

PARTNERS HUMAN RESEARCH COMMITTEE DETAILED PROTOCOL

Title

COVID-19 Real-time Symptom Epidemiology Tracker (CORSET)

NCT04331509

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1 Background & Rationale

In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei, China¹. Deep sequencing analysis from lower respiratory tract samples indicated a novel coronavirus, which was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (previously known as 2019-nCoV)². Despite efforts to contain the outbreak, the infection soon spread to over 180 countries and was declared a pandemic by the World Health Organization on 11 March 2020³.

COVID-19 infection causes a spectrum of respiratory illness that includes symptoms of dry cough and fever which can progress to dyspnea and severe respiratory distress syndromes⁴⁻⁶. Symptoms can be slowly progressive to acute in onset. More recently, non-respiratory symptoms, including malaise, fatigue, and gastrointestinal distress (e.g. diarrhea, abdominal pain) have been appreciated and can precede respiratory symptoms^{7,8}. Moreover, it is increasingly clear that individuals may harbor infection without clinical symptoms⁹, which has made containment of the virus a significant challenge. To date, our hospitals are also seeing unprecedented numbers of patients presenting with clinical symptoms potentially consistent with COVID-19. However, after those patients interact with our providers, they are often sent home without a method of follow-up and check-in about symptoms. Thus, there is a high unmet need for methods to prospectively collect high-quality, real-time data from patients in the community using a rapidly adaptable data-capture platform for COVID-19 infection that encompasses the spectrum of symptom onset, diagnosis, treatment, vaccination, and clinical outcomes

Because of their background and work environments, health care workers (HCW) have heightened awareness of the onset of potential COVID-19 symptoms and greater access to testing and care, thereby offering unique insights into the trajectory of symptom onset, diagnosis, treatment, and clinical outcomes. HCW are also at high personal risk of infection, leading to subsequent community spread. Limited availability of adequate personal protective equipment (PPE) has raised concern about their vulnerability to infection, work stress, and absenteeism, which further strains our response to the crisis. Thus, there is an urgent need to prospectively collect high-quality, real-time, data from HCW using a rapidly adaptable data-capture platform for COVID-19 infection that encompasses the spectrum of symptom onset, diagnosis, treatment, vaccination and clinical outcomes. Further, there is an imperative for more accurate estimates of disease incidence; identification of characteristics for risk stratification to improve guidelines for testing, quarantine, treatment, vaccination, and hospitalization; and assessment of PPE effectiveness in reducing infection, stress, and absenteeism. Such data are critical for not only protecting our healthcare workforce but to optimally allocate resources for the general population.

To address these urgent priorities, we have established a partnership with physicians and epidemiologists at King's College London (KCL) and Guy's and St. Thomas' Hospital London and software engineers at Zoe Global Ltd, a health data science company focused on developing mobile phone apps to generate high-dimensional datasets for predictive machine learning approaches. We will survey populations of patients and HCW in real-time and rapidly advance our understanding of COVID-19 at population scale. Together, we are launching COVID-19 Symptom Study App, a "symptom tracking app" that has been built for both Apple and Android platforms and is currently approved in their UK app stores and in submission to their US app stores. To differentiate this study using the app from other apps that "track" individual locations for contact tracing, the app and the study are also referred to as the COVID Symptom Study. The app is supported through emergency funds provide by the UK National Health Service National Institute for Healthcare Research and the Wellcome

Trust. On first use, the app records location, age, and core health risk factors. With continued use, participants can provide daily updates on symptoms, health care visits, and COVID testing results. They can also indicate if they are self-quarantining or seeking health care. If they seek healthcare, they can share the level of intervention and related outcomes. Healthcare workers will be asked specific questions about intensity of patient exposure, use of PPE, and stress/anxiety. The use of an app will facilitate prospective collection of data related to COVID-19 and capture the dynamic nature of exposure, onset of symptoms, disease trajectory, and clinical outcomes currently observed. In addition, participants will receive a one-time COVID Diet Quality and Habits Questionnaire, a supplemental questionnaire that collects additional data on changes in diet, alcohol consumption, the use of supplements and physical activity. It is our intention to perform pooled data analyses using data collected from this study, and de-identified data from other sources that collect complementary data for COVID-related exposures, onset of symptoms, disease trajectory, and clinical outcomes (e.g. HowWeFeel; covidnearyou.org). This secondary use of data by investigators will be detailed through individual data use agreements via the COPE Consortium, but broadly will be used to address the objectives presented here.

