Remote Population Surveillance for COVID-19 in the Fenland Cohort:

Fenland COVID-19 sub-study protocol
Kirsten, Rennie
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Study Investigators

Fenland COVID-19 Study investigators:

Prof Nick Wareham[1]: Study Chief Investigator
Dr Kirsten Rennie[1]
Dr Albert Koulman[1]
Dr Effrossyni Gkrania-Klotsas [1]
Dr Carina Tyrrell[1]
Dr Vickie Braithwaite[1]
Dr Golam Khandaker[2]
Dr Ben Perry[2]

Fenland Study Investigators:

Prof Simon Griffin[1]
Prof Nita Forouhi[1]
Dr Soren Brage[1]
Claudia Langenberg[1]
[1] MRC Epidemiology Unit, University of Cambridge
[2] Department of Psychiatry, University of Cambridge

Study Co-ordinators

Richard Salisbury
Hannah Pettet

MRC Epidemiology Unit, University of Cambridge

Sponsor

University of Cambridge

Ethics

South West Cornwall and Plymouth Research Ethics Committee (20/SW/0100; 30 June 2020)

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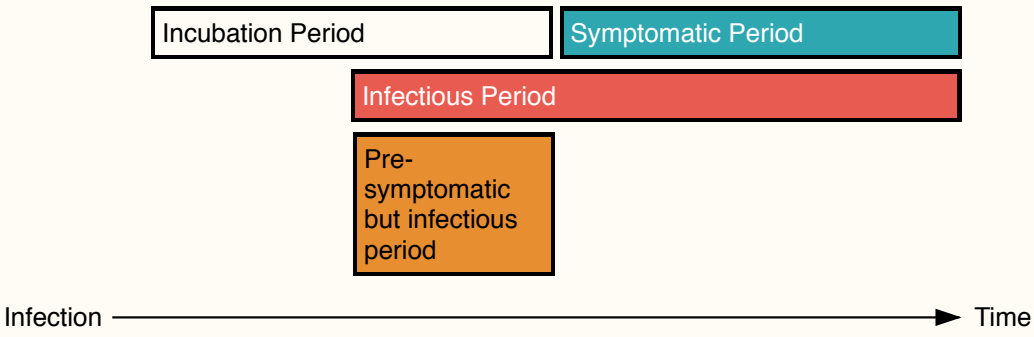
1.0 Background

The rapid spread of coronavirus disease 2019 (COVID-19) is an unprecedented global public health emergency. There is an urgent need for accurate epidemiological data to understand how to mitigate the pandemic and support decision-making over the coming months. Until recently, the focus of attention has been on organising healthcare resources to manage the immediate consequences of COVID-19 infection. However, now that lockdown is being gradually released in the UK, other issues come to the fore, particularly the avoidance of further waves of infection.

One key unknown is the extent of previous infection in the wider community because antigen testing in symptomatic individuals outside of the hospital setting was limited during the first wave. As yet, there have been few population-based studies that have measured antibodies to determine who has previously been affected. Estimates from one sero-prevalence survey in the USA (1), suggest that the under-ascertainment of cases based on confirmed cases in hospital is considerable and that as many as one hundred times as many people have actually been infected than have currently been reported. The proportion of the population who have had COVID-19 and who are thus likely to be immune to re-infection is unknown, but it is important to quantify this as part of the pandemic management. Currently, no antibody test has been rolled out for community testing. Population-based cohort studies, such as the Fenland study, in which individuals are randomly selected from a universal population-based sampling frame, are well placed to contribute to the estimation of sero-prevalence as results from such studies are generalisable.

Now that the first surge in cases is diminishing, a major challenge will be to determine how to monitor the emergence of new cases in the population to be able to rapidly institute contact tracing and isolation to avoid additional waves of infection. A particular concern is the possibility that individuals may be infected, and therefore likely to transmit the disease to others, in the pre-symptomatic phase. This asymptomatic transmission has been estimated to be a significant contribution to the overall spread of COVID-19 (2).



