COVID-RED

innovative medicines initiative

101005177 - COVID-RED

COVID-19 infections - Remote Early Detection

WP7 – Project management, coordination, and sustainability

D7.5 Second biannual report on COVID-RED progress, including ethics report and impact assessment

Period covered by the report: from 1 July 2020 to 31 December 2021

Lead contributor	1- UMCU
Other contributors	2 – Ava AG 3 – Julius Clinical 4 – University College London 5 – VIVE 6 – Stichting Sanquin Bloedvoorziening 7 – Takeda Pharmaceuticals International AG 8 – Roche Diagnostics Nederland 9 – Labormedizinosches Zentrum Dr. Risch Ostschweiz AG

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Document History

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V1.2	25.04.2022	Initial version updated
V2.0	26.04.2022	Final version

Contents

1. Explanation of the work carried out by the beneficiaries and Overview of the progress

1.1 Objectives

In this project, we will 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 populations. At the same time, a mobile application will be used to track participant-reported symptoms. A prospective, observational study will follow 13,000 individuals from the general population and 7,000 high-risk individuals 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 could potentially have a SARS-CoV-2 infection and thus are referred for further testing.

To evaluate algorithm performance, the cohort will be tested for COVID-19 antibodies at the end of follow-up, with stored baseline samples of participants who have tested positive also being tested to determine whether the participant was already seropositive at baseline or was exposed to SARS- CoV-2 during follow-up. COVID-19 seropositivity in the intervention cohort will be compared to seropositivity in a control population of 10,000 individuals drawn from the same populations using an application only.

Thus, this project will deliver a large body of information on COVID-19 PCR testing and antibodies that can be used to develop additional diagnostics and therapeutics in addition to validating remote vital signs and self-reported symptoms monitoring systems.

The COVID-RED consortium has summarized in the below table the main outputs produced in the first period to achieve the project's objectives. Those outputs are further detailed in section 1.2 of this report.

Progress towards COVID-RED project objectives
1. To assess the diagnostic and prognostic value of monitoring vital signs (such as breathing rate, pulse rate, skin temperature, and heart rate variability) by the Ava bracelet in users at home (for early COVID-19 case identification)
Realisations: •Feasibility study (D3.2) has been completed based upon collaboration with COVI-GAPP. Best practices have been implemented and a formal report has been finalized. •Within the main COVID-RED study, the wearable bracelet and complementary smartphone app have been deployed to 17,824 study participants. •The vital signs monitored by this bracelet are, in combination with a self-completed symptom diary, being used to develop and evaluate a predictive algorithm for COVID-19 case identification.
2. To monitor individuals after the diagnosis to detect deterioration and that are under medical supervision (for early identification of COVID-19 patients requiring mechanical ventilation and/or intensive care) (WP 1)
Realisations: •D1.1 Functional and validated real-live monitoring device tailored for COVID-RED for tracking changes in physiological parameters associated with early signs of infection completed. •D1.2 Functional and tested novel app to collect biophysical data and patient reported outcomes for the detection of early signs of COVID-19 infection (1st iteration) completed. •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) completed. •D1.4 Algorithm to generate signals on patients to be tested for SARS-CoV-2 (1st iteration) completed.

• D1.5 Algorithm to generate signals on patients to be tested for SARS-CoV-2 (improved version) completed. • D1.7 Updated data capture and transmission strategies completed.
3. To study the added value of these remotely measured vital signs to the patient reported outcomes (WP3)
Realisations: • 17,824 participants (57k registrations) randomized at enrolment closure by implementing various recruitment strategies. • D3.1 study protocol written, regulatory/ethics approvals obtained and protocol amended twice. Study has in addition been executed according to protocol • D3.2 Report on small feasibility study & proposed adaptations to the protocol & operational study conduct • D3.3 Study subject approvals package • D3.4 Midterm recruitment report • Subject recruitment and data collection completed • Data processing completed and analyses are in progress
4. To assess on the economic and clinical effects of monitoring vital signs for the early detection of COVID19 and in the detection of deterioration after the diagnosis (WP4)
Realisations: • D4.1 Report on the interventions costs/price of the Ava monitoring device
5. To generate a large database on vital signs and symptoms over time, and health care usage, that can be linked to COVID-19 antibody presence (as a marker of past COVID-19 infection) at the end of the data collection period (WP2)
Realisations: • D2.1 Testing protocols + appendixes. • D2.2 Interim report on testing results for SARS-CoV-2 virus • D.2.1 Resubmission of deliverable 2.1 based • Samples at end of P2 collected and preparation for analysis
6. To deliver large open-source databases that are GDPR compliant (WP5)
Realisations: • In-app Daily Symptom Diary List of questions developed and deployed. • In-app onboarding questions list developed and deployed. • Data transfer of all data up to and including Period 1 from all sources to the Central Analytics Platform • Consortium members onboarded on Data Science Platform which will function as Central Analytics Platform. • Data collection from participant follow-up almost completed • D5.1 Full data management plan (1st iteration) • D5.2 Full data management plan (2nd iteration v1) – finalised and submitted • D5.3 Data management plan (3rd iteration v1) - nearing recirculation to IMI – finalised and submitted • D5.5 Deploy technology infrastructure components I, II and III • D5.6 Deploy tech infrastructure component IV • D5.7 Initial CRF development completed.
7. To partner with stakeholders and other related projects to create a network and maximize project impact (WP6)
Realisations: • Communication strategy was developed (D6.1) and communication activities ongoing via our website, Twitter, and Instagram (D6.2). • For some of the stakeholder engagement, COVID-RED will be collaborating with HI-NL. The first stakeholder tables are being organised. HI-NL will support the activities of the consortium but the

consortium partners will be closely involved in each step of the stakeholder engagement activities. HI-NL will also provide input for the regulatory plan.
8. To ensure the efficient & effective management of the consortium and sustainability of results, in compliance with the Grant Agreement and Consortium Agreement. (WP7)
Realisations: •A project handbook (D7.1), contact database (D7.2), project plans (D7.3) and a description of the tendering procedure (D7.11) are in place •The progress of WPs is being monitored in monthly Managing Board meetings where each WP provides an update, and bi-weekly Managing Team meetings. Risk assessment regarding the clinical trial was discussed biweekly during the trial execution. Deliverable progress is tracked in an Excel document by PMO. A SharePoint environment has been set up to ensure smooth transfer of results between WPs. •UMCU is managing the overall project communication, including the project website and Twitter. A report was developed describing the internal and external communication outputs (7.10) •A first interim progress report was provided to IMI in summer 2021 (D7.4) •The Advisory Board was installed and provided input in July 2021 (D7.7) and December 2021 (D7.8), following update meetings with the Advisory Board and Work Package leads. •UMCU manages legal topics and contracts. The Consortium Agreement was finalised by December 2021 (D7.12). The Grant Agreement was amended in December 2021 to extend the project with six months. Another amendment will follow to update the DoA with the changes in study design and tasks as discussed with IMI. •A first attempt was made to understand the potential interest of commercial partners for collaboration, investment or purchase of the project device (i.e., algorithm, app and study results), but it was concluded that we should pursue these efforts only once the algorithm was finalized and the study results are available. We will continue this work as part of the sustainability plan (D7.13) and the business plan (D7.14). •COVID-RED is actively participating in the join activities of the projects that are a result of IMI Call 21 •

1.2 Explanation of the work carried per work package

1.2.1 Work package 1

Objectives

The aim of WP1 is to tailor an existing remote monitoring infrastructure (the Ava bracelet, app, data analysis, computer algorithms, and application program interfaces [APIs]) from its original (pre- project) application to the application of COVID-19 remote monitoring. To address this aim, we have devised the below sub-objectives.

Sub-objectives:

- Modify the Ava monitoring device output and data analysis process for detection of changes in physiological parameters that could be indicative of a COVID-19 infection.
- Develop a novel app (Ava COVID-RED) based off Ava's existing architecture that gathers baseline data, clinical symptoms, biophysical parameters and potential exposure status that then transfers this raw data to a backend server for pre-processing and sends algorithm- derived testing recommendations back to the user in real-time.
- Build a machine learning algorithm based on data from the wearable device, clinical symptoms and risk class to adjudicate participants to testing for SARS-CoV-2.
- Build and maintain a GDPR-compliant infrastructure for extracting, cleaning, storing, analysing and transferring data from deployed measurement technologies in conjunction with WP5.

Work carried out in this period towards the achievement of these objectives (referring to tasks, milestones and deliverables as mentioned in the DoA)
Task-by-task updates:

1.1 Extending the functionality of technology and software of an existing remote monitoring wearable device to the specific situation of COVID-19

The Ava device was repurposed for capturing general infection and potentially COVID-19 specific changes in temperature, breathing rate, pulse rate, heart rate variability (HRV), perfusion, and/or sleep quality and quantity. These physiological parameters were used to create a machine learning algorithm (v1) designed to aid in the detection of early signs of COVID-19 infection (see Task 1.3).

While the hardware of the device itself was not modified as a result of WP1, Task 1.1 extended and altered the functionality of the current Ava app specifically for the purposes of the COVID-RED project. The pre-study trial in Liechtenstein (n=1,186) to validate the Ava bracelet's ability to register biophysical changes indicative of COVID-19 infection was completed. The pre-study required users to log their symptoms and sync the wearable device through Ava's existing fertility tracking app, which could be freely downloaded from mobile App/Play stores. Prior to first use, the app required user registration, background demographic details, and login information. In M1-M6 of WP1, Ava's team of software engineers, user experience (UX) designers, and data scientists adapted the existing user interface (UI) and APIs to display changes in the key physiological parameters of interest that may signal a COVID-19 infection. Whereas the standard fertility Ava app allows users to log menstrual symptoms like abdominal cramping, the COVID-19 iteration allows COVID-RED participants to report the presence and severity of illness symptoms on a daily basis. Potential logging options in the updated app now include dry cough, fatigue, chills, aches, nasal congestion, sore throat, diarrhoea, and/or loss of taste and smell. Additionally, COVID-RED participants can record potential confounds that may interfere with biophysical data measured by the Ava bracelet (e.g., taking anti-febrile medication or drinking alcohol) in the updated app. Development of the iOS and Android versions of the COVID- RED app occurred in parallel. The novel app (Ava COVID-RED) was submitted to the Google play and Apple mobile stores for approval in December 2020 (M6); final approval was granted and the app became available for download on February 4, 2021 (M8).

