COVID-RED

innovative medicines initiative

101005177 — COVID-RED

COVID-RED

WP3 – Study design, execution and analysis

D3.2 Report on small feasibility study & proposed adaptations to the protocol to be made

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Document History

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Contents

Summary

Following lessons learned in the COVI-GAPP study (https://www.covi-gapp.li/), which is conducted by consortium partner Dr Risch Medical Laboratories in Liechtenstein using a customized version of the Ava Fertility Tracker app, some best practices were adapted for the COVID-RED study. In summary, the following items were adapted or developed based, at least partially, upon the COVI-GAPP study:

1. The Ava COVID-RED App
2. Version 1 of the COVID-19 infection detection algorithm;
3. The onboarding materials for study participants
4. The contact points & communication plan to increase compliance & reduce participant dropout

The Ava COVID-RED app

Deliverable 1.2 describes the data analysis prototype (DAP) application implemented for COVI-GAPP, while Deliverable 1.3 details the improvements live in the Ava COVID-RED smartphone application. Both apps allowed participants to sync data from their Ava bracelet to their smartphone and finally to a cloud-based server. The COVI-GAPP ran on the proprietary Ava Fertility Tracker app while the Ava COVID-RED app stands alone and is only available to current COVID-RED participants. We highlight how the COVI-GAPP app informed the COVID-RED study briefly below.

After first downloading the Ava Fertility Tracker app, COVI-GAPP participants logged into the app with their pre-assigned, anonymous username and password. On the backend, the participants were marked with a special user role which enacted conditional changes to the app. In the Ava Fertility Tracker app, women who have purchased the Ava bracelet for menstrual cycle tracking or as a conceptive aid receive a daily fertility indicator based on their prior night's physiological parameters. However, COVI-GAPP participants saw a "Fertility Unknown" alert in-app instead. The Ava Fertility Tracker app also allows women to log fertility-related items in a Daily Diary; for example, women can report results of pregnancy and luteinizing hormone tests, or symptoms associated with premenstrual syndrome. The COVI-GAPP version of the app focused on confounds and COVID-19 related information. Participants could report specific symptoms or whether they had taken antipyretic medication that may mask infection-driven change in physiological parameters. The COVI-GAPP app used the same color scheme as the Ava Fertility Tracker app and included all the same content shown to conceptive-seeking women

who purchased the Ava bracelet. Thus, while it served the purposes of the pilot trial, it was not ideally suited for a large-scale clinical trial.

Designed specifically for the COVID-RED study, the Ava COVID-RED app adapted the Ava Fertility Tracker's codebase and corresponding features. Visually, it has its own unique color scheme; the manufacturer's design team chose calming blues and muted yellows, avoiding reds which they felt came off as alarming during an already tension-fraught global pandemic. As with COVI-GAPP DAP, the app had a login screen which required pre-authorization by the study team. Only eligible participants can access the app, in line with its limited regulatory approval for clinical investigational use. After first login, participants responded to a series of onboarding questions designed to help better tailor the real-time infection detection algorithm (see Deliverable 1.4 for a detailed explanation).

In the Ava COVID-RED iteration of the app, participants see real-time indicators about their potential infection status. This feature was developed and deployed in January 2021, available only to COVID-RED participants in the Netherlands. COVI-GAPP participants, in contrast, were instructed to adhere to national testing guidelines to know when to seek medical attention or a diagnostic test. The Daily Diary section of the app was further adapted from the DAP, allowing participants to log more features (e.g., recent vaccinations). The app had a more detailed COVID-19 symptom list, organized by affected body area. Although COVI-GAPP participants could log a positive diagnostic test for SARS-CoV-2, the app would remain unchanged; it looked the same and the home screen indicator would still show "Fertility Unknown". In contrast, if a participant logged a positive SARS-CoV-2 diagnostic test in the Ava COVID-RED app, a pop-up would ask them to confirm the test result. Logging a positive test result will trigger the app to switch modes from "COVID-19 tracking" to "COVID-19 confirmed" on the backend, stopping the algorithm from running for that user for the remaining duration of the study. The participant can still wear and sync their Ava bracelet with the Ava COVID-RED app to see their nightly physiological parameters. However, the health indicator algorithm will no longer run on the backend. Instead, the user will see a constant message on their home screen asking them to continue to check in with the Ava COVID-RED app and contact a medical professional if their symptoms worsen. In "COVID-19 confirmed" mode, participants can still view graphs of their data over time and log symptoms in their Daily Diary. If the participant accidentally logs a positive COVID-19 test, they can always de-select the positive test result button on that date in the Daily Diary, and the app will switch back to "COVID-19 tracking" mode.