Symptom trackers have been widely deployed in the UK and may help identify individuals with classical symptoms who can seek medical attention and get early testing. For those who test positive, the UK Government has recently reinstated contact tracing and isolation for contacts who test positive, which was abandoned when the number of new cases surged. This strategy is a key element of efforts to diminish the likelihood of secondary outbreaks recurring in the population as restrictions are lifted (3,4). However, there is a potential gap in the strategy between the detection of infected symptomatic individuals and the establishment of track and trace approaches. One of the aims of this project is seeking to improve the detection of early pre-symptomatic COVID-19 infection using a set of signs and/or digital biomarkers plus self-report health indicators.

Understanding the pre-symptomatic phase and identifying infected individuals at this stage will ultimately enable better management with earlier diagnosis, isolation and contact tracing. The set of signs and digital biomarkers that could form part of a predictive test of the pre-symptomatic phase would need to be highly sensitive as the consequences of a false negative test would be high, i.e. individuals who were truly infected would be missed. Ideally the test would also be highly specific, but if a trade-off were necessary, a lower specificity could be tolerated since the consequence of being a false positive would be an unnecessary definitive diagnostic test for the viral antigen. Since this definitive diagnostic test could be done rapidly now that testing facilities have been scaled up sufficiently, the consequences for that individual and any contacts of being a false positive would be minimised.

The imposition of social distancing measures in the UK has had the desired effect of flattening the curve and avoiding a surge in cases that could have overwhelmed the NHS. However,

there have been other impacts on health and health-related behaviours. It is unknown how social distancing measures have impacted on health-related behaviours such as diet and physical activity behaviour, nor has the impact of the pandemic itself and of the disease mitigation strategies of wellbeing and mental health been quantified. Although data sources from providers of wearable technologies have suggested declines in physical activity following the restrictions, such data are from select groups who may well be at the upper end of the general population distribution of physical activity (5). From a public health perspective, it is important to quantify the impact of the social distancing measures on physical activity levels across the whole population since the impact may be influenced by the initial level of usual activity and could well be socially patterned. It would also be important to quantify whether any impact on physical activity levels was lasting or not, since small shifts in population-level physical activity, if maintained, could have sizable impacts on long-term health outcomes. The same considerations apply to dietary behaviour.

Fortunately, the serious health consequences of COVID-19 are relatively uncommon but there is likely to be significant heterogeneity in the risk of those adverse outcomes between individuals. Although this is in part explained by age, sex and co-morbidities, it is likely that there are other factors that influence prognosis, the study of which may contribute to understanding the progression of the disease and to the identification of therapeutic strategies. Within individual cohort studies, the number of affected individuals will be relatively small, making the precision with which disease progression and prognosis can be studied low in any single study. Thus, there is a need to combine data and undertake multi-cohort analyses to have sufficient statistical precision to examine COVID-19 progression and prognosis by different risk profiles.

2.0 Study objectives

The Fenland COVID-19 study has the following objectives:

1. To deploy established and approved methods of serological testing at scale to determine the prevalence of previous infection with COVID-19 in a population-based study of well-characterised individuals in Cambridgeshire
2. Within a sub-sample of the cohort, to understand the natural history of COVID-19 from the pre-symptomatic to the symptomatic stages by tracking digital markers, symptom logs and other self-report health indicators in this population
3. Within a sub-sample of the cohort, to develop a pre-symptomatic prediction model for the early detection of COVID-19 infection using signs, digital biomarkers and other self-report health indicators and results from serological testing

4. To evaluate the impact of the COVID-19 national restrictions including social distancing measures on health-related behaviours, mental health and well-being.
5. To contribute data and results to multi-cohort analyses to study the prognosis of COVID-19 infection according to different risk factor profiles.

3.0 Why the Fenland Cohort?

The Fenland cohort study has followed 12,435 participants from 2005 to 2020 to investigate the interaction between environmental and genetic factors in determining obesity, type 2 diabetes and related metabolic disorders. Participants born between 1950 and 1975 were originally recruited from GP registers in Cambridgeshire as a population-based sampling frame. This area of Eastern England has had a relatively low number of confirmed cases of COVID-19; ~1000 out of total population of ~650,000 in Cambridgeshire, although the true figure is likely to be at least 10-fold if not 100-fold higher.

This cohort is unique in its population-based sampling frame which has generated a study broadly representative of the population of the county of this age, not least because it employed three original testing centres and thus recruited individuals living in the cities of Ely and Cambridge and the town of Wisbech as well as the surrounding rural areas. Thus, the study has broad socio-economic representativeness in contrast to other studies which sample individuals based on convenience and thus not representative of the general population.