1.2 Maximize novel app's clinical research potential and alignment with other WP objectives.

Task 1.2 ensured that the design and features specified in the novel Ava COVID-RED app align with the objectives of the other work packages. Work Package 5 (WP5), for example, aims to develop a questionnaire to capture individual subject signs and log symptoms longitudinally; accordingly, WP1 worked closely with WP5 to ensure efficient allocations of resources and minimize potential redundancies in trial design and survey responses. Similarly, coordination between members involved in WP1 and Work Package 2 (WP2) helped determine whether a self-report log of antibody or PCR tests in-app made sense; ultimately, the collaboration led WP1 to include self-report PCR logs in-app while removing the logging of antibody test results (which will be objectively verified by WP2's seroprevalence analysis

1.3 Developing machine-learning algorithm

Simultaneous to the Ava COVID-RED app's development, Ava's data science and machine learning Subject Matter Experts (SME) developed a novel algorithm to detect early signs of COVID-19 infection. Version 1 (v1) uses a user's nightly and past physiological parameters recorded by the Ava bracelet along with their self-reported data to return a signal determining whether the user has early signs of COVID-19 and should be contacted for medical follow-up. At a later stage, signals generated in the study could also form the basis for prophylactic treatment.

The algorithm development will continue across the course of the COVID-RED study, refined and retrained on data collected during the Learning Phase, Phase 1 and Phase 2. The initial iteration of the algorithm (v1) was trained on data from the Liechtenstein pre-study (n=1,186) now completed; only data collected through January 2021 was included in the training and validation datasets. Through data exploration, feature selection and model specification, Ava's data science team trained a novel COVID-19 detection algorithm ingesting temperature and breathing rate together with self- reported symptoms to generate potential alarms about the existence of an infection. The algorithm included a state-of-the-art recurrent neural network based on Long Short-Term Memory units that leverages time series data to detect deviations in physiological parameters compared each participant's healthy baseline. The v1 model performance of COVID-19 infection detection measured on the holdout test dataset gave a sensitivity of 68% and a specificity of 36%. The algorithm was deployed to Ava's backend infrastructure and integrated to the COVID-RED app's API prior to the study's start. An updated version of the algorithm (v1.1), based on combined data from the Learning Phase and the COVI-GAPP clinical trial, was released at the beginning of Phase 1, on June 3, 2021. It does not have a corresponding deliverable, as it was not initially planned in the DoA. Minor improvements included refining the RNN in an attempt to reduce the number of false positives triggered by the algorithm.

The second iteration of the algorithm (v2) was based on data collected during the full Learning Period and released in September 2021, at the start of Phase 2. As a major improvement in this iteration, Ava's data science team incorporated transfer learning to train the model. This version of the algorithm ingests heart rate variability as an additional feature, further increasing its overall accuracy. The model performance measured on the holdout validation dataset yielded a sensitivity of 80% and a specificity of 23%. As compared to v1, we were thus able to increase the algorithm's sensitivity at the cost of specificity. Evaluating v2 on an independent test set derived from the Liechtenstein study population yielded a sensitivity of 61% and 29% specificity. The test results, even with the lower sensitivity, are comparable to the validation dataset considering the relative relation between sensitivity and specificity. This speaks to the model's overall good generalizability.

The planned third and final iteration of the algorithm (v3) will be developed after all data have been collected. Current work suggests that further improvement of specificity is likely. Serology test results will be incorporated into v3 and may improve the algorithm's performance. In particular, we expect these data to help increase the model's specificity. Additionally, the influence of potential confounds (e.g., alcohol intake, drug and medication use) and naturally occurring fluctuations in physiological parameters due to the menstrual cycle among female participants will be considered when revising v2. Finally, future models will also consider asymptomatic cases based on seroconversion over the course of the study

1.4 Creating the necessary data infrastructure for data extraction and analysis

In order to make sure that the data generated by the Ava bracelet and the Ava COVID-RED app can be included in the data platform in Work Package 4 (WP4), we reviewed, analysed and adjusted Ava's data generating mechanisms. Ava's internal database from its current fertility app user base was duplicated and customized for the COVID-RED clinical trial in M1-M6, thereby fulfilling the set-up requirements of Task 1.4. Data collection and storage began in M8, upon enrolment of the first participant in the COVID-RED clinical trial. Following the first transfer of serology and PCR data from the pre-study in Liechtenstein, data analysis started in M6 and contributed towards v1 of the COVID- RED algorithm (see Task 1.3). Reporting has been ongoing since M1, with communication between WP1, other WPs and the COVID-RED management board necessary to ensure the app and bracelet's compatibility with COVID-RED's primary and secondary research objectives.

Deliverable-by-deliverable updates:
D1.1: Functional and validated real-live monitoring device tailored to COVID-RED for tracking changes in physiological parameters associated with early signs of infection – Completed.
D1.2: Functional and tested novel app to collect biophysical data and patient reported outcomes for the detection of early signs of COVID-19 infection (1st iteration) – Completed.

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) – Completed.
D1.4: Algorithm to generate signals on patients to be tested for SARS-CoV-2 – Completed.
D1.5: Algorithm to generate signals on patients to be tested for SARS-CoV-2 (improved version) – Completed.
D1.6: Algorithm to generate signals on patients to be tested for SARS-CoV-2 (final version) – Planned to begin after the end of data collection and will be completed in June 2022
D1.7: Updated data capture and transmission strategies – Completed.

Significant exploitable results delivered during this period (if any) No significant exploitable results at this stage yet.

Contribution from beneficiaries	
Beneficiary	**Work carried out for this WP (e.g. task, deliverable)**
UMCU Utrecht	T1.1, T1.2, T1.3, D1.1, D1.2, D1.3, D1.4, D1.5, D1.7
Ava	T1.1, T1.2, T1.3, T1.4, D1.1, D1.2, D1.3, D1.4, D1.5, D1.7
Julius Clinical	T1.1, T1.2, T1.3, T1.4, D1.1, D1.2, D1.3, D1.4, D1.5, D1.7
Takeda	T1.1, T1.3, T1.4, D1.1, D.2, D1.3, D1.4, D1.5, D1.7
Roche	T1.2
LMZ Dr. Risch	D1.2, D1.3, D1.4, D1.5, D1.7

1.2.2 Work package 2

Objectives
The following objectives have been identified as part of the WP2:

- Develop protocols and procedures for study participant testing in the cohort study.
- Test study participants who have a positive signal using the algorithm developed in WP1 for SARS-CoV-2 virus.
- Test all study participants for SARS-CoV-2-specific antibodies at the end of their follow-up period, and if positive, also test their stored baseline samples.
- Collect information on positive cases and their clinical follow-up.

Work carried out in this period towards the achievement of these objectives (referring to tasks, milestones and deliverables as mentioned in the DoA)

Task-by-task updates:
2.1 Develop protocols and procedures for testing and for follow-up of positive cases –
Procedures for serological sampling and evaluation for SARS-CoV-2 antibodies have been established and participant samples are being collected and evaluated. Procedures for sampling and evaluation for SARS-CoV-2 infections using PCR and antigen testing has also been established and are currently underway.

2.2 Testing study participants for SARS-CoV-2 virus
As of June 23, 2021, a total of 556 participants that both received a positive signal from the Ava COVID-RED app and were unable to get tested using the government test centres have received a test kit provided by WP2. Sanquin has received and reported the results for 396 of those tests (71%).

2.3 Testing study participantsfor SARS-CoV-2 antibodies
To date, 11,906 Learning Phase (LP) and 13,348 baseline serological samples have been received of which 6,358 (53%) have been tested by Sanquin

Deliverable-by-deliverable updates:
D2.1: Testing protocols – Completed.
D2.2: Interim report on testing results – Started but Delayed, due to delayed start of recruitment.
D2.3: Final report on testing results – Delayed, due to delayed start of recruitment.

Significant exploitable results delivered during this period (if any)

- No significant exploitable results at this stage yet.

Contribution from beneficiaries	
Beneficiary	**Work carried out for this WP (e.g. task, deliverable)**
UMCU Utrecht	T2.1, D2.1, D2.2
Sanquin	T2.1, T2.2, T2.3 D2.1, D2.2
Roche	T2.1, T2.3, D2.1, D2.2
LMZ Dr. Risch + Risch services	T2.1, D2.1, D2.2
Julius Clinical	T2.1, D2.1, D2.2

1.2.3 Work package 3 Study design, execution and analysis

Objectives
The objective of WP3 is to evaluate the ability of the Ava Bracelet when coupled with a signs and symptoms diary to detect early indicators of COVID-19 infections accurately and reliably enough to be used to make early triage recommendations regarding need for further testing and treatment. The following sub-objectives have been devised.
Sub-objectives:
1.2.3.1 Develop study protocol for cohort study.
1.2.3.2 Acquire relevant regulatory/ethics approvals (including feasibility of e-consent/data privacy aspects).
1.2.3.3 Analyse data from study and interpret results.
1.2.3.4 Develop advice for further use of tested approach.
1.2.3.5 Pilot testing.
1.2.3.6 Full study execution including recruitment & retention of participants & monitoring the study for operational quality.

A protocol for the COVID-RED was developed and approved by the ethics committee of the Universitair Medisch Centrum Utrecht (UMCU) on 27 January 2021. The design addressed key logistical constraints (e.g., informed consent regulations within decentralized trials, testing kits for COVID-19, number of devices available, and single-user limitation for the devices). Due to the introduction of COVID-19 vaccines into the Netherlands beginning in early 2021, the eligibility criteria in the protocol were amended to allow for vaccination prior to and during the trial. Additionally, the serology testing methods needed to be adjusted to ensure that infection could be detected distinctly from vaccination (in collaboration with WP2). Enrolment began on 19 February 2021 and was closed on 3 June 2021. The trial enrolled 17,824 participants of the target 20,000 (89% of goal).

End-of-trial analyses is underway based on the v1.0 of the statistical analysis plan and Tables, Listings and Figures Specification provided on 05 August 2021. Further progress on the remaining objectives of WP3 await the completion of the trial..

Work carried out in this period towards the achievement of these objectives.

Task-by-task updates:
3.1 Protocol development – Completed.
3.2 Feasibility study – Feasibility study has been completed based upon collaboration with COVI-GAPP. Formal report has been finalized.
3.3 Execution of the cohort study – Recruitment began on 19 February 2021 with extensive public campaigns and closed on 3 June 2021. All ongoing subjects reached End of Trial by November 2021. Report has been finalized.
3.4 Monitor the cohort study for operational quality – Monitoring plan was in place prior to recruitment with ongoing data review, helpdesk interactions, and follow-up for select participant clinical events (I.e. Adverse Device Effects) by qualified safety physicians.
3.5 Clinical Analysis of study results and future recommendations – 1st version of Statistical analysis plan and Tables, Listings and Figures Specification completed. All data transferred to central analytics platform for data processing an data analysis. Central analytics platform is in production and in use. First draft of several analyses have been completed and are subject to Quality Control and a thorough review process by the consortium..
3.6 Develop advice for further use of tested approach – First brainstorms completed.