Our **overall goal** is to identify risk factors for incidence and outcomes related to COVID-19 across the spectrum of disease presentation and severity to provide a resolution snapshot on the current pandemic as well as develop an infrastructure within infected populations for long-term follow-up and molecular studies to prevent the next global outbreak.

There is an urgent need to deploy this app in real time to maximize the collection of information as the COVID-19 pandemic accelerates and is likely to peak in the coming weeks.

2 Study Aim and Objectives

Overview: The proposed study will contact health care professionals working at Mass General Brigham (Partners Healthcare) or participants enrolled in the Harvard Nurses' Health Study, Harvard Nurses' Health Study II, Harvard Nurses' Health Study III (NHSII/NHSIII), Growing Up Today Study (GUTS), Health Professionals Follow-up Study (HPFS), American Cancer Society Cancer Prevention Study 3 cohorts and direct them to use "COVID-19 Symptom Tracker," a novel app for mobile devices designed to specifically capture self-reported information regarding symptoms associated with COVID-19 and use of PPE during the current COVID-19 pandemic. In addition, we will enroll individuals in other cohorts who may use this protocol as a cede protocol to recruit their participants to the research study by seeking formal approval of recruitment materials. We will also use this app to track patients who are enrolled in additional protocols across Mass General Brigham who under investigation for COVID-19 ("CoV-Risk."), including Partners IRB Protocol: 2020P000804 or individuals in the general public who enroll in this app on their own. This app is a joint development between Zoe Global Ltd and a team of physicians and epidemiologists at King's College London, Guys and St. Thomas' Hospital London, MGH, BWH, and the Harvard T.H. Chan School of Public Health. These data will be collected by Zoe Global Ltd and returned to the PI and co-investigators.

Specific objectives include:

1. Collect real-time data on COVID-19 symptoms from general public individuals and

healthcare workers (HCW) during the 2020 pandemic using mobile digital technology. These data will allow for the construction of more accurate models of disease incidence and outcomes which can inform risk stratification for testing, algorithms for management (i.e. quarantine and hospitalization), and allocation of PPE. These data will also be used to understand the role of PPE in preventing infection and alleviating work-related stress and absenteeism.

2. Link real-time data on COVID-19 symptoms with ongoing collection of data on lifestyle, diet, health conditions, vaccination, and psychosocial stress among HCW enrolled in the Nurses' Health Study II that have been extensively phenotyped over the last 30 years and genetically profiled to examine the role of these factors in COVID-19 disease, chronic complications, and psychosocial stress.
3. Collect real-time data on COVID-19 symptoms from patient or external cohorts that are being enrolled who are being investigated for COVID-19 ("CoV Risk"). These data will allow us to link the presentation of symptoms with clinical course, including likelihood of testing positive for COVID-19, development of new symptoms, vaccination, and clinical outcomes. These data can be linked with other clinical data or biospecimens that are being collected in other protocols (e.g. Partners 2020P000804). These data may be linked back to parent cohorts according to other Data Use Agreements.
4. Use deidentified data collected from other external or internal sources to pool with our collected data to perform proposed analyses. This will include data collected by other investigators using similarly designed tools and made available to investigators on this protocol according to other Data Use Agreements as they pertain to the analyses outlined in this detailed protocol.