It is also unique in the extent and depth of the previous characterisation of the health and lifestyle of the participants including detailed quantitative metabolic trait outcomes linked to glycaemia, insulin resistance and the overall level and regional distribution of body fat, physiological assessment of hepatic steatosis, cardio-respiratory fitness and resting metabolic rate and in-depth assessment of dietary and physical activity behaviours plus genetics, metabolomics and proteomics. Individuals in the cohort have previously consented to linkage of their data to routine health records and this creates an opportunity to link the cohort to primary and secondary health care data.

4.0 Recruitment of participants

The University of Cambridge MRC Epidemiology Unit will approach all 12,110 participants recruited to the Fenland study who are known to be living and who have not been lost to follow-up. They will be invited, either by email, telephone call, by letter or SMS message from July 2020, to join a 6-month Fenland sub-study of remote population monitoring for COVID-19 with

the patient information sheet and consent form delivered on-line. Participants will be consented to join this overall remote population monitoring study. Separate consent also will be obtained by the MRC Epidemiology Unit for those participating in the sub-study involving the collection of information through a smartphone application (App).

All individuals who agree to participate will be asked to indicate whether they have a smartphone (firmware iOS version 13.0 or above / Android 6.0 or above) or not. Those without a smartphone will be invited to participate in the study by provision of information through on-line questionnaires only.

5.0 Measurements

5.1 Serological testing

After consent to participate in the study has been obtained, a testing kit will be delivered to all participants to enable them to collect a blood sample for serology testing using dried blood spot (DBS) technology for analysis using established antibody tests. Participants will be asked to repeat the test at 3-monthly intervals during the study period.

The use of DBS represents a novel and clinically relevant method for remote testing for COVID-19. The advantages are the ability for participants to provide a sample without needing to visit a clinical setting or be visited at home by a healthcare professional. The method itself offers minimal invasiveness, minimal blood volume required, simplified shipping and storage compared to a blood sample (6). DBS technology has routinely been used for serological testing for other conditions including such as HIV, Malaria and other infectious diseases (7–9).

5.1.1 Blood draw method

Participants who consent to participate will be sent a DBS sample collection kit. These will be delivered to the participants complying with Category B (UN3373) regulations. Two sample collection kit options are being considered. Our preferred option is to use a OneDraw device. We report below the steps that we are taking to ensure that use of this novel technology is feasible in this context. If, for whatever reason, this proves not to be the case, we will use a standard finger prick to obtain a dry blood spot sample.

The OneDraw blood collection device is intended to collect capillary blood from the upper arm of adults onto filter (matrix) paper within the collection device. This is a single-use, sterile, whole blood specimen collection method to provide a stabilised sample that can readily be transported in the sealed cartridge transport sleeve.

The device incorporates lancets securely enclosed in the device. The device applies a vacuum to the subject's skin and the lancets make two small incisions on the surface of the skin. The vacuum draws capillary blood to the surface of the skin and into the device, where it is deposited into a closed cartridge containing two stabilisation matrices. The matrices absorb and stabilise the blood and analytes in the blood. The cartridge can then be easily removed from the device and placed in a transport sleeve for posting. In Drawbridge Health clinical studies, the median draw time was 3 minutes and 58 seconds (range 1-10 minutes) with draw time depending on participant characteristics such as hydration status and capillary bed factors. Participants who have used OneDraw compared with finger-prick blood collection performed on them using a lancet have rated the device to be less painful using a pain rating score of 0-10 (OneDraw mean 1.02 versus fingerprick mean 2.60 in 260 participants) and 80% preferred using the device compared with fingerprick (12%) and venepuncture (8%) respectively. This makes it a desirable choice for use in a population-based study with repeated blood collection measures. The choice of blood draw method and other aspects of the study have been discussed with the Fenland Study participant panel. They concluded that they were more comfortable with the use of this device than a finger-prick test as they considered it to be more user friendly for those who may be adverse to needles or squeamish about seeing blood.