Deliverable-by-deliverable updates:
D3.1: Study protocol - Completed.
D3.2: Report on small feasibility study & proposed adaptations to the protocol to be made - Protocol has incorporated learnings from COVI-GAPP including practices for participant retention. Creation of formal report is finalized.
D3.3 Study subject approvals package - Completed.
D3.4 Midterm recruitment report – 17,824 of 20,000 participants recruited. A recruitment report has been developed for this phase. As recruitment has been front-loaded as part of the cross-over trial design, further reporting on recruitment is no longer relevant.
D3.5 Report on final analysis of results – Outline created and ready to accept content from all the analyses.
D3.6: Report on the status of posting results in the study registry - The trial has been registered in the Netherlands Trial Register (NTR). As the NTR permanently closed for new study registrations and is not suitable for posting study results, a substitute registry will be identified.
D3.7: Report on lessons learned to inform checklist creation - brainstorms on the topic have been completed.

Significant exploitable results delivered during this period (if any)
No significant exploitable results at this stage of the trial, except for the protocol being published (available at https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-021-05643-5).

Contribution from beneficiaries	
Beneficiary	**Work carried out for this WP (e.g. task, deliverable)**
UMCU Utrecht	T3.1, T3.2, T3.3, T3.4, T3.5, D3.1, D3.2, D3.3, D3.4
Ava	T3.1, T3.2, T3.3, T3.4, T3.5, D3.1, D3.2, D3.3
Julius Clinical	T3.1, T3.2, T3.3, T3.4, T3.5, D3.1, D3.2, D3.3, D3.4
Roche	T3.1, T3.2, T3.3, T3.5, D3.1, D3.2, D3.3

1.2.4 Work package 4 Health Economics Analysis

Objectives
The objective of WP4 is to explore the health economics of the health economics of the Ava bracelet and complementary Ava COVID-RED app for SARS-CoV-2 detection. This will include collection of data related to use of healthcare resources for both the AVA monitoring device and in the hospital system. Moreover, a cost-consequence analysis will be performed to relate the incremental costs to the clinical advantages of the Ava monitoring system.
Sub-objectives:
1.2.3.7 To assess the costs of implementing and operating the Ava bracelet and complementary Ava COVID-RED app for SARS-CoV-2 detection.
1.2.3.8 To assess the economic outcomes of the Ava bracelet and complementary Ava COVID-RED app for SARS-CoV-2 detection.
1.2.3.9 To assess the Ava bracelet and complementary Ava COVID-RED app for SARS-CoV-2 detection using a cost-consequence analysis.

Work carried out in this period towards the achievement of these objectives (referring to tasks, milestones and deliverables as mentioned in the DoA)

Task-by-task updates:
4.1 Determining the intervention costs – Intervention costs have been identified through communications with members of WP1, WP2 and WP3. The intervention costs have being registered and accumulated by Ava and Julius Clinical. The costs associated with the intervention have been reported in deliverable D4.1 by December 2021.
4.2 Assessing the economic outcomes – The economic outcomes have been identified through communications with members of WP2, WP3 and WP5. The economic outcomes are collected through a bi-weekly questionnaire administered to the study participants and will be ready for analysis when the trial finalises.
4.3 Cost-consequence analysis – There are ongoing collaborations with WP3 on the relevant outcomes and how these are estimated. A statistical analysis plan (SAP) is under development. The costs in the cost consequence analysis consists of the costs estimated in the tasks above.

Deliverable-by-deliverable updates:
D4.1: Report on the intervention costs/price of the Ava monitoring device – The report was finalized in December 2021.
D4.2: Report on the outcomes and associated hospital costs – The report on the outcomes and costs will be constructed when the trial is finalised.
D4.3: A first draft of a scientific paper reporting on the results of the cost-consequence analysis for publication in an international peer-review journal – Not yet begun.

Significant exploitable results delivered during this period (if any)
Report on the interventions (deliverable D4.1) costs/price of the Ava monitoring device have been finalized.

Contribution from beneficiaries	
Beneficiary	**Work carried out for this WP (e.g. task, deliverable)**
UMCU Utrecht	T4.1
VIVE	T4.1, T4.2, T4.3

1.2.5 Work package 5 Data Management

Objectives

WP5 will develop a full 'data management plan' (DMP) as well as a data sustainability plan. The overall objective is to provide an infrastructure to host all data, or features extracted from the data, collected and analysed in the study with the same level of annotation, pseudo-anonymization and accessibility for model development as during the research phase. The plan should comprise financial, legal, ethical and structural aspects as well as scalability of the storage/ access capacity. For WP5, we have devised the following sub-objectives:

Sub-objectives:

1.2.5.1 Develop electronic questionnaire(s) capturing individual subject signs and symptoms longitudinally directly from the patients.

1.2.5.2 Develop case report forms (CRFs) to capture additional data as collected/or available by the site for each patient including baseline demographics, baseline comorbidities, baseline COVID-19 risk factors, polymerase chain reaction (PCR) test results, serology results, health resource utilization, adverse events, and clinical outcomes.

1.2.5.3 Create the infrastructure to host signs and symptoms data, CRF data, and device data (or parameterized results from the device data).

1.2.5.4 Implement a long-term, sustainable model for data storage meeting FAIR requirements.

Work carried out in this period towards the achievement of these objectives.

Longitudinal data capture of signs and symptoms was incorporated into the Ava COVID-RED app. Electronic case-report forms (CRFs) were developed with broad consortium feedback which addressed each of the data domains listed in the sub-objectives. Infrastructure for the individual data sources was in place prior to start of the trial. Infrastructure for hosting each of the pseudo- anonymized data sources, linking, and analysing those data was decided on by the Consortium in February 2021 and has been deployed for production work. Where necessary data transfers have been specified and completed. A long-term, sustainable FAIR data storage platform is still under discussion with different options being compared for cost-effectiveness and utility for external researchers.

Task-by-task update:

5.1 – Data Management Plan – The DMP has reached the 3rd iteration (D5.3)with final version (D5.4) on target for end-of-trial. The last and final version of the DMP will be developed towards the end of the trial to encompass all updates to the Data Management of the trial up to that point.

5.2 - Deploy and maintain the technology infrastructure to underpin the cohort study - Infrastructure for hosting of signs, symptoms and physiological data has been set-up by Ava. eCRF and survey data is hosted by software of an external party hired by Julius Clinical. A customized Amazon Web Services (AWS) environment has been developed by Julius Clinical which meets the requirements of COVID-RED to host the pseudonymized trial data from all sources for final analysis. This environment has been released for production programming. The infrastructure used and set up for this trial is described in D5.5 and D5.6. Relevant consortium members have been onboarded to the platform and are collaborating on programming. Final data available by Dec 2021 has been transferred to the data science platform to support programming work. The eCRF and surveys database was locked in Feb 2022.

5.3 - CRF Development – Completed. eCRFs and surveys were developed (D5.8) and implemented for the collection of screening and baseline data as well as for longitudinal details on testing behaviour, behavioural changes, vaccination status, healthcare resource use, and more, as stated in the protocol. The app developed by Ava in WP1 was used to collect individual signs and symptoms data necessary for both algorithm development and evaluation. The last questionnaires to participants were sent out in November 2021 when follow-up ended.

5.4 - Implement a long-term, sustainable model for data storage meeting FAIR requirements – A first proposal for a sustainable model has been circulated for review by the consortium. Efforts are underway

to incorporate feedback as well discuss further details prior to finalization of the deliverable (D5.8) and implementation.

Deliverable-by-deliverable update:
D5.1: Full data management plan (1st iteration) - Completed and submitted to IHI
D5.2: Data management plan (2nd iteration) – Completed and submitted to IHI
D5.3: Data management plan (3rd iteration) - Completed
D5.4: Data management plan (final version) - Not yet begun.
D5.5: Deploy technology infrastructure components I, II and III - Completed.
D5.6: Deploy technology infrastructure component IV - Completed
D5.7: Initial CRF development completed - Completed.
D5.8: Report on sustainability model for data storage - First version reviewed by consortium and to be further finalized.

Significant exploitable results delivered during this period (if any) No significant exploitable results at this stage yet.

Contribution from beneficiaries	
Beneficiary	**Work carried out for this WP (e.g. task, deliverable)**
UMCU Utrecht	T5.1, T5.3, T5.4, D5.1, D5.2, D5.3, D5.6, D5.7
Ava	T5.1, T5.2, T5.3, T5.4, D5.1, D5.2, D5.3, D5.5, D5.6, D5.7
Julius Clinical	T5.1, T5.2, T5.3, T5.4, D5.1, D5.2, D5.3, D5.5, D5.6, D5.7
UCL	T5.1, T5.2, T5.3, T5.4, D5.1, D5.2, D5.3, D5.5, D5.6, D5.7
Takeda	T5.1, T5.2, T5.3, D5.1, D5.5, D5.6, D5.7
Roche	T5.1, T5.2, T5.3, D5.1, D5.2, D5.3, D5.5, D5.6, D5.7

1.2.6 Work package 6 Communication, dissemination and stakeholder outreach

Objectives
WP6 will work to serve the needs of the project acting as a facilitator of the work, connecting information sources from key stakeholder groups to improve the value, quality and harmonization of information disseminated on evidence related to COVID-19 remote monitoring and its utility in early detection of illness incidence and triage decisions. The aim of WP6 is to help maximize the impact of project outcomes on stakeholders.
Sub-objectives:

- Identify and incorporate stakeholders' perspectives on the barriers and enablers of remote monitoring devices and apps for monitoring physiological parameters in detecting early signs of a COVID-19 infection into project roadmap.
- Development and execution of an appropriate regulatory strategy.

Work carried out in this period towards the achievement of these objectives.
Task 6.1 Develop dissemination and exploitation plan (D6.1, D6.2, D6.9)
Communication activities have started and were reported on in D7.10 and D6.1 and D6.2. For example, in D7.10, we described our communication strategy. In addition, we have created a communication plan for the clinical trial specifically, and a social media plan for our Twitter (@CovidRed) and Instagram (@covidredproject) accounts. External communication was mainly focused on participant recruitment and retention during this first study period. Now that the clinical trial has ended, we have shifted towards project dissemination and adopted a more international-oriented approach. An update of the communication, dissemination, and exploitation plan, D6.9, is in preparation. Other progress that has been made towards this task includes the development of the logo, website, Twitter, Instagram, manual,

and templates, and development of press campaign to capture press attention for our clinical trial within the Dutch, Liechtensteinian, Swiss, and American media.

