101005177 — COVID-RED

COVID-RED

WP7

D7.8 Second Report from the Advisory Board

Lead contributor	1. UMCU
Other contributors	2. AVA AG (Ava) 3. JULIUS CLINICAL RESEARCH BV (JCR) 4. UNIVERSITY COLLEGE LONDON (UCL) 5. VIVE - DET NATIONALE FORSKNINGS- OG ANALYSECENTER FOR VELFAERD (VIVE) 6. Stichting Sanquin Bloedvoorziening (Sanquin) 8. ROCHE DIAGNOSTICS NEDERLAND BV (Roche)

Document History

Version	Date	Description
V1.1	24.12.2021	First version
V1.2	25.01.2022	Final version

Publishable summary

As part of the COVID-RED project, a scientific and ethical Advisory Board (AB) is set up, which will act as an independent consulting body for the management of the consortium, and provide non-binding strategic advice to the Managing Board on the scientific progress and problems that may arise during the implementation of the IMI COVID-RED initiative.

In this report, AB members have shared their questions and comments on several aspects of the study, including GDPR compliance, algorithm design, study design, participant retention, data analysis. The AB feedback was carefully considered by the consortium and the consortium responses are included in this report. The consortium will take the received feedback into account in the further course of the COVID-RED project.

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Introduction

COVID-RED is a public-private partnership, funded by the Innovative Medicines Initiative running from 1 July 2020 until 30 June 2022. The overall goal of COVID-RED is to evaluate the use and performance of a CE-marked device (wearable), which uses sensors to measure breathing rate, pulse rate, skin temperature, and heart rate variability for the purpose of early detection and monitoring of COVID-19 in general and high-risk Dutch populations. At the same time, a mobile application will be used to track participant-reported symptoms.

A prospective, randomised crossover trial is following amost 18,000 individuals from the Dutch population wearing the device and responding to participant self-report parameters via a purpose-designed app. Based on this data, an algorithm will indicate which individuals require COVID-19 diagnostic testing. To evaluate algorithm performance, the cohort will be tested for COVID-19 antibodies at baseline and the end of each period of the design, with stored samples at the beginning of each period of participants who have tested positive also being tested to determine whether the participant was already positive at baseline or was exposed to SARS-CoV-2 during follow-up.

As part of this project, a scientific and ethical Advisory Board (AB) is set up, which will act as an independent consulting body for the management of the consortium, and provide non-binding strategic advice to the Managing Board (MB) on the scientific progress and problems that may arise during the implementation of the IMI COVID-RED initiative.
This report is the second of a series of three public reports, and its aim is to share the assessment and recommendations on the scientific quality of the work conducted during the second period of the project (M12-M17).

COVID-RED Advisory Board

We set up a diverse Advisory Board (AB) specialised in the relevant scientific and ethical fields, and have thus invited six suitable experts to join the AB. The following expertise is represented in the Advisory Board: ethicist, patient advocate, representative from the Dutch National Institute for Public Health and the Environment, healthcare provider, wearable device specialist, clinical trials expert. All AB members are individuals with extensive experience, scientific and/or industrial prominence and leadership in the field of the project.
All appointed Advisory Board Members have signed an Advisory agreement, and are routinely asked to disclose any conflict of interest with the objectives of the COVID-RED project.

Our six appointed Advisory Board members are:

First name	Surname	Organization
Cees	Smit	Patient Advocate

Susan	van den Hof	The National Institute for Public Health and the Environment (RIVM) – Representative
Martine	de Vries	The Leiden University Medical Center (LUMC) - Ethicist
Manuel	Castro Cabezas	Julius Clinical - Healthcare provider
Björn	Eskofier	Friedrich-Alexander University – Wearable device specialist
Frank W.	Rockhold	Duke University – Clinical trials expert

Following a kick-off meeting on 2 July 2021 and a follow up meeting on 17 November 2021, our Advisory Board members were asked to deliver the second review of the outcomes developed from month 12 (June 2021) to month 17 (November 2021) of the project, and to provide, from their expert perspective, feedback on the progress of the COVID-RED scientific initiative so far.
The main activities and/or milestones developed during this period (M12-M17) are listed below:

