



Study Title: Incidence of COVID-19 (SARS-CoV-2) infection and prevalence of immunity to COVID-19 (SARS-CoV-2) in the UK general population as assessed through repeated cross-sectional household surveys with additional serial sampling and longitudinal follow-up - an Office for National Statistics Survey

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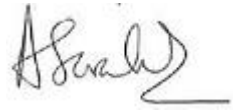
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The investigators have no potential conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, Health Research Authority, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

TABLE OF CONTENTS

1.	KEY CONTACTS.....	7
2.	LAY SUMMARY.....	10
3.	SYNOPSIS	13
4.	ABBREVIATIONS.....	16
5.	BACKGROUND AND RATIONALE.....	17
6.	OBJECTIVES AND OUTCOME MEASURES.....	21
7.	STUDY DESIGN	24
8.	PARTICIPANT IDENTIFICATION	33
8.1.	Study Participants.....	33
8.2.	Inclusion Criteria.....	33
8.3.	Exclusion Criteria	33
8.4.	Blood sampling	33
8.5.	Co-enrolment	33
9.	PROTOCOL PROCEDURES	35
9.1.	Recruitment.....	39
9.1.1.	Registration, consent and home visits through protocol v15.0	40
9.1.2.	Registration, consent and study assessments from protocol v16.0.....	40
9.2.	Screening and Eligibility Assessment.....	42
9.3.	Informed Consent.....	42
9.3.1.	Transition to extended period of data linkage in protocol v14.0.....	44
9.4.	Enrolment.....	45
9.4.1.	Post enrolment recruitment into providing monthly blood samples and extending follow-up in those providing blood samples to April 2022 (from protocol v7.0).....	45
9.4.2.	Post enrolment recruitment into extending follow-up in those only providing swab samples to April 2022 (from protocol v9.1)	46
9.4.3.	Post enrolment recruitment into providing monthly blood samples for those aged under 16 years (from protocol v11.1 (initial phase), v13.1 (main phase))	46
9.4.4.	Post enrolment transition from study worker home visits (protocol v16.0)	50
9.4.4.1.	Collection of quantitative and qualitative data for process evaluation during the transition	54
9.5.	Blinding and code-breaking.....	56
9.6.	Description of study intervention(s), comparators and study procedures (clinical).....	56
9.6.1.	Description of study procedure(s).....	56

9.7.	Baseline Assessments	59
9.8.	Subsequent Visits	59
9.9.	Sample Handling.....	60
9.9.1	Sample handling for study purposes	60
9.9.2	Return of results	61
9.10.	Early Discontinuation/Withdrawal of Participants.....	62
9.11.	Definition of End of Study	63
10.	SAFETY REPORTING	64
10.1.	Reporting Procedures for Serious Adverse Events.....	64
11.	STATISTICS AND ANALYSIS.....	65
11.1.	Statistical Analysis Plan (SAP)	65
11.2.	Description of the Statistical Methods.....	65
11.3.	Sample Size Determination	66
11.4.	Analysis populations.....	69
11.5.	Decision points	70
11.6.	Stopping rules.....	70
11.7.	The Level of Statistical Significance	70
11.8.	Procedure for Accounting for Missing, Unused, and Spurious Data.....	70
11.9.	Procedures for Reporting any Deviation(s) from the Original Statistical Plan.....	71
12.	DATA MANAGEMENT	72
12.1.	Source Data	73
12.2.	Access to Data	73
12.3.	Data Recording and Record Keeping.....	74
13.	QUALITY ASSURANCE PROCEDURES	75
13.1.	Risk assessment.....	75
13.2.	Study monitoring.....	75
13.3.	Study Committees	75
14.	PROTOCOL DEVIATIONS	76
15.	SERIOUS BREACHES	77
16.	ETHICAL AND REGULATORY CONSIDERATIONS.....	78
16.1.	Declaration of Helsinki.....	78
16.2.	Guidelines for Good Clinical Practice	78
16.3.	Approvals.....	78
16.4.	Other Ethical Considerations.....	78

16.5.	Reporting	78
16.6.	Transparency in Research.....	78
16.7.	Participant Confidentiality.....	79
16.8.	Expenses and Benefits	79
17.	FINANCE AND INSURANCE	81
17.1.	Funding	81
17.2.	Insurance	81
17.3.	Contractual arrangements	81
18.	PUBLICATION POLICY.....	82
19.	DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY	82
20.	ARCHIVING.....	82
21.	REFERENCES	83
22.	APPENDIX I: PARTICIPANT FLOW AND MATERIALS.....	85
23.	APPENDIX II: AMENDMENT HISTORY	98

TABLE OF TABLES

Table 1	Original planned recruitment of households in England* †	29
Table 2	Schedule of investigations for each new cohort	37

TABLE OF FIGURES

Figure 1	Repeated cross sectional survey design through protocol v15.0.....	30
Figure 2	Serial sampling frequency and tests.....	31
Figure 3	Flow diagram	35
Figure 4	Illustration of the impact of staged approach to transition a theoretical 100,000 participants on the number of completed tests per week.....	53
Figure 5	Impact of sample size on precision for various estimates of prevalence	68
Figure 6	Participant types.....	85
Figure 7	Study enrolment – new participants	86
Figure 8	New participants – worked example of time from first consent in each household	87
Figure 9	Communications flow - new participants.....	88
Figure 10	Participant journey – online questionnaire, postal return of samples	89
Figure 11	Participant journey – online questionnaire, courier return of samples.....	90
Figure 12	Participant journey – telephone questionnaire, postal return of samples	91
Figure 13	Participant journey – telephone questionnaire, courier return of samples	92
Figure 14	Test kit logistics flow	93
Figure 15	Questionnaire completion flow.....	94
Figure 16	Existing participants – opt in	95

Figure 17 Existing participants – worked example of time from first opt in each household 96
Figure 18 Communications flow - existing participants 97

1. KEY CONTACTS

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Committees	A study management group will provide oversight, including investigators named above as representatives of participating organisations, a representative of the Devolved Administrations, the Chief Investigator, and with an independent Chair.
Website	https://www.ndm.ox.ac.uk/covid-19/covid-19-infection-survey Results available on: https://www.ndm.ox.ac.uk/covid-19/covid-19-infection-survey /results

2. LAY SUMMARY

The COVID-19 pandemic has had, and continues to have, a profound impact across the UK. This study aims to find out how many people are still getting the infection and how many are likely to have had the infection, even if they haven't realised it at the time. This is particularly important as more people have multiple vaccinations against COVID-19. Although the vaccines work very well, they are not 100% protective, and it is necessary to monitor how well they work in the real-world.

One way to find out whether a person has an infection is to directly look for the microbe in their nose and throat. The main test used to diagnose COVID-19 uses a swab taken from someone's nose and throat. Once an individual has recovered from the infection, the virus cannot be found any longer. One way the body fights infections like COVID-19 is by producing small particles in the blood called "antibodies". It takes 2-3 weeks for the body to make enough of these antibodies to fight the infection. But once a person recovers, they still stay in the blood at low levels and give some protection against future infection. Getting vaccinated against COVID-19 is another way that people can get antibodies that can protect them against getting COVID-19. So scientists try to measure levels of both the virus and these antibodies to work out who has COVID-19 now (with or without symptoms) and who has had it in the past, or has developed antibodies against it after getting vaccinated.

In this study we want to find out how many people of different ages across the UK have COVID-19 over time, particularly as people go back to work or school and as more and more people get multiple vaccinations, and how many have had COVID-19 in the past. We do this by testing for the virus in the nose and throat of people and by measuring levels of antibody in the blood. We also want to find out how many people have COVID-19 with symptoms or without knowing they have the infection because they don't have any symptoms. We want to do this in a group of people that reflects the population of the UK – so a range of ages and places where people live. We will ask everyone aged 2 years or older in each randomly selected household to have a nose and throat swab, and for those aged 12 years and older to answer a few short questions (parents/carers will answer for younger children). Up to protocol v16.0, this will be done at a home visit undertaken by a trained individual; from protocol v16.0 we will move to posting sample kits to participants, with questions being completed online or over the telephone. Those aged 12 years and older can take their own swabs using self-swabbing kits, and parents/carers will use the same kits to take swabs from their children aged 2-11 years. Self-swabbing is to reduce the risk to the study workers at home visits. We will ask adults aged 16 years or older from a randomly selected subset of these enrolled households to also give a sample of blood. At the start of the study, this was taken from a vein by a trained nurse, phlebotomist or healthcare assistant, but later it was taken by a fingerprick by the participant themselves, so that all visits could happen without study workers and participants needing to come into close contact (<2m) or using posted sample kits. Where an adult in the household is already giving blood, from September 2021 we also asked children and young people aged 8-15 years whether they would be happy to give a sample of blood (plus those aged 5-7 years in an initial pilot in October 2021 only). We will take swabs from all households, whether anyone is reporting symptoms or not. At the start of the study, we did not take blood from a vein from anyone in a household where someone had symptoms compatible with COVID-19 infection, or was currently self-isolating or shielding, to make sure that study workers stayed at least 2m away from them at all times. Using a fingerprick done by each participant means that study staff can maintain recommended distancing at all study visits (or sample kits will be posted from protocol v16.0), so blood can be collected by fingerprick at every visit, including in households where anyone has symptoms or is currently isolating/shielding. The choice of a minimum of 2m for home visits was to reduce risk as much

as possible, based on the fact that prevalence may vary over time as different COVID-19 variants emerge and in practice, transmission risk is directly related to actual distance rather than suddenly changing at 1m or 2m, with the choice of thresholds for other activities based on pragmatic as well as scientific justifications. When conducting home visits, the trained study workers will use all the recommended precautions to protect themselves and everyone in the household from getting the virus.

Up to protocol v15.0, we will ask people who have this first home visit whether they would be happy to have the same kind of visit and nose and throat swabs repeatedly, every week for the first month (swab and questionnaire only, no blood draw), and then every month from their first visit until the study ends (including monthly blood draws for those with blood taken originally). Over 95% of participants chose to have repeated monthly visits, and so from protocol v16.0, we will ask everyone joining the study to do the tests and complete the questionnaires every week for the first month and then every month until the study ends. Participants are free to withdraw from the study at any time. This is to find out how rates of infection and immunity change over time in individual people, and whether they can get the virus again with or without having symptoms.

In April 2020, we began by inviting 20,000 households to participate with an assumed 50% opt-in rate, and a target enrolment of 10,000 households (2,500 per week over around one month). Around 2,000 of these households (500 per week) were asked to give blood. After this, in Phase II we invited new groups of around 5,000 households in England, around 500 households in Wales and around 500 households in Northern Ireland approximately every week, targeting recruitment of around 2,500, 250 and 250 new households per week respectively (total 3,000 households per week; assuming 50% consent rate; numbers approached will be increased if consent rate is lower to achieve the target enrolment). A mean of 2.1 individuals were recruited per household. In order to achieve a cohort of ~150,000 individuals sampled at least once a fortnight from October 2020 onwards when the winter season of respiratory infections starts, and monitoring for a possible “second wave” of infections was critical, from the end of July 2020 we scaled this up to inviting new groups of around 18,000 households in England, around 1,800 households in Wales, up to 1,800 households in Northern Ireland and around 4,500 households in Scotland approximately every week, targeting recruitment of around 9,000, 900, up to 900, and 2,250 new households per week respectively (total around 13,000 households per week; assuming 50% consent rate; numbers approached to be increased if consent rate is lower to achieve the target enrolment). **Ultimately the swab target from October 2020 to March 2022 inclusive was to achieve ~150,000 individuals with swab test results at least every fortnight in England, ~9,000 in Wales, ~5,000 in Northern Ireland and ~15,000 in Scotland (~179,000 total across the UK)** (absolute numbers reflecting the relative size of the underlying populations). To January 2021, we approached 10-20% of invited households to also give a sample of blood from enrolment. This is to find out how the number of people infected at any one time, the levels of immunity to COVID-19, and the rates of infection with and without symptoms, are changing across the country. From February 2021, we asked a representative sample of those already recruited to the study but only giving swabs to also give blood at their monthly visits, and for everyone giving blood samples to stay in the study until April 2022. **The blood target from April 2021 to March 2022 inclusive was to achieve up to ~125,500 adults 16 years and older with blood test results every month in England, and up to ~7,500, ~4,500 and ~12,500 per month in Wales, Northern Ireland and Scotland (~150,000 in total across the UK)** (absolute numbers reflecting the relative size of the underlying populations). This is to monitor how vaccination affects immunity at both the population and the individual level. For those aged 8-15 years, the target from December 2021 to

March 2022 inclusive was to achieve ~3,600 blood test results from older children/adolescents every month.

From April 2021 to March 2022, we maintained the targets for both swab results per fortnight and blood results per month above by

- inviting everyone who was currently active in the study to remain on monthly follow-up visits (additional consent)
- inviting additional households who were only giving swabs at their monthly visits to additionally give blood by fingerprick at these visits (additional consent)
- until January 2022 continuing to enrol new households into the study and have follow-up visits in order to replace participants who stop follow-up or supplement current numbers in order to maintain targets despite possible missed visits.

From April 2022 onwards (protocol v16.0), we will invite existing participants to transition from study worker home visits to posted sample kits and completing questionnaires online/by telephone. From April 2022, the swab targets will be reduced by ~25% and the blood targets by ~20% (i.e. retaining a greater percentage of those giving blood in order to maintain as much precision to monitor declines in antibodies as possible), to achieve the following:

- Swab target: up to ~227,300 swab samples taken from individuals 2 years and older every 28 days in England, ~15,650 in Wales, ~10,050 in Northern Ireland and ~23,200 in Scotland (~276,200 total across the UK every 28 days, ~300,000 swab samples in total across the UK per month)
- Blood target: up to ~90,850 blood samples taken from individuals 8 years and older every 28 days in England, ~6,300 in Wales, ~4,150 in Northern Ireland and ~9,200 in Scotland (~110,500 in total across the UK every 28 days, ~120,000 blood samples in total across the UK per month)

Reductions are proportionately less in Wales and Northern Ireland in order to maintain power within these countries, and proportionately more in England to meet the overall reductions. The goal is to transition sufficiently large numbers of existing participants to maintain these targets through 31 March 2023. However, if necessary new households will also be enrolled into the study up to 31 January 2023 and have follow-up assessments (using posted sample kits and completing questionnaires online/by telephone from enrolment) in order to replace participants who stop follow-up or supplement current numbers in order to maintain targets.

The information gained from the survey will help scientists and the government work out how to manage the pandemic better moving forwards and protect the health system from being overwhelmed.

3. SYNOPSIS

Study Title	Incidence of COVID-19 (SARS-CoV-2) infection and prevalence of immunity to COVID-19 (SARS-CoV-2) in the UK general population as assessed through repeated cross-sectional household surveys with additional serial sampling and longitudinal follow-up
Internal ref. no. / short title	COVID-19 Infection Survey
Study registration	ISRCTN21086382
Sponsor	University of Oxford Joint Research Office Boundary Brook House Churchill Drive, Headington, Oxford OX3 7GB
Funder	UK Health Security Agency, previously the Department of Health and Social Care The Welsh Government (in-kind contribution) The Department of Health on behalf of the Northern Ireland Government (in-kind contribution) The Scottish Government (in-kind contribution) The Northern Ireland Statistics and Research Agency (in-kind contribution) Office for National Statistics (in-kind contribution) University of Oxford (in-kind contribution through the Biomedical Research Centre and the Health Protection Research Unit)
Study Design	Repeated cross-sectional surveys of representative households across the UK, with nested serial sampling of a subset of participants providing additional optional consent for this
Study Participants	Adults, adolescents and children aged 2 years or older, in households who have either participated in Office for National Statistics (ONS) or Northern Ireland Statistics and Research Agency (NISRA) surveys or in households that have been randomly selected from databases of addresses.
Sample Size	Phase I started with 20,000 households in England being approached for the initial cross-sectional survey and approximately 10,000 households being recruited over approximately one month (around 2,500 per week). All consenting/assenting adults, adolescents and children aged 2 years and older within each enrolled household were recruited (approximately 21,000 individuals from approximately 10,000 households). Phase II started by approaching approximately 5,000 new households in England, around 500 households in Wales and around 500 households in Northern Ireland approximately every week in new cross-sectional surveys, targeting enrolment of around 2,500, 250 and 250 new households per week respectively (total ~3,000 households per week/~12,000 households per month; assuming 50% consent rate). From the end of July 2020, recruitment was scaled up to inviting new groups of around 18,000 households in England, around 1,800 households in Wales, up to 1,800 households in Northern Ireland and around 4,500 households in Scotland approximately every week, targeting recruitment of around 9,000, 900, up to 900, and 2,250 new households per week respectively (total around 13,000 households per week). The swab target from October 2020 to March 2022 inclusive was to achieve a cohort of ~150,000 individuals providing swab test results at least once a fortnight in England, ~9,000 in

	<p>Wales, ~5,000 in Northern Ireland and ~15,000 in Scotland (total 179,000 across the UK) (absolute numbers reflecting the relative size of the underlying populations). Numbers approached will be increased if the consent rate is lower to achieve the target enrolment.</p> <p>In total, to achieve this, to 12 April 2021, we recruited 371,996 individuals from 182,007 households in England, plus 23,461 individuals from 11,957 households in Wales, 12,687 individuals from 6,311 households in Northern Ireland and 32,206 individuals from 17,936 households in Scotland.</p> <p>To January 2021, between 10-20% of those recruited also provided blood samples as well as swab samples, with the remainder giving swabs only. From February 2021, we asked a representative sample of those already recruited to the study but only giving swabs to also give blood at their monthly visits, and for everyone giving blood to stay in the study until its planned end. The blood target from April 2021 to March 2022 inclusive was to achieve up to ~125,500 adults 16 years and older with blood test results every month in England, and up to ~7,500, ~4,500 and ~12,500 per month in Wales, Northern Ireland and Scotland (~150,000 in total across the UK) (absolute numbers reflecting the relative size of the underlying populations). Where an adult in the household is already giving blood, from September 2021 we also asked children and young people aged 8-15 years whether they would be happy to give a sample of blood (5-7 years in an initial pilot in October 2021 only). For those aged 8-15 years, from December 2021 to March 2022 the target was to achieve ~3,600 blood test results from older children/adolescents every month.</p> <p>From April 2021 to March 2022, we continued to maintain the targets for swab results per fortnight and blood results per month above by</p> <ul style="list-style-type: none"> • inviting everyone who is currently active in the study to remain on monthly follow-up visits (additional consent) • inviting additional households who were only giving swabs at their monthly visits to additionally give blood by fingerprick at these visits (additional consent) • until January 2022, enrolling new households into the study and having follow-up visits up until the end of the study in order to replace participants who stop follow-up or supplement current numbers in order to maintain targets despite possible missed visits. <p>From April 2022 onwards (protocol v16.0), we will invite existing participants to transition from study worker home visits to posted sample kits and completing questionnaires online/by telephone. From April 2022, the swab targets will be reduced by ~25% and the blood targets by ~20% (i.e. retaining a greater percentage of those giving blood in order to maintain as much precision to monitor declines in antibodies as possible), to achieve the following:</p> <ul style="list-style-type: none"> • Swab target: up to ~227,300 swab samples taken from individuals 2 years and older every 28 days in England, ~15,560 in Wales, ~10,050 in Northern Ireland and ~23,200 in Scotland (~276,200 total across the UK every 28 days, ~300,000 swab samples in total across the UK per month) • Blood target: up to ~90,850 blood samples taken from individuals 8 years and older every 28 days in England, ~6,300 in Wales, ~4,150 in Northern Ireland and ~9,200 in Scotland (~110,500 in total across
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	<p>the UK every 28 days, ~120,000 blood samples in total across the UK per month)</p> <p>The goal is to transition sufficiently large numbers of existing participants to maintain these targets through 31 March 2023. However, if necessary, new households will also be enrolled into the study up to 31 January 2023 and have follow-up assessments in order to replace participants who stop follow-up or supplement current numbers in order to maintain targets.</p>
Planned Study Period	<p>Up to protocol v15.0, depending on the consent/assent provided by each individual participant, their involvement may be</p> <ul style="list-style-type: none"> • for one home visit only (cross-sectional survey) • for five home visits (cross-sectional survey then optional to repeat visits every week for the next month) • for at least 6 home visits (cross-sectional survey then optional to repeat visits every week for the next month and then monthly through to the end of the study). <p>From protocol v16.0, each participant would complete questionnaires online or by telephone and return samples weekly for one month from enrolment and then monthly until the end of the study. Participants can withdraw at any time.</p> <p>All participants would have follow-up through available routine electronic health records for up to 15 years from their final study assessment to evaluate use of healthcare, results from tests for COVID-19 infection done within the NHS and equivalent bodies in Devolved Administrations, and mortality. Consent for this electronic follow-up is required to join the study.</p> <p>The total study duration is 18 years (3 years recruitment and serial sampling to 31 March 2023), plus 15 years additional follow-up after the end of serial sampling through existing electronic records from the final serial sampling timepoint).</p>
Planned Recruitment period	<p>24 April 2020 to 31 January 2022 (1.75 years) from protocol v1.0 through v15.0</p> <p>1 May 2022 through to 31 January 2023 (8 months) from protocol v16.0, if necessary to maintain targets</p>
Planned study duration	<p>24 April 2020 to 31 March 2023 for study assessments (3 years), including any closeout; and to 31 March 2038 (3 years + 15 years) for data linkage</p>
Objectives and Endpoints	<p>See Section 6 below.</p>
Intervention(s) and Comparator	<p>Not applicable, non-interventional study</p>

4. ABBREVIATIONS

A&E	Accident and Emergency
CDDO	Central Digital and Data Office
CI	Chief Investigator
CT	Cycle threshold
DHSC	Department of Health and Social Care
eCRF	Electronic Case Report Form
ePCR	Endpoint polymerase chain reaction
GCP	Good Clinical Practice
HCP	Healthcare professional
HRA	Health Research Authority
HSC	Health and Social Care (Northern Ireland)
MHRA	Medicines and Healthcare Products Research Agency
NHS	National Health Service
NISRA	Northern Ireland Statistics and Research Agency
ONS	Office for National Statistics
PPE	Personal protective equipment
REC	Research Ethics Committee
RGEA	Research Governance, Ethics and Assurance University of Oxford
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcriptase polymerase chain reaction
SGSS	Second Generation Surveillance System
SOP	Standard Operating Procedure
UKHSA	UK Health Security Agency
WHO	World Health Organisation

Note: All references to the NHS in this protocol also include NHS Wales, the Health and Social Care (HSC) in Northern Ireland, and NHS Scotland.

5. BACKGROUND AND RATIONALEⁱ

The first cases of infection with a novel coronavirus, subsequently designated SARS-CoV-2 (commonly called COVID-19), emerged in Wuhan, China on 31st December 2019.¹ Despite intensive containment efforts, there was rapid international spread and by 17 April 2020, SARS-CoV-2 had caused over 2 million confirmed infections and 140,000 reported deaths globally.² A global pandemic was declared by the World Health Organisation (WHO) on 12th March 2020.³

Containment efforts have relied heavily on population quarantine ('lock-down') measures to restrict population movement and reduce individual contacts.^{4,5} In order to develop public health strategies for exit from lock-down, there is an urgent need for scale-up of diagnostic testing, in parallel with collection of robust data that describe recent and past SARS-CoV-2 exposure at an individual and population level.

In most settings, laboratory diagnosis of infection has been based on real-time reverse transcriptase polymerase chain reaction (RT-PCR). Diagnostic RT-PCR typically targets the viral ribonucleic acid (RNA)-dependent RNA polymerase (RdRp) or nucleocapsid (N) genes using swabs collected from the upper respiratory tract (nose and throat).^{6,7} However, the requirement for specialist equipment, skilled laboratory staff, and PCR reagents has created bottlenecks. Clinical care and public health containment efforts are thus impeded by diagnostic delays even for clinically unwell patients, and further limited by a lack of wider testing including both mass screening, and specific high-risk groups (contacts of confirmed cases, and healthcare workers and their families). Further the numbers who are asymptotically infected are currently completely unknown. Poor population-level data adds uncertainty to dynamic models that inform planning of lockdown restrictions (as exemplified by experiences in other countries⁸). Furthermore, even when available, RT-PCR from upper respiratory tract swabs may be falsely negative, due to quality or timing of collection; viral titres in upper respiratory tract secretions peak in the first week of symptoms,⁹ but may have declined below the limit of detection in patients who present with symptoms beyond this time frame.¹⁰ In individuals who have been infected and recovered, RT-PCR provides no information about prior exposure or immunity.

For these reasons, attention has turned to the potential for antibody testing to provide data to support individual or population-level release from lock-down and inform mathematical models to predict the future trajectory of the pandemic, as well as supporting diagnosis of individuals with a clinical COVID syndrome. In contrast to RT-PCR, assays that reliably detect antibody responses specific to SARS-CoV-2 could contribute to diagnosis of both acute infection (via rises in IgM and IgG levels) and identify those who have been exposed and recovered with or without symptoms (via persisting IgG).¹¹ Receptor-mediated viral entry to the host cell occurs as a result of the interaction between the unique and highly conserved trimeric SARS-CoV-2 spike (S) glycoprotein and the ACE2 cell receptor.¹² This S protein is the primary target of specific neutralising antibodies, and serology assays for SARS-CoV-2 therefore typically seek to identify these antibodies (see Figure 1 in ¹³). Within this study we plan to use an antibody assay for the anti-spike IgG immunoglobulin in all participants with blood draws; we will also assay neutralising antibodies directly in a subset of participants with blood draws. From February 2021, we will combine this anti-spike assay with an anti-N (nucleocapsid) assay to try to distinguish between those with immunity due to natural infection (expected to be anti-S and anti-N positive) and vaccination (expected to be anti-S positive, anti-N negative because the vaccines produce antibodies to spike only). From April 2022, anti-N antibodies will only be assayed in a subset of participants, depending on capacity.

ⁱ With grateful thanks to Dr Philippa Matthews and Dr David Eyre for most of the introductory text.