Task 6.2 Understand stakeholder needs and perceptions and align with project outcomes (D6.3, D6.4, D6.5, D6.6)
For some of the stakeholder engagement, COVID-RED will be collaborating with HI-NL. This is an initiative based in the Netherlands but with an international scope which organizes stakeholder round tables with innovators/consortia and key public and private sector players (e.g. health care payers, HTA bodies, health care professionals, patients etc). HI-NL is supported by the Dutch Ministry of Health, but also has an international scope. By working with HI-NL, we believe we can organise our stakeholder engagement in a more efficient and effective manner by working with an experienced party. The costs of the HI-NL services are, in the assessment of the consortium, reasonable and potentially lower than the investments that the consortium would make to organise the activities themselves. It has to be emphasised that HI-NL will support the activities of the consortium and that the consortium partners are closely involved in each step of the stakeholder engagement activities. The responsibility for the related deliverables stays with the consortium but will be based on HI-NL input. These activities will be included in the next amendment.

Task 6.3 Develop and execute regulatory plan (D6.7, D6.8)
This activity was not started yet. It is related to the T6.2 and awaiting the HI-NL input.

Significant exploitable results delivered during this period (if any)
No significant exploitable results at this stage yet, we have mainly supported the COVID-RED project via communication and dissemination and expect exploitable results after engaging with HI-NL.

Contribution from beneficiaries	
Beneficiary	**Work carried out for this WP (e.g. task, deliverable)**
UMCU Utrecht	Led and completed T6.1, D6.1, D6.2, are coordinating contact with HI-NL
Ava	Provided inputs to D6.1.
Roche	Provided inputs to D6.1.

1.2.7 Work package 7 Project management, coordination, and sustainability

Objectives
The objective of WP7 is to run effective project management for the COVID-RED consortium and to guarantee the project's capacity to respond to the urgent need for remote detection of COVID-19, and to facilitate an improved understanding of the spread of and capacity to remotely detect COVID-19. Sub-objectives:

- Project management: Providing detailed follow-up and tracking, via regular work package reports, early reports of any unexpected organisational or structural issues or delays with respect to the project deployment and intermediate objectives.
- Set-up an effective communication infrastructure and foster the integrative process within the consortium.
- Ensure the consortium's contractual duties are carried out. Advise and guide the participants to comply with the IMI regulations and their contractual and legal requirements. Abide by the "good practice" of resources management as presented in the Financial Guidelines.
- Prepare and execute a sustainability plan, to ensure the most efficient exploitation of project results and to achieve the highest possible benefit for scientists, industry and the European society.

Work carried out in this period towards the achievement of these objectives.

Task 7.1 Scientific coordination and progress management (D7.1

UMCU is coordinating the general progress management and provided project management plans (D7.1 and D7.3) and a contact database (D7.2). The progress of WPs is being monitored in monthly Managing Board meetings where each WP provides an update. In bi-weekly Managing Team meetings, important points are being discussed in a smaller group. Risk assessment regarding the clinical trial was discussed biweekly during the trial execution and was assessed by a working group composed of UMCU and Julius Clinical, this group reporting directly to the Managing Board. Deliverable progress is tracked in an Excel document by PMO. A first interim progress report was provided to IMI in summer 2021 (D7.4). Furthermore, a SharePoint environment has been set up to ensure smooth transfer of results between WPs. The Advisory Board was installed and provided input in July 2021 (D7.7) and December 2021 (D7.8), following update meetings with the Advisory Board and Work Package leads.

Task 7.2 Communication management

UMCU is managing the overall project communication, including the project website and Twitter. Reddit was also used for a short period in the phase of participant recruitment as well. As such, they delivered a report describing the communication plan (D7.10). Communication about the study (focused on recruitment and retention) is mainly managed by Julius Clinical. They also manage the Instagram account focused on study participants. Task 7.2 is closely linked to Task 6.1.

Task 7.3 Financial and periodic reporting

UMCU manages overall budget and budget transfer. As part of the amendment to extend the project timelines, an extra financial and periodic reporting was added to early 2022, which will be followed by the final reporting after June 2022. UMCU is responsible for ensuring a smooth process and timely submission to IMI. They have also provided a tendering procedure description (D7.11).

Task 7.4 Legal and contractual management

UMCU manages legal topics and contracts. The Consortium Agreement was finalised by December 2021 (D7.12). The Grant Agreement was amended in December 2021 to extend the project with six months. Another amendment will follow to update the DoA with the changes in study design and tasks as discussed with IMI. Contracts with Advisory Board members were all fully signed by June 2021.

Task 7.5 Sustainability and business development

At an early stage in the project, we made a first attempt to understand the potential interest of commercial partners for collaboration, investment or purchase of the project device (i.e., algorithm, app and study results). To this end, we reached out to an extended list of potential stakeholders, including the business development teams of the consortium's industry partners. Initial discussions led to the conclusion that it was too early in the project to garner distribution interest. Consequently, we concluded we should pursue these efforts only once the algorithm was finalized and the study results are available. We will continue this work as part of the sustainability plan (D7.13) and the business plan (D7.14) during the extended project duration.

To date, one patent has been applied for but not yet granted to the manufacturer of the wearable device, Ava AG. This application work was begun very early in the project—some of it in parallel to the COVID-RED application process—to ensure a timely submission prior toother potential competing parties. Additionally, it drew on data collected by the manufacturer's original application, Ava Fertility, as a proof-of-concept. Once the COVID-RED study results are available, the entire consortium will assess additional intellectual property (IP) opportunities. All IP will be considered in the sustainability plan, this will also detail how the results can benefit the wider digital health industry in a balanced manner.

Task 7.6 Support collaboration activities and potential synergies with grants awarded under the CallIMI2-2020-21-01

COVID-RED is actively participating in the join activities of the projects that are a result of IMI Call 21. Up until now, the conversations have had an exploratory character from the side of COVID-RED, although we expect a more intense collaboration with other projects once results from IMI COVID-RED come available. UMCU has also joined the DRAGON stakeholder community. More details can be found in section 1.5 of this report.

Significant exploitable results delivered during this period (if any)

The two reports by the Advisory Board are publicly available on our website and contain relevant questions and suggestions both for COVID-RED and for other projects with overlapping elements.

Contribution from beneficiaries	
Beneficiary	**Work carried out for this WP (e.g. task, deliverable)**
UMCU Utrecht	T7.1, T7.2, T7.3, T7.4, T7.5, T7.6, D7.1, D7.2, D7.3, D7.4, D7.7, D7.8, D7.10, D7.11, D7.12
Ava	Provided contents to project Handbook; detailed project plans; report describing internal and external communication procedures and tendering procedures description; sustainability and business development discussions; and the advisory board reports.
Julius Clinical	Provided contents to project Handbook; detailed project plans; report describing internal and external communication procedures and tendering procedures description; and the advisory board reports.
UCL	Provided contents to project Handbook; detailed project plans; report describing internal and external communication procedures and tendering procedures description; and the advisory board reports.
VIVE	Provided contents to project Handbook; detailed project plans; report describing internal and external communication procedures and tendering procedures description; and the advisory board reports.
Sanquin	Provided contents to project Handbook; detailed project plans; report describing internal and external communication procedures and tendering procedures description; and the advisory board reports.
Roche	Provided contents to project Handbook; detailed project plans; report describing internal and external communication procedures and tendering procedures description; and the advisory board reports.
LMZ Dr. Risch	Provided contents to project Handbook; detailed project plans; report describing internal and external communication procedures and tendering procedures description; and the advisory board reports.

1.2.8 Work package 8 Ethics requirements

Objectives
This work package sets out the 'ethics requirements' that the project must comply with.

Work carried out in this period towards the achievement of these objectives.
Deliverable-by-deliverable update:
D8.1: Human cells or tissues (HCT) - Requirement No. 2 obtained all the relevant documents for using, producing or collecting human cells or tissues – completed.
D8.2: Non-EU Countries (NEC) - Requirement No. 4 adequate import/export authorisations – completed.
D8.3: General (GEN) - Requirement No. 5 appointing an independent ethics advisor – completed.

Significant exploitable results delivered during this period (if any) No significant exploitable results at this stage.

Contribution from beneficiaries	
Beneficiary	**Work carried out for this WP (e.g. task, deliverable)**
UMCU Utrecht	Led and completed D8.1, D8.2, D8.3

1.3 Impact assessment

The table below contains an overview of the expected impacts of the COVID-RED project and how the work carried out in this period contributes to these impacts.

How the work carried out contributes to the expected impacts
1. Leveraging an existing medical-grade technology may allow clinicians and researchers to more rapidly evaluate patients' well-being, thereby enabling faster case detection and management.
Realisations: • There have been 219 confirmed cases of SARS-CoV-2 (as of 24.11.2021) for which the app reported a red signal 0-3 days prior to any reported symptoms by the participant or up to 4 days before or after the positive diagnostic test for asymptomatic cases.
2. Healthcare professionals and researchers may benefit from using this device to monitor confirmed cases of COVID-19
Realisations: • The forthcoming analysis of the data that is now fully collected will determine the benefit of this device for monitoring. Several research questions have been formulated that will shed light on this topic.
3. By reducing the in-person contact between patients and their care team, the AVA Bracelet could lower potential transmission rates among nurses, doctors, and/or researchers studying COVID- 19's development.
Realisations: • 219 confirmed cases of SARS-CoV-2 (as of 24.11.2021) were individually notified in real-time by the Ava COVID-RED app and encouraged to self-isolate and/or seek testing since the beginning of the project, thus positively impacting the transmission rate in general population
4. The repurposed Ava Bracelet could contribute to fast-track development and availability of therapeutics and/or diagnostics to be used in the clinical management of patients infected by COVID-19 and/or future outbreaks of coronaviruses, and patients with similar infectious diseases, and to ensure that a variety of drugs are available for patients, including tackling resistance, and combination therapy.
Realisations: • No significant impact confirmed yet.
5. Contribution to public health preparedness and response in the context of the ongoing epidemic of COVID-19 and/or future outbreaks of pan-coronaviruses
Realisations: • The study itself resulted in a number of public campaigns including social media campaigns which reached a large number of Dutch nationals and residents. This activity raised awareness of COVID-19 and the degree to which it, in its asymptomatic or pre-symptomatic form, can still bring infection risks to others. Data collection has been completed and the forthcoming data analysis will shed light on the important research questions formulated and determine the impact for public health preparedness. In addition, the fully remote nature of this trial has provided many lessons learned which will improve the ability to perform essential research in the midst of a pandemic or epidemic.
6. Significant impact on global health, both at the individual and the public health level by leading to results that have a direct impact on people at risk of exposure to coronavirus or on patients suffering from coronavirus disease.
Realisations: • Data collection has been completed and the first steps of the data analysis have been taken. Planned analyses have been formulated and documented which will not only evaluate the wearable