The Ava bracelet captures 3 million data points per user per night, syncing with the Ava COVID-RED app built under Deliverable 1.3. Adapted from Ava Fertility Tracker's proprietary codebase, new features introduced in Ava COVID-RED include a Daily Diary customized for COVID-RED and real-time home screen health indicators based on the previous 24 hours' physiological data and/or self-reported symptoms. With development completed on December 1, 2020, Ava COVID-RED achieved its stated purpose of improving upon the COVI-GAPP DAP. It was submitted to the Apple iOS and Google Play Stores for review in mid-December and was available for download by participants beginning February 4, 2021.

Version 1 of the health indicator algorithm

As explained in Deliverable 1.2, COVI-GAPP's primary objective was to collect physiological data from participants prior to and during a SARS-CoV-2 infection, in an effort to gather data for training version 1 of the COVID-RED health indicator algorithm. Subjects in the COVI-GAPP study

did not receive a real-time alert about their likelihood to have a current SARS-CoV-2 infection, unlike subjects in the COVID-RED study. Version 1 of the health indicator algorithm deployed in the COVID-RED study was trained and validated on physiological data from COVI-GAPP participants who tested positive for SARS-CoV-2 via a laboratory-confirmed diagnostic or antibody test. While the learning phase went live with version 1, iterative versions of the algorithm will be deployed in Phases 1 and 2 based on cumulative data from COVID-RED participants. Thus, the data collected during the learning phase will help improve the algorithm further.

Onboarding materials for the study participants

Based on lessons learned in the COVI-GAPP study, the onboarding materials for subjects enrolling in the COVID-RED study will contain plain-language instructions on how to install and use the Ava COVID-RED app, how to use the bracelet and how to perform self-testing (nasal swabs and finger pricks).
Due to the considerable amount of actions that the participants will have to take themselves after being randomized into the study, it is important to ensure that the instructions are clear and unequivocal. To this end, we created a step-by-step instruction booklet to walk participants through each necessary onboarding requirement. This instruction booklet contained:

- An introductory paragraph, welcoming the participant to the study;
- Contact information for general trial support and for technical Ava COVID-RED app support
- How to install the Ava COVID-RED app;
- How to pair the Ava bracelet with the Ava COVID-RED app;
- How and when to use the app (all aspects of the app);
- How and when to complete bi-weekly surveys;
- How and when to perform self-testing, including baseline/follow-up antibody tests and nasal Polymerase Chain Reaction (PCR) tests; and,
- Where and when to deliver specimens collected via self-testing.

The COVI-GAPP team observed that not all study participants read through the entire instruction booklet; consequently, the COVID-RED team decided to create additional instructional to facilitate the onboarding process.

Communication plan & reducing drop-out

Based on learnings from the COVI-GAPP study, COVID-RED researchers attempted to streamline the support process for participants. Ensuring participants knew who to contact for which types of questions, the study materials included the helpdesk numbers for both the Julius Clinical study site and Ava's technical call center. When experiencing issues with the Ava bracelet or the Ava COVID-RED app, participants were instructed to contact Ava's dedicated COVID-RED customer support team. For more general study questions or questions related to self-testing kits, participants should contact the Julius Clinical support center (facilitated by WP3). The COVID-RED website also includes a Frequently Asked Questions (FAQ) section (www.covid-red.eu/en/veelgestelde-vragen), where participants can find easy-to-implement responses before escalating their concern to a helpdesk. This FAQ will be updated continuously by WP3's

operations team to address commonly asked and emerging questions.