In this study, we aim to address crucial unknowns regarding the extent of transmission and ongoing rates of infection in the UK. We will use a repeated cross-sectional survey design. In Phase I, we will invite approximately 5,000 households from England to participate every week with an assumed 50% opt-in rate, and a target enrolment of 2,500 households, providing a cohort of approximately 10,000 population-representative households in the first month. In Phase II, we will start by recruiting new cohorts of approximately 2,500 households per week from England (approximately 10,000 each month) together with approximately 250 households per week from Wales and 250 households per week from Northern Ireland (each approximately 1,000 each month; total households across all regions approximately 3,000 per week and 12,000 per month) to estimate the proportion of the population that are currently infected with SARS-CoV-2, symptomatically and asymptotically, based on diagnostic RT-PCR performed on a nose and throat swab collected by the participant (self-swabbing) or by a parent/carer from participants aged 2-11 years, and self-reported symptoms. Numbers approached will be increased if the consent rate is lower to achieve the target enrolment. In approximately 300-600 enrolled households per week (1,200-2,400 households per month; 10-20%, including 100-200 households per month from each of Wales and Northern Ireland), a trained healthcare professional (HCP) will also collect venous blood to estimate seroprevalence using antibody assays, to quantify the percentage of the adult population in the UK that has previously been infected with SARS-CoV-2. This would substantially improve/decrease uncertainty of models that have been used to predict the effect of school closures, social distancing, and other interventions aimed at reducing the spread of the virus.

However, in order to achieve a cohort of ~150,000 individuals sampled at least once a fortnight in England from October 2020 when the winter season of respiratory infections starts, and monitoring for a possible “second wave” of infections is critical, from the end of July 2020 we will scale this up to inviting new groups of around 18,000 households in England, around 1,800 households in Wales, up to 1,800 households in Northern Ireland and around 4,500 households in Scotland approximately every week, targeting recruitment of around 9,000, 900, up to 900, and 2,250 new households per week respectively (total approximately 13,000 households per week; assuming 50% consent rate; numbers approached will be increased if consent rate is lower to achieve the target enrolment). **Ultimately the swab target from October 2020 to March 2022 inclusive is to achieve ~150,000 individuals with swab test results at least every fortnight from October 2020 onwards in England, ~9,000 in Wales, ~5,000 in Northern Ireland and ~15,000 in Scotland (total 179,000 across the UK)** (absolute numbers reflecting the relative size of the underlying populations) (see *Table 1* below for initial planned recruitment in 2020). The same proportions will be approached for blood draws.

However, additional critically important questions remain about onward transmission and waning immunity in individuals who are positive, whether such individuals can be re-infected symptomatically or asymptotically, and about incidence of new infection in individuals without prior exposure. Incorporating nested serial sampling of consenting individuals can efficiently provide estimates of these outcomes in different subgroups. We will therefore also serial sample individuals from these cross-sectional surveys who provide additional consent 1, 2, 3 and 4 weeks (1 month) after their first assessment (counted as week 0); if further consent is provided, we will continue this sampling at 2 months and every month thereafter to assess this over the longer term. Over 95% of participants offered these options through to protocol v15.0 chose to have repeated monthly visits over the longer term, and so from protocol v16.0, we will ask everyone joining the study to have study assessments every week for the first month and then every month until the study ends. Participants are free to withdraw at any time. Infection (nose and throat swab) will be assessed at every assessment and immunity (antibodies) every

month. In Phase I and II to date, acceptance of additional visits was very high and therefore follow-up visits are also included in the target of 150,000 individuals sampled every fortnight in England from October 2020 onwards (and equivalently in Devolved Administrations). We will also approach anyone with a positive test for virus (i.e. new infection) in the study to undergo a blood draw as quickly as possible after their positive test and then at monthly visits to contribute additional information to analyses of how immunity after infection changes over time, where this does not lead to targets for blood sampling being exceeded by >5% (which impacts the capacity of the laboratory to conduct all the required tests).

However, in order to monitor the impact of vaccination on both immunity and infection, from February 2021, we will ask a representative sample of those already recruited to the study but only giving swabs to also give blood at their monthly visits, and for everyone giving blood samples to stay in the study until April 2022 (i.e. to have additional visits beyond their original 12 month study period). Blood will initially either be taken through a venous blood draw as previously or through a capillary blood draw (fingerprick) done by the participant. From protocol v9.0, all blood draws will be capillary so that all visits can be conducted without any contact. **The blood target from April 2021 to March 2022 is to achieve up to ~125,500 adults 16 years and older with blood test results every month in England, and up to ~7,500, ~4,500 and ~12,500 per month in Wales, Northern Ireland and Scotland (~150,000 in total across the UK)** (absolute numbers reflecting the relative size of the underlying populations). Where an adult in the household is already giving blood, in order to monitor the impact of immunity as well as infection in younger individuals, from September 2021 we will also ask children and young people aged 8-15 years whether they would be happy to give a sample of blood (5-7 years in an initial pilot in October 2021 only). See Section 9.4.3 for rationale and details. For those aged 8-15 years, from December 2021 to March 2022, the target is to achieve ~3,600 blood test results from older children/adolescents every month.

In total, from 24 April 2020 to 12 April 2021, we recruited 371,996 individuals from 182,007 households in England, plus 23,461 individuals from 11,957 households in Wales, 12,687 individuals from 6,311 households in Northern Ireland and 32,206 individuals from 17,936 households in Scotland.

From April 2021 to March 2022, we continued to maintain the targets for both swab results per fortnight and blood results per month by

- inviting everyone who was currently active in the study to remain on monthly follow-up visits (additional consent)
- inviting additional households who were only giving swabs at their monthly visits to additionally give blood by fingerprick at these visits (additional consent)
- until January 2022, enrolling new households into the study and having follow-up visits up in order to replace participants who stop follow-up or supplement current numbers in order to maintain targets despite possible missed visits.

The reason for following already recruited participants for longer, rather than only recruiting new participants, is the importance of assessing the duration of protection provided by vaccination and previous infection against new infection. Power to do this is maximised by having longer higher quality survey follow-up, including SARS-CoV-2 tests regardless of symptoms and antibody data, on the same individuals, rather than recruiting large numbers of new participants whose SARS-CoV-2 history is

unknown or much less clearly documented (e.g. only symptomatic testing for current infection through national testing programmes, and no prior antibody test data).

From April 2022 onwards (protocol v16.0), we will invite existing participants to transition from study worker home visits to posted sample kits and completing questionnaires online/by telephone. From April 2022, the swab targets will be reduced by ~25% and the blood targets by ~20% (i.e. retaining a greater percentage of those giving blood in order to maintain as much precision as possible to monitor declines in antibodies), to achieve the following:

- Swab target: up to ~227,300 swab samples taken from individuals 2 years and older every 28 days in England, ~15,650 in Wales, ~10,050 in Northern Ireland and ~23,200 in Scotland (~276,200 total across the UK every 28 days, ~300,000 swab samples in total across the UK per month)
- Blood target: up to ~90,850 blood samples taken from individuals 8 years and older every 28 days in England, ~6,300 in Wales, ~4,150 in Northern Ireland and ~9,200 in Scotland (~110,500 in total across the UK every 28 days, ~120,000 blood samples in total across the UK per month)

Reductions are proportionately less in Wales and Northern Ireland in order to maintain power within these countries, and proportionately more in England to meet the overall reductions. The goal is to transition sufficiently large numbers of existing participants to maintain these targets through 31 March 2023. However, if necessary new households will also be enrolled into the study up to 31 January 2023 and have follow-up assessments (using posted sample kits and completing questionnaires online/by telephone from enrolment) in order to replace participants who stop follow-up or supplement current numbers in order to maintain targets.

In addition, for planning the continuing response to the pandemic, it is essential to understand the relationship between symptomatic/asymptomatic infection, immune status and use of health resource within the NHS, and with mortality. In this study, we will therefore seek consent to link study results to NHS data for up to 15 years after the last study visit for each participant to estimate the impact of COVID-19 on the development of future health conditions, and hence on the NHS and future requirements, to available data from the UK Health Security Agency's (UKHSA's) Second Generation Surveillance System (SGSS) and equivalent national test databases in Wales, Northern Ireland and Scotland to ensure that we have information on other tests for SARS-CoV-2, and to ONS and relevant national mortality data to estimate the impact on mortality.

The goal is to obtain results which can be generalised across all the countries in the UK and help manage the pandemic moving forward.

Risks to participants will be minimised by the use of non-contact home visits. Study workers will follow appropriate government guidance regarding personal protective equipment. From protocol v16.0 onwards, sample kits will be posted to participants, and questionnaires completed online or by telephone, reducing risks to participants even further.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
<p>Primary Objective</p> <p>To estimate prevalence of symptomatic and asymptomatic SARS-CoV-2 infection in the general population and how this varies over time</p>	<p>Presence or absence of SARS-CoV-2 virus assayed from a nose and throat swab</p>	<p>Every calendar day from the start of the study, with analysis based on continuous time and the latest test available in the prior 2 weeks</p>
<p>Secondary Objectives</p> <p>To estimate the incidence of new symptomatic and asymptomatic SARS-CoV-2 infection in the general population, and how this varies over time</p> <p>To estimate immunity to SARS-CoV-2 in the general adult population and how this varies over time, as reflected by anti-S and anti-N immunoglobins (anti-N in all participants to protocol v15.0 only)</p> <p>To estimate the association between prevalence of symptomatic and asymptomatic infection in individual members of households</p> <p>To estimate the association between immunity to SARS-CoV-2 across individual members of households</p>	<p>Presence of SARS-CoV-2 virus in a nose and throat swab, separately in previously negative and previously positive individuals (to estimate re-infection after clearing the virus)</p> <p>Optical density readings for anti-S(spike) and anti-N(nucleocapsid) IgG from a ELISA assay for SARS-CoV-2 antibodies assayed from blood, categorised according to predefined thresholds based on pre-pandemic plasma as positive or negative</p> <p>Presence or absence of SARS-CoV-2 virus assayed from nose and throat swabs taken from different members of the same household*</p> <p>Concentrations and thresholds of IgG to SARS-CoV-2 assayed from blood of different members of the same households*</p>	<p>Every calendar day from the start of the study</p> <p>Every calendar day from the start of the study, with analysis based on continuous time and the latest test available in the last month</p> <p>Each household visit</p> <p>Each household visit</p>

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
<p>Exploratory Objectives</p> <p>To assess how prevalence and incidence of symptomatic and asymptomatic infection, and of immunity to SARS-CoV-2 (outcomes) varies by participant characteristics, particularly age, geographical location and time, but also other characteristics collected or linked including vaccination and comorbidities or other characteristics from GP records and for prevalence and incidence of symptomatic and asymptomatic infection, how this varies by immunity to SARS-CoV-2, both natural and following vaccination</p>	<p>Presence or absence of SARS-CoV-2 virus assayed from a nose and throat swab</p> <p>Presence of SARS-CoV-2 virus in a nose and throat swab, separately in previously negative and previously positive individuals on nose and throat swabs (to estimate re-infection after clearing the virus), as assessed by immunity determined by IgG to SARS-CoV-2 assayed from blood, and by vaccination status and time from vaccination</p> <p>Concentrations and thresholds of IgG from an ELISA assay for SARS-CoV-2 antibodies assayed from blood</p>	<p>In individual cross-sectional surveys; repeated at each follow-up timepoint in those consenting to serial sampling</p>
<p>To assess how immunity to SARS-CoV-2, and having had SARS-CoV-2 infection, affects future use of NHS resources, development of specific conditions, and mortality</p>	<p>Inpatient admissions, outpatient attendances, A&E attendances, consultations with a General Practitioner, development of new conditions such as diabetes, heart failure, dementia and other conditions that could be related to SARS-CoV-2 infection as collected from available routine electronic NHS health records; overall mortality and cause of death as collected from ONS and relevant national mortality databases</p>	<p>Over time following each visit and after SARS-CoV-2 infection compared with not being infected, for up to fifteen years</p>
<p>To compare immunity to SARS-CoV-2 in the general adult population, as reflected by neutralising antibodies and IgG</p>	<p>Concentration of neutralising antibodies to SARS-CoV-2 assayed from blood, categorised according to predefined thresholds¹⁴ as positive or negative</p> <p>Concentrations and thresholds of anti-S and anti-N IgG from an ELISA assay for SARS-CoV-2 antibodies assayed from blood</p>	<p>Specific study visits where neutralising antibody assays performed</p>

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
To estimate the prevalence of “long COVID” and whether this varies by participant characteristics	Repeated and continued reporting of specific symptoms over time from a first positive swab test Self-reported long COVID	Over time following each first positive swab; at cross-sectional visits
To estimate prevalence of other respiratory infections in the general population and how these vary over time (depending on funding)	Presence or absence of other respiratory viruses assayed from the same nose and throat swab as for SARS-CoV-2	Every calendar day from the start of sampling, with analysis based on continuous time and the latest test available in the prior 2 weeks

* estimated from statistical random effects models, see Section 11.

7. STUDY DESIGN

The overall study design is repeated cross-sectional surveys of representative households across the UK, identified either by one adult from the household having participated in existing surveys conducted by ONS or the Northern Ireland Statistics and Research Agency (NISRA) and providing consent for future contact regarding research or by the household being randomly selected from a commercially available source such as AddressBase, which is maintained by the Ordnance Survey, or equivalent databases including in the Devolved Administrations. This will ensure that the sample remains representative in terms of the country throughout its duration and also facilitate proportionate increases where there is evidence of increasing prevalence in Phase II, as described below.

All adults and adolescents aged 16 years and above in the household who are present in the household at the enrolment visit and willing and able to consent will be included in the study, as will all adolescents and children aged 2 years and older for whom a parent/carer is willing and able to consent to their participation. Assent will be sought from adolescents and children aged 10 years or older. Children are included in this study because it is essential to understand prevalence and incidence of symptomatic and asymptomatic infection in children, particularly to inform regarding continuation of school closures.

These cross-sectional surveys will be repeated over time, recruiting new households each week, following standard sampling methods (for example as employed in the Labour Force Survey) to ensure that the study represents the UK population and can estimate reliably prevalence over time of symptomatic and asymptomatic infection and immunity (as assessed by various antibody profiles) (Figure 1). In each cross-sectional survey, up to protocol v15.0 study participants who provide additional optional consent/assent will undergo repeated serial sampling at 1, 2, 3 and 4 weeks (approximately 1 month) after their enrolment visit (week 0) to assess incidence of new infection, viral clearance and changes over time in immunity. If further additional consent is given, this will then be further repeated at month 2 and every month thereafter from their first study visit to assess these outcomes over the longer term. Up to protocol v15.0, the choice of participating once at enrolment, weekly for the first month, or weekly for the first month and then monthly will be made at the enrolment visit; participants will not be offered the option to extend if they initially choose weekly visits for one month only. Over 95% of participants offered these options through to protocol v15.0 chose to have repeated monthly visits over the longer term, and a number of those who initially chose 1 or 5 visits requested to then extend their participation (which was not possible under the approved protocol). Therefore from protocol v16.0, we will ask everyone joining the study to have study assessments every week for the first month and then every month until the study ends. Participants are free to withdraw at any time.

Up to protocol v16.0, data collection will be done via home visits (phased out from protocol v16.0). This method is used to minimise risk to the participant from having to attend a central facility. In order to reduce risks to participants and study workers, all home visits will be “non-contact” visits where study workers do not enter the household and stay 2m away from the household at all times, passing any necessary sterile equipment for self-swabbing using standard precautions. Blood for the antibody test will be drawn via a fingerprick by the participant, since the antibody tests being used in this study have similar performance regardless of source of blood. Self-fingerprick has been successfully used with these antibody assays (which require very small sample volumes) in very large numbers in the UK BioBank serology study (https://www.ukbiobank.ac.uk/media/zusjljce/ukb_serologystudy_report_month2_final-1.pdf). From protocol v16.0, sample kits for nose and throat swabs and for fingerprick blood tests will be posted to participants for self-completion and return, with no further home visits.

At every assessment (contact or non-contact home visit or self-completion), all participants will take a self-swab of their nose and throat and complete a short questionnaire (online or by telephone from protocol v16.0). The self-swab can be done by those aged 12 years and older and has been successfully used in drive through testing centres; those 2-11 years will be swabbed by their parent/carer. The swab is the same size as that used routinely in paediatric practice and there is no modification to the technique needed. Self-swabbing minimises the risk to study workers of contracting SARS-CoV-2 from an asymptotically infected individual at a home visit. In a subset of households, optional consent will also be sought for adults aged 16 years or older to have a blood draw. In the first cross-sectional survey (Phase I, see below), the invitation to undergo additional blood sampling was sent to those sampled from the ONS Opinions COVID-19 Survey for practical reasons and to enable future data linkage to more detailed data on reported self-isolation behaviours. In subsequent surveys, of the 6,000 households invited to participate each week (24,000 per month), approximately 600-1200 households per week (2,400-4,800 per month; 10%-20%; including 200-400 households per month from each of Wales and Northern Ireland) will be randomly selected to receive an invitation for adults aged 16 years and older in the household to have a blood draw, as well as for all individuals 2 years and older to self-swab, targeting enrolment of a minimum of 300 households per month for blood sampling (10% of the target enrolment; including at minimum 50 households per month from each of Wales and Northern Ireland). From the end of July 2020, the percentage randomly selected to receive an invitation for blood draw was increased to 20%, to assess the potential for prior immunity to affect future infection. In order to monitor the impact of vaccination on both immunity and infection, from February 2021, we asked a representative sample of those already recruited to the study but only giving swabs to also give blood at their monthly visits, and for everyone giving blood samples to stay in the study until April 2022 (i.e. to have additional visits beyond their original 12 month study period). **The blood target from April 2021 to March 2022 was to achieve up to ~125,500 adults 16 years and older with blood test results every month in England, and up to ~7,500, ~4,500 and ~12,500 per month in Wales, Northern Ireland and Scotland (~150,000 in total across the UK).** All households who are approached for blood sampling will be included in the blood sampling cohort if anyone in the household is willing to provide consent for blood draws, and blood will be drawn from all participants in the households selected for blood sampling who are willing to provide blood, so the precise percentage randomly selected to receive this invitation to provide blood samples will be adjusted based on opt-in rates. If participants consent to serial sampling, blood will also be drawn monthly for the duration of their consented serial sampling. The choices available to participants are illustrated in **Figure 2**. Where an adult in the household is already giving blood, from September 2021 we will also ask children and young people aged 8-15 years whether they would be happy to give a sample of blood (5-7 years in an initial pilot in October 2021 only). For those aged 8-15 years, from December 2021 to March 2022 the target is to achieve ~3,600 blood test results from older children/adolescents every month.

In order to contribute additional information to analyses of how immunity after infection changes over time, the household of any participant with a positive nose and throat swab for virus from a study sample would also be approached for consent for a blood draw as quickly as possible after the first positive test in the household and then at subsequent monthly visits to the end of their participation, where this does not lead to targets for blood sampling being exceeded by >5% (which impacts the capacity of the laboratory to conduct all the required tests). Each individual participant within these households would make their own decision about agreeing to these additional blood draws or not, but the entire household would be approached. They would re-consent in order to provide consent for blood sampling. For participants recruited under protocol v6.0 and later, consent for blood draws after testing

positive on a nose and throat swab within the study will be sought at enrolment, to avoid needing to reconsent individuals after they test positive on a nose and throat swab. However, those in the household of anyone testing positive will be offered the opportunity to change their minds at the time when someone in the household tests positive, and either not provide blood samples (even if they originally consented to this) or to consent and provide blood samples (even if they did not originally consent to this).

Given the scale of Phase II and the fact that it will run across the Devolved Administrations, the lead organisation (IQVIA) will be supported by a number of similarly-qualified data collection organisations conducting home visits up to protocol v16.0 (see Section 12). Fieldwork will be managed through a specific contact centre, and the number provided on the household's invitation letter and participant information.

Up to protocol v15.0, participants who consent to one cross-sectional survey would have just one visit. Participants who consent to serial sampling would have either five study visits over one month (enrolment, weeks 1, 2, 3, 4) or at least 6 study visits over one year (enrolment; weeks 1, 2, 3, 4; then every month subsequently). The precise duration of follow-up would depend on when the participant was recruited and what they consented to – however, participants who agreed to monthly visits can withdraw permanently at any time and can also miss individual visits. From protocol v9.0 to protocol v15.0, the majority of participants agreeing to multiple follow-up visits after one month would have monthly visits through to April 2022. However, if some participants recruited before protocol v9.0 choose not to provide optional consent for follow-up through to April 2022, they would be followed for a maximum of 12 months (as the original consent form specified participation for a maximum of 12 months). Participants newly recruited under protocol v9.0 to v15.0 would be followed up monthly until April 2022, which would be between 3 and 9 months, depending on specific date of recruitment. From protocol v16.0, all participants will be followed up until the end of the study.

All participants would also have follow-up through routine electronic health records for health utilisation (particularly rates of hospitalisation and visits to primary care), development of conditions that may be related to having had SARS-CoV-2 (for example diabetes, heart failure and dementia) and mortality for up to 15 years from their final study visit. Over the coming decades it will be essential to understand the contribution of SARS-CoV-2 infection to potentially increased rates of multiple long-term health conditions; the extensive testing for SARS-CoV-2 in survey participants makes them ideal to be able to identify who has and has not been infected as accurately as possible. To reduce burden on participants, the survey does not ask detailed questions about medical history (see Section 9.6.1): we will also therefore link health data for each participant back to January 2016 (4 calendar years before the start of the COVID-19 epidemic) to ensure that analyses assessing the impact of COVID-19 on the risk of developing subsequent health conditions properly adjust for conditions that people had before they joined the survey. Linkage to routine data would be performed both during and after active study participation, to allow the impact of COVID-19 and vaccination on hospitalisations and primary care utilisation to be assessed.

The study will start with one approach to 20,000 households from England in Phase I, aiming to enrol 10,000 households (approximately 2,500 per week over one month), based on respondents to waves 1-4 of the ongoing ONS Opinions COVID-19 Survey and other ONS surveys. Households in England where an adult participant has agreed to future contact regarding research will be targeted ($n \sim 20,000$), assuming a 50% response rate. All eligible participants in these households who consent to serial sampling will be

included in the serial sampling component, and approximately 2,000 households from the ONS Opinions COVID-19 survey who were approached for consent to the blood draw will be included in that component.

In Phase II, sampling will be from households who have participated in ongoing and further ONS and NISRA surveys and from databases of addresses held in Devolved Administrations. **For assessment of current infection, from October 2020 to March 2022, the swab target is to achieve ~150,000 individuals with swab test results at least every fortnight in England, ~9,000 in Wales, ~5,000 in Northern Ireland and ~15,000 in Scotland (total 179,000 across the UK)** (absolute numbers reflecting the relative size of the underlying populations). For assessment of immunity, from April 2021 to March 2022, **the blood target is to achieve up to ~125,500 adults 16 years and older with blood test results every month in England, and up to ~7,500, ~4,500 and ~12,500 per month in Wales, Northern Ireland and Scotland (~150,000 in total across the UK)** (also giving paired swab samples at the same timepoints) (absolute numbers reflecting the relative size of the underlying populations). For those aged 8-15 years, from December 2021 to March 2022, the target is to achieve ~3,600 blood test results from older children/adolescents every month.

From April 2021 to March 2022, we maintained the targets for swab results per fortnight and blood results per month above by

- inviting everyone who was currently active in the study to remain on monthly follow-up visits (additional consent)
- inviting additional households who were only giving swabs at their monthly visits to additionally give blood by fingerprick at these visits (additional consent)
- until January 2022, continuing to enrol new households into the study and have follow-up visits up in order to replace participants who stop follow-up or supplement current numbers in order to meet targets despite possible missed visits.

From April 2022 onwards (protocol v16.0), we will invite existing participants to transition from study worker home visits to posted sample kits and completing questionnaires online/by telephone. From April 2022, the swab targets will be reduced by ~25% and the blood targets by ~20% (i.e. retaining a greater percentage of those giving blood in order to maintain as much precision to monitor declines in antibodies as possible), to achieve the following:

- Swab target: up to ~227,300 swab samples taken from individuals 2 years and older every 28 days in England, ~15,650 in Wales, ~10,050 in Northern Ireland and ~23,200 in Scotland (~276,200 total across the UK every 28 days, ~300,000 swab samples in total across the UK per month)
- Blood target: up to ~90,850 blood samples taken from individuals 8 years and older every 28 days in England, ~6,300 in Wales, ~4,150 in Northern Ireland and ~9,200 in Scotland (~110,500 in total across the UK every 28 days, ~120,000 blood samples in total across the UK per month)

Reductions are proportionately less in Wales and Northern Ireland in order to maintain power within these countries, and proportionately more in England to meet the overall reductions. The goal is to transition sufficiently large numbers of existing participants to maintain these targets through 31 March 2023 (see Section 9.4.1 for details of the transition). However, if necessary new households will also be enrolled into the study up to 31 January 2023 and have follow-up assessments (using posted sample kits

and completing questionnaires online/by telephone from enrolment) in order to replace participants who stop follow-up or supplement current numbers in order to maintain targets.

Initial sampling for recruitment will be stratified by geographical location in order to provide more precise regional estimates of incidence and seroprevalence. Where possible, sampling will also be stratified by ethnicity to ensure sufficient numbers for appropriate representation in final weighted estimates of prevalence. From Phase II, sampling may be proportionately increased in regions or occupations or other groups with any evidence of increasing prevalence, in order to provide greater certainty regarding the probability of increasing infection rates as opposed to sampling variation. Sampling will also take into consideration local non-response rates to ensure those recruited remain regionally representative as much as possible. Those approached to provide blood samples from enrolment were selected completely at random from the initial recruitment invitation letters. To ensure that the expanded cohort providing blood samples is representative of the different regions, has the greatest possible power to investigate the impact of ethnicity, and places the least burden on participants, invitations to households to join the blood cohort after recruitment will be randomly selected stratified by sub-regional geographical area, but proportionately increased in households where anyone reports coming from an ethnic group other than White. Only households where anyone originally consented to repeated follow-up for longer than one month will be approached for consent for additional blood sampling. Sampling will also be proportionately adjusted to take into consideration non-response rates to the invitation to provide additional blood samples by factors including sub-region and age, to ensure those providing blood samples remain representative as much as possible.