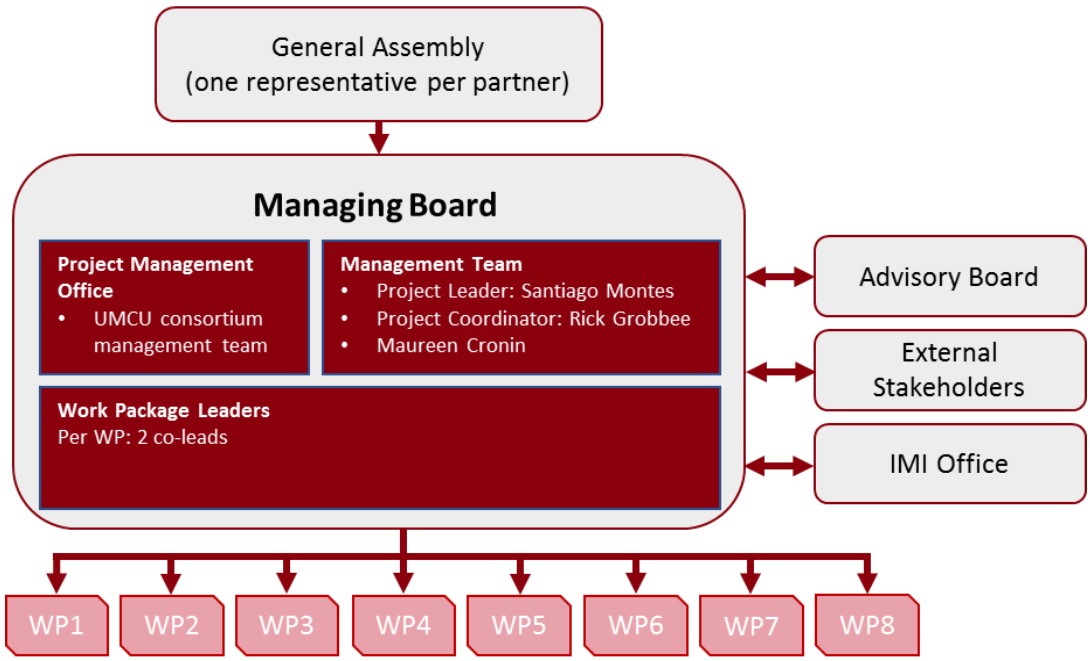
performance but also investigate many other significant research questions which can directly contribute to both public and individual health for those at risk of exposure or those who have been infected by SARS-CoV-
7. Impact on competitiveness and growth of companies including SMEs
Realisations: • No significant impact confirmed yet.

1.4 Consortium management

A project such as COVID-RED requires a well-designed management structure and expertise in order to ensure project deliverables are of the highest quality and respond to the urgent needs of COVID-19 as quickly as possible. COVID-RED builds upon extensive experience of involved partners and people in IMI and projects of similar complexity. Santiago Montes serves as the Project Leader while professor Diederick Grobbee serves as the Project Coordinator.
During the first period, the set up and consolidation of a multi-layered governance structure was prioritized to ensure that COVID-RED operates in a transparent and efficient manner and will effectively meet the goals and objectives described in the Grant Agreement. The governance structure of COVID-RED has been strategically designed to ensure the concerns and expertise of all participant organizations, as well as external and tangential stakeholders, are considered in project decisions. The structure is organized in such a way to ensure the consortium can remain flexible, given the evolving nature of the COVID-19 pandemic to which this project is responding. Clearly defined roles, responsibilities, decision-making authorities, processes and procedures have been implemented for the efficient and effective functioning of this consortium.

As outlined in the figure below, the governance structure covers 4 essential management components:

1. Action: represented by WP teams.
2. Coordination: Managing Board, including the WP Leads, Managing Team and PMO.
3. Advice and review: the Advisory Board (AB).
4. Approval: The General Assembly.



No significant challenges arose within the team during the first period of the project. The public-private partnership is working well and in a transparent manner, resolving conflicts, if any, using the escalation model detailed in the DoA. The partnership is also working pragmatically towards resolving clinical questions, making use of additional working groups; attendance at ad-hoc meetings is high, and topics are discussed and agreed upon collaboratively.

The consortium did not experience major changes in its composition during the period. Two Advisory Board meetings have taken please during this period of the project, and results of those interactions are publicly available on the COVID-RED website.

1.5 Collaborations/synergies with other initiatives

Collaboration with other IMI initiatives under Call IMI2-2020-21-01

IMI supported via the European Commission's Horizon 2020 Framework Programme for Research & Innovation, launched a special fast-track call (Call 21) on "*Development of therapeutics and diagnostics combatting coronavirus infections*". Selected projects are expected to advance knowledge of SARS-CoV-2 and of the wider coronavirus family, with the aim of contributing to an efficient patient management and/or public health preparedness and response to current and future outbreaks of coronavirus infection. The total funding in respect to Call 21 is €117 million which is distributed across the 8 selected projects. There are 5 diagnostics projects (COVID-RED, DECISION, KRONO, RAPID-COVID, DRAGON) and 3 treatment projects (CARE, Imprentri, MAD-CoV 2).

It is expected that all 8 projects will interact with each other, with the aim of finding synergies to help maximize the impacts of each project. The ultimate aim would be to create an IMI2 COVID-19 Projects Community which not only fosters collaboration among the projects but also the field at large, both during project duration and after.

During the first period, the set up and collaborative definition of a practical way of working together was prioritized to help facilitate discussions and follow-up decisions on executable collaborations. A series of actions have illustrated the work done by the multi-project approach led by DRAGON. These are:

- Signing of the collaboration agreement – nearing completion
- Identify and agree on modes of engagement, communication & dissemination – completed.
- Continue discussions on synergies – ongoing.
- Partake in IMI recommended meetings and activities – ongoing.

To help facilitating exchanges, a working methodology was agreed amongst all collaborative partners. It consists of

- Identifying key modes and tools to be used within the community are critical to facilitate engagement and communication, and putting in place a shared communication platform via MS Teams (Achieved in February 2021).
- Creating a shared contact database – achieved, Excel sheet entitled *'IMI2 COVID-19 Community_Key Info'* uploaded to Microsoft (MS) Teams
- Housing pertinent information related to each project – ongoing, Excel sheet entitled *'IMI2 COVID-19 Community_Key Info'* uploaded to MS Teams.
- Planning a series of collaborative meeting – achieved, the table below shows the meetings that have taken place within the COVID-19 projects.

Date	Meeting Description	Participants & Attendance
2 December 2021	IMI2 Collaboration Agreement Meeting among Call 21 projects on COVID-19	
16 July 2021	IMI COVID-19 projects - Diagnostic - 1st REGULTORY MASTERMIND	

18 June 2021	IMI COVID-19 Projects call in June	reps of 8 COVID-19 projects
16 April 2021	IMI COVID-19 Projects - Diagnostic - Design sprint call.	reps of DECISION, COVID-RED, KRONO, DRAGON and RAPID-COVID
11 Feb 2021	Signing of Collaboration Agreement	Reps of 5 projects KRONO & DECISION not in attendance
15 Jan 2021	DRAGON-Impentri to discuss proteomics testing	DRAGON & Impentri reps
1 Dec 2020	DRAGON initiated meeting with all 8 projects to discuss potential areas of collaboration	Reps of 7 projects. COVID-RED not in attendance
8 Oct 2020	IMI meeting with projects	IMI & reps of 8 COVID-19 projects

COVID-RED and DRAGON have also met together outside the above schedule as both projects use AI technologies to combat the COVID-19 pandemic. DRAGON's use of machine learning in diagnosing and predicting healthcare outcomes following a confirmed SARS-CoV-2 infection complement our at-home monitoring approach. Our first kick-off meeting with DRAGON took place on 28 June 2021.

Beyond tangible collaborations in research which are either yet to be defined or require further discussion, other ideas the projects could participate in are outlined below, and could be executed in the second period of the COVID-RED project:

- Communication Activities, such as supporting other projects with social media amplification; organize science day or mini conference with open registration with sessions, networking tables and 1-1 networking or content focused around sharing key project results; organize workshops on data standards, AI, apps or invitation to events organized by the project or project partner. Below are some examples proposed by DRAGON:
  - COVID-19: State of the art – DRAGON IMI project on 29 April 2021
  - 1st DRAGON Roleplay Roundtable to be scheduled end June-early July 2021
- Ethics & Regulatory Activities, such as formation of Ethics Advisory Board (including regulatory experts) for all 8 projects.
- Stakeholder engagement Activities, such as providing access to broader stakeholders by forming a community.

<u>Collaboration with other IMI initiatives</u>

The IMI COVID-RED initiative was contacted in June 2021 by beneficiaries of the IMI Trials@Home initiative to support qualitative interviews. Trials@Home Work Package BEST (Best practices in Remote Decentralized Clinical Trials - DCTs), led by academic partner University of Dundee, and EPFIA partner Sanofi, have asked whether they could interview COVID-RED Leaders, as part of BEST call for additional DCTs initiatives. The interviews were conducted in quarter 4 of 2021.

2. Update of the plan for exploitation and dissemination and sustainability of results

In month 3 of the project (October 2020), WP7 coordinated the development of a report describing internal and external communication outputs
The purpose of the plan is to:

- Define target audiences, communication channels, and key messages for COVID-RED.
- Establish clear goals, objectives, and timelines for communication activities.
- Provide guidance to project participants for the development of communication activities and the preparation and use of materials.

The overall aim is to maximize the impact of COVID-RED by ensuring full use of available communication channels both within and outside of the project.

This plan is intended to function as a foundation for the planning and execution of communication activities by members of the project in a professional and coordinated manner. This plan outlined the target audiences, communication channels, and key messages for COVID-RED. The adoption of this plan encourages the full use of available communication channels from the project. Furthermore, it should ensure quality and consistency of communication.
Key messages for different audiences (stakeholders) relating to project deliverables and overall objectives are identified in advance, and a matrix is used to map these to project timings, appropriate channels of communication, and the intended impact on stakeholders. Communication activities and, where necessary, key messages will be updated periodically as the project progresses and as feedback from stakeholders is obtained.
High quality internal and external communication is key to the success of COVID-RED, underpinning effective collaboration between project partners and maximizing the impact of the project's findings.