- Clinical trial execution progressing; close to study end (First batch of subjects reached EoT on 3-Nov; second batch on 18-Nov).
- Planned and implemented necessary data management infrastructure for a fully decentralized trial, and developed and managed a cloud-based centralized analytics platform with qualified statistical software for the hosting and analysis of study data collected through all of the different sources (EDC; Ava Bracelet; Ava COVID-RED app; and Lab data).
- Shifted focus from participant recruitment to participant retention, using a communication plan for the clinical trial specifically. Hired a social media expert for managing Twitter and Instagram.
- Assessed compliance with study procedures (i.e. bracelet sync, survey completion) throughout the project.
- Tested participants for antibodies using serology testing. In order to expand the testing of SARS-CoV-2-antibody (Task 2.3) to identify those who have been vaccinated, WP2 has incorporated additional testing for anti-nucleocapsid antibodies.
- Developed algorithm version 2 (launched at start of study Phase 1)
- Bracelet return campaign set up and already being executed for first batch of subjects.
- Data on the intervention costs are being collected and delivered.
- Identification of possible solutions for long-term FAIR data storage and access by external researchers.

They were especially requested to look critically at key steps, activities, and/or missing elements in the work packages that may represent a risk for the realization of the scientific programme, and/or may affect its quality or implementation.
Ultimately, they were tasked with qualifying, according to their own expertise, the main risks attached to the scientific progress achieved by the COVID-RED project in month 12 to 17, and, wherever possible, to suggest remedial actions.

The materials made available for the first review were:

- Recording and slides of the kick-off meeting, including project presentation.

- First bi-annual report (D7.4) describing the project's progress from month 1 to month 11 (July 2020 – April 2021);
- Publication of COVID-RED study protocol as available in July 2021;
- The project's website: www.covid-red.eu, as well as access to the project's Twitter account (@CovidRed) and Instagram account (covidredproject);
- Highlight of press releases about COVID-RED from month 1 to month 13:
    - Promising results from our pilot study in Liechtenstein: COVI-GAPP;
    - IMI recruitment message about COVID-RED;
    - Interview with Rick Grobbee about the project (in Dutch only);
    - Press article written by a participant, interviewing Rick Grobbee and other participants about their experiences (in Dutch only).

New materials for the second review were:

- Recording and slides of the follow up meeting, including project presentation.

Advisory Board comments

Summary table of proposed follow-ups

Observations from AB advisers	Action follow-up	Where to be implemented	When	By whom
Dropout rate	A thorough analysis of the dropout rate will be performed during the analyses of the final data after participant follow-up has ended	Follow-up in TASK 3.5 – Clinical Analysis of study results and future recommendation and D3.5	Final data after participant follow-up has ended	WP3
Risk that some primary endpoints required may be lower than required	Propose to investigate appropriate Machine Learning approaches to ensure that the envisioned analyses can be conducted	TASK 1.3 - Developing machine-learning algorithm and D1.3 Functional and tested novel app to collect biophysical data and patient reported outcomes for the detection of early signs of COVID-19 infection (improved version)	Final data after participant follow-up has ended (February 2022)	WP1

Vaccination status	Vaccination status is stratified at app level Antibody testing expanded to be able to differentiate between the participants that were vaccinated and those that had a COVID-infection	TASK 2.3 – Testing study participants for SARS-CoV-2 antibodies and D2.3: Final report on testing results	Final data after participant follow-up has ended	WP3
Asymptomatic cases	Propose to explore if we can develop an algorithm that allows us to detect asymptomatic infections.	TASK 1.3 - Developing machine-learning algorithm and D1.3 Functional and tested novel app to collect biophysical data and patient reported outcomes for the detection of early signs of COVID-19 infection (improved version)	Final data after participant follow-up has ended (February 2022)	WP1
Algorithm performance	The current evaluation of the algorithm was based on data collected during the first period of the trial. The final evaluation will also include the follow-up period and thus a higher number of registered infections.	Proposed follow-up in TASK 3.5 – Clinical Analysis of study results and future recommendations and D3.5	Final data after participant follow-up has ended	WP3
Marketing	Depending on the initial outcomes of the studies, COVID-RED will design an exploitation strategy	Proposed follow-up in TASK 7.5 – Sustainability and business development and D7.14 Business plans	After data has been analysed	WP7