Table 1 Original planned recruitment of households in England* †

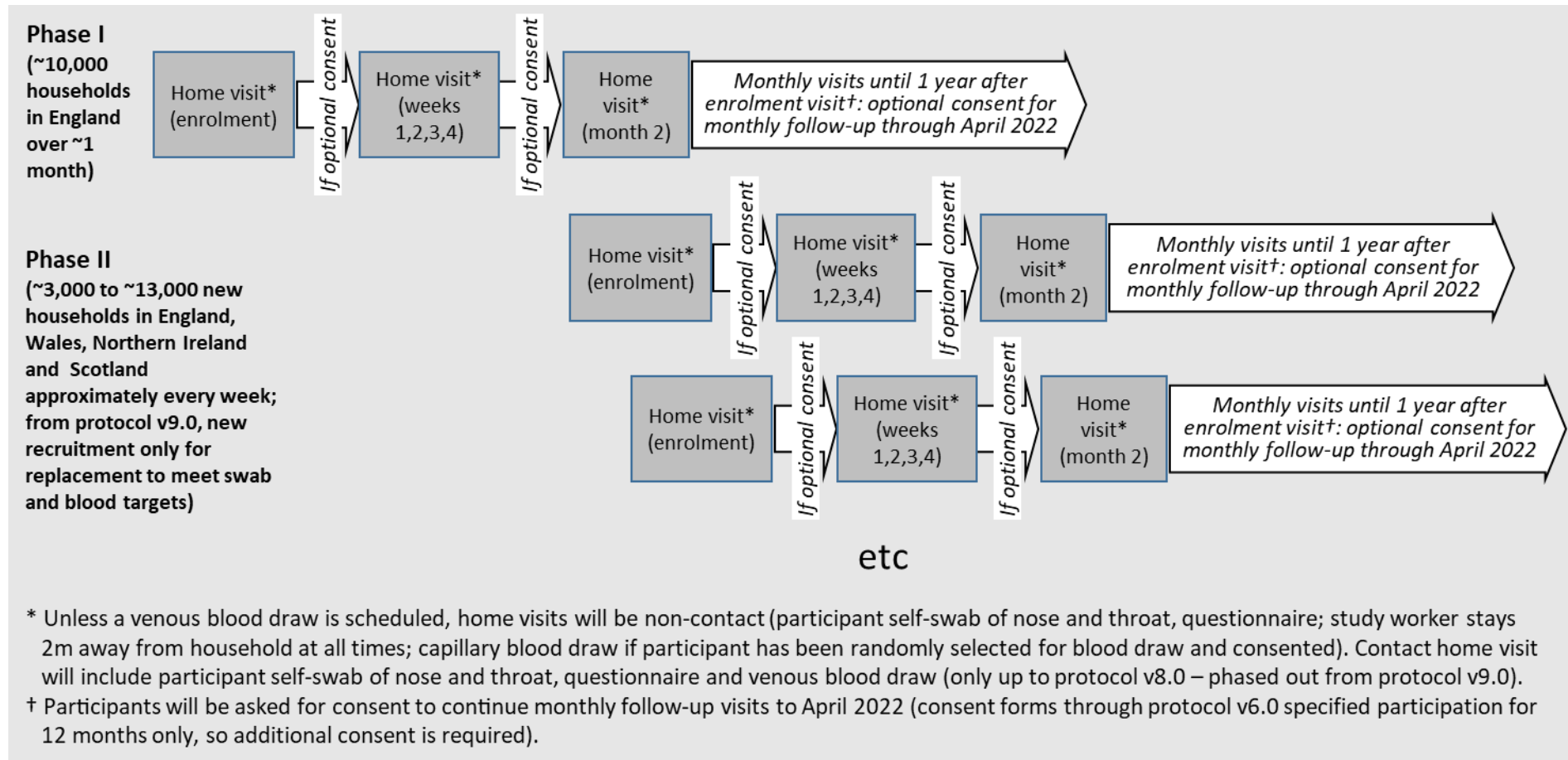
Week starting	Newly recruited households in England (actual or approx planned)	Newly recruited individuals in England (actual or approx planned)
27 April 2020	2523	5483
04 May 2020	3156	7038
11 May 2020	2436	5406
18 May 2020	1365	3092
25 May 2020	442	999
01 June 2020	1163	2526
08 June 2020	2008	4207
15 June 2020	2261	4550
22 June 2020	1778	3622
29 June 2020	1645	3469
06 July 2020	1598	3244
13 July 2020	2500	5388
20 July 2020	2500	5388
27 July 2020	3000	6466
03 August 2020	5000	10776
10 August 2020	7500	16164
17 August 2020	8250	17780
24 August 2020	9000	19397
31 August 2020	9000	19397
07 September 2020	9000	19397
14 September 2020	9000	19397
21 September 2020	9000	19397
28 September 2020	9000	19397
05 October 2020	9000	19397
12 October 2020	9000	19397
19 October 2020	7500	16164
26 October 2020	7500	16164
02 November 2020	5000	10776
09 November 2020	5000	10776
16 November 2020	5000	10776
23 November 2020	5000	10776
30 November 2020	2500	5388
07 December 2020	2500	5388
14 December 2020	2500	5388
21 December 2020	2500	5388
28 December 2020	1500	3233
04 January 2021	1500	3233
11 January 2021	1500	3233
18 January 2021	1500	3233
25 January 2021	1500	3233
01 February 2021	1500	3233
08 February 2021	500	1078
15 February 2021	500	1078
22 February 2021	500	1078
01 March 2021	500	1078
08 March 2021	500	1078
15 March 2021	500	1078
22 March 2021	500	1078
29 March 2021	500	1078
Total enrolled	176602	380292
Average ratio individual: household		2.16

* targets for each of Wales and Northern Ireland are 10% of those shown for England. Target for Scotland is to recruit 2,250 households per week from September, in order to achieve 15,000 individuals sampled every fortnight from October 2020 onwards. Targets are approximate and may vary depending on speed of scale-up and other factors, such as consent rates.

† From April 2021 to March 2022, to maintain the targets for swab results per fortnight and blood results per month above, we will invite already recruited participants to remain in follow-up through April 2022, with either swabs or swabs and fingerprick blood tests, and we will continue to invite new households to join the study.

Note: Gray shading shows data to July 2020, and white cells plans thereafter. Numbers approached given in the main text are based on 50% consent; more will be approached to achieve the numbers recruited above.

Figure 1 Repeated cross sectional survey design through protocol v15.0

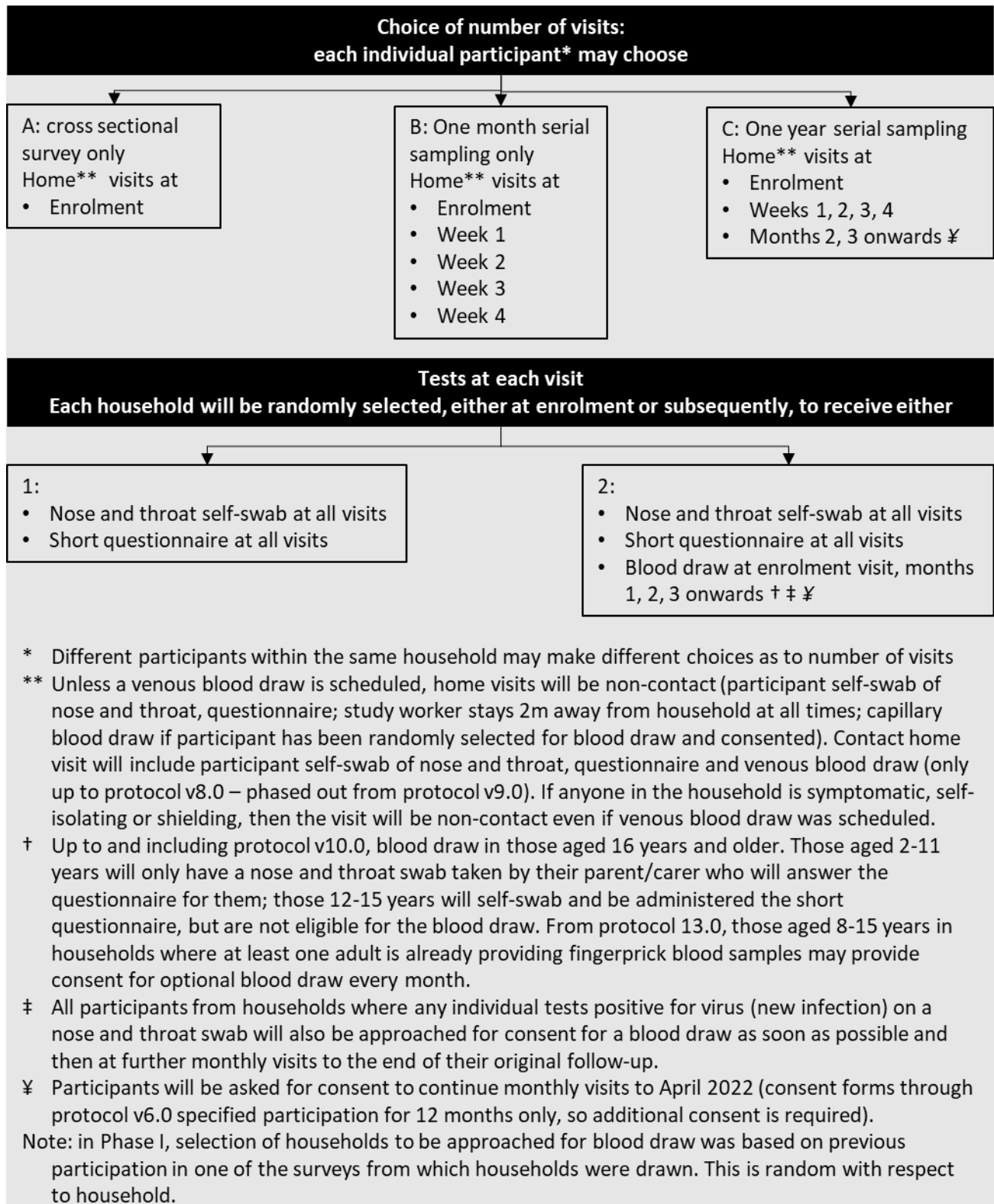


Note: in Phase I a single invitation letter was sent simultaneously to 20,000 households, with households then enrolled at ~2,500 per week for 4 weeks. In Phase II, between 6,000 and 24,000 invitations will be issued per week (will be increased if consent falls below 50% to achieve targeted recruitment) with continuous recruitment from these issues, hence Phase II is shown on multiple lines.

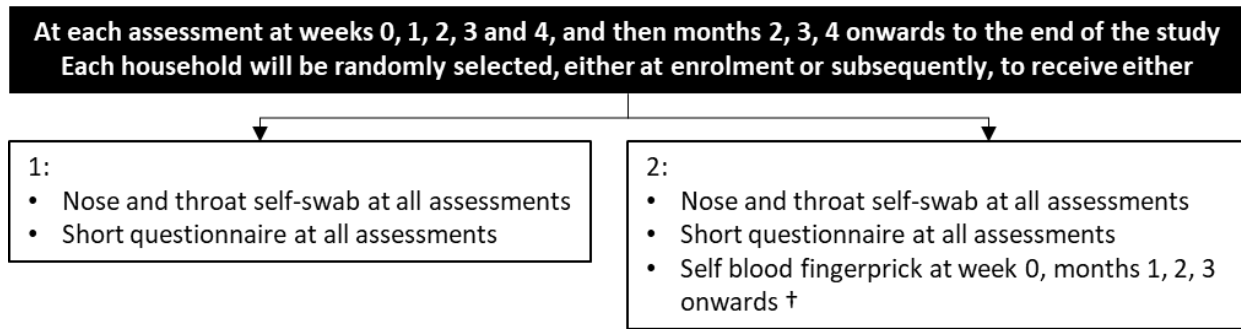
From protocol v16.0, home visits replaced with posted swab and fingerprick blood kits, and completion of questionnaires online or by telephone. New participants provide consent for weekly visits for a month and then monthly visits until the end of the study (monthly visits continue in existing participants). All participants can withdraw at any time.

Figure 2 Serial sampling frequency and tests

(A) through protocol v15.0



(B) from protocol v16.0



† Fingerprick blood draw from enrolment in those aged 16 years and older. Those aged 2-11 years will only have a nose and throat swab taken by their parent/carer who will answer the questionnaire for them; those 12-15 years will self-swab and be administered the short questionnaire, but are not eligible for the blood draw from enrolment. Those aged 8-15 years in households where at least one adult is already providing fingerprick blood samples may subsequently provide consent for optional blood draw every month.

Note: all participants from households where any individual tests positive for virus (new infection) on a nose and throat swab will also be approached for consent for a blood draw as soon as possible and then at further monthly visits to the end of their original follow-up, where this does not lead to targets for blood sampling being exceeded by >5% (which impacts the capacity of the laboratory to conduct all the required tests).

Note: from protocol v16.0, assessments will be carried out remotely, with sample kits posted to participants and questionnaires completed online or on the telephone

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Healthy volunteers aged 2 years or older (no upper age limit), who are currently resident in a household where an adult member has either participated in an ONS or NISRA survey and has consented to be approached for future research or where the household has been randomly selected from databases of addresses.

8.2. Inclusion Criteria

- Adult, adolescent or child aged 2 years or older, male or female
- Currently resident in a household where a household member has participated in an ONS or NISRA Survey and has consented to be approached for future research or where the household has been randomly selected from databases of addresses. 'Currently resident' is defined according to 2011 Census definitions:
 - A 'resident' is defined as a person who typically stays overnight in the address at least 4 nights out of 7
 - A 'household' is defined as one person living alone; or a group of people (not necessarily related) living at the same address who share cooking facilities and share a living room or sitting room or dining area
- If 16 years or older: Participant is willing and able to give informed consent for participation in the study.
- If 2-15 years at last birthday: A parent/carer is able to give informed consent for participation in the study; those aged 10 years and older should also provide assent.

8.3. Exclusion Criteria

There are no exclusion criteria.

8.4. Blood sampling

Those approached for blood sampling from recruitment will be a random sample of invited addresses.

Those aged 16 years and older approached for optional additional blood sampling after recruitment will be restricted to those households where at least one person gave consent for follow-up beyond 1 month, in order to monitor antibody positivity over time. Households which have ceased active follow-up will also not be eligible to be approached for optional additional blood sampling and extended follow-up.

Those aged 8-15 years approached for optional additional blood sampling after recruitment will be restricted to those households where at least one adult is currently providing fingerprick blood samples (plus those aged 5-7 years in an initial pilot in October 2021 only). No child or young person aged 8-15 years will be approached to provide blood samples at household recruitment.

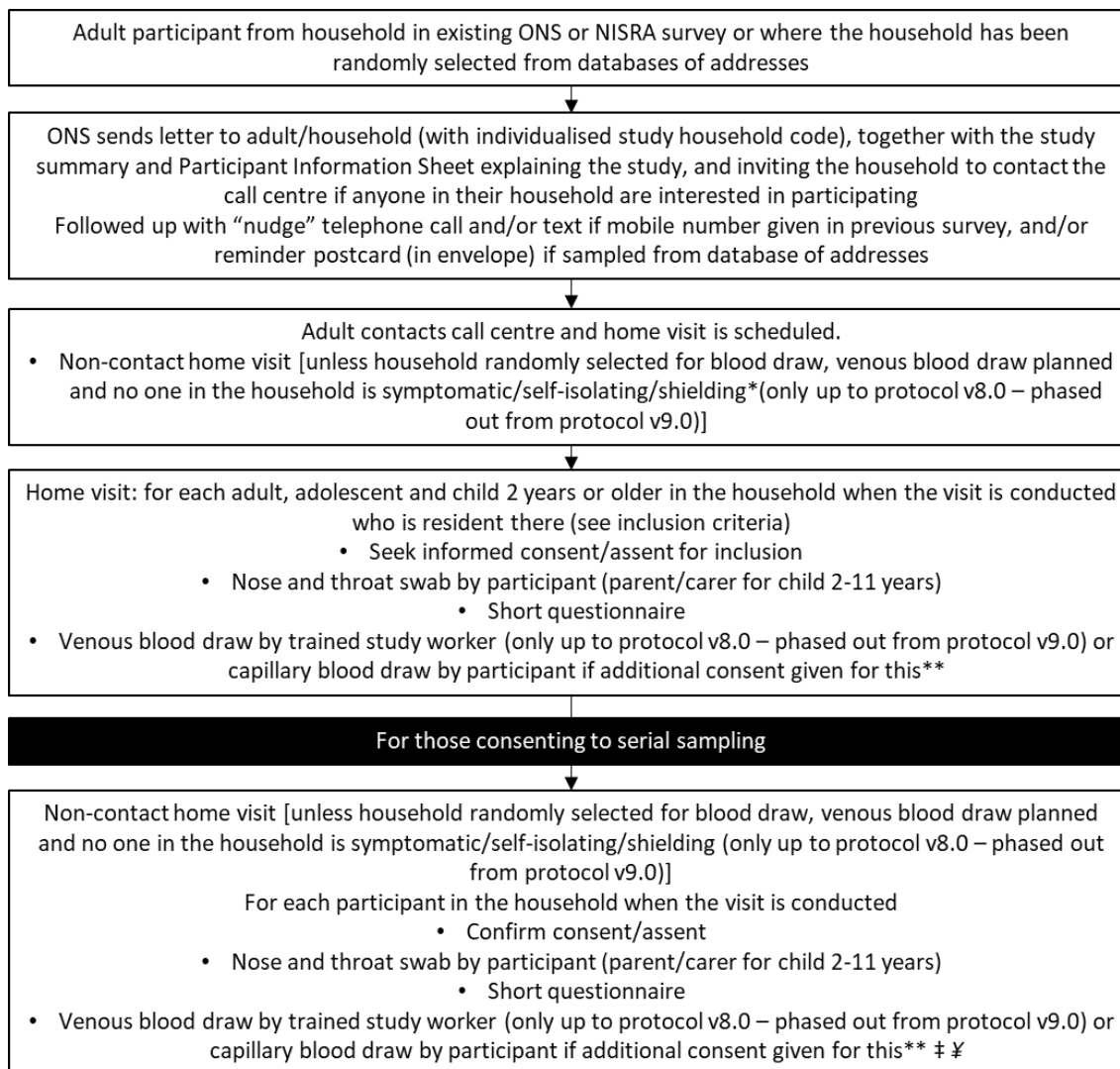
8.5. Co-enrolment

As this is an observational study with no intervention, co-enrolment is allowed with any other interventional or observational research study.

9. PROTOCOL PROCEDURES

Figure 3 Flow diagram

(A) up to protocol v15.0



* Unless a venous blood draw is scheduled, home visits will be non-contact (participant self-swab of nose and throat, questionnaire; study worker stays 2m away from household at all times; capillary blood draw if participant has been randomly selected for blood draw and consented). Contact home visit will include participant self-swab of nose and throat, questionnaire and blood draw (only up to protocol v8.0 – phased out from protocol v9.0). If anyone in the household is symptomatic, self-isolating or shielding, then the visit will be non-contact even if venous blood draw was scheduled.

** Blood draws initially planned in a minimum of 300 enrolled households per week. Households will be randomly selected before being invited and therefore each household with either be approached for swabs and blood or swabs alone. As the consent rate for blood is not known in Phase II, 10-20% of targeted households will be invited to consent for blood samples: all invited households who consent will be included in blood draws.

‡ All participants from households where any individual tests positive for virus (new infection) on a nose and throat swab in the study will also be approached for consent for a blood draw as soon as possible and then at further monthly visits to the end of their original follow-up.

¥ Participants will be asked for consent to continue these monthly visits to April 2022 (consent forms through protocol v6.0 specified participation for 12 months only, so additional consent is required).

Note: only individuals present in the household at the original enrolment visit and who originally provided consent/assent will be included in the serial sampling. Any individuals who join the household after the enrolment will not be included. Any individuals who originally consented to serial sampling and leave the household will be considered withdrawn from the study.

(B) from protocol v16.0

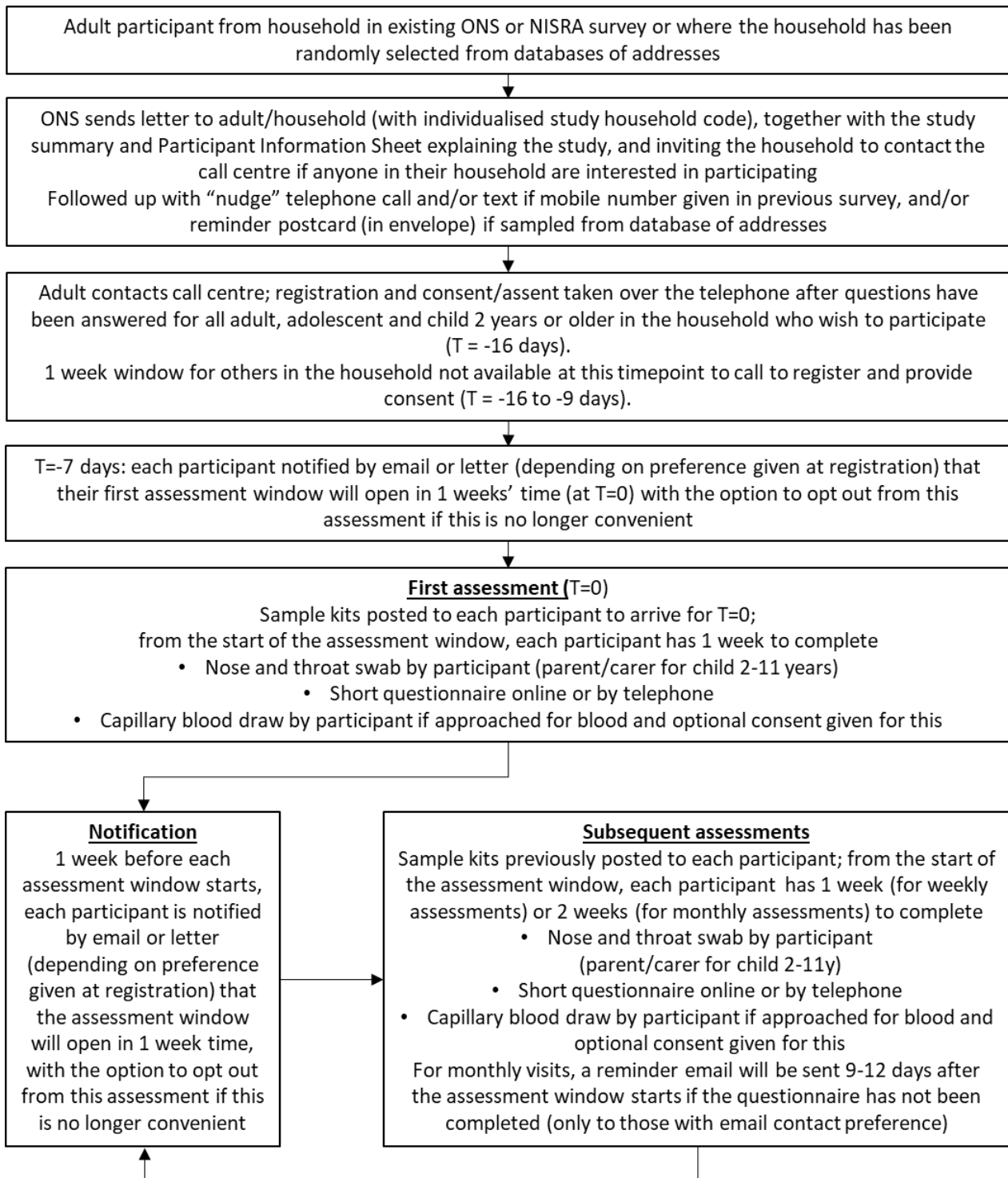


Table 2 Schedule of investigations for each new cohort

(A) up to protocol v15.0

	Initial letter from ONS	Tele-phone contact with contact centre †	Enrol-ment home visit*	Week 1, 2, 3 home visit	Week 4/ month 1, months 2- ¥ home visit
All participants					
Participant Information Sheet(s) (including Welsh translation for households in Wales)	X				
Eligibility screen		X			
Informed consent/assent			X		
Participant nose and throat self-swab (done by parent/carer for child 2-11 years)			X		
Short questionnaire			X		
Capillary blood draw by participant if participant is in a household randomly selected for blood sampling, is 16 years or older, and provides consent (see Figure 2)			X*		
If consent provided for visits at weeks 1, 2, 3					
Informed consent/assent confirmed				X	
Participant nose and throat self-swab (done by parent/carer for child 2-11 years)				X	
Short questionnaire				X	
If consent provided for visit at week 4/month 1 or subsequent monthly visits (see Figure 2)					
Informed consent/assent confirmed					X
Participant nose and throat self-swab (done by parent/carer for child 2-11 years)					X
Short questionnaire					X
Capillary blood draw by participant if participant is 16 years or older and provides consent, and is either in a household randomly selected for blood sampling (starting from recruitment or subsequently), or is from a household where a participant has had a positive nose and throat swab in the study (see Figure 2)					X*
Capillary blood draw by participant or parent/carer if participant is 8-15 years (5-7 years in an initial pilot in October 2021 only) and consent (and assent) is provided, and is in a household where one or more adults are already giving capillary blood monthly					X

† A contact email will be available for those unable to telephone (eg due to hearing or speech impairment). Each household's invitation letter and participant information sheet will have the specific contact centre number.

* Home visits are non-contact (participant self-swab of nose and throat, questionnaire; capillary blood draw if participant has been randomly selected for blood draw and consented; study workers stay 2m away from household at all times).

¥ Participants will be asked for additional consent to continue monthly visits to April 2022.

(B) from protocol v16.0

	Initial letter from ONS	Telephone contact with contact centre † T = -16 days	First assessment (Week 0)*	Week 1, 2, 3*	Week 4/ month 1, months 2, 3, 4 etc to end of study*
All participants					
Participant Information Sheet(s) (including Welsh translation for households in Wales)	X				
Eligibility screen		X			
Informed consent/assent by telephone		X †			
Notification of assessment window 1 week before assessment window starts‡, with option to opt out of this assessment			X	X	X
Participant nose and throat self-swab (done by parent/carer for child 2-11 years)			X	X	X
Short questionnaire			X	X	X
Capillary blood draw by participant if participant is 16 years or older and provides optional consent, and is in a household randomly selected for blood sampling starting from recruitment			X		X
Capillary blood draw by participant who has provided consent for blood sampling from recruitment or subsequently, or by parent/carer if participant is 8-15 years and consent (and assent) has been provided					X

† A contact email will be available for those unable to telephone (eg due to hearing or speech impairment). Each household’s invitation letter and participant information sheet will have the specific contact centre number. Others in the household may call to consent at any time up to -9 days (1 week after the first consent in each household).

* The assessment window is 7 days for weekly assessments and 14 days for monthly assessments. Compensation vouchers will only be issued for samples and questionnaires completed within the assessment window.

‡ aim is to send assessment window notifications 7 days before each assessment window opens; may be 5-7 days before depending on e.g. postal deliveries and capacity.

Note: the assessment window is termed the “testing window” in materials for participants. Monthly visits will initially be implemented as 31 days apart, but given substantial uncertainty in the percentage of testing windows that will be completed under the new approach, this schedule may be extended by up to 5 days (to 36 days) or shortened by up to 3 days (to 28 days) in order to achieve the overall sample targets with the (unknown) number of participants who choose to opt in to the new approach. This does not impact analysis as the key objectives relate to rates over calendar time.