In the first project period, WPs have achieved the following communication and dissemination of results:

- Align all parties on dissemination standards and present a strong external project's image, by generating a strong visual COVID-RED identity and online representation with the creation of logo, dedicated website and communication materials
- Defining key stakeholders and audiences
- Creating a dedicated media campaign to support the recruitment of study participants. Here the project benefitted from the support of a public relations (PR) and media specialist from UMCU, who helped shape the key messages and target the right audience including Dutch national media for the recruitment campaign.
- Creating appeal for the recruitment campaign, by conducting a series of news interviews and participating in prominent Dutch media initiatives (*see table below for details*).
- Maintaining a list of external media initiatives and organisations of relevance, with key contacts
- Creating and maintaining effective communication messages for community building. In support of these activities, specific materials have been developed to promote COVID-RED and to ensure that outputs have impact beyond the scope of defined project activities. These materials are described in this deliverable (D6.1).
- Managing the COVID-RED social media community, by ensuring a strong presence on social media (dedicated Facebook groups, Twitter and Instagram feeds) and hiring a social media community manager

- Creating retention storyline and disseminate key adherence messages throughout the project lifetime, to ensure that participants stay engaged while the study environment may slightly change (for example, with the increased number of participants that may negatively affect their willingness to adhere to the study) - ongoing
- Maintaining statistics and feedback on the use, quality and impact of communications activities, for example website visits, Twitter 'likes' and feedback from participants themselves. These will be made available to MB so that the success/impact of communication activities can be evaluated

The Managing Team (MT) and Managing Board (MB) of COVID-RED have also provided oversight of communication activities (including evaluation of their effectiveness), signing off all public project deliverables to IMI and approving communications strategy, such as key messages, interviews, internal publications and/or internal targeted communication (storyline proposals ect)

Next steps include extending our communication and dissemination by shifting the focus from study participants to the scientific community and industry. As a results, communications will be primarily in English instead of in Dutch and we actively aim to target an international audience.

Sustainability plan (TASK 7.5 – Sustainability and business development – M6-M18
The sustainability report due in February 2021 (D7.13) has been postponed to the project end.
The report will include, as per DoA, an extensive identification of additional business models beyond those making the use of datasets for commercial developments subjected to fees, whilst facilitating open access for research purposes described in WP4.

At an early stage in the project, we made a first attempt to understand the potential interest of commercial partners for collaboration, investment or purchase of the project device (i.e., algorithm, app and study results). To this end, we reached out to an extended list of potential stakeholders, including the business development teams of the consortium's industry partners. Initial discussions led to the conclusion that it was too early in the project to garner distribution interest. Consequently, we concluded we should pursue these efforts only once the algorithm was finalized and the study results are available. We will continue this work as part of the sustainability plan (D7.13) and the business plan (D7.14) during the extended project duration.
To date, one patent has been applied for but not yet granted to the manufacturer of the wearable device, Ava AG. This application work was begun very early in the project—some of it in parallel to the COVID-RED application process—to ensure a timely submission prior toother potential competing parties. Additionally, it drew on data collected by the manufacturer's original application, Ava Fertility, as a proof-of-concept. Once the COVID-RED study results are available, the entire consortium will assess additional intellectual property (IP) opportunities. All IP will be considered in the sustainability plan, this will also detail how the results can benefit the wider digital health industry in a balanced manner.

Additionally, the consortium has agreed to a proven phased approach to implement a successful sustainability strategy:
(1) mapping: identifying valuable use cases for a repository of COVID-19 datasets, as well as further applications of the remote monitoring system beyond COVID-19, by assessing key clinical/societal needs, market/commercial opportunities and operational/technical feasibility, inventorying possible strategic partners, and investigating best practices amongst comparable initiatives;
(2) brainstorming business case development;
(3) validating: together with a selection of key stakeholders and possible funders/payers, the business cases will be validated (including cost-effectiveness modelling);
(4) planning: positive business cases will be further detailed in a sustainability plan;

(5) business development: activities (promotions for industry and not-for-profit organisations) and contacts(key funders/decision makers/payers) will be initiated to realize seed funding/initial revenue/commercial deals.
The sustainability plan will present a roadmap for long-term sustainability of the consortium and network after the official end of COVID-RED to ensure that this valuable collaborative effort will endure.

3. Update of the data management plan

The Data Management Plan (DMP) has been iteratively updated throughout the project, culminating into the 3rd version being submitted (D5.3). In this version, the DMPwas updated to reflect the latest operational changes within the study, with the main focus on the use of the data science platform managed and maintained by Julius Clinical instead of AnDREa as the main tool for data analysis within the study. The DMP contains details on what data is collected, how FAIR principles are adhered to, what resources are allocated for data management, how data security is ensured and how ethical standard are upheld.

The long-term storage and sharing of the data for approved future research is not described in detail in the DMP as this is part of an upcoming deliverable, D5.8: Report on sustainability model for data storage, which encompasses Task 5.4 ("Implement a long-term, sustainable model for data storage meeting FAIR requirements"). The short- and long-term value of the data collected from this study is hard to overstate. D5.8 will describe how the data collected in the study are structured to meet the requirements of the FAIR Data Principles and how data assets will be made available for further approved research requests in the long-term. For this, a long-term sustainable model is needed for curating data and metadata and providing access to researchers with approved requests after the project itself is finished. This deliverable focuses on how the longevity of data storage and access is ensured for future research in a FAIR manner. After defining requirements as a consortium, several platforms have been considered for this purpose which have suitable capabilities such as data archiving, publishing, and secured, separated workspaces. A final decision on the platform to be used has not been made yet, but platforms such as YODA, hosted by Utrecht University, are candidates. A process will be set up where requests for access from external researchers will be evaluated by the consortium prior to access being provided by data managers hired for this purpose.

The above information as well as what is described in Deliverable D5.8 will also be updated in the final version of the DMP (D5.4) to be completed by the end of the project.

In the 3rd iteration of the DMP, the section use of existing data was updated to better reflect the data that is being re-used and what it is used for in the study. In addition, the description of data was updated to reflect what will not be part of the public dataset due to commercial sensitivity and intellectual property.

4. Follow-up of recommendations and comments from previous review(s) (if applicable)

Action plan for COVID-RED, in response to midterm project review report received on the 24th of November 2021.

1. Project extension

As mentioned by the reviewers, the project is making progress overall. However, the project has faced a rapidly evolving COVID-19 situation and significant delays. Therefore, the consortium has requested a six-month extension, which was first discussed with our IMI Scientific Office in Q2 of 2021. As part of the action plan, the extension has been included in an amendment of the Grant Agreement.

The reviewers indicated that the consortium has justified the project extension by their description of delays in ethics approvals, in recruitment for clinical trials, and in resolving data protection aspects. However, they also pointed out that, besides the changing landscape of the pandemic, the deviations were the results of not thorough enough planning for the necessary regulatory requirements, data protection, and the lower number of available bracelets for the study because the bracelets could not be reused as anticipated. The consortium acknowledges that the start-up of the study ideally should have been earlier than was realized. However, while acknowledging it could not have prepared for all possible scenarios that could have been encountered for the start of such a study, the consortium is confident that it did take all possible steps to ensure as fast a start as possible. As the reviewers identify, there were several important factors that hampered preparations and progress. If we zoom in on the first reason given, the changing landscape of the pandemic, this had an immense impact on how the study could have been set up. A concrete example: The question if it was possible to obtain wet-ink, in-person, signatures on the Informed Consent while conducting the rest of the study remote was thoroughly explored and quickly thwarted when it became clear that lockdowns and further governmental regulations were to be expected. Another example is that investigations into the exact difference between Wet medisch-wetenschappelijk onderzoek met mensen (WMO) and non-WMO studies according to Dutch law were also unclear and required contact with many experts from the Ethics committee as well as governmental officials before a decision was reached. This came on top of the other challenging obstacles that are mentioned, including the setup of infrastructure for a fully remote trial, availability of testing materials in the Netherlands as a whole, and changing objectives and design of the study given the fluctuating infection rates in the Netherlands and impending availability of vaccinations rolled-out in record speeds. These were all obstacles that impacted the development of the study protocol.

In addition, it is worth clarifying that the time from finalization of the protocol until full ethics approval was obtained was short: 6 weeks, which included the holiday period for December 2020 as well as 2 resubmissions. As approval of the regulatory authority in the Netherlands (CCMO) could not be obtained until after ethics approval. This added another 3 weeks to the timeline, which again is fast relative to standard practice. Full ethical approval of the protocol was also necessary to obtain approval by Google and Apple for the Ava COVID-RED app, meaning that processes could not be done in parallel despite our best efforts.

2. Meeting project objectives

As requested, supporting data for each objective will be reported in the periodic report. For two of the objectives, the reviewers had added more comments which are addressed below.

A general comment was that, reflecting on the difficulties faced in the project and the resulting delay, the consortium should focus on priority aspects, which can be achieved early. The consortium fully agrees with the reviewers that priority should go towards the evaluation of the primary objective and key secondary objectives. All efforts will be put towards these goals and, where necessary, tangential analyses that do not contribute to the primary aims of the project and which could potentially cause delay in deliverables will be abandoned.

In line with this, we appreciate the reviewers' suggestion to maintain a strict focus on COVID-RED's most important goal. The evolving COVID-19 landscape including vaccinations should be factored in, but the consortium should avoid deviations from the original scope. It is indeed the case that there are many different interesting scientific questions to be answered in this study which have led to the list of secondary and tertiary analyses besides the defined primary analyses. The consortium will make sure to prioritize the 3 different primary analyses which each provide unique and relevant perspectives to the primary objective. Subsequently the consortium will prioritize those secondary and tertiary objectives that are of greatest importance and minimize any time or effort lost on tangential analyses which don't contribute to the main aims of this study. Where deemed worthwhile consortium partners may also pursue tertiary analyses after the completion of the study. Indeed, we will follow your advice to refine the most suitable use case—for instance early COVID-19 detection—and will focus on fine tuning the algorithm with an emphasis on the most suitable user group and the highest clinical need. We agree this approach should improve our business case for the exploitation of the results in a commercial setting.

