Serological testing for COVID-19 in ALSPAC (G0/G1)

Lay title: COVID-19 home antibody testing study

Study Protocol

Key study information	
Protocol version/date	v2.1 01/08/2020
Ethics Committee Reference	Ref number 110264 (approved 21 July 2020) ALSPAC Ethics and Law Committee (ALEC), University of Bristol
Sponsor	University of Bristol
Funder	Supported by core ALSPAC funding, The UK Medical Research Council and Wellcome (Grant ref: 217065/Z/19/Z) and the University of Bristol provide core support for ALSPAC. and, Wellcome Trust Investigator grant support for PI Nic Timpson.
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ALSPAC Reference	B3566

Introduction

Serological testing for COVID-19 in ALSPAC (G0/G1) (Lay title: COVID-19 home antibody testing study) will invite ALSPAC participants who have previously completed COVID-19 questionnaire to complete a home antibody test.

This is part of a collaborative effort across UK cohorts to collect serological data on past infection status. In particular a set of cohorts have been selected to provide information on prevalence across 4 important areas of variation – ethnicity, age, socio-economic status and geography. (Please note each cohort is running their studies separately and are have their own protocol and route to ethics approval).

Background

Our outcome measure is lateral flow test derived evidence of positive antibody response to COVID-19 given knowledge of the sensitivity and specificity of the Fortress Home Test kit. This is relevant given our objectives in this work.

The broad objective of this work (and contribution to the work already underway by REACT and UKBiobank) is the collection of epidemiological-grade biological test data for COVID-19 infection across a series of select studies across the UK which provide information on prevalence across 4 main axes of variation important for developing mitigation strategy relevant evidence (age, geography, socio-economic position, ethnicity/ancestry) and with the ability to assess this against information on existing comorbidities. Our aim is to have results that are policy useful in a short period of time reflecting the burden of COVID-19 retrospectively across these important gradients, but also to allow for the effective planning of research into the nature of the events before, during and after infection. This can only be done in longitudinal studies with retrospective data and that are continuing (and part of funded examinations into COVID-19 studies) in the future. The Avon Longitudinal Study of Parents and Children (ALSPAC) is the first of 5 studies to have DHSC procured Fortress lateral flow tests available to do this.