OneDraw is currently licenced for use by a healthcare professional for HbA1c testing where it has shown excellent inter-operator and lot-to-lot precision (mean CV 1.2% (range 0.1-4.8%); 1.1% (range 0%-3.6%); respectively). We have discussed the use of OneDraw with the MHRA who have approved the use of the device to obtain a sample for COVID-19 antibodies in this study. We are currently conducting studies to validate its use for COVID-19 serological testing against routine venous blood samples within Cambridge University Hospital Trust. Further, we are conducting a feasibility study for its use in adults without the need of a healthcare professional present to ensure that the device can be operated effectively. Preliminary work has been conducted by Drawbridge Health for instructions of use without a healthcare professional and we are revising these user instructions for this study and testing their validity in a group of participants as part of the feasibility study.

If OneDraw is not feasible to use, a DBS sample collection kit using a CE marked device under Article 22 of the Medical Device Regulation 2017/745 will be used. This will contain relevant materials and instructions to allow participants to complete and submit DBS samples including safety lancet devices, standard Guthrie card (with filter paper for blood spot collection), an alcohol wipe, cleaning wipe, plaster, freepost return packaging for the DBS and an instruction leaflet on how to take the sample. An instruction leaflet and related video will be developed and tested before deployment.

Participants will be provided with rigid plastic sharps boxes to place the used OneDraw devices/lancets after each blood sample taken. At the end of the study, the participants will be asked to return the sharp box to participating pharmacies for safe disposal or to arrange a clinical disposal collection from the local council.

The DBS sample will be placed in a leak-proof receptacle and a leak-proof secondary packaging into appropriate outer packaging pre-paid to be posted back to the MRC Epidemiology Unit on the day of collection. Clear instructions will be provided only to provide a DBS sample and mail them on Monday-Thursday (to ensure receipt when the laboratory is open), and to adhere to social isolation guidelines and social distancing measures that may be in place when mailing them.

5.1.2 Laboratory testing

The samples will be tested for SARS-CoV-2 IgG antibodies using an updated protocol for the test is a semi-quantitative assay developed by Mologic and marketed by Omega Diagnostics. This is an ELISA kit for detection of IgG antibodies to SARS-CoV-2 in human serum or plasma, as an aid to diagnosis of active or recent COVID-19 infection in symptomatic and asymptomatic individuals.

Diluted serum/plasma samples are incubated with COVID-19 antigens immobilised on microtitre wells. After washing away unbound serum/plasma components, anti-human IgG conjugated to horseradish peroxidase is added to the wells, and this binds to surface-bound antibodies in the second incubation. Unbound conjugate is removed by washing, and a solution containing 3,3',5,5'-tetramethylbenzidine (TMB) and enzyme substrate is added to indicate antibody binding. Addition of Stop Solution terminates the reaction and provides the

appropriate pH for colour development. The optical densities of the cut-off control, positive control and samples are measured using a microplate reader at 450nm wavelength.

DBS samples will be stored for potential future analyses for other COVID-19 antibody tests and for COVID-19 related biomarkers.

5.2 Collection of web-based data from all participants

All individuals who agree to participate will be invited to use webforms to provide information regarding behaviour quantification including diet and physical activity (PA) measures. These will be the validated Recent Physical Activity Questionnaire (RPAQ) and Food Frequency Questionnaire (FFQ) previously used in the Fenland cohort. The only adjustment that has been made is to the FFQ where the timeframe has been adjusted from 12-months to 4-weeks in line with the RPAQ for the purposes of this study. Participants will be asked to complete both of these questionnaires every 3 months.

Participants without a suitable smartphone will be asked to use webforms to provide COVID-19 symptoms and history (as baseline and on a monthly basis), as well as weight measures (via self-reported weight in light clothing on a monthly basis using their own weighing scales). Table 1 details the scheduling of these measures. The webforms will be accessed using a unique identifier specific to each participant, and the information collected will be transferred to a secure encrypted database. The information cannot be viewed or retrieved by the webform and can only be accessed by the study team working within the secure research drive from the encrypted database.

Within the initial questionnaire, those with a compatible smartphone will be invited to participate in a sub-study involving an App to collect more detailed information including logging of COVID-19 symptoms, mental health, vital signs, etc. on a more frequent basis.