9.1. Recruitment

Households will be recruited from databases of addresses (Phase II) and existing and ongoing ONS and NISRA surveys, including the ONS Opinions COVID-19 Survey in Phase I. This survey is wave 6 of the Labour Force Survey and recruits one adult per household across the UK to ask non-medical questions about the impact of SARS-CoV-2. The survey is voluntary and is conducted in compliance with the Code of Practice for Official Statistics. As part of this survey, participants indicate whether they are happy to be approached for future research and those who have indicated that they are willing will be approached for recruitment into Phase I of this study.

As of 18 April 2020, approximately 5,000 adults from across the UK have agreed to be approached for future research from this survey. Phase I will approach all these adults in England for feasibility reasons relating to initial availability of study workers, together with other households identified from the Labour Force Survey who have similarly agreed to be approached for future research. Recruitment into the Opinions COVID-19 Survey is continuing, with approximately 4,000 adults being recruited per month for at least May and June 2020. Given its size and scale, Phase II will extend this approach to sampling, by continuing to recruit individuals who have indicated that they are willing to be approached about future studies from other ONS and NISRA surveys and also include participants in the Devolved Administrations, and also by selecting households randomly from a commercially available source such as AddressBase, which is maintained by the Ordnance Survey, or equivalent databases including in the Devolved Administrations. This will ensure that the sample remains representative in terms of the country throughout its duration and also facilitate proportionate increases where there is evidence of increasing prevalence.

Regardless of phase, ONS will send a letter to all targeted households, explaining the nature of the study, together with the main Participant Information Sheet and a short summary of the study and will follow this up with one telephone call and/or text reminder following standard practice where contact numbers have been provided through participation in a previous survey or are available via the address list from which households are sampled. Households, including those sampled through databases of addresses, may also receive a postcard reminder (in an envelope to ensure that the households study code remains private). Welsh translations will also be sent to households in Wales. The invite letter will direct participants to a website where some additional translations will be available. Only the short summary (in leaflet form) and the Participant Information Sheet for adults 16 years and older will be sent with the invitation letter (and not other Participant Information Sheets), since the point of contact from previous surveys is an adult or the household as a whole in Phase II and it will not be known whether there will be children or adolescents in the household. This Participant Information Sheet includes relevant information for parents/carers about any children in the household. Up to protocol v15.0, additional age-appropriate information will be provided at home visits where appropriate; from protocol v16.0, weblinks to additional age-appropriate information sheets will be provided in the Participant Information Sheet for adults 16 years and older, along with advice on introducing the study to younger household members where relevant. From protocol v16.0, the initial invitation will also include a step-by-step guide to the process of joining the study and a blank copy of the consent form watermarked as an example, not to be used.

Each household will be assigned a unique code at the point they are selected to be approached for the study: this code will be used on subsequent study correspondence. After recruitment, different

household members who consent to participation will be uniquely identified by a pseudonymised study number. The invitation letter will ask an adult to telephone the contact centre if anyone in the household is interested in taking part. A contact email will be available for those unable to telephone (eg due to hearing or speech impairment). One or multiple members of the household may participate, regardless of whether the originally targeted adult chooses to participate, but those outside the household are not eligible.

9.1.1. Registration, consent and home visits through protocol v15.0

When an adult from the household telephones the contact centre, any immediate questions will be answered and a home visit from a study worker will be arranged. Verbal consent will be obtained for this home visit, and documented. At each non-contact home visit, the participant(s) aged 12 years and older will self-swab their nose and throat (methods currently being successfully used in those 12 years and older at drive through testing centres and in Phase I) and study workers will administer the short questionnaire (details below). For children aged 2-11 years, the parent/carer will self-swab the child (minimising risk to study workers) and will complete the questionnaire on behalf of the child. Study workers will stay 2m away from household at all times, passing the necessary equipment to the participant(s). In practice in Phase I, non-contact visits have either been conducted at the doorstep, or the study worker has telephoned the household from their car for the majority of the visit, coming to the doorstep only to pass over consent/assent forms (enrolment only) and the self-swabbing materials, with the choice left to the individual participants in the household. Given its acceptability and the fact that the information collected in the study has a low risk for confidentiality (the questions about health are about COVID-related symptoms now and in the past), a similar approach will be used in Phase II. If the household has been selected for blood draw, blood may be taken from a capillary (fingerprick) by the participant (aged 16 years or older) at a non-contact home visit. The study workers will bring all the recommended personal protective equipment (PPE) to these home visits.

Full consent (and assent where relevant) will be taken at this enrolment home visit (see below).

9.1.2. Registration, consent and study assessments from protocol v16.0

When an adult from the household telephones the contact centre, any immediate questions will be answered. If the adult wishes to provide consent at this point, this may be taken over the telephone (see below); otherwise, they will be invited to call back at their convenience. Anyone else from the household who wishes to participate may also have their questions answered and consent taken at this telephone call, or they may call back to consent to join the study at any time over the next 7 days from the first person consenting in the household (set as time -16 days (before the first assessment window), see Table 2B above). The maximum time from the first to last person in each household consenting is set at 1 week (-9 days), to allow notifications of the first assessment window to be sent to all participants in the household 1 week (7 days) before the first assessment starts at T=0. If all eligible individuals in the household provide consent at this initial phone call, this consent window may close sooner. Each participant who consents will be asked their preference for questionnaire completion (online or by telephone), future contact regarding study communications (e.g. notification of assessment windows) and test results (email or letter) and whether they have the ability to use a priority post box in general or will need to use a courier (see below). Participants will also be asked whether they would like to receive compensation for study assessments (see Section 16.8), and if yes, whether they wish to receive these

vouchers by email or post (separate preference to study communications). The different preferences available to participants are summarised in Appendix I, Figure 6.

Following consent and before their first assessment window, new participants will be emailed links or posted a guide on how to take a swab and how to take blood if consent has been provided for this, together with step by step guide to what will happen in the survey. These materials will also be available at all times on the study website. A copy of their consent for the study will also be sent securely (see Section 9.3), together with their unique participant ID. Flow and example timeline for new participants is summarised in Appendix I, Figures 7 and 8, and communications with new participants summarised in Appendix I, Figure 9.

One week before the first assessment at T=0, and every subsequent assessment (see Table 2B above), each participant will receive a notification of their upcoming assessment window for sending notifications -7 to -5 days before each assessment window starts). This will be via individual email where participants state a preference for email notification at registration, otherwise by a single letter to the household. Each participant will have the option to opt out of the upcoming assessment on an individual basis if this is no longer convenient up to 4 days before the assessment window opens, in order to avoid sending sample kits that will not be used. Opt out will initially be by telephone, but an online opt out process will be provided as soon as possible. Participants who have consented to blood sampling may opt out of blood sampling but still complete a swab test and the questionnaire at any assessment. The participant's experience of each assessment is summarised, according to their preferences, in Appendix I, Figures 10-13.

Each participant who has not opted out of an assessment will be posted a swab kit, and if consented to blood and not opted out of blood sampling at this assessment, a blood kit. The dates of the period during which tests/questionnaires should be completed will be included in the notification email/letter, and will be 1 week from the start of the window for weekly assessments and 2 weeks from the start of the window for monthly assessments. The notification email/letter will also contain the weblink to the questionnaire and the telephone number to call to complete the questionnaire. Samples (self-swab of nose and throat, fingerprick blood sample) should be taken on the same day as the questionnaire is completed, regardless of which method of completion is used. The logistics of sending and returning sample kits and completing the questionnaire are summarised in Appendix I, Figures 14 and 15. A short summary of key information will be included with the sample kits, together with the barcodes identifying the samples which each participant will confirm when completing the questionnaire.

Those with a preference for email communication will be sent a reminder 9-12 days after the start of each assessment window if the questionnaire has not been completed at this time (precise timing to be determined based on when questionnaire/test returns start to reach a maximum). Given potential delays in post, those with a preference for communication by letter will not receive a reminder.

The main method for returning swab and blood samples will be through Royal Mail priority postboxes. If participants are not able to get to a priority post box themselves, anyone can take the sample kits to the post box for them. Alternatively, participants can book a courier to return their samples if they do not have anyone else to take samples to a priority post box and:

- they cannot get to a Royal Mail priority post box without using public transport
- there are no Royal Mail priority post boxes where they live

- they are classed as vulnerable or clinically extremely vulnerable
- they are too unwell to leave their home
- they have limited mobility.

9.2. Screening and Eligibility Assessment

There is no maximum duration between receiving the invitation letter and recruitment. The time will depend on participant convenience (and availability of study workers through protocol v15.0), but will be as short as possible in order to maintain the serial survey design. In the case of late response, the household will be analysed according to the date the household was enrolled (first study assessment).

9.3. Informed Consent

Up to protocol v15.0, verbal consent for the home visit will be obtained during the telephone call in which the appointment is made. At this enrolment home visit, each participant in the household aged 16 years or older must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed. The person who obtains the consent must be suitably qualified and experienced, and have been authorised to do so by IQVIA (responsibility delegated to IQVIA from the Chief Investigator and Sponsor). An Informed Consent document will be signed; the original paper form will be left at the household with the participant (or parent/carer) and the consent form scanned securely to obtain the research copy.

From protocol v16.0, consent for participation in the study will be taken over the telephone. Each participant in the household aged 16 years or older must personally confirm their consent to each of the statements in the Informed Consent form before any study specific procedures are performed. The person who obtains and records the consent must be suitably qualified and experienced, and have been authorised to do so by IQVIA (responsibility delegated to IQVIA from the Chief Investigator and Sponsor). A hard or electronic copy of each Informed Consent document completed remotely will be sent securely to each participant (or parent/carer) in the household, including their name and pseudonymised study number.

The same process will be followed to obtain consent from a parent/carer for participation of a child or adolescent aged 2-15 years, and for assent from older children and adolescents aged 10-15 years. Up to protocol v15.0, age-appropriate information will be provided at the home visit; from protocol v16.0 weblinks to additional age-appropriate information sheets will be provided in the Participant Information Sheet for adults 16 years and older, along with advice on introducing the study to younger household members where relevant.

Each potentially eligible household member may choose to participate or not to participate individually – all those who consent/assent will be included, but not every member of the household is required to consent/assent. Up to protocol v15.0, only those individuals present in the household at the time of the enrolment home visit will be approached for consent/assent. Any individuals who join the household after the enrolment home visit will not be included, nor will any individuals who were members of the household at the time of the enrolment home visit but not present at the enrolment home visit. From protocol v16.0, other potentially eligible members of the household may telephone to ask questions and provide consent at any time up to 1 week after the first person in the household provides consent.

Written versions of the Participant Information Sheets will have been provided to the participants together with the original invitation letter (via post) detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason, including at the initial home visit up to protocol v15.0, and with no obligation to give the reason for withdrawal. Up to protocol v15.0, information will also be presented verbally at the home visit or during the telephone call to make the home visit appointment; from protocol v16.0, information will be provided during the registration and consent phone call (participants may also call back later to provide consent subsequently at any time over the 7 days following the first person consenting in the household).

Consent will include:

- Required: To provide a small amount of additional data on questionnaires (see below).
- Required: For linking their data and sample results from this study to available data already held by ONS and relevant national mortality databases (because this is where we will obtain geographic data from, and to obtain overall mortality and cause of death), to NHS records (and equivalent national databases in Devolved Administrations) from January 2016 to 15 years from their last assessment (in order to assess the impact of results gained from the study on future healthcare utilisation) and to UKHSA and equivalent national test databases in Wales, Northern Ireland and Scotland from January 2016 to 15 years from their last assessment to ensure that we have information on other tests for SARS-CoV-2. It will be stated in the Participant Information Sheet that this linkage will require the study to hold name, address, sex and date of birth.
- If household selected for blood sampling: Optional: Blood sampling in those 16 years and older (where requested).
- If household selected for blood sampling: Optional: For any leftover material from blood samples taken at the study visits (see below) to be saved for future better tests relating to SARS-CoV-2.
- Optional up to protocol v15.0: To repeated assessments to collect the same samples and information, see **Figure 2A** for options. Up to protocol v15.0, the choice of participating once at enrolment, weekly for the first month, or weekly for the first month and then monthly will be made at the enrolment visit; participants will not be offered the option to extend if they initially choose weekly visits for one month only. As over 95% of participants offered these options through to protocol v15.0 chose to have repeated monthly visits over the longer term, and a number of those who initially chose 1 or 5 visits requested to then extend their participation (which was not possible under the approved protocol), from protocol v16.0, we will ask everyone joining the study to have study assessments every week for the first month and then every month until the study ends. Participants are free to withdraw at any time.
- Optional: For the study to approach them in future with details of other ethically approved research studies or other programmes approved by DHSC or UKHSA (or equivalent in Devolved Administrations) for them to consider for potential participation (see below). (A list of DHSC or UKHSA (or equivalent) approved programmes is maintained on the study website with further details for participants.)
- Optional: if originally approached for swab tests only, to provide swab and blood tests if any member of their household tests positive on a swab test (as described in Section 7 above).

The reason for asking whether individuals would be happy to be approached in future for other ethically approved research studies or other programmes run by the NHS (or equivalent in Devolved Administrations) is because several other studies are trying to recruit individuals, for example, for human genetic studies led by Genomics England (<https://www.genomicsengland.co.uk/covid-19/>). However, if participants indicate that they are happy to be approached for future ethically approved research or other programmes run by the NHS (or equivalent in Devolved Administrations) (optional consent), this study would forward to them information about other studies/programmes for their consideration. This information would also be maintained on the study website.

The Participant Information Sheet will have been posted to the household with the original invitation letter, ensuring that households have adequate time to consider whether they wish to call to discuss participation in the study. Up to protocol v15.0, age appropriate documentation will be brought to the home visit for adolescents and children; from protocol v16.0, weblinks to additional age-appropriate information sheets will be provided in the Participant Information Sheet for adults 16 years and older, along with advice on introducing the study to younger household members where relevant. Up to protocol v15.0, it is not possible to give potential participants unlimited time to consider the study at the home visit. However, they will have had the opportunity to cancel the appointment at any time between the original telephone call and the home visit.

Each potentially eligible household member will be recorded as either having consented/assented to the study or not. For those who do not consent/assent, the reason will be recorded if the person is willing to provide this, and their age in years.

Any individual household member who assented to the study at enrolment but attains 16 years during the study will be consented individually at the first study visit after their 16th birthday. After study worker visits are no longer being conducted, participants would receive an initial invitation (using their preferred method of communication, email or letter) to consent individually following their 16th birthday, with no testing windows scheduled after this invitation has been sent. Consent would be taken over the telephone, as for new participants. They would receive a reminder about consenting themselves 20-40 days after the first invitation (currently 30 days but may be varied depending on the response rate to communications over time as for invitations to opt in to the new approach, see below), and a final reminder 60-80 days after the initial invitation (currently 70 days, but may be varied as above). In order to use mixed modes to reach participants, this second reminder would be by letter wherever possible. After this second reminder, a previous adolescent participant will receive no further communication about the study.

9.3.1. Transition to extended period of data linkage in protocol v14.0

The protocol originally sought consent for linkage of survey data to health records from the beginning of 2020 to 1 year after the last study visit (required, not optional, for participation as secondary endpoints relied on this data linkage for ascertainment). Given the ongoing nature of the pandemic and the importance of quantifying the risk of future health conditions associated with having had COVID-19, adjusting for pre-existing health conditions (as described in Section 7 above), in protocol v14, this consent was extended to run from 1 January 2016 to 15 years after the last study visit. All active participants at the time of extension (substantial amendment 13, protocol v14.0) were contacted to inform them of this change, with the option to opt out of additional data linkage compared with their original consent. Similarly, all participants who had completed their study follow-up or left the study for reasons such as moving house, without formally withdrawing from study participation, and who had

agreed to be approached in the future about research (>97% of participants) were approached in the interests of transparency, and provided with the same option to opt out of additional data linkage compared with their original consent. Participants who had completed follow-up but who had not consented to be approached in future about research (<3%) and those who had been withdrawn (e.g. due to loss of capacity or unreasonable behaviour) were not approached and will not have data linkage extended.

9.4. Enrolment

There is no intervention.

Whether a household is approached for blood sampling is randomly allocated (whether at recruitment or subsequently).

Participants will be enrolled at the first home visit up to protocol v15.0, or at a telephone call at which consent is taken, 16 to 9 days before the first assessment from protocol v16.0.

9.4.1. Post enrolment recruitment into providing monthly blood samples and extending follow-up in those providing blood samples to April 2022 (from protocol v7.0)

A random sample of 10-20% households has been approached for consent to provide blood samples from the point of recruitment for the duration of their follow-up in the study. However, larger numbers are required to assess the impact of vaccine rollout on population level immunity (see Section 11.3 below). Therefore from February 2021, a randomly selected sample of already enrolled households who are currently providing swab but not blood samples, and where at least one person originally provided consent for 12 months' follow-up, will be invited to additionally provide blood samples at their monthly visits and extend their follow-up through to April 2022. This will be optional, and will be on an individual basis in those aged 16 years and older, but will be for both components (follow-up to April 2022 and monthly blood draws). Those aged 16 years or older who do not provide consent for this optional blood sampling will remain on monthly follow-up from the original household recruitment date with swabs only. If anyone in the household provides additional consent, then parents/carers of anyone aged under 16 years in the household will be approached for consent to extend follow-up to April 2022 only for these individuals (to ensure that the household continues follow-up together).

At the same time, those households who were approached for blood draws from enrolment, and where one or more person has already consented to blood draws from enrolment, will be approached for optional consent to extend their monthly follow-up to April 2022. This is because the original consent form for these participants specified the duration of study participation as one year. Similarly, if anyone in the household provides additional consent, then parents/carers of anyone aged under 16 years in the household will be approached for consent to extend follow-up to April 2022 only for these individuals (to ensure that the household continues follow-up together). From May 2021 (protocol v9.0), all blood draws will be capillary using a fingerprick.

The reason for not consenting will be recorded if the participant is willing to provide one, but this is not required. Regardless of consent, study participants may refuse a blood draw at any individual visit according to their preference at that visit.

As consent to be approached in future for other ethically approved research studies or other programmes run by the NHS (or equivalent in Devolved Administrations) (see Section 9.3 above) was only added for all participants, regardless of positivity, in protocol v6.0, this option will be sought from all those being approached about additional blood draws and extended follow-up until April 2022.

Selected households will receive an invitation letter explaining the additional blood draws and visits. This may be sent by email where participants have provided email addresses to receive vouchers and information about the study; participants without email addresses will be sent the invitation by post. A reminder may be sent where relevant, either by post or email. Anyone who is willing to consent can do so either by informing their study worker at their next scheduled visit or by contacting the contact centre. They will then be asked to sign an additional consent form at their next scheduled visit, before any blood is drawn.

9.4.2. Post enrolment recruitment into extending follow-up in those only providing swab samples to April 2022 (from protocol v9.1)

In order to maintain swab targets through April 2022, from May 2021, we will approach all participants providing swab samples only and who originally agreed to 12 months follow-up for consent to extend their monthly visits to April 2022. This will be optional, and will be on an individual basis for each participant (i.e. is not dependent on agreement of the whole household). This is because the original consent form for these participants specified the duration of study participation as one year. The reason for not consenting will be recorded if the participant is willing to provide one, but this is not required. Regardless of consent, study participants may refuse any individual visit according to their preference.

As consent to be approached in future for other ethically approved research studies or other programmes run by the NHS (or equivalent in Devolved Administrations) (see Section 9.3 above) was only added for all participants, regardless of positivity, in protocol v6.0, this option will be sought from all those being approached about extended follow-up until April 2022.

Selected households will receive an invitation letter explaining the additional blood draws and visits. This may be sent by email where participants have provided email addresses to receive vouchers and information about the study; participants without email addresses will be sent the invitation by post. A reminder may be sent where relevant, either by post or email. Anyone who is willing to consent can do so either by informing their study worker at their next scheduled visit or by contacting the contact centre. They will then be asked to sign an additional consent form at their next scheduled visit.

9.4.3. Post enrolment recruitment into providing monthly blood samples for those aged under 16 years (from protocol v11.1 (initial phase), v13.1 (main phase))

Through protocol version 10.0, fingerprick blood testing for antibodies in the survey was done only in those aged 16 years and older. However, as schools re-opened in Autumn 2021, positivity rates were 1.41% the week ending 27 August 2021 compared with 0.05% the week ending 25 August 2020. COVID-19 vaccinations were recommended only for those 12-15 years with long-term health conditions leaving them at higher risk of serious illness from COVID-19 or living with someone at higher risk of serious illness, meaning the majority of school age children remained unvaccinated. However, positivity rates are far higher in school age children than adults, leaving key questions relating to the degree of immunity school-aged children might already possess due to higher previous rates of natural infection and how

much this might mitigate effects of return to school on positivity rates, and hence onward transmission, within this critical age group. For example, despite historically higher positivity rates in children, between September-December 2020, 13% of both students and staff in eighteen schools in six regions in the SKIDsPLUS study were SARS-CoV-2 sero-positive¹⁵. In March 2021, 13% of primary and 17% of secondary school pupils tested positive for SARS-CoV-2 antibodies in the ONS Schools Infection Survey, although this varied between 5% and 28% across secondary school pupils in different areas¹⁶. In the same survey, in June 2021, 25% of primary school staff and 23% of secondary school staff tested positive for SARS-CoV-2 antibodies¹⁷ (pupil data not yet available). How antibody prevalence in children relates more generally to antibody prevalence in adults in the same household and adults in the same communities is unknown, particularly in a general population representative sample.

From protocol v11.0, the option for their child to participate in fingerprick blood testing for SARS-CoV-2 antibodies will be offered to parents of children aged 5-15 years already enrolled in the survey, where at least one adult in the household is themselves already providing fingerprick blood samples (amended to 8-15 years in protocol v13.0 following results of an initial phase in October 2021, see below). This is to ensure that the parent/carer providing consent for the child has a clear understanding of the procedure and what it means to provide the fingerprick blood sample. In an initial pilot phase sampling in October 2021, consent from the parent/carer will be to provide a fingerprick sample every other month (i.e. not monthly as for adult participants) in order to estimate how antibody levels change over time in children and adolescents, in the same way as adults. Views of parent/carers will be elicited to determine frequency of testing if wider rollout proceeds (see below; monthly testing from protocol v13.0 based on parent/carer views). Children will be asked for their verbal assent for the blood draw and any dissent will always be respected. Regardless of initial consent/assent, participants aged under 16 years may refuse a blood draw at any individual visit according to their preference at that visit, and/or their parent/carer may refuse on their behalf. Those aged under 16 years for whom consent is not provided for this optional blood sampling will remain on monthly follow-up for swabs only. The reason for not consenting and assenting will be recorded if the participant is willing to provide one, but this is not required.

As all visits are non-contact with the study worker staying at least 2m away at all times, the parent/carer will take the fingerprick sample for the child, using the same instructions as they use themselves (adolescents may take the sample themselves following the fingerprick guide) (see Section 9.6.1 below). The sampling kits for adults and children are identical, except that a paediatric lancet will be available for children who need it (adolescents may prefer to use the adult lancet depending on age and body size). Fingerprick samples will be processed using exactly the same methods and assay as for adult participants (see Section 9.9 below), and antibody results will be returned in the same way as for adult participants (see section 9.9.2 below). One important reason for using identical testing methods is to ensure comparability in antibody positivity results across the age range, rather than using a different test in those under 16 years from those 16 years and older. Use of identical methods and assays will mean the data are directly comparable. In contrast, saliva antibody tests used in the ONS Schools Infection Survey have an estimated sensitivity of only 80%¹⁶, meaning methods of analysis firstly need to make adjustments for this and secondly also need to account for different positivity thresholds. The minimum blood volume marked on the tube is 250µL, although the laboratory are able to process samples down to 200µL, but this provides a quantitative antibody level as well as a positive/negative result. This is essential moving forwards in the pandemic as it provides the flexibility to look at higher antibody levels which appear likely to be needed to neutralise different variants. This is also a major limitation of point of care lateral flow antibody tests, which do require smaller blood volumes, but each use their own

individual threshold and again have much poorer sensitivity. For example the FORTRESS assay used in adults in the REACT study had sensitivity 84% and specificity 99% for PCR-confirmed cases/pre-pandemic sera (compared with >99% for the assay currently used in adults in the survey¹⁸), again leading to the same challenges with analysis as saliva based tests.

Support for fingerprick testing with a quantitative assay comes from a large online public engagement study (n=4,290) carried out in June 2020 by REACT¹⁹. Key findings from their Executive Summary were

- There is high willingness among parents/carers to perform finger-prick antibody testing on children, even if just for research purposes.
- Young people also showed high willingness to be tested to see if they've had COVID-19, although to a slightly lesser extent than parents/carers.
- Overall preference was for the test to be performed at home by the parent or young person.
- Whilst 59% chose “saliva test (spit into tube)” as their preferred test approach, “finger-prick test” was the second most common choice (25%) and further comments suggested preference was generally for whichever test is more accurate.

We have also discussed parent/carer supervised/performed fingerprick testing with highly experienced research nurses from the Oxford Vaccine Group and they confirm that it would be a feasible and acceptable approach.

Therefore, households where at least one adult participant is already providing fingerprick samples and where one or more children/adolescents aged 8-15 years are participating in the survey will receive an invitation letter explaining the additional blood draws (5-7 years also included in an initial pilot in October 2021, see below). By definition this will be at a post-enrolment visit. This invitation may be sent by email where participants have provided email addresses to receive vouchers and information about the study; any participants without email addresses will be sent the invitation by post. Any parent/carer who is willing to provide consent for their child/adolescent can do so by informing their study worker at their next scheduled visit. They will then be asked to sign an additional consent form at their next scheduled visit, before any blood is drawn. Children will be asked for their verbal assent for the blood draw at this visit and any dissent will always be respected. Children and young people who attempt the blood draw will receive a sticker as a “thank you” in the initial phase only.

However, reflecting the fact that uptake is unknown, invitations will be sent using a phased approach. We will first sent invitations to all adults aged 24 years or older in around 1,100 eligible households focussed around specific geographic regions (to facilitate additional study worker training) and targeting invitation letters to as even a spread of around 1,000 approached children between 5-15 years as possible (taking into account non-response/missed visits). Assessment of feasibility of proceeding across all eligible households would be based on the number of fingerprick tests attempted and antibody test results obtained per child/adolescent in whom consent was sought (so incorporating both parent/carer consent and ability to provide a blood sample of sufficient volume to run the test successfully). This outcome would be modelled by age from 5-15 years, and separately in those 5-9 and 10-15 years. If test results are obtained in <5% in either age group, then no further households would be approached for recruitment. Age ranges or age groups with >25% test results and >50% agreeing to do the test again in future (see below) would proceed to full implementation. For rates between 5 and 25% the funder would take a decision about proceeding to full implementation based on exact rates and association with age, and anticipated future participation. If a decision is made not to proceed, then any households

invited into the pilot who have not yet had a study visit (e.g. due to dates not being convenient/personal preference) would not be subsequently approached.