2a. Objective: development of a diagnostic device

The reviewers requested that the project team clarify its statement that the project device is not a diagnostic medical device. We want to re-confirm that we see COVID-RED as a project that is part of the EU Innovative Medicines Initiative evaluating the use and performance of a CE-marked device (wearable), which uses sensors to measure respiratory 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 populations. However, in pointing this out in the Mid-Term review, we sought to ensure that it was understood that the device being used in the project is CE-marked for Fertility and not yet commercially available for diagnosing and/or monitoring COVID-19. As part of Work Package (WP) 1, the consortium applied for a clinical device exemption to repurpose the Ava bracelet for SARS-CoV-2 detection and use in the COVID-RED study. An Investigational Medical Device Dossier (IMDD) was submitted to the Medische Ethische Toetsingscommissie (METC) Utrecht and discussed by the committee on December 22, 2020. After iterative review and requests for more than 500 additional pages of documentation (which WP1 members produced in less than three weeks), the METC approved the use of the Ava bracelet and novel Ava COVID-RED app for the COVID-RED clinical trial on January 27, 2021. Data collected during this clinical investigation will be paramount in providing pre-market clinical evidence of the device's safety and performance for infection detection and diagnosis, per accordance with the European Medical Device Regulation 2017/745 (MDR). Therefore, based on European regulatory definitions, we cannot yet formally call Ava COVID-RED app and algorithm a CE-marked diagnostic medical device. Nevertheless, in this project we have accomplished several important steps in a process that could lead to this formal designation in the future. After evaluating the device's suitability for identification of COVID-19 cases prior to symptom onset, we will outline in our sustainability plan how the device could be best utilized in the market and the regulatory steps necessary to achieve an exploitable commercial product, leveraging COVID-RED data to pursue the device's CE-marking as a diagnostic medical device.

2b. Objective: monitoring individuals after a COVID-19 diagnosis to detect deterioration (for including early identification of COVID-19 patients requiring mechanical ventilation and/or intensive care).

Regarding the data collected related to this objective, when subjects log a positive diagnostic test in the AVA COVID-RED app, the app moves to a COVID-19 positive mode where subjects no longer receive daily indications if they have a potential SARS-CoV-2 infection. Symptoms and biophysical parameters monitored through the app and wearable device are still collected. In addition, subjects can indicate in the biweekly surveys if they have been hospitalized due to COVID-19. This survey includes questions on the number of days on the Intensive Care Unit (ICU) the participant may have experienced, if applicable, and the number of days on mechanical ventilation, if applicable. Where possible, subjects who have indicated a SARS-CoV-2 infection have been contacted again to provide

additional details. The collection of this data allows us to monitor participants' healthcare utilization in addition to their symptoms and infection-associated biophysical parameters.

Data on healthcare utilization are used for 3 different objectives defined in the Protocol and Statistical Analysis Plan (SAP; Secondary Analyses #1, 9 and 10). Together these analyses provide several perspectives on the broader objective defined in WP1. The first analysis in the SAP examines overall health economic utilization. Objective 9 in the SAP analyzes the relationship between reported long-term symptoms and changes in biophysical parameters in subjects who reported a positive SARS-CoV-2 test. Finally, objective 10 characterizes longitudinal symptoms and recovery dynamics in COVID-19 positive subjects. With these analyses, we can monitor and characterize the deterioration of individuals following a COVID-19 diagnosis in terms of their experienced symptoms, changes in biophysical parameters and healthcare resource utilization. At the time of the midterm review, the COVID-RED study follow-up period was underway. Accordingly, analysis of SARS-CoV-2 positive participants' healthcare utilization and disease trajectory had not yet been analyzed. In line with WP1's objectives and pending database locking, we can proceed with these analyses now that the last participant has exited the study.

WP1 will also investigate the possibility of developing an algorithm to detect COVID-19 infection deterioration and report on it as part of Deliverable 1.6. However, given the low number of anticipated mechanical ventilation and/or ICU usage reported by participants to date, it may be impossible to employ machine learning methods given the small sample size. The smaller number of reported medical events arising from a SARS-CoV-2 infection can at least in part be attributed to the widespread adoption of vaccines in the Netherlands, which has largely reduced the severity of breakthrough infections and are credited with keeping more individuals out of the hospitals. Accordingly, WP1 has had to adapt to the changing landscape and will, at the least, strive to meet its pre-stated objectives by working with WP3 to analyze the existing healthcare utilization even if an algorithm's development is not possible.

3. Feasibility study

The IMI reviewers correctly identified that no feasibility study was performed and instead that an existing study, COVI-GAPP (a sub-study of the GAPP study), was chosen as a replacement. While this marks a deviation from the original Description of Action (DoA), the consortium carefully weighed COVI-GAPP's potential merit as a replacement before moving ahead with this decision. At the time of the decision to move forward with using COVI-GAPP in lieu of a new feasibility study, it had already recruited 2170 subjects and employed clinical operations which paralleled the intentions of the originally described pilot study. In line with the reviewers' request, Deliverable 3.2 will be updated to properly reflect the arrangement and implications. All COVI-GAPP investigators are members of the COVID-RED consortium, which is how its potential as a pilot study first came to light. Subsequent budget implications from the decision to substitute COVI-GAPP for a feasibility study will be addressed in the next amendment to the Grant Agreement.

The consortium would like to highlight that at the time of the initial submission of the COVID-RED proposal, the COVI-GAPP sub study was only beginning and its success at that time was uncertain. By the time that the consortium would have needed to launch a full-blown pilot study, the COVI-GAPP study had been running for six months and was more similar to the COVID-RED study than initially anticipated. Data from COVI-GAPP could, through its inclusion as a pilot study, be used to train the initial version of the Ava COVID-RED algorithm for use during the study's initial Learning Phase. In addition, COVI-GAPP was testing operational processes including helpdesk support and a recruitment strategy which the consortium saw as adaptable to COVID-RED. Given this, the consortium considered that setting up a feasibility study while having an appropriate alternative in place would waste time which could be pivoted towards the COVID-RED study and would help in identifying SARS-CoV-2 similarities. Given the temporal and financial savings as well

as potential to leverage operational learnings, the deliberate decision was taken to repurpose the COVI-GAPP study as COVID-RED's feasibility study.

4. Study design

The consortium changed the original study design from 'prospective, observational study in a set of three, clearly-defined cohorts' to 'a randomized, single-blinded, two-period, two-sequence crossover trial'. In addition, the participant number of the clinical trial has decreased from 40,000 to 20,000, and the final number of recruited participants was 17,824. Deliverable 3.1 will be amended to provide further justification and detail on how changes to the study design impact the project's execution, outcome and exploitation. Edits to Deliverable D3.4 will also provide a justification for the decision to recruit 20,000 participants and a description of its impact on study execution, budget, outcome, and exploitation In addition to the formal amendments to D3.2, we have presented a clarification and explanation changes in the COVID-RED study design below.

The Description of Actions for this study and thus the initial study design was developed rapidly at the start of the COVID-19 pandemic. The pandemic's highly volatile nature and its societal impact affected study execution as well as the start of recruitment. In addition to setbacks outlined elsewhere in this document, we have outlined various statistical and study design obstacles faced by the COVID-RED consortium. As was the case for the whole project, this process was highly iterative and required frequent last-minute modifications to deal with the rapidly changing circumstances. Obstacles that arose at various moments in the beginning of the project that required further modification of the study set up and design included:

- Due to delays in study recruitment and the pandemic's volatile nature, there was concern about the number of SARS-CoV-2 infections that would circulate in the general population (given governments implementing society-wide restrictions) and thus our study sample during the study.
- The shorter follow-up time in the original study design could prevent the accumulation of enough SARS-CoV-2 infections to iteratively train multiple versions of an algorithm and evaluate them.
- A within-participant, cross-over randomized trial would allow a more definitive answer to the formulated research questions and objectives, while inherently controlling for confounding factors (e.g., each participant's medical history).
- As per the original DoA and project budget, 20,000 bracelets were available for the study; this necessarily limited the upper value of participants we could recruit using a cross-over design.
- Willingness of individuals to participate in the study and comply for the whole follow-up period would likely be less if individuals knew that there was a chance that they would not get to use the bracelet at all. The cross-over design alleviated this concern; all participants were equipped with an Ava bracelet and could see their real-time health data on the Ava COVID-RED app. Furthermore, participants were blinded to condition. They did not know whether their physiological data was incorporated into the algorithm at any given moment or if their health indicators were based on standard of care (i.e., self-reported symptoms). In the prior study design, participants would have known whether they were assigned to standard of care versus wearable algorithm. The lack of blinding could have influenced their behavior and drop-out rate, confounding statistical analyses outlined in the SAP. The new design mitigated this risk by minimizing participants' certainty about their randomization to a given condition at any given moment.
- Concerns about the feasibility of recruiting 40,000 subjects within several months and supporting them in a remote trial setting with fluctuating governmental restrictions,
- Very limited supply of testing availability and materials (both serology and PCR) in the Netherlands as a whole and thus also in our study. Being independent of the national testing service provided by the municipal health services would be highly infeasible from a budgetary perspective.

These obstacles, in addition to more minor considerations not highlighted here, meant

that we considered different study designs and methodology to arrive at the best possible approach to obtain our research objectives. Ultimately, 'a randomized, single-blinded, two-period, two-sequence crossover trial' recruiting 20,000 subjects best addressed the above concerns. This design allowed us to:

- Analyze the efficacy of a wearable-driven algorithm for COVID-19 detection by controlling for possible participant-level confounders.
- Analyze within-person differences in behaviors and outcomes due to standard of care (e.g., symptom-based testing) versus the novel algorithm.
- To increase statistical power through the crossover design as compared to a parallel-arm randomized trial with 20,000 subjects.
- Ensure that recruitment and compliance would be more successful as all subjects would receive and use the Ava bracelet.
- Uniquely allow for participant blinding to condition, increasing the comparability between the control and experimental arms.
- Set a more feasible recruitment goal given the circumstances while obtaining more power than a normal parallel arm design through the use of cross-over periods.
- Increase the follow-up period, thereby increasing the number of possible infections that could be detected and allowing more time for algorithm development, roll-out and evaluation.

This study design was evaluated by a sample size and power calculation (see the SAP Section 3) and deemed to be sufficient to answer the project's primary research objectives.

5. Study execution

Overall, subject retention was a challenge in the study. This was caused by multiple factors, including an overall lower urgency of COVID-19 in public perception following the Netherlands' mass vaccination campaign. Due to the project's innovative nature and unique siteless study design, effective subject retention strategies had to be tailor crafted. In addition, the length of the period which the subjects would participate in the trial (ranging from 6.5 to 9 months) made effective long-term retention strategies less effective. Instead, the consortium anticipated lower subject compliance during holiday periods, having to react quickly and efficiently once subject compliance dwindled.