Table 1: Frequency of web-based data collection

Module	Measures	Measurement frequency
All participants		
Behaviours	Diet (FFQ) and physical activity (RPAQ)	At baseline and every 3 months
Only participants without smartphones		
Weight measures	Self-reported weight	At baseline and at monthly intervals
COVID-19 questionnaire		At baseline and at monthly intervals

5.3 Smartphone App data

Those participants with an appropriate smartphone will be separately consented by MRC Epidemiology Unit and invited to provide information through an App being developed by Huma (https://huma.com/ previously Medopad) specifically for this study. The participant information sheet (PIS) and consent form will be delivered on-line by the MRC Epidemiology Unit, and once consented, participants in this sub-study will be sent a link to download the App as well as an unique identifier to join. The PIS for this sub-study summarises the research and explains how the information collected will be used. It also describes how the University and Huma will share data.

The participant will access different modules within the App which provide the facility to take different measurements at different frequencies. Hardware will be provided to make the measurements respecting social distancing rules in operation at the time of delivery. Participants will be asked to input the measurement results from these devices into the App.

There will be the following modules in the App;

1. COVID-19 baseline questionnaire including risk factors and changes in physical activity and diet behaviour since before COVID-19 government restrictions
2. COVID-19 symptom checker
3. COVID-19 signs and digital biomarkers; resting heart rate (HR), oximetry and body temperature
4. mental health
5. monthly COVID-19 risk factor update questionnaire
6. medication and supplement use

7. body weight
8. physical activity and diet behaviour changes
9. digital measure of physical activity.

These modules are described in more detail below and the frequency of testing is given in Table 2. Participants will receive prompts on their phones to remind them to complete the necessary measures. Participants will also be able to set their own time reminders for completion of individual modules. The App content will be tested with the Fenland participant panel to ensure the questions, instructions and accompanying Learn/About sections are clear and un-ambiguous for the study participants before the App sub-study starts.

Table 2: Frequency of measurements in the Smartphone App sub-study

Module	**Measurement**	**Frequency**		
		3x week	**Monthly**	**Other**
1. Baseline COVID-19				At baseline only
2. COVID-19 symptoms		x		
3.COVID-19 digital biomarkers	Resting heart rate, oximetry, and temperature	x		
4. Mental health	PHQ-8, GAD-7 and PSS		x	
5. COVID-19 risk factor update			x	
6. Medication and supplement use				Participants will be prompted monthly to access this module if there are changes to record
7. Body Weight	Self-reported body weight		x	
8. Change in PA and diet			x	alternate weeks to the mental health module
9. Digital PA				Continuous

5.3.1 Baseline COVID-19 module

The module will collect information for risk factors for infection relevant to the ongoing data collection at baseline including:

- Pregnancy status
- Has had a COVID-19 test and if yes, if result was positive, negative or are waiting for results
- Smoking and vaping status, length of smoking status and how many cigarettes smoked
- Self-reported health quality
- Presence of relevant pre-existing co-morbidities e.g. diabetes
- Family history of disease
- Allergy history
- Prompt to collect medication and supplement use
- Previous COVID-19 symptom experience and date symptoms started
- Living situation
- How are you feeling now
- Recent changes in diet and physical activity by domain relative to pre-COVID-19 government restrictions

Participants will be asked to update a sub-set of questions from this questionnaire monthly for changes in these risk factors [see section 5.3.5 below].

5.3.2 COVID-19 symptom module

Participants will be asked to record symptoms three times a week throughout the study period to give sufficient data for the pre-symptomatic objective. Participants will be asked to select the symptoms they are experiencing from the list given and if no symptoms to select “next” to confirm no symptoms and skip these questions.

5.3.3 COVID-19 digital biomarker modules

A repeated set of signs or digital biomarkers will be collected in a standardised manner three times a week at the same time as the symptom recording to determine whether changes in these biomarkers are associated with pre-symptomatic or asymptomatic phases of the infection. The biomarkers have been selected on the basis of reports from early studies in pre-symptomatic signs and also symptoms associated with COVID-19. For example, a drop-in oxygen levels have been reported in patients before the onset of symptoms.

Participants will be provided with a digital thermometer and pulse oximeter to measure their temperature and oxygen saturation respectively. Participants will be asked to take the measurements and then manually enter the result into the App. Participants will be asked to measure their resting heart rate by placing their finger over the camera on their smartphone. This measure takes approximately 60 seconds and will provide estimates of respiratory rate and heart rate variability as well as the measure of resting heart rate.