Sustainability	Publishing key information about the trial as well as the results of the project in peer-reviewed open-access journals Making essential study data available via developping a plan for a sustainable model for data storage	Follow-up in Task 5.4 - *Implement a long-term, sustainable model for data storage meeting FAIR requirements* and D5.8	After data has been analysed	WP5
eConsent	N/A – Resolved			
Randomization	N/A – Resolved			
Training	N/A – Resolved			
COVID-19 waves	N/A – Resolved			
Data management platform	N/A – Resolved			
Opportunities for collaboration	N/A – Resolved			

General observations

The Advisory Board members commented that the project progress looks very good, and that the quality of the work is evolving well. The issues encountered have been dealt with as well as possible. It looks encouraging that the bracelet and app are working better and better. The preparations for the final analysis look thorough. They would like to emphasize the value of the work done. They congratulate the consortium on this major accomplishment in these harsh times. Despite the fact that the external boundary conditions are changing, the consortium always adapted well to a moving target.

Challenges observed

A major challenge remains the dropout rate: how to explain it, understand it, and deal with it for future planning purposes. In addition, a risk is that the number of primary endpoints required for robust conclusions on the algorithms for relevant subgroups (e.g. vaccinated versus unvaccinated) or by calendar period (e.g. summer versus winter, dominant SARS-CoV-2 variants) may be lower than required; but that is not be influenced by the researchers. And the consortium itself as well as the reviews came up with identifying the „moving target“ (due to vaccinations, dropouts, etc.) as a challenge - this could be addressed by appropriate Machine Learning / Signal Processing approaches.

Consortium response

A thorough analysis of the dropout rate will be performed during the analyses of the final data after participant follow-up has ended. Due to the unique and challenging circumstances it was very difficult to predict the amount of dropout to be expected during the trial. All possible methods were employed in this decentralised trial to keep people engaged and participating in the study. For example, prediction modelling was used during the study to identify subgroups at higher risk of dropout for more targetted reminders. Nevertheless there was substantial dropout of which the impact on the final analyses will be assessed when all the data has been collected. If this impact proves to be significant, we will investigate appropriate Machine Learning approaches to ensure that the envisioned analyses can be conducted. Thus far, we have attempted to account for the potentially relevant factors such as vaccinations in algorithm development. However, we will not know the extent of the impact of dropout rate on algorithm's performance until all data has been collected.

eConsent

How was eConsent managed for this trial, as it can be challenging?

Consortium response

In order to implement eConsent & eSignature for the COVID-RED trial, the trial had to be regarded by the by the central ethics committee as a non-WMO trial, which is the Dutch law on medical research with human subjects. After thorough discussions with the ethics committee, the COVID-RED was classified as non-WMO. This allowed the consortium to implement an eConsent platform, ensuring a fully remote way of obtaining consent from all trial subjects.

Randomization

Does the trial involve randomization? Were there any issues with participants not being content with the group they were randomized to?

Consortium response

Participants were randomized at the study start in a cross-over setup: all participants wore the bracelet and filled out the eDiary, but for only half of the participants, the bracelet data was fed back to the diary. The two groups switched halfway through the study. This was a blind randomization; participants didn't know in which group they were, as it was designed to maintain participants engaged during the entire duration of the study.

Training

How was training handled? Did participants understand well enough what was expected?

Consortium response

Participants were informed of the study through a tiered approach:

- First, during the onboarding process, (potential) participants were instructed of what was expected of them and what the study would entail by means of the electronic consent form;
- Second, if a participant confirmed his/her understanding of the study and provided consent through the eConsent module, the participant would be randomized into the study. The patient was then sent a starter package, which included an Instruction Booklet, which contained step-by-step details on all aspects of the study;
- Third, online video's were made available to all COVID-RED participants which provided information on:
    - The purpose & conduct of the study;
    - How to use the app;
    - How to use the bracelet
    - How to perform a fingerprick.
- Fourth, a list with frequently asked questions were made available through the website which provided information on all aspects of the study, and was iteratively updated during the course of the study;
- Fifth, all randomized participants received monthly newsletters with additional instructions and general updates on the study;

- Finally, support was provided through all participants through a helpdesk that could be contacted by e-mail or phone throughout the entire course of the study. Technical support in case of issues with the app or bracelet was available as well (through Ava's customer support team). COVID-RED social media accounts were also maintained and monitored by the consortium, allowing participants to engage and ask questions through social media as well.

As such, the consortium felt that sufficient support was provided to the participants, and in case of any questions or comments, the subjects could always reach out to the helpdesk or technical support.