Investigator Team and study location

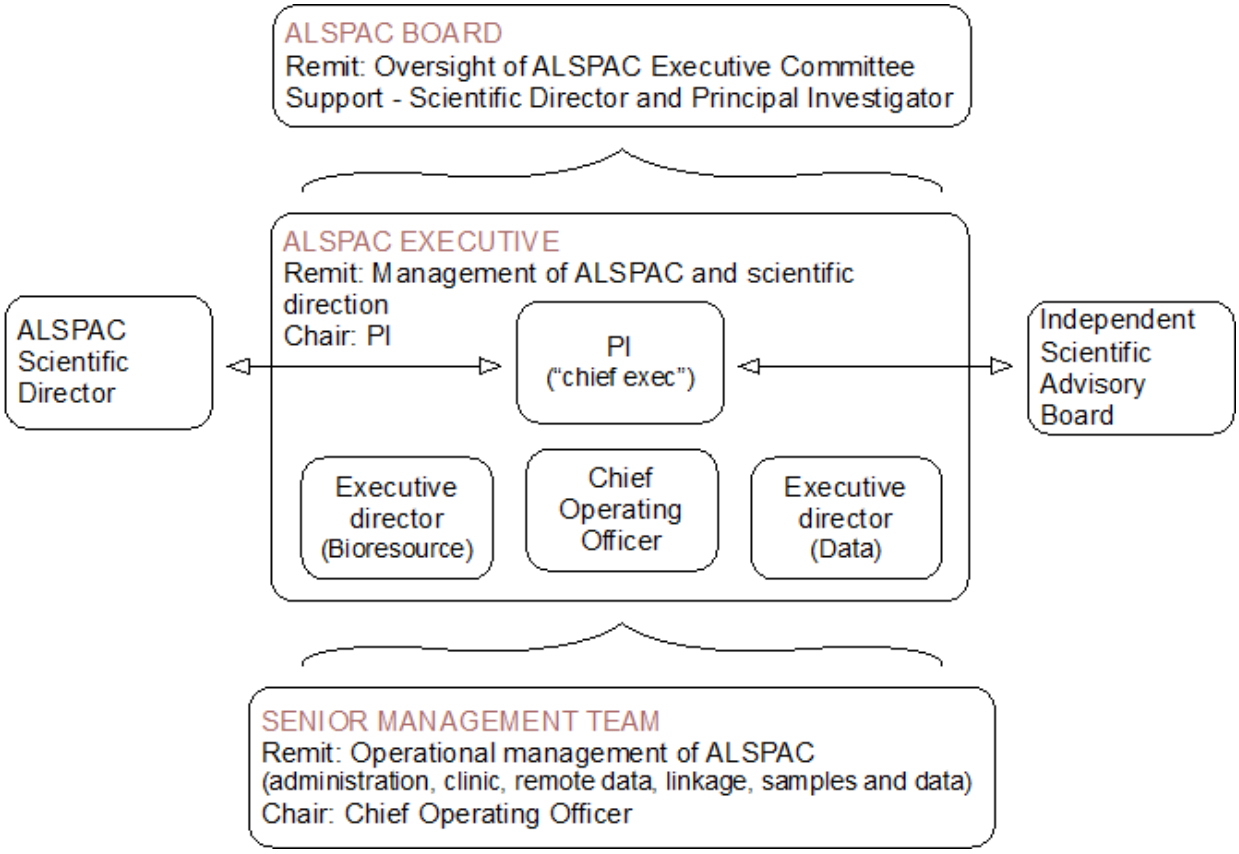
ALSPAC resides in the Population Health Science division of the Bristol Medical School in the Faculty of Health Sciences. The University of Bristol is committed to population health science and ALSPAC - evidenced by maintained support and major initiatives such as the Population Health Science Institute (www.bristol.ac.uk/research/institutes/population-health). The ALSPAC PI (Prof Nicholas Timpson) is ultimately responsible for all parts of ALSPAC activity including this specific project which has been planned in collaboration with the REACT study, but led internally. The ALSPAC Executive (Chaired by the PI and composed of the PI, the Chief Operating Officer of the study (Lynn Molloy) and Executive Directors for bioresource and data (Dr Sue Ring and Dr Kate Northstone)) have co-led the planning of this specific project. This work also sits within the broader remit of the Wellcome Trust supported Longitudinal Population Studies COVID-19 secretariat and steering group – details of which can be seen here http://www.bristol.ac.uk/alspac/researchers/wellcome-covid-19/. This work has received oversight by the ALSPAC Board (Chair Prof Matt Hickman), the Scientific Director (Prof Davey Smith) and the Independent Scientific Advisory Board (Non-CoI/independent chair Professor Tim Frayling – University of Exeter).

ALSPAC Study Management

ALSPAC has an effective an efficient team of professional service staff who will integrate with the leads for this specific research. A *Senior Management Team* is responsible for day to day activity required to deliver ALSPAC objectives. Information concerning the job of running ALSPAC and this

work flows from this group to the *ALSPAC Executive* weekly. The ALSPAC Executive is effectively held to account by the *ALSPAC Board* and questions regarding governance, science or strategy can be referred to one or more of the ALSPAC Board, The *Independent Scientific Advisory Board* or the Scientific Director.

Figure 1. ALSPAC management structure



The structure of ALSPAC management has been set up to specifically enable clear and effective flow of information from the operating ALSPAC teams (clinic/data/linkage/lab/operation and administration) through the Senior Management Team (SMT) to the ALSPAC Executive.

Aims and Objectives

Our objective is to coordinate the collection of epidemiological-grade biological test data using (home-based serological testing kits) for COVID-19 infection across a series of select studies across the UK. This aims to complement existing studies based on COVID-19 serology and provide information on prevalence across 4 main axes of variation important for developing mitigation strategy relevant evidence (age, geography, socio-economic position, ethnicity/ancestry) and with the ability to assess this against information on existing co-morbidities.

In ALSPAC specifically we will **firstly** address prevalence across those of differing age range in the South West of the UK. We now know (UKBiobank preliminary data – **Figure 1**) that there is likely to be both a detectable number and age gradient of infection exposure in the South West (reflecting a broader trend in the UK) and would be able to provide an important estimate in our sample of parents and "children of the 90s" participants.