For reasons of practicality and to control diurnal variation, participants will be asked to take all measurements first thing in the morning after awaking. Participants will be able to set specific time reminders for it to accommodate their daily schedule. It is anticipated that this would take less than 6 minutes per measurement session.

All individuals who agree to participate will be sent a digital pulse oximeter (ChoiceMMed MD300C29) and a sublingual thermometer (Genial Digital Thermometer T12L). The App will be programmed to provide prompts for when these measures need to be taken and participants will be able to set specific time reminders for the measurements. The field team within the MRC Epidemiology Unit will create online Standard Operating Procedures (SOPs) and videos for participants to access online to aid them in taking the measurements consistently with these devices.

5.3.4 Mental health modules

Measures of depression, anxiety and perceived stress will be made throughout the study period.

Depression will be measured using the Patient health questionnaire (PHQ-8), a validated self-report tool widely used to assess depression in community and clinical samples including UK primary care (10). An online version of this questionnaire was administered to over 150,000 participants in the UK Biobank cohort. PHQ-8 assesses depressive symptoms occurring in the past two weeks.

PHQ-8 Scoring: Each item is rated as not present (0), several days (1), more than half the days (2), and nearly every day (3), giving a total depression symptom score of 0-24. Using

established thresholds, the score can provide categorical outcome of depression. The full PHQ-9 score ≥10 has a sensitivity of 88% and a specificity of 88% for major depression.
Anxiety will be measured using the Generalised Anxiety Disorder questionnaire (GAD-7), a validated self-report tool widely used to assess anxiety in community and clinical samples (11). This questionnaire was administered online to over 150,000 participants in the UK Biobank cohort. GAD-7 Scoring: Similar to PHQ-9, GAD-7 assesses symptoms occurring in the past two weeks; item rating is also identical (total score 0-21). A score of ≥10 identifies generalized anxiety disorder (GAD) with sensitivity 89%, specificity 82%.

Perceived stress will be measured using the Perceived Stress Scale (PSS), which is one of the most widely used validated self-report tools for assessing psychological stress in community and clinical samples (12). PSS assesses stress over the past month. Items are designed to measure how unpredictable, uncontrollable, and overloaded respondents find their lives. Higher PSS scores are associated with increased depression, poor control of blood sugar levels in diabetes patients, and risk of infections.

PSS Scoring: PSS scores are obtained by reversing responses (e.g., 0 = 4, 1 = 3, 2 = 2, 3 = 1 & 4 = 0) to the four positively stated items (items 4, 5, 7, & 8) and then summing across all 10 items. A short 4-item scale can be made from questions 2, 4, 5 and 10 of the PSS 10-item scale.

Frequency of Measurement: PHQ-8, GAD-7 and PSS will be administered monthly.

5.3.5 COVID-19 risk factor update module

This module will be used to track changes in the risk factors for COVID-19 and prompted to access the medication and supplement use module if any changes have occurred since the previous update.

5.3.6 Medication and supplement use module

Participants will be asked to complete all medications and supplements taken at baseline and to record any changes to their medication or nutrition/non-nutrition supplement, dose and frequency of administration on a monthly basis.

5.3.7 Body weight module

During the study period, there could be changes to participant's body weight status. Participants will be asked to self-report their body weight in light clothing on a monthly basis using the same weighing scales.

5.3.8 Changes in physical activity and diet module

Simple questions of recent changes in diet and physical activity by domain will be included in the last 7 days as a frame of reference. Participants will be prompted to complete these questions every month. Participants will complete FFQ and RPAQ questionnaires every 3 months via the webforms in Section 5.2.

5.3.9 Digital measure of physical activity

Participants will be asked whether they consent to sharing the movement recorded in their smartphones to be used as part of this study. For those with iOS firmware, step counts are automatically stored on the phone in the Apple Health App and for those with Android firmware, the Google Fit app will need to be installed if it has not been installed already. From both platforms, the highest possible resolution data will be exported every fortnight and stored on central servers for later processing, whilst the App will store and display the last 7 days of hourly step counts.