In addition to the two quantitative outcomes (consenting and finger prick test attempted/approached, valid blood test result/approached), we would also record the parent/carers views on acceptability of fingerprick testing for each child approached, specifically regarding whether or not the test was completed successfully, how easy or hard they found the test, and how often in future would they be willing to try fingerprick testing again (including a never option), as well as any free text comments regarding the pilot. As this feedback would be sought only within the pilot, it will either be recorded on the main study database (depending on time needed to develop this) or using a separate survey tool (Smart Survey) to the main study database. On Smart Survey, child participants would be identified only by their age in years at last birthday, sex, and pseudonymised household identifier (no personal identifiable information).

In the initial pilot phase, 1,465 participants aged 5-15 years were visited and blood samples were obtained from 265 participants (18.1%). Blood samples were obtained from 5.5% aged 5-7 years, 17.3% aged 8-10 years, 21.9% aged 11-13 years and 24.9% aged 14-15 years. Of those parents/carers completing the questionnaire and reporting that they took part in the pilot (n=282), the majority (59.2%) reported they would be willing to participate once every month; however this percentage was greater in those aged 8 years or older. The next most commonly chosen frequencies were once every 2 months (12.1%) and once every 3 months (12.4%). An equal percentage reported they would not do the test again or were not sure (both 7.1%). Questionnaire responses suggested mixed experiences of how easy they found the test, with 8.2% reporting that it was very easy, 35.1% easy, 22.0% difficult, 15.2% very difficult and 19.1% giving a neutral response.

Based on the results of this initial pilot phase, from protocol v13.0, households where at least one adult participant is already providing fingerprick samples and where one or more children/adolescents aged 8-15 years are participating in the survey will receive an invitation letter explaining the additional blood draws and inviting those aged 8-15 years to participate and provide a blood draw monthly. As for adult participants, regardless of initial consent/assent, participants aged 8-15 years may refuse a blood draw at any individual visit according to their preference at that visit, and/or their parent/carer may refuse on their behalf, meaning that those who prefer less frequent blood draws may do so within the protocol.

Given the low uptake rate (5.5%) those aged 5-7 years will not be invited to participate from protocol v13.0 onwards.

In terms of targets, protocol v11.0 included a maximum target of 5,500 blood test results per month across the entire age range of 5-15 year olds, based on sampling ~4,000 children aged 5-9 years and ~7,000 older children/adolescents aged 10-15 years every other month, and 25% uptake. Based on the results of the pilot, 5-7 year olds will not be included and the proposed frequency of testing changed to monthly in 8-15 year olds (as described above). The net result of these two changes, plus slightly lower uptake than originally estimated in those aged 8-15 years (~20% vs 25%) leads to a new target of 3,600 blood test results per month across 8-15 year olds only. As an observational study, the justification for sample size is based on the precision around estimates of positivity obtained, and is considered to still provide acceptable precision (see Section 11.3). From protocol v17.0, reflecting the reduced sample size across the study as a whole, from April 2022, there is no specific target for 8-15 year olds across the UK every 28 days, given higher than anticipated antibody positivity rates in this age group and numbers

providing blood are achieving reasonable precision (e.g.

<https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronaviruscovid19infectionsurveyantibodyandvaccinationdatafortheuk/23february2022>).

9.4.4. Post enrolment transition from study worker home visits (protocol v16.0)

To 3 March 2022, there were 450,275 individuals are currently active in the study (still receiving home visits). Under protocol v16.0, a phased approach will be taken to offer existing active participants the option to transition from study worker home visits to posted sample kits with either online or telephone completion of the questionnaire. The phased approach enables the study to comply with the Central Digital and Data Office (CDDO) requirements (<https://www.gov.uk/service-manual/service-standard>; mandatory for the study to comply with given the government funding of a digital service), whilst also ensuring that procedures are tested before being rolled out to many thousands of participants and that statistical comparisons can be made between answers to questionnaires administered by study workers or online/over the telephone.

Specifically, we envisage a four stage approach, described below with approximate timings; however, these may be accelerated or delayed depending on any logistical or other issues identified. In each stage, participants will receive an email or letter (depending on their existing preference for receiving study information) informing them of the future cessation of study home visits and the arrangements for future assessments, including a step-by-step guide to the process of opting to continue in the study. This will be based on the main Participant Information Sheet for adults aged 16 years and older, excluding the information about registration and consent, and weekly visits for the first month, since all existing participants will have been in the study for at least 3 months at the time they move to the new approach to delivery. The communication will be sent between the scheduled penultimate and final home visit wherever possible, providing an additional opportunity for participants to discuss the future approach to delivery with their study worker. Some invitations may only be sent after the final scheduled home visit; however, all participants have already been informed through an approved communication about the changes to the mechanism of delivery (Substantial Amendment 16). Further, study workers will also provide participants with a short leaflet highlighting the action needed to remain in the survey at study worker visits in June and July 2022, to further increase awareness of the changes. After the initial communication inviting them to remain in the study under the new approach, participants will have the option to register their interest in continuing in the study either immediately or subsequently. There is no time limit to participants registering interest, but there would be no further communications from the study to the participant after a second reminder 60-80 days after the initial communication (see below). Each participant would initially opt-in by telephone, but an online process to register interest in continuing the study will be provided as soon as possible. Participants would receive an initial reminder about registering for the new approach 20-40 days after the first communication (currently 30 days but may be varied depending on the response rate over time), and a final reminder 60-80 days after the initial communication (currently 70 days, but may be varied depending on the response rate over time), approximately following the times when participants would have expected to have study worker visits. In order to use mixed modes to reach participants, this second reminder would be by letter wherever possible (dependent on the total numbers not opted in by this timepoint given the fixed funding to support this) (if necessary, prioritising letters based on participant characteristics with lower opt-in rates after email invitation and email first reminder (as per original communications preference), for example older participants). After this second reminder, a previous participant will receive no further

communication about the study. Whilst limiting the period of transition would avoid large gaps in individual participant's longitudinal data, any specific time period is arbitrary. Early data from Stage 1 indicate that a continued increase in opt-in rates over time from the first week after the initial communication; as the UK moves to 'living with COVID-19' and participants return to work, school and previous activities, with a lower priority being placed on COVID-19, it is important to maximise opt-in from existing participants, even if there is a short gap in their longitudinal data, rather than having to recruit new participants with no prior longitudinal data at all in order to meet targets, and to allow existing participants who wish to move to the new approach the opportunity to do so.

Contact to register willingness to continue in the study will be understood to extend existing consent since no other procedures (self-swab, self-fingerprick by the participant, questionnaire) will change, only the mode by which these are delivered. Each participant who registers interest in continuing will be asked their preference for questionnaire completion (online or by telephone), future contact regarding study communications (e.g. notification of assessment windows) and test results (email or letter) and whether they have the ability to use a priority post box in general or will need to use a courier (as per Section 9.1.2 above, summarised in Appendix I, Figure 6). Participants will also be asked whether they would like to continue to receive compensation for study assessments (see Section 16.8), and if yes, whether they wish to receive these vouchers by email or post (separate preference to study communications). Email addresses and telephone numbers will be verified for those who telephone to opt in to ensure security of this information; participants wishing to provide an email address for the first time will be asked to call the contact centre. All participants from a household who register interest in continuing will have the same first assessment window for the new approach; this will be scheduled to continue the household's monthly visit schedule, within the existing study windows wherever possible with the aim of achieving as smooth a transition in completed test results as possible (see Figure 4 below). The start of this first assessment window will become T=0 for the new system, with assessments scheduled monthly from this point onwards. Flow and example timeline for existing participants opting in is summarised in Appendix I, Figures 16 and 17, and communications with existing participants summarised in Appendix I, Figure 18. Participants who opt to continue in the study will be emailed links or posted a guide on how to take a swab and how to take blood if consent has previously been provided for this, together with step by step guide to what will happen in the survey given their preferences (post box vs courier etc).

The required reduction in sample size and transition to the new approach to delivery from 1 April 2022 will be achieved as follows. First, all participants will be informed that from 1 April 2022, the compensation vouchers will reduce from £25 to £20 per assessment, and that, if they prefer not to continue the study, they should contact the contact centre to withdraw. The numbers choosing to withdraw are unknown, but could be 5-25%. Depending on this, up to 20% of existing participants will be contacted in April 2022 to thank them for their participation and explain that the study has a reduced sample size and it will no longer be possible to continue to include them. Priority will be given to retaining participants with under-represented characteristics, including non-White ethnicity, higher deprivation, smaller household sizes, giving blood by fingerprick and with longest participation and fewest missed visits in the study wherever possible, to improve overall representativeness and maximise the value of the most complete histories of SARS-CoV-2 infections to meet objectives.

Remaining participants will be invited to transition to the new approach to delivery in four stages. Stages 2-4 form a randomised stepped wedge design, enabling statistical comparisons to be made between

answers to questionnaires administered by study workers or online/over the telephone, and swabs/bloods returned by different mechanisms, and ensuring that the study retains sufficient numbers under plausible assumptions to continue to report on positivity (see below).

- Stage 1 (target start date for opt in invitations 21 March 2022²) is a small scale transition of up to 2,000 households, sampled purposively to capture the experience of a range of ages, ethnicities, deprivation, household size and reported long-term health conditions, in transitioning to the new approach. All participants in Stage 1 will be asked to provide feedback on their experience of the new arrangements in order to improve logistics through short surveys; a purposively selected sub-sample will be invited to qualitative interviews (see Section 9.4.4.1 below for details). CDDO term this small scale initial transition the “private beta”. CDDO approval is required to proceed to Stage 2.
- Stage 2 (~4 weeks, target start date for opt in invitations 18 April 2022) is a larger transition of a random 25% of participants not included in Stage 1 (and not dropped from the study, as described above) who would have had study worker visits due in each of the following 4 weeks. CDDO term this small scale initial transition the “public beta”. Participants in Stage 2 will have the opportunity to provide feedback on their experience of the new arrangements through the same short surveys as Stage 1.
- Stage 3 (~4 weeks target start date for opt in invitations 16 May 2022) is a larger transition of a random 35% of participants not included in Stage 1 who would have had study worker visits due in each of the following 4 weeks.
- Stage 4 (~4 weeks target start date for opt in invitations 13 June 2022) is the final transition of the remaining 40% participants.

Assuming that 90% of participants respond to the initial communication, increasing to 99% after the 20-40 day reminder, that ultimately 81% of participants chose to transition to the new format (increasing gradually predominantly over the 6 weeks from the initial communication), that 90% respond in any given assessment window, that individual assessment window non-response is 10%, that overall 97% of sample kits posted that are returned are done so a median 7 days after the start of each assessment window, this staged approach would lead to the number of completed swab tests shown below in Figure 4 over weeks from start of Stage 2, assuming that a theoretical 100,000 participants are currently visited each week (approximately the case). If a greater percentage chose to continue in the study, then the final numbers will be higher, but the trends will be similar. As the percentages who will choose to continue are unknown, randomisation will be stratified, with households with under-represented characteristics, longest participation and fewest missed visits prioritised for randomisation in Stage 2 and 3, and other participants randomised across Stages 3 and 4. Depending on the percentage who agree to continue, some participants originally planned to be randomised to Stage 4 may need to be contacted to explain that it will no longer be possible to continue to include them, given the reduced sample size.

During each of Stages 2, 3 and 4, adjusted estimates of swab and antibody positivity (adjusting for sex, age, ethnicity and region as used in the post-stratification (see Section 11.2), and also further adjusting for deprivation and household size) would be compared between those randomised to transition to the new approach to delivery and returning swab tests and those randomised to still receive study worker

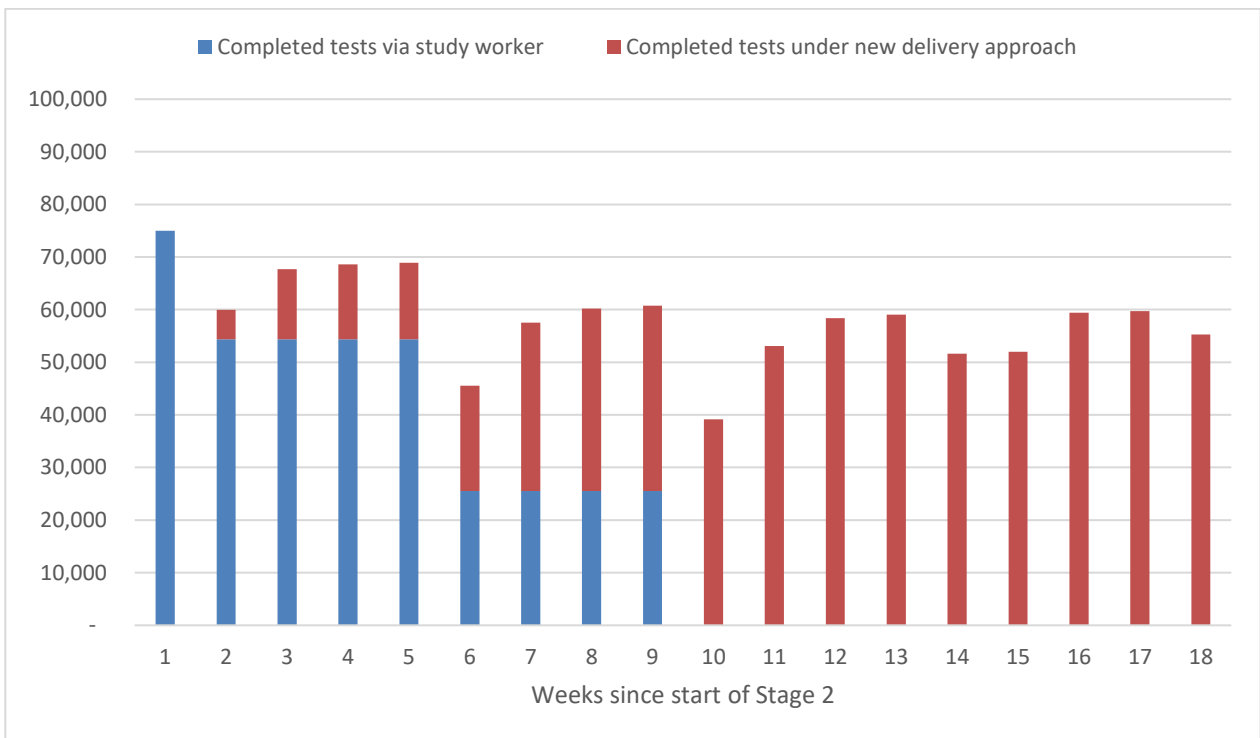
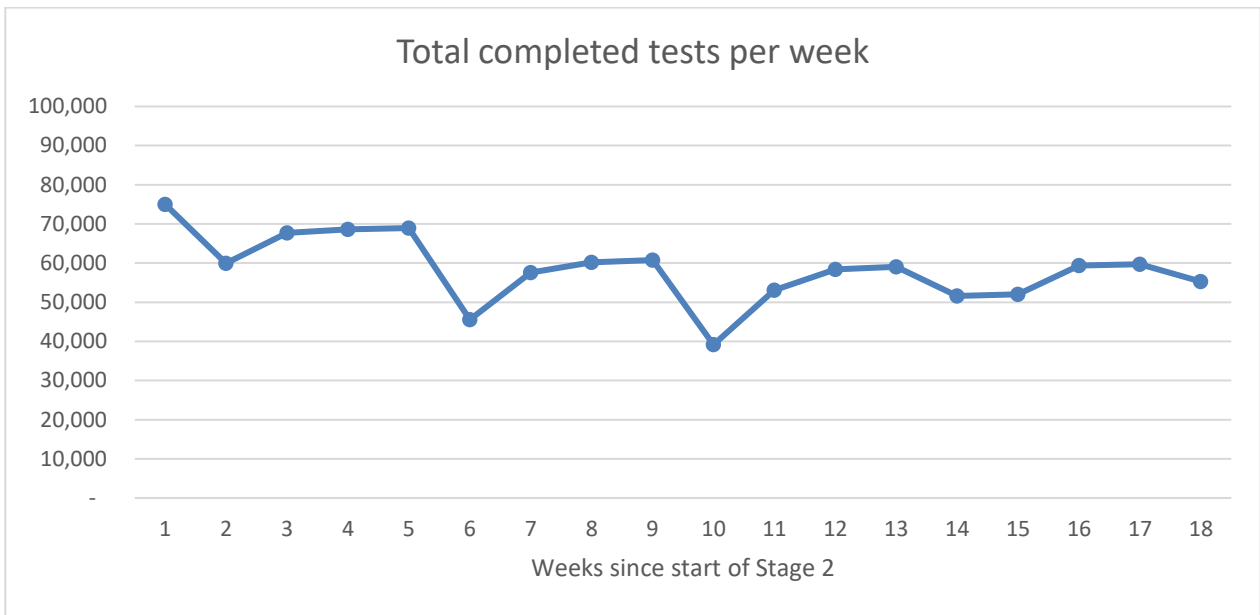
² All dates are indicative targets, depending on approval from the Research Ethics Committee, completion of the database for online/telephone questionnaire completion, and, for later stages, approval from CDDO and absence of need to make other changes based on participant feedback.

visits. This, together with analyses of response rates by these factors, will enable an assessment of whether future adjustments for response rates are necessary.

Study worker visits will continue to be scheduled under protocol v16.0 for all participants who have not yet received their invitation to continue the study under the new approach (up to one home visit will be scheduled after this invitation, but if the household does not attend, no further home visits will be scheduled). Study visits will stop as soon as these final scheduled visit dates have passed.

Monthly visits will initially be implemented as 31 days apart, but given substantial uncertainty in the percentage of testing windows that will be completed under the new approach, this schedule may be extended by up to 5 days (to 36 days) or shortened by up to 3 days (to 28 days) in order to achieve the overall sample targets with the (unknown) number of participants who choose to opt in to the new approach. This does not impact analysis as the key objectives relate to rates over calendar time, not by time since participants joined the study.

Figure 4 Illustration of the impact of staged approach to transition a theoretical 100,000 participants on the number of completed tests per week



9.4.4.1. Collection of quantitative and qualitative data for process evaluation during the transition

The goal of the quantitative and qualitative process evaluation 1 is to test how the new approach to delivery was actually used and received in practice. Process evaluation will include surveys offered to all

participants invited to and opting to continue the study in Stages 1 and 2, and interviews in a sub-sample of those from Stage 1.

Quantitative process evaluation

We will approach all participants invited to and opting to continue the study in Stages 1 and 2 to record their experiences of the new approach to delivery. To ensure that we capture their views at each stage of the process, this will involve the option to complete ~5 short questions after opt in (online or by phone) for existing participants, ~5 short questions after any participant opts out of the testing window and a slightly longer survey (~20 questions) after completing the questionnaire to cover the overall end-to-end process, the questionnaire itself (e.g. layout, clarity of questions, any problems with browsers if online), and the home testing/returns (e.g. getting to a postbox, booking couriers). Questions will include ease of use, understanding of the system from the communications provided, clarity of instructions and the general approach, and use Likert scales to capture strength of views. We will include free text boxes for participants to add further information about experiences regarding the transition, and explicitly elicit suggestions for improvement. Completing these questions would be understood consent to participate in this component of the process evaluation. Participants would be offered the option of completing these questions by phone if they call to opt in/opt out of a testing window or complete the questionnaire by telephone, or could be emailed a link to complete the questions online. The link to the final questions will be included at the end of the questionnaire for those choosing to complete the main survey questionnaire online. As this feedback would be sought only within Stages 1 and 2, it will be recorded using a separate survey tool (Smart Survey) to the main study database. On Smart Survey, participants would be identified only by their age in years at last birthday, sex, region and household size (no personal identifiable information). Analysis will be conducted at least every 2 weeks to ensure that problems with the logistics of the transition are addressed swiftly.

Qualitative process evaluation

All interviews will be semi-structured and conducted by the Office for National Statistics either by telephone or online. Interviews will be audio recorded by the interviewers (and explicit consent will be sought for this). Participants invited and opting to continue the study in Stage 1 will be eligible for inclusion regardless of age or sex, provided they are willing and able to give informed consent for participation in the qualitative study. Consent will be collected verbally and recorded by the interviewer before any interview starts, and a copy of the consent form sent securely to each participant. Participants invited to interviews will be purposively sampled by gender, age and whether they chose to complete questionnaires online or by telephone, and return samples by post or courier; and if possible also by geography, deprivation and other under-represented characteristics until saturation of experiences/views (expect 20-30 interviews). Participants would be approached by staff from the Office for National Statistics once they have completed their first assessment under the new approach to delivery, and interviewed at a time convenient to them. The information provided to participants invited to join Stage 1 will include the possibility that they may be approached for interview (which is optional) and that they will be asked to provide feedback via a survey (also optional).

Interviews will last approximately 30-45 minutes and participants will receive a voucher worth £20 as compensation for their time. Semi-structured, open ended questions will be used to explore individual experiences of using the new approach to delivery.

Interviews will all be audio-recorded and fully transcribed by ONS staff. Transcription will be done using Microsoft Teams transcription software and the audio recording will be captured through a separate computer program. Once the transcriptions are sense checked, the interviewers will anonymise them, by replacing any names or personal identifiers with a participant number and pseudonym in the saved copy of the transcript which will be stored in a limited access Sharepoint folder at the Office for National Statistics. Personal data will be linked with participant numbers stored on a secure network drive at the Office for National Statistics. Pseudonyms are used so that results can be easily discussed whilst protecting participants' identities. Direct quotations used in any reports or other outputs from the study will be anonymous with all identifying details removed.

To ensure that we remain open to and grounded in participants' perspectives, we will carry out thematic analysis of all textual data. Coding frameworks will be developed by two researchers and then iteratively refined, with agreement on all final coding by two independent researchers. Themes and interpretation of findings will be discussed with the wider team, to ensure consistency, particularly comparing and contrasting themes identified from the different approaches to delivery.

9.5. Blinding and code-breaking

There is no blinding and there is no intervention in this study.

9.6. Description of study intervention(s), comparators and study procedures (clinical)

There is no intervention in this study and hence no comparator either.

9.6.1. Description of study procedure(s)

At each study assessment, each participant aged 12 years or older will be provided with a self-swabbing kit, and asked to take their own nose and throat swab (one swab from the nose and throat). These kits are identical to those currently being used successfully for self-swabbing in those aged 12 years and older at the drive through testing centres and in Phase I. Parents/carers will be asked to take the swab from children aged 2-11 years, after first taking their own swab so they can be confident that it is not painful. The study workers will be able explain and demonstrate the technique to each participant in the household. A self-swabbing guide will also be available. The self-swabbing kit includes viral transport media which the swab is placed directly into. This will be labelled with a unique barcode (for this sample) linked directly to the participant's unique study number on the study database. Results from this accredited test will be returned directly to the participant (see Section 9.9.2 below).

Up to protocol v16.0 (when study worker visits are phased out), the study workers will ask each participant (including those under 16 years old) a short set of specific questions (COVID-19 related symptoms based on those recommended by the WHO).²⁰ From protocol v16.0, each participant will complete these questions online or over the telephone, according to their preference.

The following questions will be asked at the enrolment home visit up to protocol v15.0, or during the registration/initial consent telephone call from protocol v16.0:

- Date of birth (required for unique participant identification and for linkage to NHS/ONS/UKHSA records and those from relevant databases in Devolved Administrations); sex; ethnicity
- Telephone number if participants are happy to provide it for contact purposes (e.g. in the case of errors in test results being identified, multiple missing samples etc)

- Email if participant would like to receive communication about the study (eg assessment window notifications) or test results (results will be returned by the study identified by month and year of birth only (not person-identifiable), or vouchers for participation directly by this route, and also to receive updates on results and news about the study (see Section 16.8). Participants may opt out of emails with updates on results from and news about the study, but may not opt out (unsubscribe) from emails about the study procedures or test results, or any communication about the study that has been approved by the Research Ethics Committee.

The following questions will be asked at each assessment (including the enrolment home visit up to protocol v15.0 and the first time the questionnaire is completed online or by telephone for new participants from protocol v16.0), with only changes (where relevant) being elicited at any follow-up assessments:

- Is the participant currently symptomatic or self-isolating? If self-isolating is this because of symptoms in self or others in the household
- Do they have any of the following symptoms today (yes/no for each of fever (including high temperature), muscle ache (myalgia), fatigue, sore throat, cough, shortness of breath (dyspnea), chest pain, headache, nausea/vomiting, abdominal pain, diarrhoea, loss of taste, loss of smell, trouble sleeping, loss of appetite/eating less than usual, runny nose/sneezing, noisy breathing (wheezing), chest pain, palpitations, vertigo/dizziness, memory loss/confusion, difficulty concentrating, worry/anxiety, low mood/not enjoying anything, other symptoms) or since the last visit, or otherwise consider that they currently have COVID-19
- Have they recently been in contact with someone that they definitely know (based on a positive test) or suspect (no positive test) was infected with COVID-19 at the time of contact? Yes/No for each type of contact and for each
 - If yes, date of last contact
 - If yes, was this someone in their own household or someone outside their household
- Occupation (available from ONS or NISRA for the adult targeted in the original letter where identified from previous surveys, but not for the rest of the household or those identified through address lists)
- Working status (employed, not working, retired, student etc) and work location (at home, outside of home etc), including number of days per week usually spent working outside the home or at school/nursery, and mode of transport to get to work/school/nursery
- Healthcare and social care contacts including currently working in health/social care in roles which primarily directly interact with patients/residents/clients or not, recently visited hospital or residential/nursing care home
- Contacts with other individuals inside the household (eg social distancing within the household) and outside the household, including through work, school/nursery, shopping, exercise etc including duration and number of individuals, how easy they find it to maintain social distancing and use of face coverings or masks
- Do they have long-term health problems, and do these limit their activities?
- Current smoking status
- Have they recently travelled abroad? If yes, to which countries?
- Have they received or been offered a vaccine against COVID-19? If yes, type, number of doses, dates.
- Have they received a vaccine against influenza? If yes, date.
- Do they think/know they have been infected by COVID-19? Yes/No

- If yes, date first symptoms and what symptoms (yes/no for each of fever (including high temperature), muscle ache (myalgia), fatigue, sore throat, cough, shortness of breath (dyspnea), chest pain, headache, nausea/vomiting, abdominal pain, diarrhoea, loss of taste, loss of smell, trouble sleeping, loss of appetite/eating less than usual, runny nose/sneezing, noisy breathing (wheezing), chest pain, palpitations, vertigo/dizziness, memory loss/confusion, difficulty concentrating, worry/anxiety, low mood/not enjoying anything, other symptoms)
- If yes, did they contact the NHS about this (suspected) COVID-19 infection? Yes/No
- If yes, were they tested? Yes/No
 - If tested, were they positive/negative/test failed/results not yet received?
- If yes, were they hospitalised Yes/No?
- If yes, do they think that they are suffering from “long COVID” and with what symptoms? How is this limiting their activities?