Figure 2. Seroprevalence estimates for the South West UK – UKBiobank

Counts:

<30 - 149

30-39 - 172

40-49 - 168

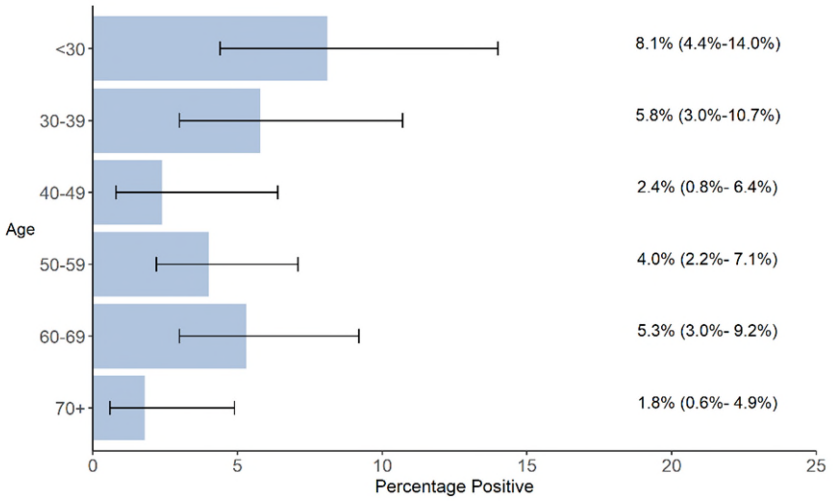
50-59 - 297

60-69 - 244

70+ - 218

Total UKBiobank

n (South West)=1,248



Source data - UK Biobank SARS-CoV-2 Serology Study (https://www.ukbiobank.ac.uk/wp-content/uploads/2020/07/UKB_SerologyStudy_month1_report.pdf, specific data release – Personal communication - Naomi Allen, Senior Epidemiologist – UKBiobank.

Secondly, we will assess the extent of disparity between symptoms and infection (i.e. the importance of covariables/morbidities for the presentation of events). Through our COVID-19 questionnaires (https://wellcomeopenresearch.org/articles/5-127, http://www.bristol.ac.uk/alspac/covid-19/) we now have a collection of material stretching from October 2019 to present reflecting self-reported symptoms. These have been cross-referenced to those used and analysed by the COVID-19 Symptom Tracker (https://covid.joinzoe.com/) and have been mobilised into a Wellcome Trust supported, standardised, questionnaire which is supported by a dedicated secretariat (http://www.bristol.ac.uk/alspac/researchers/wellcome-covid-19/). A key objective to the analysis of new serological data will be the cross-referencing of questionnaire/symptom based estimates of prevalence and case status with overall estimates from home based testing.

Thirdly, as a long-standing prospective birth cohort initiated in the early 1990s and still ongoing, ALSPAC is able to bring together new COVID-19 specific data (here serological data) with record linkage, symptoms (association with data from new questionnaires - https://wellcomeopenresearch.org/articles/5-127, http://www.bristol.ac.uk/alspac/covid-19/), severity, and retrospective data on life course health (www.bristol.ac.uk/alspac). The infrastructure to align testing to questionnaire data collection is already present and is able to ask questions as to factors important for susceptibility, severity, outcomes and for the long term importance of the condition and how this relates (or doesn't) with mitigation as a uniform change unlike infection. This platform has already been exploited in the design of new science and forms the basis of the inclusion of ALSPAC in the, now awarded, examination of convalescent cases over the coming year. In this instance, the availability of love course and deep phenotypic data on active participants provides an important chance to capture information on factors that impact COVID-19 immunological responses. Part of this work will be contingent on locating those once infected by COVID-19 and whilst no one measure is perfect for this, the composite collection of serology, questionnaire and record linkage is likely to be the best approach for detecting and locating cases – symptomatic and non-symptomatic.

All of these three outcomes require serological data to be viable and sit in the context of (i) the REACT study which has already and effectively deployed the proposed test here, (ii) the ALSPAC participant and ethical and legal committees giving approval for this work and (iii) a time pressure given the likely waning performance of the specific tests here which are reliant on the persistence of the IgG response after infection (Seow et al, Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection https://doi.org/10.1101/2020.07.09.20148429, Long et al Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections https://www.nature.com/articles/s41591-020-0965-6, Wajnberg et al SARS-CoV-2 infection induces robust, neutralizing antibody responses that are stable for at least three months https://doi.org/10.1101/2020.07.14.20151126).