Furthermore, the COVI-GAPP study revealed that several factors throughout a year may reduce participants' compliance in wearing the Ava bracelet or completing the daily symptom logger. For example, summer, national and school holidays, during which participants go on vacation, may impact compliance. In order to keep compliance as high as possible, the COVID-RED team will regularly review which participants complete the bi-weekly surveys, synchronize their bracelet with the app and perform the fingerprick serology test. Should compliance with any of these 3 procedures decrease, participants will be contacted by the team via e-mail to remind them to complete the necessary study procedures. Additionally, prior to any holiday in the Netherlands, the COVID-RED team will send reminders to the participants asking them to continue to wear their bracelet and complete in-app questionnaires. We will also communicate the trial progress in plain language so that participants are aware of their participation's impact, including sharing any interim results and findings.

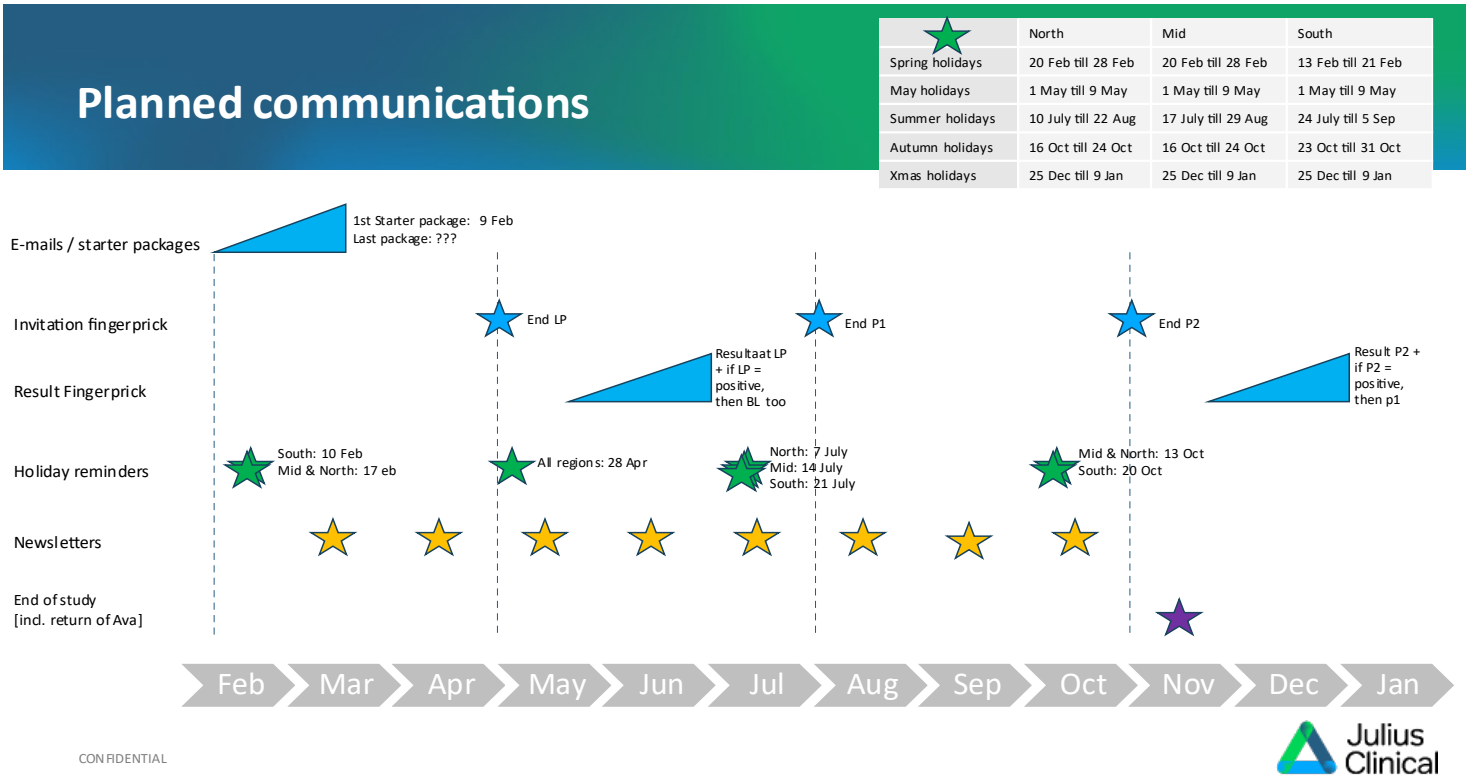

Figure 1: *Initial version of the participant communication plan. Each star represent a moment in time where a communication is sent to the participants.*