3 Subject Selection

3.1 Study population

We will recruit individuals who wish to have their COVID-19 symptoms tracked. This will include nurses, advanced practice providers, physicians, and other health care workers (HCW) within Mass General Brigham via appropriate channels through consultation with the office of the Chief Information Officer and Incident Command leadership. The app is also being offered in Spanish.

Possible methods may include direct emails or advertisements, including through the Partners Broadcast email system from the relevant nursing and physician organizations at each Partners Hospital. We also will recruit participants/HCW enrolled in the Growing Up Today Study (GUTS), the Nurses' Health Study (NHS), Nurses' Health Study II (NHS II) or Nurses' Health Study III (NHS III) which are based at Brigham and Women's Hospital as well as the Health Professionals Follow-up Study (HPFS) which is based at Harvard T.H. Chan School of Public Health. We will additionally enroll individuals from other prospective cohorts. For some cohorts that are not based at Partners, the investigators may submit, through a cede protocol, recruitment materials for their cohorts to recruit participants to use the COVID symptoms tracker app and allow us to collect data on their cohorts.

NHS was established in 1976 and recruited 121,700 female nurses. The original focus of the study was on contraceptive methods, smoking, cancer, and heart disease, but has expanded over time to include research on many other lifestyle factors, behaviors, personal characteristics, and more than 30 diseases.

NHS II was begun in 1989 with the recruitment of 116,430 female nurses from across the US who have completed follow-up questionnaires every other year. Participants have

provided a variety of biological specimens over the course of follow-up and participated in digital phenotyping studies.

GUTS recruited children of Nurses' Health Study II participants. The first phase of the study began in 1996 during which 16,882 girls & boys between the ages of 9 & 14 were enrolled into the study. The second phase of GUTS (GUTS2) was rolled out in 2004, with the enrollment of an additional 10,923 children between the ages of 10 & 17. This is a cross-generational study allowing for exploration of the relation between early life exposures and health in adulthood.

NHS III cohort is an expansion of the NHS II that began enrolling female RNs, LPNs, and nursing students in 2010. In 2015, eligibility was expanded to include male nurses. More than 45,000 female and male nurses and nursing students currently participate.

HPFS is a male study designed to complement the female NHS. It began in 1986 and enlisted 51,529 men in health professions to participate in the study. The purpose of the study is to evaluate a series of hypotheses about men's health relating nutritional factors to the incidence of serious illnesses, such as cancer, heart disease, and other vascular diseases.

The American Cancer Society would like to enroll participants in their Cancer Prevention Study 3 (CPS3). In December 2013, the American Cancer Society completed the initial recruitment of its newest study, Cancer Prevention Study-3, with over 304,000 participants. The American Cancer Society's Epidemiology Research Program invited men and women between the ages of 30 and 65 years who had no personal history of cancer to join this historic research study. The ultimate goal was to enroll at least 300,000 adults from various racial and ethnic backgrounds from across the United States and Puerto Rico.

Although we recognize that members of the NHS, NHS II, NHS III and HPFS may not be active HCW, we will still include them to provide comparative data among a population without sustained occupational exposure to potential COVID-19.

We will also encourage "CoV-risk" patients to enroll in the app as a means to provide clinical information, data on symptoms, vaccination, and clinical outcomes for linkage with data collected through other protocols (Partners 2020P000804). Other protocols enrolling CoV-risk patients may add use of the app to their own IRB protocols and point to this protocol to cover data collection using the app. These studies may directly inform participants about this tool.

As the crisis continues, we may develop additional sub-studies that users of the app may be interested in participating in. We will provide an opt-in checkbox (defaults to opted out) to allow app users to denote whether they are interested in learning about additional studies being performed by the research team. The question that will be asked is "Are you interested in being contacted to learn about additional studies related to COVID-19 or use of this app?" It will be added as a separate question within the app at the end of the questionnaire set. Individuals who record their interest may be contacted directly with recruitment materials in the future for research studies (submitted as independent IRB protocols) related to their being a user of the app.