Methods

This approach will use the same testing approach as the existing REACT-2 study (https://www.reactstudy.org) and consequently, methods are based directly on this successful investigation who have recruited and tested over 100,000 participants. The study team have been kind enough to share expertise and documentation. It is noted in Appendix 1 where documents are adaptations of the REACT study documents.

Recruitment

Eligibility and exclusion criteria

Inclusion:

ALSPAC G0, G1 and G1 partners who responded 'Yes' to the question in the 'Learning more about COVID-19' questionnaire asking if they would be happy for us to send information about research involving testing for COVID-19.

OR

ALSPAC G0, G1 and G1 partners who only completed the first COVID-19 questionnaire and have not had the opportunity to let us know about these types of further research.

Exclusions:

Any participant who responded 'No' to the question in 'Learning more about COVID-19' questionnaire asking if they would be happy for us to send information about research involving testing for COVID-19.

Participants at increased risk of bleeding (participants will be asked at the consenting stage to self-declare any issues related to bleeding disorders)

Participants outside the UK. Costs and timescales for postage outside the UK make this impractical.

Participants flagged as deceased, withdrawn, no to questionnaires and no to contact.

Methods

Participants meeting the Eligibility Criteria described above will be invited to take part via email (See Appendix I). The initial invite provides information about the study and ask them to consent online if they wish to take part. (see Data Collection – Consent section for further details on the consent process).

If a response is not received with ~3 days a reminder email will be sent (See Appendix I).

A timeline, included the recruitment phase, is shown in Appendix II.

Sample Size

Based on the inclusion criteria above, there are 5,830 participants who responded Yes to follow-up (G0 – 3254, G1 – 2493, G1 partners - 83 G1 partners)

Plus, an additional 1345 participants who completed the first COVID-19 questionnaire but not the second.

Study power

Throughout the planning of this work we have worked with Professor Peter Diggle (who has also advised the REACT team) with respect to the assessment of whether the sampling frame we can provide is viable for our analytical questions (objectives). Is it clear that the linkage of data from regional and national cohorts represents, in combination with results from other current or prospective national-level COVID-19 studies, presents an opportunity to conduct a wide range of analyses covering various aspects of COVID-19 epidemiology. Relevant to ALSPAC, however, the assessment of the performance of data collected is can be presented in terms of a single sample being able to recruit 4-5000 participants (based on deploying 5000 home kits to those consented from a pool of more than 7000 COVID-19 questionnaire completers).

For the purpose of illustration, we considered the performance of this sample (which is adequately sized for estimating prevalence) for estimating the association of BMI with local prevalence (one of our main objectives and the most power demanding). In the context of the sample and the performance of the test being used here, the precision of estimates depends on the range of the spatial correlation in prevalence, increasing with the range of the spatial correlation. The table below shows estimates of standard error for the relationship between local prevalence (assumed here to be approximately 5%) and body mass index (BMI) for different prevalence correlation range (a key metric of prevalence variation). We find that not only is there a general improvement in precision with increasing prevalence correlation range, but also a low magnitude of error given the likely prevalence of COVID-19 in the ALSPAC sample.

Prevalence correlation range (km)	**0**	**3**	**10**
SE (BMI/prevalence association or beta)	0.026	0.019	0.016

The rate limiting factor to the sampling frame in this case is the completion of ALSPAC COVID-19 questionnaire(s) which determine the pool of active participants who are both aware of the work and are active in this part of the study. These are all participants who have valid contact details and who, following their participation in the COVID-19 data collection since May, can be contacted for the open and PIS led consenting process for this home based testing. This is the maximum sample size available for this work and will provide greatest available analytical power for our main objectives. As mentioned above, this sample is adequately powered for this work which is – given the sampling frame – unique and contributory. It is important to maximise sample size for this work not only to provide the best estimates for main analyses, but also to allow for maximised followup sample size given inevitable attrition over time (as seen in all cohorts followed longitudinally).

Data Collection

Consent

Participants will be sent a suite of information describing the study, what is involved and how to take part. These include a Participant Information Sheet, Instruction booklet and Instructional video (See

Appendix I for full documents). They are also given details of the ALSPAC participation team to contact if they have further queries.

If, after reading the documents, participants wish to take part they are directed to an online consent form (See Appendix I) hosted on REDCap (https://projectredcap.org/). There are several declarations to ensure that they have read and understood the study documentation and what is required of them.

