.0.6), purrr, rlang
Suggests:	testthat (≥ 3.0.0), knitr, rmarkdown, graphics
Published:	2022-02-01
Author:	Rosanne Turner [aut], Alexander Ly [cre, aut], Muriel Felipe Perez-Ortiz [ctb], Judith ter Schure [ctb], Peter Grunwald [ctb]
Maintainer:	Alexander Ly <a.ly at jasp-stats.org>
License:	LGPL (≥ 3)
NeedsCompilation:	no
Language:	en-GB
Materials:	README NEWS
CRAN checks:	safestats results

Documentation:

Reference manual: safestats.pdf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METHOD ARTICLE

ALL-IN meta-analysis: breathing life into living systematic reviews [version 1; peer review: 2 approved

The paper describing ALL-IN meta-analyis is currently under review at F1000.

We invite you to comment on this paper on the F1000 website!

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 ALL-IN meta-analysis, Safe testing and Anytime-valid confidence sequences:
  j.a.ter.schure@cwi.nl