Household postcode (required at the level of outward portion and first number of the inward portion for geospatial analyses) will be available from the original ONS or NISRA survey or the address list from which the household was sampled. However, full address will also be confirmed against the household identifier sent with the original invitation letter at registration. At a household level, the number and ages in months of any children under 2 years who are normally resident in the household (as per 2011 Census definition) but are not eligible because of their age will also be recorded at the enrolment home visit (up to protocol v15.0) or the registration/consent telephone call (from protocol v16.0), as will the number and age (years) of any individual over this age not joining the study (e.g. because they were present when the home visit was conducted up to protocol v15.0, or because they do not wish to join). Household size will thus be available from this data together with the record of who consented/assented or not (with ages, see section 9.3 above). This information will be used in analysis of transmission, to account for the fact that these individuals are not sampled within the study design.

For those participants in households randomly selected for blood draws who provide additional consent (**Figure 2**), 0.5ml blood will be collected from a capillary via fingerprick by the participant (or the participant’s parent/carer for those aged under 16 years) into a Greiner MiniCollect® tube, which will then be placed into a larger carrier tube to facilitate logistics. All the materials required for the fingerprick will be pre-packaged into a standard kit, including contact-activated lancets, alcohol and saline wipes, plasters and instruction sheets. This kit will be provided to the participant as part of the home visit up to protocol v16.0 or by post from protocol v16.0.

Each tube (or carrier tube) will be barcoded and labelled with a unique barcode (for this sample) linked directly to the participant’s unique study number on the study database. Results from the antibody test for anti-spike (S) protein will be returned to participants in the same way as for the swab test results. The test for anti-spike (S) protein has shown excellent performance in a comparison with 4 commercially available assays on a large number (>1500) samples;²¹ sensitivity and specificity to identify those previously infected with SARS-CoV-2 vs not (based on plasma from pre-pandemic blood donors) (95% confidence interval, CI) were 99.1% (97.8-99.7%) and 99.0% (98.1-99.5%) respectively, compared with 98.1% (96.6-99.1%) and 99.9% (99.4-100%) respectively for the best commercial assay (Siemens). The test is now CE marked by the Medicines and Healthcare Products Research Agency (MHRA) and commercially available as the OmniPATH™ SARS-CoV-2 IgG test. Performance is similar on capillary and venous blood drawn from the same individual, and capillary blood draws have been successfully used with this assay in the large UK Biobank serology study

(https://www.ukbiobank.ac.uk/media/zusjljce/ukb_serologystudy_report_month2_final-1.pdf). From February 2021 to March 2022, all blood samples will also be tested for antibodies against the N (nucleocapsid) protein, rather than just the S protein, on the same sample as part of the single automated workflow. This should enable antibody responses to be categorised as against S only (compatible with vaccination) or against S and N (compatible with natural infection). Because anti-S is common to protection from both vaccination and natural infection, anti-S results will be returned to participants, but anti-N will not (this N-antibody test is currently for research uses only). From protocol v16.0, N-antibody will not be assayed on all samples due to capacity, but may be assayed in a subset determined either by random sampling, sampling according to date, or in specific groups of participants to test for missed infections. S-antibody results will be returned as positive or negative at the standard threshold used to identify those previously infected with SARS-CoV-2 vs not (based on plasma from pre-pandemic blood donors) as described above, in line with the MHRA CE marking for the test. However, this standard antibody threshold (42 ng/mL) was determined prior to vaccines being developed. This corresponds to 23.5 binding antibody units (BAU)/ml using the World Health Organization's (WHO) standardised units enabling comparison across different antibody assays. Currently, >97% of individuals are positive at this threshold²², meaning the vast majority get a positive result returned. A recent study of COVID-19 Infection Survey data comparing the risk of new COVID-19 infections with the most common COVID-19 variant at the time, the Delta variant, across different antibody levels, showed that a higher level, 179 ng/ml (100 BAU/ml), was needed to provide a 67% lower risk of getting a new COVID-19 infection with the Delta variant after two vaccinations with either Pfizer or AstraZeneca vaccines but without previous infection, compared with someone who was unvaccinated and had not had COVID-19 before²³. In those who had had COVID-19 before and not been vaccinated, the level of antibodies providing a 67% reduction in the risk of a new infection compared with those unvaccinated and not previously infected was 59 ng/mL, very close to the standard threshold. From protocol v15.0, we will therefore return results as positive vs negative at the standard threshold, but also inform participants as to whether their positive result reflects a lower or higher concentration of antibodies above the standard threshold, using the 179 ng/mL threshold. Percentages above this threshold are being published by the Office for National Statistics from 26 January 2022²². Further categorising results that are "positive" (above 42 ng/mL) in this way provides continuity for participants, many of whom have been receiving results at this threshold for many months, whilst providing additional information supported by research findings.

9.7. Baseline Assessments

The procedures above will be conducted at the first study assessment. If key participant characteristics are not collected at the baseline assessment in error, these may either be elicited at a follow-up assessment or by contact (phone call or email) from IQVIA. Emails given by participants that are recorded incorrectly will also be corrected by a phone call from IQVIA.

9.8. Subsequent Visits

Households from which one or more participants consent to serial sampling (up to protocol v15.0; from protocol v16.0 all households) will have assessments approximately 1, 2, 3, and 4 weeks later, and then (depending on consent up to protocol v15.0, **Figure 2**) two months after the enrolment visit and every month thereafter through to the end of the study. Up to protocol v16.0, to allow for participant convenience and study workers availability, visits should occur within equidistant windows around

scheduled study timepoints, that is within a ± 3 day window for the first three weekly visits, within a window of [-3,+16] days around the week 4 visit, or within a ± 15 day window around the visits from months 2 onwards. One home visit will be made to each household at each of these timepoints, and all consenting participants in the household at the time of the home visit will be included – additional visits will not be made if one or more participant happens not to be present at the time of an individual visit. Such participants may however be included at subsequent visits. From protocol v16.0, study assessments will be scheduled from the first study assessment under the new mode of delivery (see Table 2B), with the same windows. Participants will have the option to opt out of any assessment. Windows for completion will be 7 days from the start of the assessment window for weekly visits and 14 days from the start of the assessment window for monthly visits. Any questionnaires or samples returned after this will be used in analysis, but participants will not receive compensation if the questionnaire has been completed outside these windows or if the participant states that they have not performed one or more of the swab or the blood test (the latter if doing blood tests), in order to promote participants remaining as close to their scheduled monthly assessments as possible. Participants will continue to receive compensation if they state that they have taken a swab/blood but the sample(s) do not arrive at the respective laboratories three times (non-consecutive). On the third occasion, IQVIA will contact the participant and conduct an investigation with the logistics partner. Vouchers may be withheld for third and subsequent failures of samples to arrive at the laboratory despite participants stating that they have been taken on the questionnaire, depending on findings.

Subsequent visits (all non-contact) will be scheduled through the contact centre contacting the participant to make arrangement for a visit by the study workers, or directly with the household's study worker. Consent/assent from each participant will be confirmed at each home visit, and the procedures in Table 2 above will be conducted on all consenting/assenting participants. In order to ensure quality control of study procedures and data quality, for a small random number of follow-up visits, a member of the participant experience team will telephone the participant's household, and, if they agree, ask them a few short questions about how their visit was conducted.

From protocol v16.0, subsequent assessments will be scheduled from the date of the first assessment window (T=0). Participants will have the option to opt out of any assessment; not opting out will be considered to indicate ongoing consent for participation in the study. If participants do not complete three scheduled visits which they have not opted out of, they will be contacted by telephone or email by IQVIA to ask whether they would like to continue in the study or to withdraw.

9.9. Sample Handling

9.9.1 Sample handling for study purposes

The nose and throat swab will be sent directly to one of the government accredited laboratories in the UKHSA network (the Glasgow Lighthouse or Rosalind Franklin Laboratories), using packaging and transport in accordance with Category B transportation regulations (<https://www.gov.uk/government/publications/wuhan-novel-coronavirus-guidance-for-clinical-diagnostic-laboratories/laboratory-investigations-and-sample-requirements-for-diagnosing-and-monitoring-wn-cov-infection>). The majority of participants will return swabs using Royal Mail priority post boxes, which have been successfully used to send samples for other studies (e.g. the REACT study); the remainder will be collected via courier. Each swab will be tested for the presence of SARS-CoV-2 using reverse transcriptase or endpoint polymerase chain reaction (RT-PCR or ePCR) in an accredited test

as part of the national testing programme. Residual biological material will be discarded once testing is complete; RNA extracts will be whole genome sequenced. Depending on test validation, samples may also be tested for other respiratory viruses (e.g. influenza, respiratory syncytial virus (RSV)) and participants will be informed about this in the Participant Information Sheet. Results from any validated tests performed on swab samples will be returned to participants.

Up to protocol v16.0, blood tubes will be kept in a cool bag during the day, and then couriered to the University of Oxford within 24 hours wherever possible. From protocol v16.0, blood samples will be posted using Royal Mail priority post boxes or couriers as for the swab samples. Blood samples were successfully tested after being posted using Royal Mail priority post boxes for the Biobank study. Serum or plasma will be tested by research staff at the University of Oxford for antibodies using a novel quantitative ELISA for immunoglobulins IgG, based on tagged and purified recombinant SARS-CoV-2 trimeric spike protein in a high throughput assay.^{13,24} Antibody binding to the S protein is detected with ALP-conjugated anti-human IgG. This assay was originally developed by the University of Oxford, but has achieved CE marking for use with both venous and capillary blood and is now being marketed in collaboration with Thermo Fisher Scientific as the OmniPATH Combi SARS-CoV-2 IgG Spike ELISA. In parallel the same sample will be tested for antibodies against the N (nucleocapsid) protein, as part of the same automated workflow. Up to protocol v15.0 all samples will be tested in parallel; from protocol v16.0, N-antibody will not be assayed on all samples due to capacity and funding, but may be assayed in a subset determined either by random sampling, sampling according to date, or in specific groups of participants to test for missed infections. The platform is capable of processing very small sample volumes often encountered with finger lance capillary sampling. Serum from a subset of samples will also be tested using neutralisation assays. These neutralisation assays use a lentiviral construct which expresses SARS-Cov2 S protein, and are tested in a cell-based system described as a pseudotype microneutralisation assay (pMN), as recently used in a study of Scottish blood donors.¹⁴ Any residual material (sera and spun cells) will be stored by the University of Oxford in secure facilities; it is not expected that there will be substantial residual material following capillary blood sampling, but any remaining sample will be stored and assay plates will be stored temporarily to enable assays to be re-run if necessary (e.g. if quality control issues are identified). Any residual material collected and stored in the study that, following analysis for the study, has been clearly identified as being of no further use, may be released to other researchers for use in COVID-19 related research projects, providing consent has been provided for samples to be stored and used in future research (explicitly requested, see Section 9.3).

In all laboratories, assay results will be returned to ONS identified only by the unique barcode and date of testing. Antibody results will be returned as the quantitative optical density readings for the ELISA assays and as positive/negative together with a half maximal inhibitory concentration in the positive group for the neutralisation assay through either a secure FTP site or an encrypted and password protected file. Nose and throat swab results will be returned as positive/negative and cycle threshold (CT) values, where available.

9.9.2 Return of results

At minimum, nose and throat swab and S-antibody blood test results (at the standard and a higher threshold, see Section 9.6.1) will be returned directly to the participant through the study by email or by letter if they do not want to provide an email address for this purpose (or do not have an email address). The Participant Information Sheet will contain links to current government advice around self-isolation if

anyone tests positive on a nose and throat swab. After the enrolment assessment, subsequent swab test results will similarly be returned to participants as will S-antibody blood test results.

As required by law (Public Health Regulations (2010)), positive swab test results will also be shared with the relevant personal data (including name, contact details, postcode and ethnicity) with the relevant public health bodies for referral to national systems (UK Health Security Agency for referral to the NHS Test and Trace system <https://contact-tracing.phe.gov.uk/>; Public Health Wales for referral to the NHS Wales Test, Trace, Protect system <https://gov.wales/contact-tracing-if-you-have-tested-positive>; the Public Health Agency for referral to the HSC Northern Ireland's Test, Trace, Protect programme <https://www.publichealth.hscni.net/covid-19-coronavirus/testing-and-tracing-covid-19/contact-tracing>; and Public Health Scotland for referral to the NHS Scotland Test and Protect system www.nhsinform.scot/campaigns/test-and-protect).

The 2010 Regulations have been amended in England to require that, in addition to positive cases, indeterminate, negative and void test results must be reported by laboratories to identify the causative agents for COVID-19 (including antibody and swab test results) (in place from 23 November 2020). The required items of personal data (minimum dataset) for each sample taken will be shared with the national testing programmes as required, also to enable immediate movement of positive results into the national tracing systems (see Section 12). National tracing systems will then immediately and automatically notify participants of positive results. Participants will be informed about this automatic referral of a limited set of personal data to be linked to test results in the Participant Information Sheet, and that by taking part in this survey they agree to this disclosure taking place. In addition, all results will be returned directly to the participant by email or letter, as described above.

As described above, the household of any participant with a positive nose and throat swab for virus during the study (either from a study sample or from a test result linked to study data from national databases) would also be approached for consent for a blood draw as quickly as possible after the first positive test in the household and then at subsequent monthly visits to the end of their participation, where this does not lead to targets for blood sampling being exceeded by >5% (which impacts the capacity of the laboratory to conduct all the required tests). Consent for blood draws after testing positive on a nose and throat swab within the study will be sought at enrolment, to avoid needing to reconsent individuals. Individuals would be telephoned in order to expedite blood sampling and this would be followed up with a letter. Participants will be informed about this in the Participant Information Sheet.

9.10. Early Discontinuation/Withdrawal of Participants

During the course of the study, a participant may choose to withdraw from future study procedures. Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely. They may also withdraw consent for continued storage of their blood samples. Alternatively, they may lose the capacity to consent during the study or even die (since there is no age limit on participation). Finally, participants may withdraw from the study simply because they leave the household which was originally sampled – it is the physical household location that is sampled so if they move, their participation finishes. The study team may also withdraw a household for unreasonable behaviour in exceptional circumstances, for example, repeatedly touching study workers at non-contact visits despite being requested to maintain social distancing or being verbally abusive.

Each participant has the right to withdraw from the study at any time; individual participant withdrawal will not mean others in the household are automatically withdrawn, each participant will make their own individual decision.

De-identified data obtained up to the point of consent withdrawal will be kept and used in analysis for all participants who withdraw, regardless of type of withdrawal (described below) and this is explained in the Participant Information Sheet.

Participants who wish not to continue participation in some or all parts of the study will therefore have the following options, and the type of withdrawal recorded.

- 1) Participants may withdraw from active follow-up (i.e. future study procedures) and further communication but allow the study team to retain their personal identifiable information in order to continue to access their ONS and NHS records for future electronic follow-up. Residual serum samples would be kept for future research.
- 2) Participants can withdraw from active follow-up (i.e. future study procedures) and further communication and also request their personal identifiable information be removed so that their study records cannot be linked to ONS and NHS records for future electronic follow-up. De-identified data and samples obtained up until the point of withdrawal would be retained for use in the study analysis, and any residual serum samples to be used for future research. No further data or samples would be collected after withdrawal.
- 3) Participants can withdraw completely from the study and withdraw their samples collected up until the point of withdrawal. The data already collected would be used in the analysis, but samples would be destroyed if not already analysed and any residual serum samples already being stored would also be destroyed. Personal identifiable information would be removed so that their study records cannot be linked to ONS and NHS records for future electronic follow-up.

Participants who lose capacity to consent during the study will be withdrawn from active follow-up (option 1). Participants who withdraw for any reason will not be specifically replaced; rather ongoing recruitment will be to maintain the overall swab and blood targets described above, accounting for both withdrawals and intermittent missed visits without withdrawal. If a participant dies, immediate visits will be cancelled, and the household will be written to, asking them to call the contact centre if they would like to restart visits, but that otherwise we will not make further contact. This provides family members with the freedom to make their own personal decision about further participation.

9.11. Definition of End of Study

The end of the study is the date of the last assessment of the last participant.

10. SAFETY REPORTING

There are no interventions in this study, and the only procedures are a participant fingerprick blood draw using methods which have been widely used in other serology studies and for commercial antibody testing, and a participant self-swab (or parent/carer swab of a child) using a methodology which is being used widely at drive through testing centres across the country. Therefore, there is minimal safety risk to participants.

However, any serious adverse event **which is considered related to any of the study procedures** will be reported to the Sponsor. A serious adverse event is defined as any untoward medical occurrence that

- Results in death
- Is life-threatening (with a real, not hypothetical, risk of death at the time)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Has a real, not hypothetical, risk of one of the above

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.1. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the Health Research Authority (HRA) report of serious adverse event form (see HRA website).

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here. There is no formal Statistical Analysis Plan.

11.2. Description of the Statistical Methods

For the primary outcome, Bayesian dynamic spatiotemporal multi-level regression with post-stratification (MRP) will be used to investigate changes in positivity rates over calendar time.^{25,26} Potential spatial correlation between neighbouring areas is taken into account using a “BYM2” specification. Time will be allowed to vary in a non-linear fashion by using a first-order autoregressive term for time. Space-time, and space-age interactions will be included to allow the positivity over time to vary by age and age group. This spatiotemporal MRP is an extension of the spatial MRP method developed by Gao et al.²⁷ In extensive simulations, Gao et al found that bias was significantly reduced when using a BYM2 specification compared to a non-spatial independent identically distributed specification. Attenuation in absolute bias was most apparent with small sample sizes. Even when simulating outcome data as a multivariate independent normal, BYM2 spatial prior produced nearly same posterior estimates as independent identically distributed prior, indicating that the BYM2 spatial prior does not force spatial structure when it is not present.

The reason for using MRP as the primary method is because it allows probabilistic assessment of relatively rapid changes in positivity. MRP consists of two steps. First, a multilevel regression model is used to generate the outcome of interest as a function of (socio)demographic and geographic variables. Next, the resulting outcome estimates for each demographic-geographic respondent type are poststratified by the percentage of each type in the actual overall population. In several empirical and simulation studies MRP was superior at both the national and regional levels to classical survey weighted and unweighted approaches, including when using small sample sizes.^{26,28} Factors included in the main models - besides time, space, and a space-time interaction described above – will be sex, age, ethnicity and an age-time interaction. Whether additional interactions are needed will be determined based on the Watanabe-Akaike information criterion.

In addition, the proportion of individuals with symptomatic and asymptomatic infection (based on PCR of nose and throat swabs) based on the latest result in the last two weeks will be summarised approximately every calendar week from the start of the study, overall and by geographical region. Proportions will be calculated incorporating sampling weights for the original ONS and NISRA surveys, this survey and for non-response to this survey, with 95% confidence intervals estimated using the Korn-Grauberd method which allows for the low anticipated positivity rates. We will use Bayesian methods in sensitivity analyses assessing the impact of plausible ranges of test sensitivity and specificity on results, incorporating both the assay performance and the fact that participants are self-swabbing. Associations between various predictors and ever testing positive for infection vs never testing positive will be estimated using unweighted proportions and Fisher’s exact tests with multivariable logistic regression models to adjust for confounding. Factors considered will include sex, ethnicity, age at last birthday (as both categorical and continuous variables) and other responses to the short questionnaire. These factors will also be considered in multi-level regression models, similar to the main model over continuous time described above.

Similar spatiotemporal MRP methods will be used to estimate proportions over time with immunity defined based on the optical density readings from the ELISA assay for IgG antibodies versus the threshold defined in comparison with pre-pandemic plasma. We will also estimate the proportions with previous infection (as defined by antibodies) but no previous symptoms.

Random effects linear regression models will also be generated for the absolute optical density readings (potentially log-transformed depending on the distribution) in relation to time since onset of first symptoms, with those not reporting symptoms treated as an additional category (random effect per household – may be omitted depending on model fit). Additional factors considered in these models will include age, sex and ethnicity.

Incidence will be calculated indirectly by deconvoluting the Bayesian dynamic multi-level regression model estimate of swab positivity and an estimate of duration of PCR positivity based on those testing positive in the study. More details are provided on <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/methodologies/covid19infectionsurvey-pilot-methods-and-further-information#incidence>.

Through linkage to NHS records (and equivalent national databases in Devolved Administrations), we also aim to determine the impact of immunity and symptomatic/asymptomatic infection status on healthcare usage, in particular inpatient admissions, A&E attendances and general practitioner consultations. This linkage would be performed both during active study participation (i.e. whilst home visits are being conducted) and after active study participation has ended (for up to fifteen years). Through linkage to records from ONS and equivalent national mortality databases in the Devolved Administrations, we aim to determine the impact of immunity and symptomatic/asymptomatic infection status on mortality and cause of death. Through linkage to records from UKHSA and equivalent national test databases in Wales, Northern Ireland and Scotland on other tests for SARS-CoV-2, we will ensure that we obtain as accurate as possible associations between infection and immunity.

More information about the methods used in analysis can be found on <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/methodologies/covid19infectionsurvey-pilot-methods-and-further-information>.

11.3. Sample Size Determination

The target sample size for Phase I (around 10,000 households enrolled over one month, and around 21,000 individuals) was determined based on a conservative assumption that all members of the same household have the same infection status, and therefore each household should only be counted as one unit in the sample size calculation. If infection status varies within households, this will increase precision around our estimates.

The precision (margin of error) that various sample sizes provide around various estimates of infection rates (and seroprevalence) is illustrated in **Figure 5** below, together with the precision for smaller sample sizes, which should be achieved for specific regions and/or groups defined by other characteristics such as age. For a given prevalence p and sample size N , the expected margin of error corresponds to the expected width of the 95% confidence interval associated with the point estimate of p obtained using an exact binomial test. On balance, around 10,000 households in Phase I (around 21,000 individuals), and around 12,000 households (25,000 individuals) each subsequent month (3,000 per week) in Phase II, was

considered to provide sufficient precision across England overall, particularly at lower prevalence rates which may be expected at earlier cross-sectional surveys, as well as the possibility of assessing evidence for variation within smaller but very important subgroups, including regions and Devolved Administrations (each targeting ~1,000 households per month, ~2,100 individuals per month).

However, a major concern was the ability to monitor regions, rather than England as a whole, by October 2020 when the winter season of respiratory infections started, and monitoring for a possible “second wave” of infections was critical. Therefore scaling up of recruitment from the end of July 2020 was designed to achieve similar numbers regionally as were originally available in England as a whole in Phase I, i.e. ~15,000-20,000 individuals with swab test results at least once each fortnight in each of the nine government office regions of England and also proportionate samples in Wales, Scotland, and Northern Ireland. Overall the swab target is therefore ~150,000 individuals with swab test results at least every fortnight in October in England, ~9,000 in Wales, ~5,000 in Northern Ireland and ~15,000 in Scotland (total 179,000 across the UK) (absolute numbers reflecting the relative size of the underlying populations). Sampling may be increased in regions or occupations with any evidence of increasing prevalence, in order to provide greater certainty regarding the probability of increasing infection rates as opposed to sampling variation.

For blood sampling for seroprevalence, initially 10-20% of those enrolled providing blood samples from recruitment was considered to provide an acceptable trade-off in terms of precision, given that seroprevalence rates are expected to be higher than infection rates, and so margins of error for the former can be larger than the latter without compromising decision-making. However, in order to assess the impact of vaccination, larger numbers are needed. The total blood target of ~125,500 adults 16 years and older sampled every month in England for approximately one year from March 2021 through to April 2022 (allowing time for scale-up in additional recruitment to blood sampling) was designed to provide estimates of immunity within different regions (~10,000-15,000 per month) with a margin of error below 2%, and within different age groups over 16 years within regions (~2,000 per month) with margins of error below 5% (5(c)). For those aged 8-15 years, the target was to achieve ~3,600 blood test results every month. This will achieve a margin of error below 3.3% across the UK, regardless of the underlying true seropositivity rate, compared with below 2.7% for the original target of ~5,500 blood test results per month estimated in protocol v12.0. This modest drop is still considered to provide acceptable precision. Further, for example, 3,600 test results per month would provide 85% power to detect differences in seropositivity of 50% vs 55% between those aged 8-11 vs 12-15 (assuming these age groups are approximately equally sized), so this sample size retains excellent power to look at smaller age categories within the 8-15 year olds. Further, there are currently no representative large scale surveys of antibody positivity across the UK in this age range, where questions exist about the value of extending vaccination to younger ages, uptake of vaccination, two vs one doses etc. 3,600 blood test results per month would therefore provide a substantial increase in the information available on which to base decisions, over the current status quo.