6.0 Length of study

The study is currently designed for serology testing and digital biomarker and symptom collection for 6 months from July 2020 in the period in which lockdown is gradually released. However, due to the uncertainty of the spread or containment of the COVID-19 pandemic in the second half of 2020, we will inform participants that it is possible we will ask them if they are willing to continue with the study beyond the 6-month period if this is deemed to be informative for public health. We would confirm within the PIS and consent forms that participants understand the timelines of this study may be extended. In such case, an ethical amendment will be sought.

7.0 Participant information and advice

The App contains an information section in each module and a "Learn/About" area that participants can access for current advice on COVID-19 and mental health. This provides information and links to relevant external websites for information. The study website will

include the same information. The clinical team have contributed and reviewed the content and ensured all the content is in line with NHS and PHE guidelines.

7.1 COVID-19 information

In the App and on the study website, we will provide the following advice:

If you are concerned about your health please use the NHS 111 service (NHS 111 website - https://111.nhs.uk/covid-19/) or contact your doctor. In an emergency, call 999. For further information on COVID-19 visit https://www.nhs.uk/conditions/coronavirus-covid-19/ or https://www.gov.uk/coronavirus.

We will not follow up participants who indicate any COVID-19 related symptoms. We will monitor PHE and governmental guidance and update our recommendations to participants either in the App or on our website accordingly. It is likely that PHE guidance will evolve and may include the introduction of Apps to help track outbreaks. In order to avoid confusion, our research team will not provide advice to individuals with possible COVID-19, who will be followed up by the regular systems.

Participants will naturally be interested in the results of their antibody tests. However, at this early stage of the roll-out of a newly developed antibody measurement, we feel that provision of results back to participants could result in confusion. Our study materials make it very clear that any antibody tests have the potential for false negative and positive test results. Thus, a positive result does not confirm definitively that someone has had COVID-19 infection and similarly a negative test result does not prove that they have not. We also do not know whether a positive antibody test means that someone has immunity from repeat infection with COVID-19. There is thus a risk that provision of information about antibody status back to individuals will result to greater risk-taking behaviour is someone who is positive assumes that they are immune and therefore we will not provide these results back to participants until the end of the study. By this point, the antibody test method using DBS will have been fully validated against venous blood draw samples and finger-prick samples in a separate study with known COVID-19 positive and negative samples to confirm evidence-based cut-offs for previous COVID-19 infection. Furthermore, the antibody test results for an individual can be put into context because serial measurements over the study period will be available. Finally, it will avoid the problem of individuals changing their behaviour over the study period in response to an

individual test result. This will be done in an 'opt-in' way so that participants who would rather not know their antibody test results do not receive results.

7.2 Mental health

The measurement instrument PHQ-8 may identify individuals with high levels of depressive symptoms consistent with moderately severe or severe depression. In the Learn section we will provide the following advice:

If you are concerned about your mental wellbeing please visit (https://www.nhs.uk/conditions/stress-anxiety-depression/low-mood-and-depression/) or contact your doctor. In an emergency, call 999.

8.0 Qualitative sub-study

Once the data collection is complete, we will conduct qualitative in-depth semi-structured interviews with 20-30 of the participants recruited into the Smartphone App sub-study and those who declined to participate in the App sub-study and therefore were enrolled into the main study. Participants recruited into the Smartphone App sub-study will be double sampled as participants will provide the richest experiences of using the app and taking part in the study only. Participants then will be purposively sampled to include a range of different ages, genders, educational attainment, and differing levels of participation.

Interviews will take place via zoom or telephone depending on the preference of the participant. These will be audio recorded with participant consent, then transcribed and anonymised; additional notes may be taken by the researcher during the interviews. Questions will focus on eliciting the factors that helped participants engage in the study, the usability of the Smartphone Application, and if there were any barriers to joining the Smartphone Application part of the study and remaining in the study until completion. Questions will be worded dependent on their level of participation. Questions for those who declined to take part will focus on their reasons for not participating. We hope to use this research to inform future studies in the MRC Epidemiology Unit. The interview guide has been reviewed by the PPI panel before being finalised.

9.0 Reporting of adverse events

The Fenland study is run by the MRC Epidemiology Unit through its Cambridge Epidemiology and Trials Unit (CETU) which is accredited by UKCRC. All adverse events will be recorded by

the CETU using its standard procedures. Given the observational nature of this study, it is highly unlikely that there will be any SUSARs.

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