3.2 Inclusion criteria

Participants are eligible for inclusion if they are:

- Adults at least 18 years of age;

3.3 Exclusion criteria

- None

4 Subject Enrollment

4.1. Procedures for Recruitment/Eligibility Screening

Mass General Brigham participants will be invited to enroll through channels that are developed through collaboration with the Chief Information Officer and Incident Command leadership. This may include:

- direct email through the Partners Broadcast system;
- Rally for Research with Partners, an online platform that supports collaboration between the public and the research community;
- Direct links to the Rally Page for HCW in the COVID Pass employee symptom clearance app in use by MGB/Partners employees before entering work.
- direct email through the nursing and physician leadership after obtaining the necessary approvals through institutional processes.

Examples of digital communication, Rally with Partners communication, and physical letter communication templates have been attached.

In COVID Pass, after completing daily attestations, the app will provide a link to Rally pages for ongoing COVID studies that may be of interest to HCW. Our Rally page will be among these studies. Participants will need to voluntarily navigate to the Rally page (e.g. they are not automatically redirected) by clicking on a link for learning more about potential studies like ours or direct links to our study. We anticipate that our study may recruit people through this feature for as long as the COVID pass is in use and allows use of this feature, per Institutional Leadership recommendations. HCW who are interested in joining our study will go to the Rally page and register interest as is standard for Rally use. Registered individuals will be contacted with the IRB-approved HCW specific email (see attachments).

NHS, NHS II, NHS III, HPFS and GUTS participants will be contacted by email by the Principal Investigators of each cohort: Meir Stampfer (NHS), Walter Willett and Heather Eliassen (NHS II), Jorge Chavarro (NHS III), Jaime Hart (GUTS) and Walter Willett (HPFS). See attached example recruitment and reminder letter templates. The individual cohort name and appropriate PI name will be replaced in each case for each cohort.

CPS3 participants will be recruited by email (see attached email letter) by the Principal Investigator of CPS3, Alpa Patel, and be instructed to go through the standard research consent process and disclose their affiliation with CPS3.

“CoV at risk” patients will be told about this study as a part of their participation in additional protocols (e.g. 2020P000804). These other studies will be modified as necessary to include discussion of the application for collection of symptom data as appropriate and integrate this into their workflows/recruitment materials.

Members of the general public or other cohorts may also be recruited to the study. Specific recruitment approaches from other studies will either occur through amendment in local IRB protocols or through IRB review to this protocol. Participants in other studies that are recruited in real-time by study coordinators/research nurses may also be told about the app

They will introduce the possibility of participating in this study as another optional study to consider after individuals consent to their protocol

As a part of evolving regulations in the Respiratory Illness Clinics (RIC) at Mass General Brigham, paper products are not allowed in the RIC to limit transmission of COVID-19. Therefore, we cannot provide instruction sheets to these participants for them to take and download the app later. Leadership in the RIC have recommended that we place a laminated 8-1/2x11" sign that is capable of being disinfected in rooms where research nurses are consenting CoV at risk patients to protocols intending to use the app (see "RIC Instruction Sheet"). Once they agree to participate in these other studies, Research Nurses will point out these signs with instructions of how to download the app. Research nurse staffing has also pointed out that there is a concern that some participants may not have a phone on them. In the absence of being able to hand out a paper card with take-home instructions, the research staff of other studies may provide a direct download link for the app in email communications with their participants. The exact language for this will be included in other IRB protocols as a part of their approved email communication language.

Rally for Research is also public facing and may recruit members of the public who see this app. Any person's use of the app and subsequent data collection and ultimate consent to participate in this study will be captured via the app consent process. Anyone may voluntarily associate themselves with other research studies at MGH or other institutions in the app (like all Nurses' Health Studies/HPFS/GUTS participants do). In addition, it is possible that individuals participating in these other studies, may find our study on their own and will be given the option to self-associate with other existing studies at Mass General Brigham. This data will be treated as Personal Identifying Information and will not be shared between studies, but investigators wishing to abstract data on their study participants will be allowed access to this information to link participants back, after approval by their own IRB to collect this data (secondary use of already collected data).