However, following maintenance of COVID-19 hospitalisation rates below levels that would overwhelm the NHS during the Omicron wave in December 2021-January 2022, and given ongoing infection rates above 3%, the need to maintain this level of precision around estimates of swab positivity has reduced. Therefore, as part of adapting to live with COVID-19, from April 2022 onwards, the swab targets will be reduced by ~25% and the blood targets by ~20% (i.e. retaining a greater percentage of those giving blood

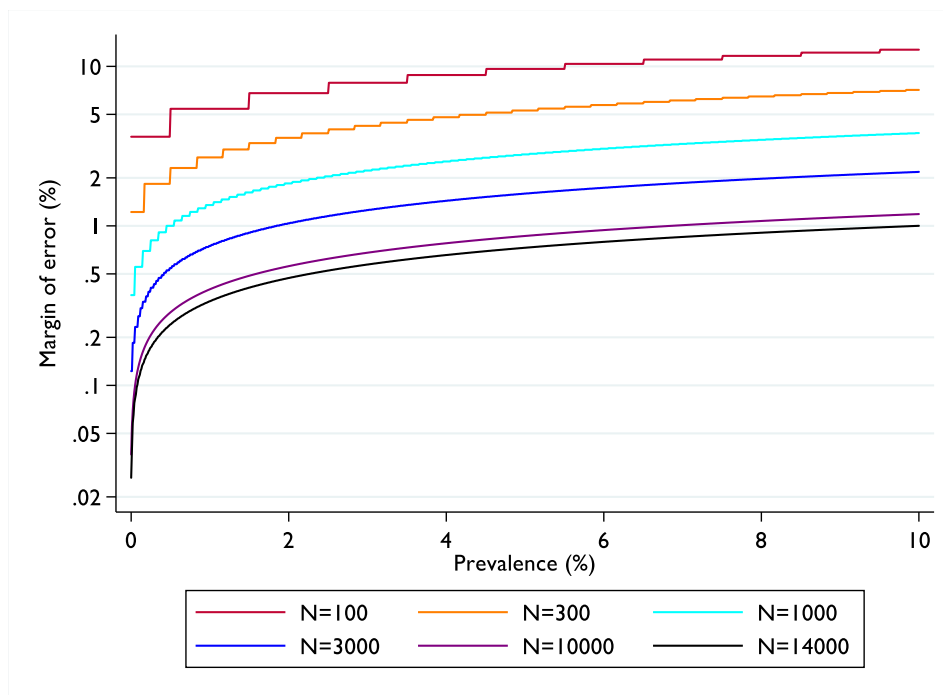
in order to maintain as much precision as possible to monitor declines in antibodies, particularly in older age groups), to achieve the following:

- Swab target: up to ~227,300 swab samples taken from individuals 2 years and older every 28 days in England, ~15,650 in Wales, ~10,050 in Northern Ireland and ~23,200 in Scotland (~276,200 total across the UK every 28 days, ~300,000 swab samples in total across the UK per month)
- Blood target: up to ~90,850 blood samples taken from individuals 8 years and older every 28 days in England, ~6,300 in Wales, ~4,150 in Northern Ireland and ~9,200 in Scotland (~110,500 in total across the UK every 28 days, ~120,000 blood samples in total across the UK per month)

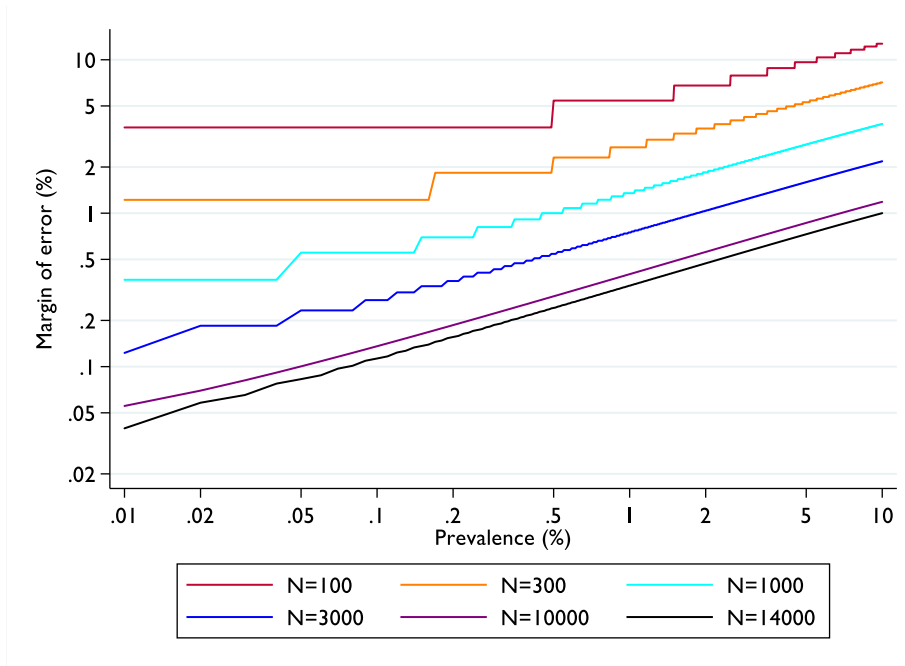
Reductions are proportionately less in Wales and Northern Ireland in order to maintain power within these countries, and proportionately more in England to meet the overall reductions. These numbers are considered to provide sufficient precision to monitoring infection rates and seroprevalence moving forwards, overall and by region/country, particularly given current levels of infection and antibody positivity. Targets are based on samples taken and arriving at the laboratories for testing rather than valid results received from the laboratories because assay failures also contribute to testing costs. Test failures with samples taken at study worker visits have generally been ~1% for swab tests and ~1.5% for blood tests; even if these increase with postal/courier return to 1-2% or 3-4% respectively, the sample targets above will retain reasonable precision. Test failure rates will be monitored closely, as will rates of samples that have been reported to have been taken failing to arrive at the laboratories (the latter are not included in the targets above).

Figure 5 Impact of sample size on precision for various estimates of prevalence

(a) With prevalence ranging from 0 to 10% on an absolute scale

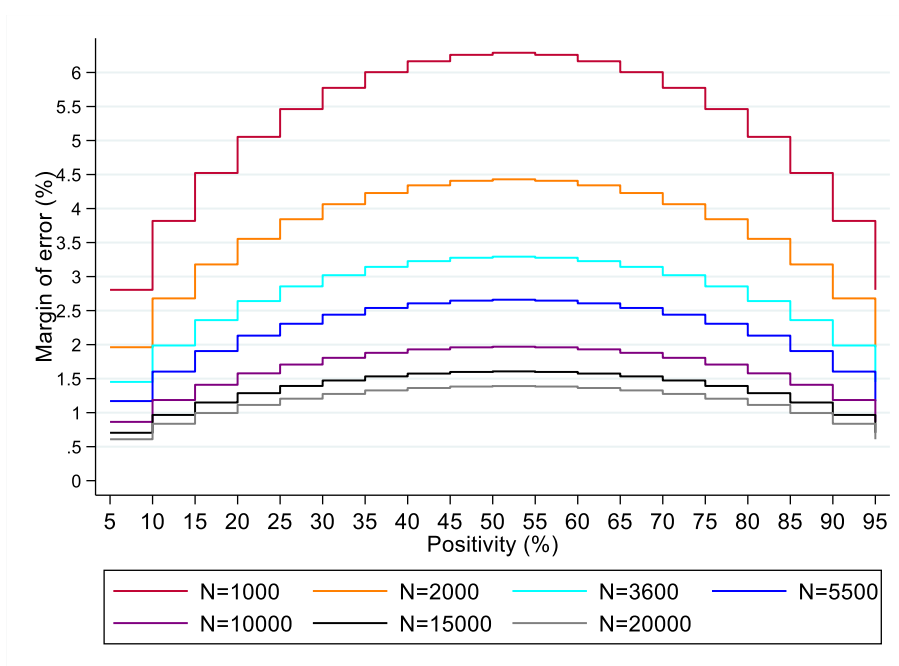


(b) With prevalence ranging from 0 to 10% on a log scale to highlight the impact at low prevalences



Note: straight lines indicate where the denominator does not allow more accurate estimation: eg out of 100 individuals, all true prevalences of under 0.5% correspond to 0/100 individuals.

(c) With prevalence ranging from 5 to 95% on an absolute scale



11.4. Analysis populations

All enrolled participants will be included in analyses, which will adjust for clustering by household wherever possible. Secondary analysis will also be conducted de-duplicating to one individual per household, for example restricting to adults targeted by ONS in the original approach letter.

11.5. Decision points

Interim analyses will be conducted at least twice a month by statisticians and analysts from the ONS, the University of Oxford and Devolved Administrations (results summarised on <https://www.ndm.ox.ac.uk/covid-19/covid-19-infection-survey/results> and published by ONS) in order to inform the UK's response to the SARS-CoV-2 pandemic. These interim analyses will follow a standardised format, and will particularly consider prevalence in key subgroups defined by region and age, with additional analyses by sex, ethnicity, occupation, region and symptoms as examples. Results will be available to all organisations involved in conducting the research. Decisions regarding subsequent cross-sectional surveys (and any necessary protocol amendments) will be made by the study management group (see section 13.3 below). Decisions will be reached by consensus wherever possible.

11.6. Stopping rules

There are no formal stopping rules for futility, efficacy or lack of power. The final decision to terminate the study will be made by the Department of Health and Social Care following appropriate consultation and agreement with the Welsh Government, the Department of Health on behalf of the Northern Ireland Government and the Scottish Government.

11.7. The Level of Statistical Significance

A nominal significance level of 5% will be used; however, results will be interpreted based on their 95% confidence intervals rather than using a rigid threshold approach.

11.8. Procedure for Accounting for Missing, Unused, and Spurious Data

Each analysis will be restricted to complete cases for the outcomes and exposures considered for that analysis. Missing assay data is expected to be extremely rare, as study workers will oversee the participant self-swabbing of nose and throat, participant capillary blood draw, and ask the specific additional questions at the home visit. From protocol v16.0, samples will be returned predominantly by post, so missing data may increase somewhat, but postal return has been used successfully by other research studies such as REACT and Biobank without substantial amounts of missing data. The RT-PCR and ePCR tests for virus have been used as a diagnostic throughout the pandemic and hence have extremely high performance. Sufficient sera will be obtained to re-run the immunological assays in case of initial assay failure. For similar reasons we do not anticipate that spurious data will be obtained.

Regular checks for data quality will be run on the small amount of predominantly self-reported data collected (see section 9.6.1). Standard range checks and plausibility checks will be run on all data fields as part of routine data processing for interim analyses. For participants agreeing to serial sampling, consistency between visits will also be checked. Given the short-time scales of the study visits, last observation carried forward and backward will be used to impute any missing data.

Standard inverse probability weighting methods or post-stratification will be used to weight observed data back to a representative UK population, based on response to the initial ONS letter in adults originally targeted, their characteristics compared with those to whom the original invite to participate in the ONS and NISRA surveys, and those characteristics vs the general UK population.

11.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Deviations from the statistical plan above will be described and justified in the analysis reports.

12. DATA MANAGEMENT

The plan for the data management of the study are outlined below. There is not a separate Data Management document in use for the study.

Given the scale of Phase II and the fact that it will run across the Devolved Administrations, the lead organisation for fieldwork, IQVIA, will sub-contract some of the field work for home visits up to protocol v16.0. IQVIA sub-contractors will use the IQVIA Voyager database.

Questionnaire data will be identified only by the household and participant code. Date of birth, name and address will be held separately using a hierarchically structured database or equivalent form of access-controlled network structure, so that only individuals with appropriate permissions (e.g. arranging home visits) can access it. The questionnaire data will be directly entered onto a secure data management system (IQVIA Voyager for home visits and for completion online or via contact centre). All study data is stored with bespoke logins and passwords unique to each user (only participants and IQVIA personnel associated with the programme). For home visits, access to the study database will be granted to an existing or new mobile device only after entering the verification code sent to a mobile phone registered in the users profile.

ONS and IQVIA sometimes share selected information with their service providers to help run studies. Sodexo (contracted by ONS) will be responsible for sending voucher compensation. HH Global and GovDelivery (contracted by ONS) will assist with communication for recruitment. IQVIA may use Capita to help resource the contact centre, through direct access to the IQVIA Voyager database. The NHS Business Services Authority will return test results to participants by email. Eight Days will print test result letters for those participants not wishing to receive results by email. Thriva will provide logistics support to package and post swab and blood test kits to participants. All will have participant contact details solely in order to undertake this contracted work. The companies involved in the survey may sub-contract out other specific services but any sub-contractors will be bound by the same duty of confidentiality and security arrangements.

The government approved laboratories (Glasgow Lighthouse or Rosalind Franklin Laboratory) will return nose and throat swab results to ONS and IQVIA to communicate results to participants (or their parent/carer, where applicable) via letter or email. At present IQVIA will also send the relevant minimum set of personal data for participants with positive swab tests to the relevant public health bodies as required by law. To enable compliance with the 2010 Regulations in England (in force from 23 November 2020) which require all test results relating to COVID-19 to be reported to public health bodies (positive/negative/Void), IQVIA will send the required minimum set of personal data for all visits where a swab was taken to the national testing programmes as required by law. The laboratories will also return nose and throat swab results directly to the national testing programmes as required by the regulations, identified by their study barcode. All results will also be returned directly to participants by IQVIA using a letter printed by Eight Days or email through the NHS Business Services Authority where participants have provided an email address to receive study test results through. In order to do this, IQVIA will send test results, along with the participant's name, email address and month and year of birth to the NHS Business Services Authority who will issue the results to participants via email, in the same way as results from the national testing programme. IQVIA will already hold the necessary personal details to enable home visits or postal tests to be arranged. The University of Oxford will return antibody results to ONS and IQVIA, who will pass these onto participants in the same way as swab test results, and to public health bodies in the required format.

In order to reduce burden on participants and reduce duplication of effort, we will ask participants for consent to retrieve information from ONS, NHS Digital and UKHSA and equivalent national databases in Wales, Northern Ireland and Scotland, to obtain information about their utilisation of NHS services (including inpatient admissions, outpatient attendances, consultations with a general practitioner, A&E admissions), their mortality status to link to their immunity and infection status and other tests for SARS-CoV-2. Linkage to NHS and test records will be done through ONS for England, and through the equivalent national bodies in the Devolved Administrations. Within ONS or the equivalent national bodies in the Devolved Administrations, linkage will use the personal information provided by the participant (name, address, date of birth and sex) to first link to an NHS number using the Personal Demographics Service or equivalent in Devolved Administrations. This linked NHS number will then be used only to identify the relevant health records in other sources, rather than trying to link to these other health sources directly based on name/address/etc, but NHS number will not be part of the study dataset nor returned to the study researchers, but used only for linkage.

For the pilot study of antibody finger prick blood testing in those aged 5-15 years old, a small amount of feedback on the parent/carer experience of attempting finger prick blood testing in their child will be sought. This will either be recorded on the main study database (depending on time needed to develop this) or on a separate survey tool (Smart Survey) to the main study database. On Smart Survey, child participants would be identified only by their age in years at last birthday, sex, and pseudonymised household identifier (no personal identifiable information).

For the Stage 1 transition from study worker home visits, feedback on participant's experience of the new arrangements will be sought. This will be recorded on the main study database (depending on time needed to develop this) or on a separate survey tool (Smart Survey) to the main study database. On Smart Survey, participants would be identified only by their age in years at last birthday, sex, and pseudonymised household identifier (no personal identifiable information). Interviews will also be conducted and recorded on audio. Once the transcriptions are sense checked, the interviewers will anonymise them, by replacing any names or personal identifiers with a participant number and pseudonym in the saved copy of the transcript which will be stored in a limited access Sharepoint folder at the Office for National Statistics.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' data are obtained. These include, but are not limited to, hospital records and laboratory records. As the electronic case record form (eCRF) is the site of the original recording of the questionnaire data for this study (i.e. there is no other written or electronic record of data), eCRF entries will be considered source data. All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent and primary household form, the participant will be referred to by their household code, participant study number, month and year of birth, and not by name. Name is required to be captured at enrolment/registration (where consent is documented) as this is needed for linkage, as stated in the Participant Information Sheet.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.3. Data Recording and Record Keeping

Data from the survey will be entered on the IQVIA Voyager platform. This uses the robust Salesforce.com platform and relies on Salesforce security measures <https://trust.salesforce.com/en/>. All versions of Voyager are validated and compliant with 21 CFR part 11. All health information is backed up within the UK.

The participants will be identified by a unique household code and participant study number in the database storing questionnaire data. The participant's name, address and contact details, including mobile telephone number to arrange visits up to protocol v16.0 and to contact e.g. in the case of errors in test results being identified, or repeated non-arrival of swabs at laboratories/non-completion of questionnaire if not opted out of an assessment window, and email address for vouchers, study updates and return of results if participants are willing to provide this, and date of birth will be included in each database but this information is primarily for the purposes of communication with participants. All information provided to IQVIA will be shared with ONS, including name and date of birth which are shared for the purposes of linkage to NHS and ONS records, and equivalent national databases in the Devolved Administrations (ONS already holds household address), but all information will not be routinely shared with other third parties involved in the study. Email addresses will be returned to ONS for provision of compensation vouchers and study updates, and these will be shared with the third parties described above that provide these services. Participants name, email and month and year of birth will be provided to NHS Business Services Authority to issue test results via email where participants are willing to receive their test results this way, and to Eight Days (together with address) to issue test results by letter otherwise. Names and addresses will be shared with Thriva to send swab and blood test kits. The companies involved in the survey may sub-contract out specific services but any sub-contractors will be bound by the same duty of confidentiality and security arrangements. Some IQVIA offices are located outside the UK, therefore IQVIA will sometimes need to process information outside the European Economic Area. Such transfers will only take place within IQVIA with appropriate safeguards in place to ensure the confidentiality and security of personal information, and participants will be informed about this in the information sheet. IQVIA will carry out a data privacy impact assessment on all personal data they collect to minimise the data protection risk to the study.

Electronic data will be stored on each database and will remain active for the duration of the study. Participants' identifiable data will then be removed and the identifiable data will be archived within each platform to be retained for a period of 5 years. This is under the joint data controllership of the University of Oxford and ONS. The University of Oxford will not process or retain any personal data. It is definitionally a data controller as sponsor of this research. ONS sets out in its privacy information its scope of processing, including for secondary purposes (<https://www.ons.gov.uk/aboutus/transparencyandgovernance/dataprotection>).

Parent/carer experience of antibody finger prick blood testing in those aged 5-15 years old in the pilot study, and of participant's experience of the transition from study worker visits in Stage 1, will either be recorded on the main study database (depending on time needed to develop this) or on a separate Smart Survey database, given the very limited number of households involved and the small number of questions. Smart Survey are hosted in the UK, hold ISO 27001 and Cyber Essentials Plus (CE+) certification, have been formally assured by ONS as part of their assurance process and approved for use in other ONS surveys.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, relevant regulations and standard operating procedures.

13.1. Risk assessment

No formal risk assessment is required. The study involves recruiting individuals at low risk in the community (rather than in a healthcare setting) who will be asked to self-swab their throat and nose and optionally provide a blood sample taken by themselves via fingerprick. Further participation in repeated assessments collecting the same samples is based on consent of the participant. The main burden of participating in the study is the time taken for the assessment and the home visits. There is minimal risk of harm to any patient from participating in the survey since it does not include any intervention. The diagnostic test for the presence of virus from the nose and throat swab will be conducted by an accredited laboratory and will be returned to the participant (or parent/carer, for children). Individual participant results of the immunity assays will not form part of patient care or interfere with routine diagnostic testing, and these results will be released to the participant. Results will be returned directly to participants as these tests are now widely available outside the study, both through the NHS and through commercial companies.

13.2. Study monitoring

No GCP monitoring will be undertaken. As described above, there are minimal risks posed to patients by this observational and non-interventional study. The only data items are either retrieved directly from electronic records (that is, are source documents in their own right against which no monitoring is possible) or are participant responses to a questionnaire which will be completed by study workers with the participant present and for which the eCRF forms the source document. The inclusion criteria are extremely simple – they will be recorded on the single study case record form. The only study procedures are completing the questionnaire and taking samples – absence of sample by definition means that research procedures were not followed.

In order to ensure quality control of study procedures and data quality for home visits up to protocol v16.0 and for study assessments thereafter, for a small random number of follow-up assessments, a member of the participant experience team will telephone the participant's household, and, if they agree, ask them a few short questions about their experience of their study assessment.

13.3. Study Committees

Oversight will be provided by a study management group, including investigators named at the start of the protocol as representatives of participating organisations, a representative of the Devolved Administrations, the Chief Investigator and an independent Chair (Professor Sir David Spiegelhalter).

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

15. SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

- (a) the safety or physical or mental integrity of the trial subjects; or
- (b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the Chief Investigator, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and any relevant host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

Following Sponsor approval the protocol, informed consent and assent form, Participant Information Sheets and summary will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Other Ethical Considerations

The main study-specific ethical consideration is the inclusion of children; other adult vulnerable participants and participants who are unable to consent for themselves are not eligible. Children are critically important to estimates of both infection status and seroprevalence, and obtaining reliable estimates in this population is essential for informing ongoing school closures amongst other decisions.

At this stage, there is no possibility that the testing will result in incidental findings that would be serious and medically actionable, as only SARS-CoV-2 antibodies will be analysed in the blood sample. Results of the PCR on the nose and throat swab will already be returned to the participant directly.

16.5. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required), host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.6. Transparency in Research

The study is registered on ISRCTN, <http://www.isrctn.com/ISRCTN21086382>. The protocol and participant information sheets are available on <https://www.ndm.ox.ac.uk/covid-19/covid-19-infection-survey>. It will be registered on HRA Summaries (<https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/>).

As well as providing a continuously updated summary of all the study results published in ONS statistical bulletins and articles to date, and in academic journals, on <https://www.ndm.ox.ac.uk/covid-19/covid->

[19-infection-survey/results](#), we will also email regular study updates and results to participants who are happy to provide an email address for this purpose and to receive vouchers.

16.7. Participant Confidentiality

The study will comply with the UK General Data Protection Regulation (UK GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s) wherever it is possible to do so, with person-identifiable information required for linkage held in an access-controlled structure. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.8. Expenses and Benefits

Up to 1 April 2022, a small compensation (£50 voucher) will be offered to each consenting/assenting participant (including child participants) for each completed enrolment home visit (contact or non-contact) to reflect their time and inconvenience. For each subsequent completed serial sampling home visit, each participant will be offered a £25 voucher. This includes any additional visits after 12 months for those invited to extend follow-up for additional monthly visits through to April 2022. Vouchers can be posted to participants, but we will offer them the option of receiving the vouchers more quickly by email if they are happy to provide an email address for this purpose (email can also be used to receive test results and study updates). The total compensation per participant would therefore be £50 for a single visit, £150 for five visits over one month and £425 for 16 visits over one year; those consenting to additional monthly visits up to April 2022 would receive £425 plus or £25 for each extra visit up to April 2022 (total depending on date of original household enrolment).

Children and young people aged 5-15 years who attempt a blood draw for finger prick testing will receive a sticker as a "thank you" in the initial phase. Feedback from children and their parents in the initial phase indicated that this was not helpful or necessarily wanted and therefore stickers will not be given in the main phase of antibody testing in children and young people aged 8-15 years (those aged 5-7 years no longer included from protocol v13.0).

From 1 April 2022, the compensation will be reduced to £20 per assessment (first or subsequent), reflecting the fact the majority of individuals have been self-swabbing for lateral flow testing during 2021 and therefore the burden of testing is less than when the study was originally set-up. From protocol v16.0, at the point where participants are offered the option of continuing in the study using post/courier for samples and without home visits, based on participant feedback, we will offer participants the option not to receive this compensation if they prefer. However, small monetary compensation has been shown to increase participation from under-represented groups, and therefore we will continue to offer it to all participants. Compensation vouchers would be sent if the questionnaire was completed within 7 or 14 calendar days from the start of weekly or monthly assessment windows (all mandatory questions completed) and they stated in the questionnaire that a swab or blood test had been performed. Participants will continue to receive compensation if they state that they have taken swabs/blood but samples do not arrive at the respective laboratories three times (non-consecutive). On the third occasion, IQVIA will contact the participant and conduct an investigation with the logistics partner. Vouchers may be withheld for third and subsequent failures of samples to arrive at the

laboratory despite participants stating that they have been taken on the questionnaire, depending on findings.

As part of the transition to the new approach to delivery, a small number of qualitative interviews will be conducted with the first participants moving to this (Stage 1). These participants will be offered a £20 voucher for their time.

17. FINANCE AND INSURANCE

17.1. Funding

Funding for the survey in England, Wales, Northern Ireland and Scotland is provided by the UK Health Security Agency, the Department of Health and Social Care, as agreed with the Treasury. In-kind support is provided by the Welsh Government, the Department of Health on behalf of the Northern Ireland Government, the Scottish Government, the ONS, the NISRA, the University of Oxford (in particular through the Oxford National Institutes of Health Research (NIHR) Biomedical Research Centre and the NIHR Health Protection Research Unit in Antimicrobial Resistance and Healthcare Associated Infections in collaboration with UK Health Security Agency [NIHR200915]) and UK Health Security Agency.

17.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

The Investigators and other relevant representatives of the collaborating organisations will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other academic publications arising from the study. Authors on academic publications will acknowledge that the study funding as detailed in Section 17.1 above. Authorship of academic publications will be determined in accordance with the International Committee of Medical Journal Editors guidelines and other contributors will be acknowledged.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the study.

20. ARCHIVING

Electronic data for the study will be de-identified and archived in the database platform at IQVIA for a period of 15 years after the end of the study.

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[stratified-seroepidemiological-investigation-protocol-for-covid-19-virus-infection](#) [accessed 17 April 2020], 2020.