Vaccination status

The vaccination status of participants can change during the trial. How was this taken into account? And how does vaccination status influence the dropout rate? The non-compliance rate will be interesting and informative.

Consortium response

Participants can indicate their vaccinations in the Ava COVID-RED app and in the biweekly surveys that they are sent. Through the biweekly surveys detailed information is collected on the date, dose, manufacturer and location of a COVID-19 vaccination. This allows the consortium to take vaccination status into account for several primary and secondary analyses by stratifying the results by vaccination status. In addition, vaccination status was also taken into account for the type of serology tests conducted so that natural SARS-CoV-2 infections could be distinguished from antibodies produced by a COVID-19 vaccine in those vaccinated. From May- to July 2021 the number of vaccinated participants

increased significantly and now it's even higher than what was initially expected, with the large majority of the study population being vaccinated. The antibody testing has been expanded to be able to differentiate between the participants that were vaccinated and those that had a COVID-infection. We will look into the influence of vaccination status on dropout rate as part of the analysis.

COVID-19 waves

Were new waves of COVID reflected in the participants, the vaccinated as well as the unvaccinated? And did new COVID-waves have an effect on the participation, resp. retention rates?

Consortium response

New waves of COVID-19 were not clearly noticeable in terms of subject recruitment and retention. The consortium did notice a decreasing interest in COVID-19 over the course of the summer period, as the vaccination campaign was at full steam and due to the seasonal character of the virus. As a result, retention rates were declining over the course of the summer period and stabilized as we moved into autumn.

Additionally, since the project does not intend to use genomic sequencing data, variant information impact on subject retention can only be assumed.

Asymptomatic cases

About machine learning for asymptomatic cases: is there anything in the data on asymptomatic cases on biosignals that can be detected for machine learning?

Consortium response

For automatic detection, the main issue is that we do not know when the infections started as they are asymptomatic, which is essential to train the algorithm. Nevertheless, we are exploring several approaches to tackle this issue and develop an algorithm that allows us to detect asymptomatic infections.

Data management platform

Which platforms do you use and can you explain that process a bit more?

Consortium response

Data is collected from different sources (Ava wearable, Ava App, Castor Surveys, Serology and PCR results hosted by Sanquin) and is transferred to the Data Science Platform (DSP) of Julius Clinical, where the combined study data is hosted and analyzed during the study. For the long term data storage and availability for future research, we are currently looking

into the YODA platform which adheres to FAIR principles. More info about YODA: https://www.uu.nl/en/research/yoda

Algorithm performance

The number of established infections seemed yet very low – will there be a second batch of participants, which may provide a higher number of registered infections to increase the power of the study?

Consortium response

The current evaluation of the algorithm was based on data collected during the first period of the trial. The final evaluation will also include the follow-up period and thus a higher number of registered infections.

Marketing

Are you anticipating on delivering something to the market at this stage, considering the current rise in infection numbers?

Consortium response

We have been exploring opportunities for bringing the algorithm to other countries as well, but it's currently still under development so it's too early now. Depending on the initial outcomes of the studies, COVID-RED will design an exploitation strategy. This could also include market delivery in the short term, but this would depend on the expected real-world value of the algorithm based on the study data.

Sustainability

One Advisory Board member advocates strongly the publication of results, but also the analysis code and especially collected data, if at all possible, for future pandemic situation preparation. Another advisor recommends disseminating project results through peer reviewed publications. A third advisor adds that in addition to scientific publications, communication to the public is important as well.

Consortium response

The consortium is committed to publishing key information about the trial as well as the results of the project in peer-reviewed open-access journals. This has already resulted in the publication of the Study Protocol and several manuscripts which are in development or have been submitted for publication. In addition, the consortium is committed to making essential study data available for future COVID-19 research upon evaluated and accepted request.

The plan for a sustainable model for data storage is currently being developed and will be submitted as deliverable D5.8

Opportunities for collaboration

There could be value in collaborating with an institute experienced in the design of pragmatic trials and the use of Electronic Medical Records (EMR) for follow-up. Besides this, the German Robert Koch Institute might be very interested in a collaboration. If needed, SAB member Bjoern Eskofier will be happy to make introductions. Other Advisory Board members would like to come back to the reflection on opportunities for collaboration at a later stage.

Consortium response

Any connecyion with institutes and or organizations interested in our study are always welcome.