4.2 Procedures for Obtaining Informed Consent

Within the app will be an informed consent page and option to digitally record consent. The consent is also being offered in Spanish. The process for and Informed Consent text is fully described in the attachment "Informed Consent Process" In brief, participants will consent on the app prior to providing responses to questions about symptoms, diagnosis of COVID-19, clinical outcomes, use of PPE. These consents will be initially collected and recorded by Zoe Global Ltd and copies provided to MGH. All participants, regardless of recruitment source, will go through this informed consent process which has been approved by the PHRC IRB.

4.3. Procedures for participation termination or withdrawal

Participants can withdraw their consent at any time during the course of the study without any reason by no longer providing data to the app.

5 Study Procedures

5.1 Recruitment and baseline enrollment

Participants will be directed to enroll through the COVID symptom tracker / COVID symptom study app, as described. Within the app, at the time of enrollment after signing informed consent within the document, each participant will provide their email address, and basic demographic information including age, sex, and zip code, and basic information on health status. They will be asked if they are an employee of Mass General Brigham or a member of the NHS, NHS II, NHS III, HPFS or GUTS cohort, or are being followed at Mass General Brigham, or other research study. If an app user participates in multiple research studies, they can select all studies they are a part of. Participants who previously could not identify with multiple studies, are now able to update their profile. If they are an employee of Mass General Brigham or a member of the NHS, NHS II, NHS III, HPFS, or CPS3 cohorts, they will have the option to provide their employee number or study ID number to facilitate downstream linkage. They will also be provided the option to provide their name. They will also be asked if they are a health professional, if so what type, and if they are currently in direct patient care roles.

5.2. Symptom tracker

At baseline, participants will be asked to provide basic demographic and health data and information on their baseline health status. They will then be asked to report if they have been tested for COVID-19 and if so, the results, as well as if they have been well over the last 24 hours. They will also be asked about symptoms. If they test positive or exhibit symptoms, they will be directed to additional questions regarding quarantine and treatment. They will also be queried about their use of PPE and work-related stress and anxiety. App users will be able to update their location (zip code) if traveling/relocating to another area. The app will track symptoms on a daily basis through July 1, 2021 based on best estimates of the duration of the current COVID-19 response crisis. However, this protocol may be terminated early if investigators deem that that crisis has receded, and a critical mass of participants are no longer logging data. Similarly, the protocol may be extended if the crisis persists beyond July 1, 2021.

Participants will also receive a one-time COVID Diet Quality and Habits Questionnaire, a supplemental questionnaire that collects additional data on changes in diet, alcohol consumption, the use of supplements and physical activity. This questionnaire will be administered through the app and the users will have the option of skipping this questionnaire if they don't want to complete it. On average it should take about 15 minutes to complete the questionnaire.

This app is built on the digital backbone of Zoe's PREDICT app, previously reviewed and approved by Partners RISO as a part of Partners IRB Protocol 2018P002078.

5.3. Data return

We will execute a data usage agreement with Zoe (submitted in parallel as the initial IRB application as Partners 2020A004627). In brief, data will be captured by Zoe Ltd and returned to Mass General Brigham for data analysis using secure Partners Enterprise Dropbox. This will include deidentified data for all users in the COVID Symptom Study as well as identified data as outlined below. This process for data sharing with Zoe Global Ltd was reviewed and approved previously by Partners RISO office as a part of Partners IRB Protocol 2018P002078. Within the Mass General Brigham population, we will associate the