At this stage we are also collecting address details to ensure that we can deliver the kits to the correct address.

Note: the following question will be added to the consent form to screen out participants with coagulation disorders (unable to update the attachment in Appendix I at this time)

> "Do you have an increased risk of bleeding (for example taking blood thinners such as Warfarin, or any medical condition that would mean a self-delivered finger prick with a lancet would not be advisable)?
>
> 1. Yes
> 2. No
> 3. Don't know

If answer is Yes participant will receive the following message.

> We cannot send you an antibody test, as there are risks associated with this test for people who have an increased risk of bleeding. Thank you for your interest."

Mailing of antibody kits

Following confirmation of consent participants address will be securely transferred to a third-party printing/mailing house (covered by a Data Processing Agreement). The antibody testing kits, instruction booklet and cover letter (See Appendix I for full documents) will be collated and set out as per the timeline in Appendix II.

If test results are not uploaded within ~3 days a reminder email will be sent (See Appendix I)

Taking the test

Participants are supplied with full instruction to complete a COVID-19 home antibody test (See Appendix I).

The kit (assembled by Una Health) consists of:

- One Orientgene test cassette in foil pouch (pouch contains test cassette and small pipette)
- One 1mL dropper bottle of buffer
- One Owen Mumford Unistik touch lancet, 23g, 2mm, yellow
- One Owen Mumford Unistik touch lancet, 21g, 2m, orange
- One sterile wipe
- One sterile cotton wool ball
- One small plaster.

In summary particpants will use the lancet to obtain a drop of blood. The blood is applied to the test cassettee and buffer is added. Once developed, 10-15 min, lines indicated the test results. These are

described in the instruction leaflet. Particpants are insturcted to take a photo of the test result to submit online

Questionnaire and submitting results

The cover letter and reminder email will contain details of the online form for submitting test results (See Appendix 1) hosted on REDCap (https://projectredcap.org/). Participants are first presented with a brief set of questions on symptom history and previous tests they may have completed. The is followed by questions on completion of the COVID-19 home antibody test, any problems encountered and asking them to report the results against a list of possible results.

We are also asking participants to upload a photo of the test result to allow for validation of the interpretation of the result. Submitting this photo is optional.

Lastly there is a section on complete the study, this includes submitting their Date of Birth, the opportunity to submit a free text comment and opt out of a Prize Draw.

Compensation

There are no individual level incentive/compensation vouchers for this study. Participants completing before the deadline will be entered into prize draw to win one of 3 £100 vouchers.

Safety and Safeguarding

Some ALSPAC participants have additional requirements or specific circumstances that require us to take a more personalised or sensitive approach. These participants are identified within our contact management system – termed safeguarding. This system enables us to shield them from inappropriate contact and to provide them with the support necessary to continue to play an active part in the study. For example, requirement for large print questionnaire, access requirements to attend a clinic. Safeguarded participants will be reviewed on a case by case basis by the participation team and a decision taken on whether it is appropriate to include them.

Adverse Events

University of Bristol has registered this study with the Yellow Card scheme. Contact details for the ALSPAC (Children of the 90s) team is included in all study documentation to participants. If a participant reports any adverse events to us via phone/email these will be reported to MHRA via the Yellow Card scheme either by ALSPAC study staff and/or we will give the participant details to report themselves via https://yellowcard.mhra.gov.uk/. Manufacturer (Fortress Diagnostics Ltd) will be informed of any device specific AEs.

Data Management

Online data collection will be managed by ALSPAC data team staff on University of Bristol servers.

To access the online data collection each participant has a unique security token in addition to a username/password. The link emailed to the participant contains their specific security token. When the participant clicks on the link, it maps the security token to the participant and logs them in. This allows access to the questionnaire and for data to be submitted. This has worked well for several years and mechanisms have been built in to minimise the risk of someone other than the participant getting hold of their details.

Each section has its own submit button, once each one has been clicked own the relevant section is completed and cannot be accessed again. Participants cannot go back to sections once they have been completed (and submitted); this reduces the risk associated with someone else being able to access the online data collection (i.e. if an email was shared/hacked and the unique linked obtained),

if someone else did access it they would not find any information only blank sections of the form. The following statement is included “Once you have clicked 'Submit' you will not be able to return to that section or edit your answers.”