Due to the recruitment strategy, which included the successful recruitment of many subjects through social media platforms such as Facebook and Instagram, the necessity for an online presence for the COVID-RED project became apparent. In response, the COVID-RED consortium set up an effective social media strategy, which included a dedicated social media manager who engaged subjects online and ensured participant questions were answered across social media platforms.

Another result of the project's scale and online recruitment strategy was that participants independently created a private Facebook group. Their shared community on the social network allowed them to discuss the COVID-RED project and discuss their experiences. After a larger discussion, the COVID-RED consortium decided to monitor the conversations in this Facebook group and ensure that questions raised by participants were answered accurately. This approach would therefore safeguard data quality while also ensuring that the consortium's presence in the group would not interfere in any other way with ongoing discussions. The COVID-RED consortium also purposely chose to not share the name of this Facebook group outside the relevant Work Package, to ensure that study staff would not interfere outside of what was agreed upon.

Participant excitement and engagement, as evidenced by the independent Facebook group's creation and general activity of the subjects on social media was encouraging. We maximized retention through regular e-mails, newsletters, social medial posts and targeted reminders for specific

activities (e.g., syncing the wearable to the Ava COVID-RED app). Email messages also adopted a gamification strategy which strove to motivate or praise subjects based on their individual study compliance. In addition, subjects with a higher likelihood of dropout, based on dropout data accrued in the beginning of the trial, were targeted with extra communications (i.e. emails and phone calls) to motivate them to continue. The potential efficacy of these retention approaches will be analyzed and, if time allows, reported upon as an example of a successful large scale, siteless clinical trial.

6. Testing procedures

As a decentralized trial the COVID-RED project made use of the national testing infrastructure and therefore relied on the tests and procedures that were available during different moments of the trial. Participants who utilized this infrastructure also reported the type of test utilized (i.e. PCR, antigen, etc.) through the biweekly surveys utilized in COVID-RED. Beyond this self-reported data we have limited insights on the type of test and specifics of the testing procedure, instrument or assays used. These aspects will be investigated in several primary and secondary analyses during the analysis of the final study results, including the reporting and accounting for (where applicable) differences in testing approaches.
In the event that participants were not able to be tested via this infrastructure, tests were provided by the COVID-RED project. We will provide a more detailed description of the tests that were provided in the case participants were not able to get testing through the national testing infrastructure in an amended Deliverable 2.1 (n.b. Deliverable 2.2 has been submitted since the mid-project report and Deliverable 2.3 will be completed once all results have been processed in February). We will also provide a more systematic analysis of user experiences and deviations between testing and app alert statuses.

7. Performance of machine learning algorithm

Due to the pandemic's rapid development and evolution, it was important for us to balance the need for flexibility in our responsiveness with the overall priority of maintaining the project's scientific rigor. Therefore, we proposed a plan that allowed us to develop and improve the project's machine learning algorithm in an iterative process based on the growing data set collected in the study, an approach commonly used for wearable algorithm development.

The mid-term results on the algorithm's performance are not our final results. In line with the DoA for D1.6, a new algorithm (version 3; v3) with expected higher specificity and accuracy is currently being developed. Furthermore, an approach to incorporate the detection of asymptomatic SARS-CoV-2 cases into the algorithm is currently being explored. Now that the last participant has exited the study (as of November 2021, following IMI's midterm review), we will be able to determine seroconversion across the project and thus objectively identify asymptomatic cases. We expect the infection detection algorithm's performance will improve during the project's final phase but can only confirm this once the planned analyses have been completed.

In our final analyses, we will report on the overall number of people who enrolled in the study that were classified as confirmed COVID-19 cases, as well as the confusion matrices across all three iterative versions of the algorithm. We anticipate that the comparison of the antibody test results with the wearable signals and reported symptoms will allow us to better understand the frequency of asymptomatic cases and if these were detected by the algorithm. In addition, we will compare the different versions of the algorithm and provide an overall assessment of the algorithm's utility in the periodic and final reports. Here it is also important to note that information on which type of diagnostic test was used and other related information was gathered through biweekly surveys. By contrast, we only collected information about the diagnostic test results in the Ava COVID-RED app. Data from these multiple sources will be reconciled to ensure assessment of the algorithm's performance derives from an accurate and objective ground truth.

8. Data management plan

The consortium has worked on the data management plan (DMP) iteratively, which is reflected in the submission of three evolving versions as deliverables D5.1 through D5.3. A final version will be submitted by the project's end . A long- term, sustainable FAIR data storage platform is still under discussion.

The IMI Reviewers indicated that the use of the dmponline platform makes it difficult to confirm if items specified in Task 5.1 were delivered. The dmponline platform was chosen as it conforms to the HORIZON2020 requirements for the data management plan. Most items identified in Task 5.1 are defined in the DMP, although we recognize some elements are missing or could be clarified. As planned in the DoA, a final version of the DMP (D5.4) will be submitted at the end of the extended project. Therefore, the consortium proposes to leave D5.3 in its current state and focus efforts on aligning Task 5.1 with the DMP when writing D5.4. Given the project's current stage, an amended version of D5.3 would be almost identical to D5.4 while requiring double the overhead.

9. Communication and dissemination

Work package 6 has worked together with WP3 on communication, with an initial focus on recruitment and retention. This communication mainly took place via our website, Twitter, and Instagram, as well as via press releases and newsletters for the study participants. Now that the study has ended, we will also direct our communication towards a scientific and expert audience. This will become especially important when our results become available, as our dissemination activities will also target the scientific and community and experts in the field of wearable technologies. To achieve this wider communication and, at a later stage, dissemination, we aim to have post more updates in English instead of Dutch and to adjust the content of our messages to the intended audience. In the meantime, we will also keep the trial participants informed, and we will make a summary of the results available in Dutch for them.

We have created Deliverable 6.1 at the start of the project, in which we describe our communication and dissemination plan. Here, we also identified our main audiences and the key messages to share with each stakeholder type. We have also written internal plans and guidance for the use of our social media and the strategy for recruitment and retention. We will update Deliverable 6.1 and submit the updated version as Deliverable 6.9, containing a more detailed plan for communication and dissemination. For the exploitation of the project outputs, our strategy will depend on the results of the algorithm performance, which are not available yet. The exploitation and innovation management will be further described in the sustainability plan (Deliverable 7.13) and the business plan (Deliverable 7.14). An exhaustive analysis of stakeholders will be described in Deliverable 6.3.

10. Collaboration

COVID-RED is participating in the join activities of the projects that are a result of IMI Call 21. Up until now, the conversations have had an exploratory character from the side of COVID-RED, although we expect a more intense collaboration with other projects once results from IMI COVID-RED come available.

11. Sustainability and business development

At an early stage in the project, we made a first attempt to understand the potential interest of commercial partners for collaboration, investment or purchase of the project device (i.e., algorithm, app and study results). To this end, we reached out to an extended list of potential stakeholders, including the business development teams of the consortium's industry

partners. Initial discussions led to the conclusion that it was too early in the project to garner distribution interest; the overwhelming feedback from potential commercial partners was that they would prefer to see the device's performance and have the real-world dataset in hand before engaging in a sustainability discussion. Consequently, we concluded we should pursue these efforts only once the algorithm was finalized and the study results are available. We will continue this work as part of the sustainability plan (Deliverable 7.13) and the business plan (Deliverable 7.14) during the extended project duration, as the final study participant exited follow-up in November 2021 and analyses according to the SAP are currently underway.

Furthermore, we agree with the IMI reviewers that there could be a benefit for the leading SME participating in the consortium as well as for the wider digital health industry that has a growing need of knowledge about clinical validation of digital tools in a compliant way. To date, one patent has been applied for but not yet granted to the manufacturer of the wearable device, Ava AG. This application work was begun very early in the project—some of it in parallel to the COVID-RED application process—to ensure a timely submission prior to other potential competing parties. Additionally, it drew on data collected by the manufacturer's original application, Ava Fertility, as a proof-of-concept. Once the COVID-RED study results are available, the entire consortium will assess additional intellectual property (IP) opportunities. All IP will be considered in the sustainability plan, this will also detail how the results can benefit the wider digital health industry in a balanced manner.

12. Project management

As the Experts point out, there were several factors that posed a challenge to efficient and effective project management, which caused an overall delay in project deliverables. Most importantly, the rapidly changing landscape of the pandemic and the fact that we are working on a moving target required a high flexibility from the entire consortium, which has (in addition) never been able to meet face to face. However, while acknowledging in hindsight that they could have processed some deliverables faster, the project management office believes that they did take the necessary steps to ensure a collaborative and clear working environment for the consortium and did sufficiently inform IMI of the challenges faced and progress made. They will keep trying their best to share future deliverables with IMI as soon as possible and to maintain open communication.

For some of the stakeholder engagement, COVID-RED will be collaborating with HI-NL. This is an initiative based in the Netherlands but with an international scope which organizes stakeholder round tables with innovators/consortia and key public and private sector players (e.g. health care payers, HTA bodies, health care profiessionals, patients etc). HI-NL is supported by the Dutch Ministry of Health, but also has an international scope. By working with HI-NL, we believe we can organise our stakeholder engagement in a more efficient and effective manner by working with an experienced party. The costs of the HI-NL services are, in the assessment of the consortium, reasonable and potentially lower than the investments that the consortium would make to organise the activities themselves. It has to be emphasised that HI-NL will support the activities of the consortium and that the consortium partners are closely involved in each step of the stakeholder engagement activities. These activities will be included in the future amendment.

One of the efforts of the project management office was the establishment of the COVID-RED Advisory Board, including an ethicist as required in the ethics deliverables. The first Advisory Board member was contracted by the end of January 2020, and the contracting of all members was completed by late April 2020. The ethicist provided several concerns and recommendations in the first bi-annual report (Deliverable 7.4). To answer the Expert's question for clarification whether they were implemented: they have all been addressed by the consortium in the Advisory Board report (Deliverable 7.7).

13. Risk management

The consortium identified several risks at the start of the project. Risks with regard to the clinical trial

are discussed in biweekly monitoring meetings between WP3 and WP7. To ensure optimal risk management and efficient risk management meetings, a risk management log was created in which risks were listed and prioritized. New risks were added to this log as well. We will update risks as listed in the EC portal during the next periodic reporting, both in terms of updating the mitigation plans and by adding the additional risks that were identified in the meantime. We will also keep monitoring the risks in our monthly Managing Board meetings, biweekly Managing Team meetings, and weekly Project Management Office meetings.