data collected in the app with internal Mass General Brigham employee databases or with data collected in other protocols (e.g. Partners 2020P000804). Within the NHS, NHS II, NHS III, HPFS, and GUTS population. Principal Investigators will link COVID-19 data by name, zip code, or cohort ID with their cohort databases for further analysis. After transfer to the MGH teams, Zoe will strip the database of names, cohort/employee IDs, or email for use in any aggregate analyses of COVID-19 incidence with other academic centers that have contributed data. Zoe will not share any name, age, IDs, or emails with any other entities other than the Mass General Brigham PIs. No other data currently maintained in the Mass General Brigham population or in the NHS, NHS II, NHS III, HPFS, GUTS or CPS3 will be shared with Zoe without additional human subjects approval or data usage agreements. Data returned to MGH will only additionally be stored and analyzed within Partners approved platforms for human subjects research data including the Channing Division of Network Medicine and Harvard FAS/Odyssey computing clusters that comply with federal, HIPAA, and Partners regulations related to protection of human data, including but not limited to encryption and two-factor authentication. Access to these systems is granted on a per user basis. Accounts are frequently reviewed for access need. Access to data is granted on an as needed basis per the P.I. permission. Channing Servers reside inside the Partners Needham Datacenter as do all Channing Data Storage devices with the exception of the data archive which is located at Simches MGH Datacenter for distancing purposes.

Data on HPFS and CPS3 participants will be handled as all participants data is and stored on Zoe Global Ltd servers until transfer to MGH as described above. Data will be shared with the Harvard T.H. Chan School of Public Health or the American Cancer Society only once Data Use Sharing agreements are in place and only according to these agreements for linkage back with their CPS3 datasets. Exported data will only include personal identifiers for members who disclosed they were a part of the CPS3 cohort.

Deidentified data relevant to the proposed analyses that have been collected by external investigators (e.g. those not included as investigators on this protocol) related to COVID-19 exposures, outcomes, symptoms, vaccination, and disease trajectory/clinical outcomes may be shared with CORSET investigators via additional data use agreements. This protocol will cover the secondary use of that data as it pertains to COVID-related analyses.

Deidentified data collected by CORSET, including data collected by the COVID Symptom Tracker / COVID Symptom Study app may be included in public databases in the future according to federal requirements related to funding sources.

6 Statistical Analysis

Given the urgent nature of the COVID-19 pandemic, there are not available numbers regarding the potential number of eligible participants within the Mass General Brigham. We estimate contacting approximately 10,000 NHS, 51,000 NHS II, 30,500 NHS III, 20,000 GUTS, 20,000 HPFS participants. "CoV at risk" protocols are currently open to enrollment. External site enrollment has no specific target, but is expected to exceed 50,000 people.

Statistical analyses will be based on traditional methods examining exposures to outcome.

Dr. Christina Astley of Boston Children's hospital will be assisting the team with analyzing data from the app.

7 Risks and Discomforts

Participants will provide their health information to COVID Symptom Tracker / COVID Symptom Study app based on consent provided in the Terms and Conditions outlined in the app (attached). This study has been designed to minimize participant burden while allowing for robust and repeated data collection necessary to obtain adequate data to assess the dynamic and brief trajectory between symptom onset, COVID-19 diagnosis, and PPE utilization. All data entered by participants is voluntary and participants can discontinue data entry at any time. They may also contact us to have their data removed from the database. No additional personal health information provided to Mass General Brigham or through their participation in the GUTS, HPFS and all Harvard Nurses' Health studies, or other protocols will be provided to Zoe.

8 Potential Benefits

There is no specific individual health benefit expected as a direct result of participating in this study. However, participants will provide vital data that will help the general public in improving our understanding of the clinical symptoms and trajectory to illness associated with COVID-19. This may inform models related to disease incidence and patterns of spread that are critical to optimize resource allocation for testing, treatment, and utilization of PPE.

9 Monitoring and Quality Assurance

We do not anticipate safety issues. The principal investigator, in collaboration with data managers at Zoe and Kings College will monitor data quality and integrity, review subject enrollment, and address any subject-related issues that might arise.

10 References

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11 Signatures

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