The consent data will be collected separately to the COVID-19 Home antibody test questionnaire under a different identifier. The consent form asks for the participants’ address to send the COVID-19 Home antibody test to. The address information will be regularly exported and deleted from the server. The address data will be compared to the administrative address on file and updated where the participant has requested this. The addresses will be stored in a secure file area accessible to only a subset of ALSPAC staff. The addresses will be encrypted and shared securely with Gemini West who will be mailing the test kits to participants.

The questionnaire that participants are asked to complete asks for the participant to upload an image of their test result. A script will strip the images of any additional information (metadata) that they main contain (such as location data) to leave just the image itself.

All data collected will be deposited in the ALSPAC data repository and data access requests will be processed via the ALSPAC executive Committee, as per the ALSPAC Access Policy.

Analysis Plan

Following the timeline in Appendix II, results from all participants undertaking home testing will arrive back via the online data collection system in a little over one week. Securely linked on return to ALSPAC, both images and results from cassettes will be first processed and validated against one another. An existing collaboration with the REACT study will look into the utility of automation at this step, but with only ~5000 results, a manual check of results against image data will be undertaken. Following this, the existing ALSPAC COVID-19 analysis team will be deployed to undertake the three main objective analyses – prevalence, association with questionnaire symptom report and lifecourse data alignment and analysis. The third and last immediate activity will then focus on the development of probabilistic assignment of case status within the cohort of those with questionnaire data, electronic health record data and a serological result.

Publication policy

Throughout the period of ALSPAC COVID-19 questionnaire data collection, three main pathways to publication have been maintained. For descriptive data and rapid release, ALSPAC researchers have been working closely with HDRUK (Clara Fennessy) to provide regular insights into data collected which is pertinent to COVID-19. There have been 4 contributions so far to the now bi-weekly SAGE report through this route and descriptive data based on new serological data will be presented in this way if it is appropriate. Secondly, ALSPAC researchers have been able to access and make descriptions of data and new analyses available in the Wellcome Open publication stream and specifically in the dedicated ALSPAC gateway found at this online, peer reviewed, publication site (https://wellcomeopenresearch.org/gateways/alspac). Lastly, all new research and work on the proposed data collected immediately following this collection (and made available through our usual channels www.bristol.ac.uk/researchers) can be published via conventional routes having submitted a publication checklist to the ALSPAC executive. This follows the ALSPAC standing publication policy, details of which can be seen here http://www.bristol.ac.uk/alspac/researchers/publishyourresearch/.

We also feel it important to mention that we maintain open communication and updates with our participants throughout the research process. Through numerous media types, the ALSPAC

communications team continue to summarise and describe the footprint of ALSPAC research (http://www.bristol.ac.uk/alspac/covid-19/). This includes usual social media routes and looks to acknowledge the diversity of the study. This is an important addition for a volunteer participant group like ALSPAC as it provides an important route to disseminate results which are aimed specifically at population-based or epidemiological findings.

Ethical Approval

Favourable opinion for this study has been given by ALSPAC Ethics and Law Committee (ALEC) at University of Bristol (http://www.bristol.ac.uk/alspac/researchers/research-ethics/). Ref Number 110264.

Appendix

I. Draft documents

Title	Full text	Adapted from REACT study?
1. Email Invite v0.1	 1. Email Invite v0.1.docx	No
2. B3566_PIS_v0.1	 B3566_PIS_v1.1_updates.doc  B3566_PIS_v1.1_updates_clean.doc	Yes Track changes showing update from Protocol v1.0 documents.
3. Instruction Booklet	 Bristol Orientgene Antibody Instruction \	Yes
4. Instructional Video v1.0	 4. Instructional Video v1.0.docx	Yes
5. Email Reminder v0.1	 5. Email Reminder v0.1.docx	No
6. Consent Form	 Covid_Antibody_Consent.pdf Plus additional screening question related to coagulation disorders will be included.	No
7. Cover Letter	 7. Cover Letter v0.1.docx	No

8. Email Test Reminder	8. Email Test Reminder v0.1.docx	No
9. Questionnaire and Results	Covid_Antibody_Questionnaire.pdf Covid_Antibody_Image_Upload.pdf Covid_Antibody_Completing_Questionnaire	Q7-13 – use in REACT study

II. Timeline

Timeline below is based on an anticipated start date of 20 July 2020.

Green boxes are contact points with participants