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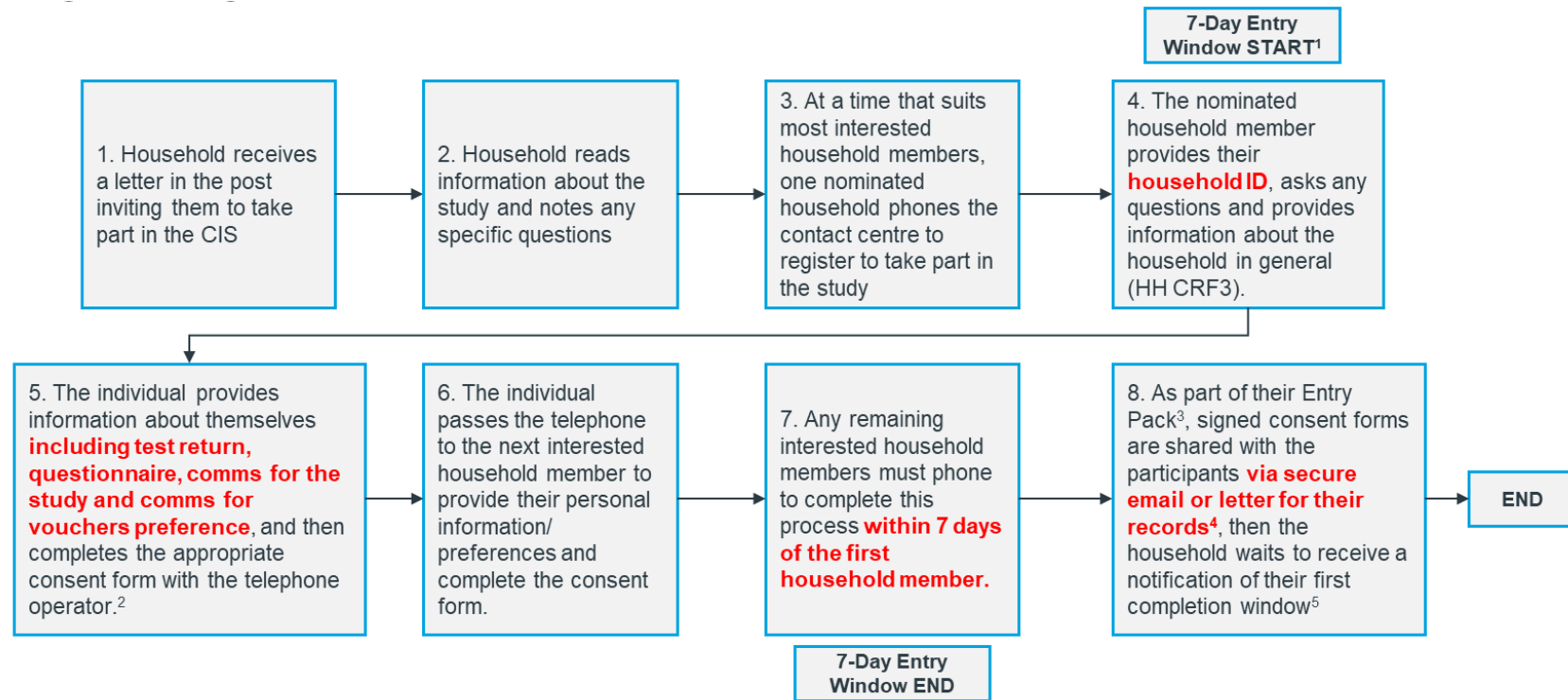
22. APPENDIX I: PARTICIPANT FLOW AND MATERIALS

Figure 6 Participant types

<i>CIS Status</i>	New Participant								Existing Participant							
<i>Post vs. Courier (Test Return)</i>	Post				Courier				Post				Courier			
<i>Digital vs. Non-Digital (Survey)</i>	Online		Telephone		Online		Telephone		Online		Telephone		Online		Telephone	
<i>Comm Preference (Notifications & Results)</i>	Email	Letter	Email	Letter	Email	Letter	Email	Letter	Email	Letter	Email	Letter	Email	Letter	Email	Letter
<i>Participant TYPE</i>	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P

<i>Voucher Delivery Preference</i>	Email/Digital				Postal/Paper				No Compensation			
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Figure 7 Study enrolment – new participants



1. No participants will be permitted to register after the 7-day entry window is complete
2. Individual participants within a household can each have differing questionnaire and comms preferences. We will encourage all members of a HH to have same test return method
3. Entry Pack includes (1) participant ID, (2) completed consent form, (3) survey storyboard tailored to stated preferences and, (4) detailed instructions for completing the test kits
4. Communication will include PII (full name), and will therefore be subject to approval by Data Controller (ONS)
5. This will occur approx. 16 days after the 1st participant of a household registers (assuming 2 days needed for scheduling and entry pack creation)

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Figure 8 New participants – worked example of time from first consent in each household

Activity:	7-Day Survey Entry Window							Scheduling & Entry Pack		Upcoming Completion Window Notification & Opt-Out Window (1)				Kit Dispatch & Arrival (1)			1st Weekly Completion Window						
Day:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
																	Upcoming Completion Window Notification & Opt-Out Window (2)				Kit Dispatch & Arrival (2)		
																	17	18	19	20	21	22	23

Activity:	2nd Weekly Completion Window							3rd Weekly Completion Window							4th Weekly Completion Window						
Day:	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Activity:	Upcoming Completion Window Notification & Opt-Out Window (3)				Kit Dispatch & Arrival (3)			Upcoming Completion Window Notification & Opt-Out Window (4)				Kit Dispatch & Arrival (4)									
Day:	24	25	26	27	28	29	30	31	32	33	34	35	36	37							

Activity:	Upcoming Completion Window Notification & Opt-Out Window				Kit Dispatch & Arrival			1st Monthly Completion Window (14 days)													
Day:	61	62	63	64	65	66	67	68	69	70	70	72	73	74	75	76	77	78	79	80	81

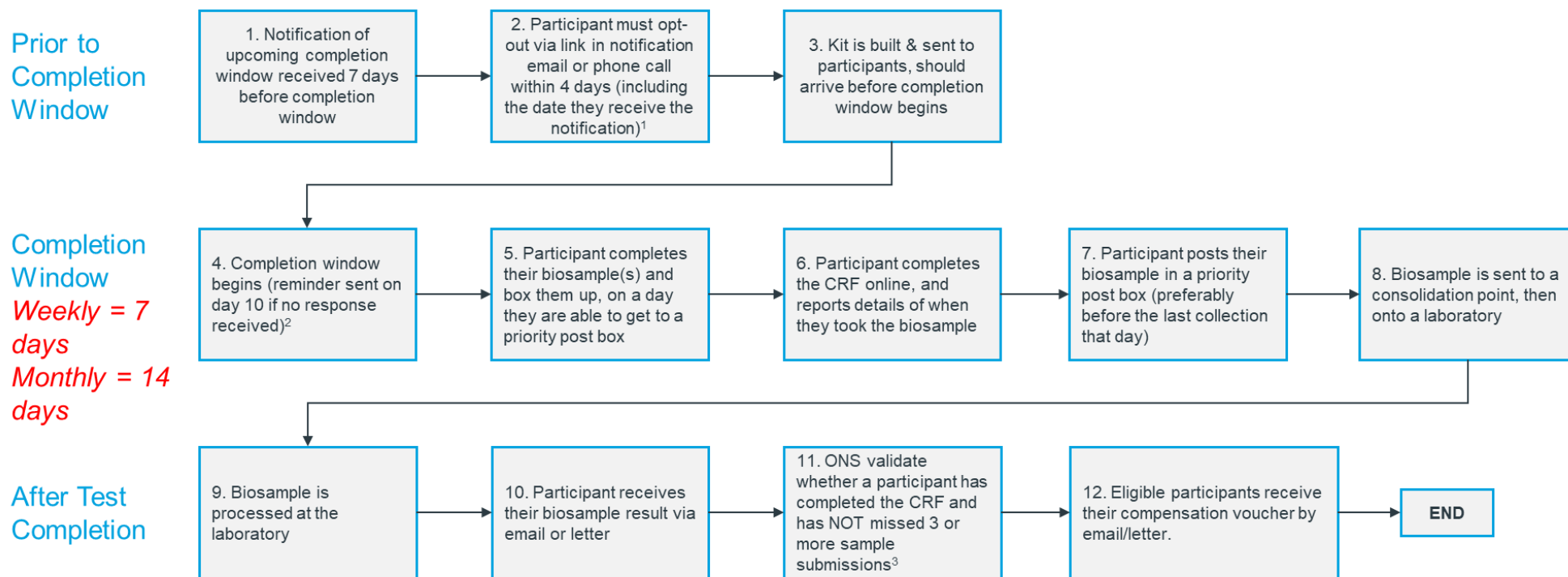
Figure 9 Communications flow - new participants

#	Name	Submitted to REC	Description	Timing	Audience	Format
1	Invitation	Invite letter PIS 16y+ PIS 10-15y child Consent form 16y+ Assent form Study summary How to take your swab sample How to take your blood sample Storyboard – register	Invitation to household to engage in CIS Digital Includes HH ID, PIS, Blank consent form & any other material Includes storyboard detailing step-by-step guide to process of registering	As required	Household	Letter
2	Invite Reminder	Invite reminder	Reminder notification if no one from the invited household has engaged	30 days after invitation	Underrepresented Households	Letter
3	Entry Pack	Consent form 16y+ Assent form Information after registration Storyboard – testing window	Communication to participant once they have registered and consented. Includes completed consent form (inc. their unique Participant ID), test kit instructions & 'storyboard' custom to courier/postal preference given ⁴	After registration	Participant	Preferred ¹
4	Upcoming Completion Window	Testing window notification	A notification to each participant advising them of their upcoming completion window & includes opt-out option	7 days prior to completion window	Participant	Preferred ³
5	Completion Window Reminder	Day 10 reminder	A reminder to each participant to complete their at-home test kit and associated survey, if not already done so. Not required if courier booked. Still sent if survey is partially complete.	Day 10 of completion window for Monthly	Participant (monthly)	Email or N/A ²
6	Courier Confirmation		A notification to confirm courier collection date and time window	On day courier is booked	Non-Mobile Participant	Email or N/A ²
7	Test Result Notification	Results return	A notification to inform participant the result of their most recent swab and/or blood test	On day result is provided by lab	Participant	Preferred ¹
8	Cohort Change Request	Swab to blood Additional blood consent	A notification to participants, currently in the swab cohort, who test positive for COVID-19, asking them to move to the blood cohort	As follow-up to 7	Swab Participant	Phone
9	Compensation Delivery		A delivery of a participants compensation voucher for completing their scheduled test and survey	Once eligible	Participant	Preferred ⁵

1. 'Preferred' means this will be determine by the participant's communication preference captured at registration
2. N/A applies to participants who have selected 'letter' as their preferred communication method at registration
3. Participants who prefer letters and have a completion starting on a Sunday, must receive this notification the day before (Saturday), so they do not lose opt-out time
4. Story board is a guide unique to that participant's chosen preferences (e.g. postal vs. courier process, online vs. telephone surveying)
5. Voucher delivery preference is de-coupled from notification/comms preference

CIS Digital - Operating Model v5.0 - Feb 2022

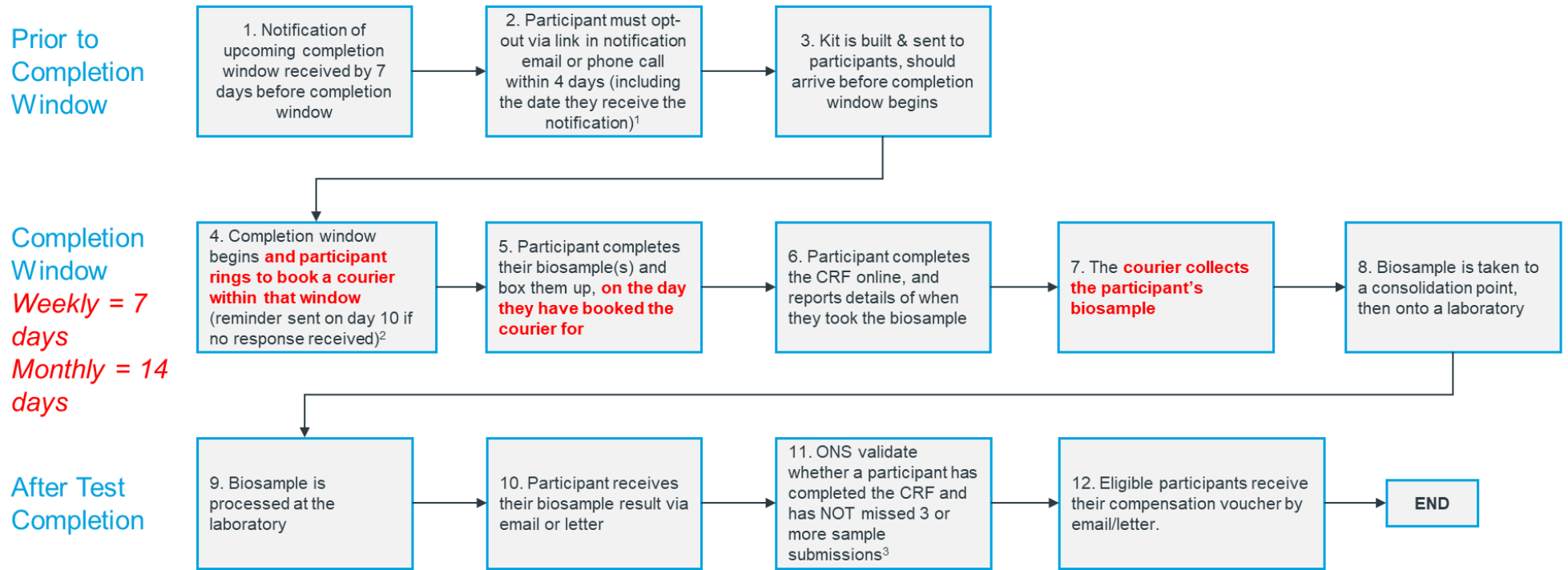
Figure 10 Participant journey – online questionnaire, postal return of samples



1. Opt-out functionality is disabled after 4 days, to prevent opt-out requests after kit has already been dispatched. Full online participant validation is not required for digital opt-out.
2. Reminder is only issued to participants on monthly completion windows, and only those who have selected email as their comms preference (at day 10)
3. If one out of a participant's blood and swab sample is received by the lab, and the participant has completed the CRF, this will count as a completion and a voucher will be issued.

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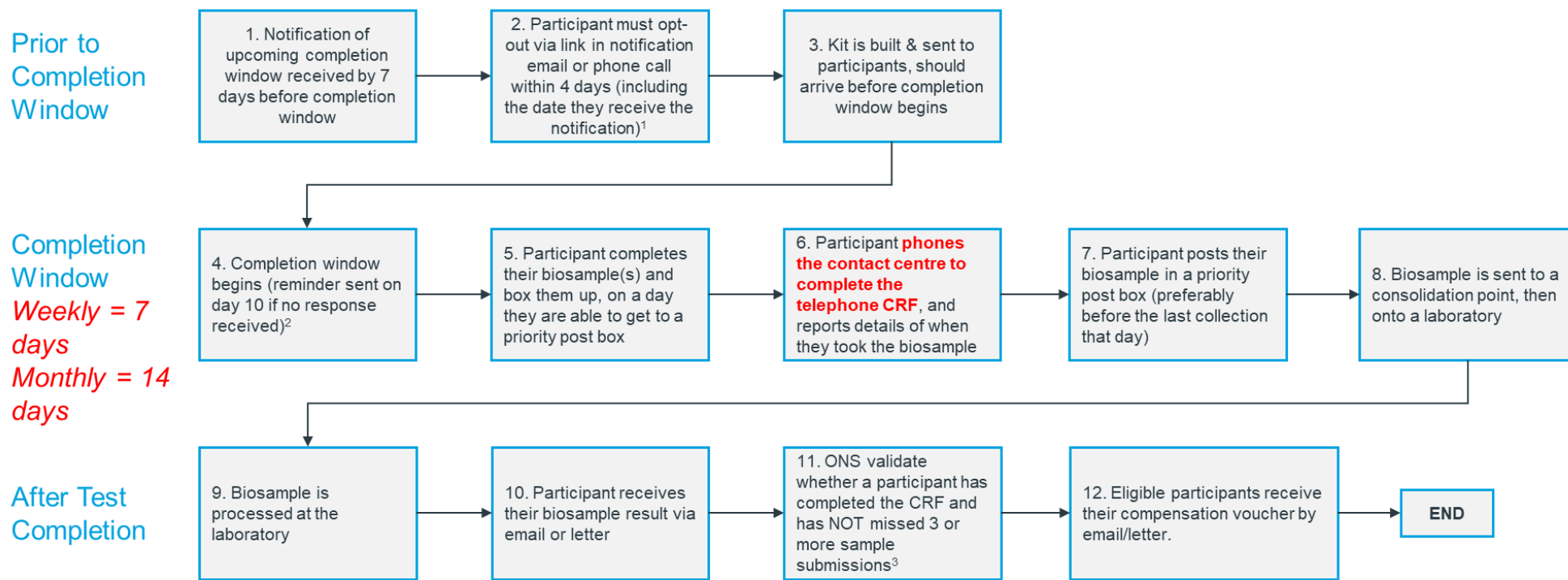
Figure 11 Participant journey – online questionnaire, courier return of samples



1. Opt-out functionality is disabled after 4 days, to prevent opt-out requests after kit has already been dispatched. Full online participant validation is not required for digital opt-out.
2. Reminder is only issued to participants on monthly completion windows, and only those who have selected email as their comms preference (at day 10)
3. If one out of a participant's blood and swab sample is received by the lab, and the participant has completed the CRF, this will count as a completion and a voucher will be issued.

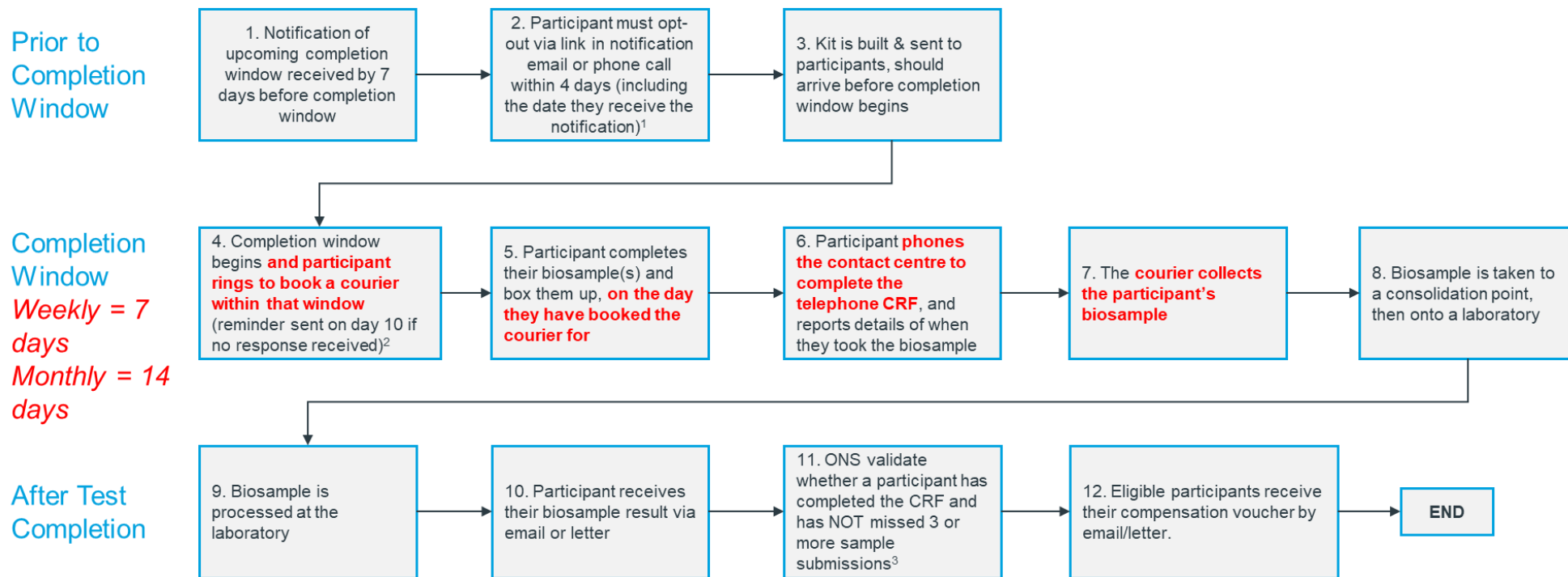
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Figure 12 Participant journey – telephone questionnaire, postal return of samples



1. Opt-out functionality is disabled after 4 days, to prevent opt-out requests after kit has already been dispatched. Full online participant validation is not required for digital opt-out.
2. Reminder is only issued to participants on monthly completion windows, and only those who have selected email as their comms preference (at day 10)
3. If one out of a participant's blood and swab sample is received by the lab, and the participant has completed the CRF, this will count as a completion and a voucher will be issued.

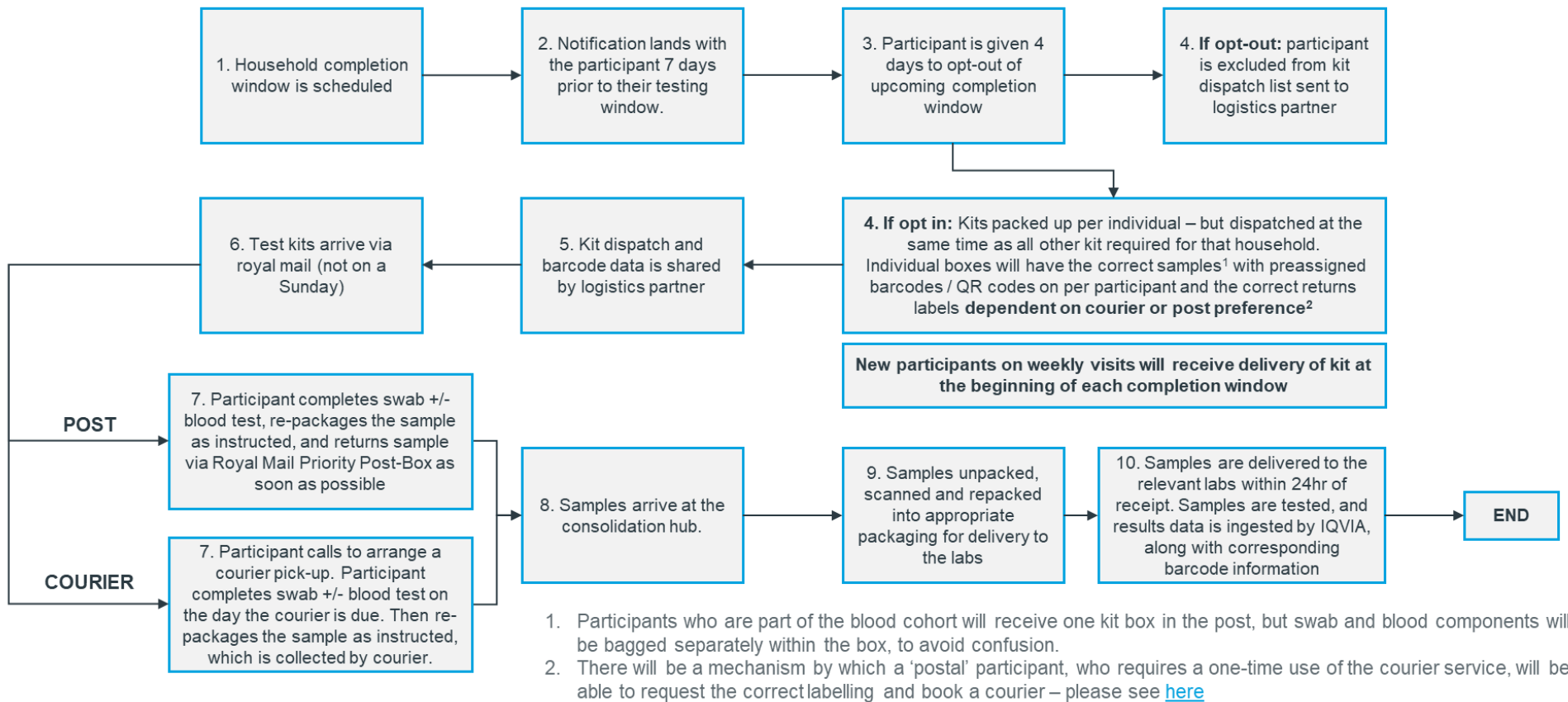
Figure 13 Participant journey – telephone questionnaire, courier return of samples



1. Opt-out functionality is disabled after 4 days, to prevent opt-out requests after kit has already been dispatched. Full online participant validation is not required for digital opt-out.
2. Reminder is only issued to participants on monthly completion windows, and only those who have selected email as their comms preference (at day 10)
3. If one out of a participant's blood and swab sample is received by the lab, and the participant has completed the CRF, this will count as a completion and a voucher will be issued.

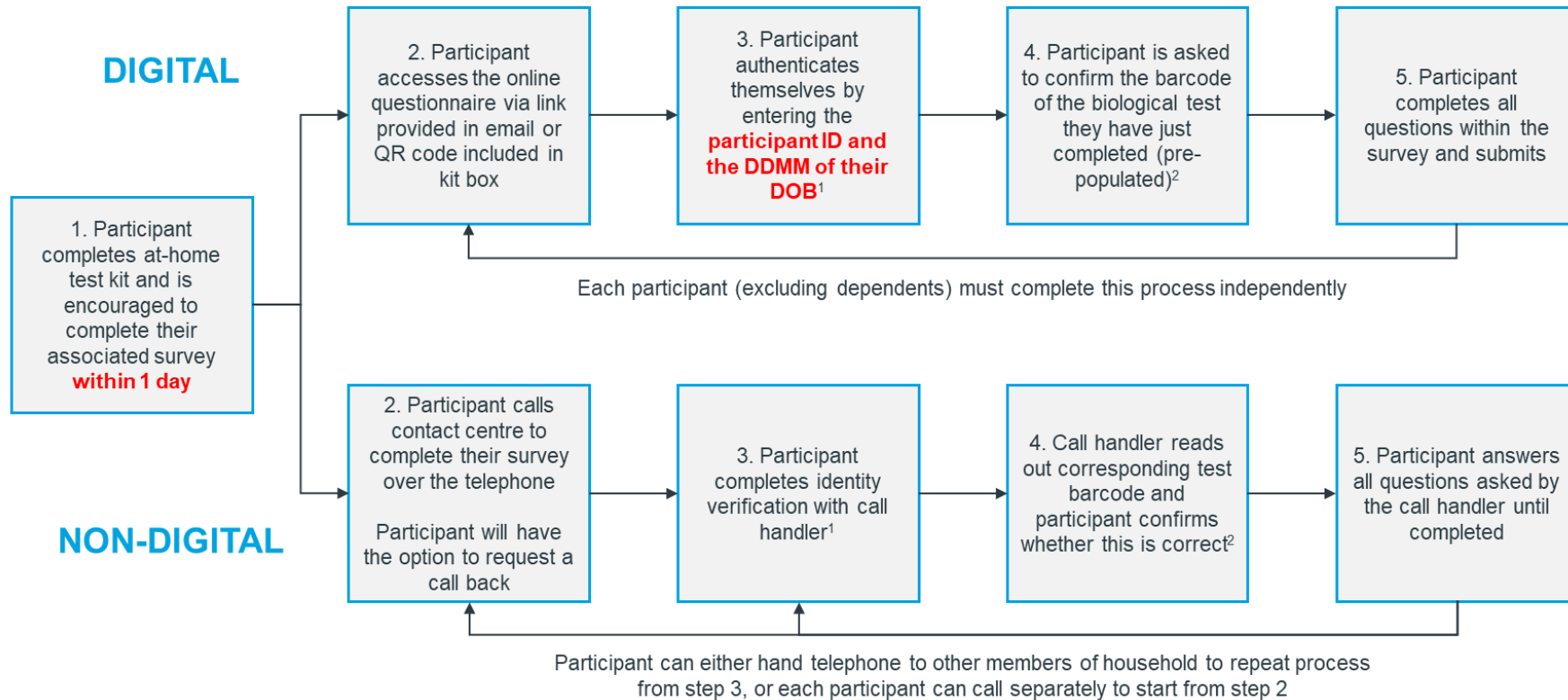
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Figure 14 Test kit logistics flow



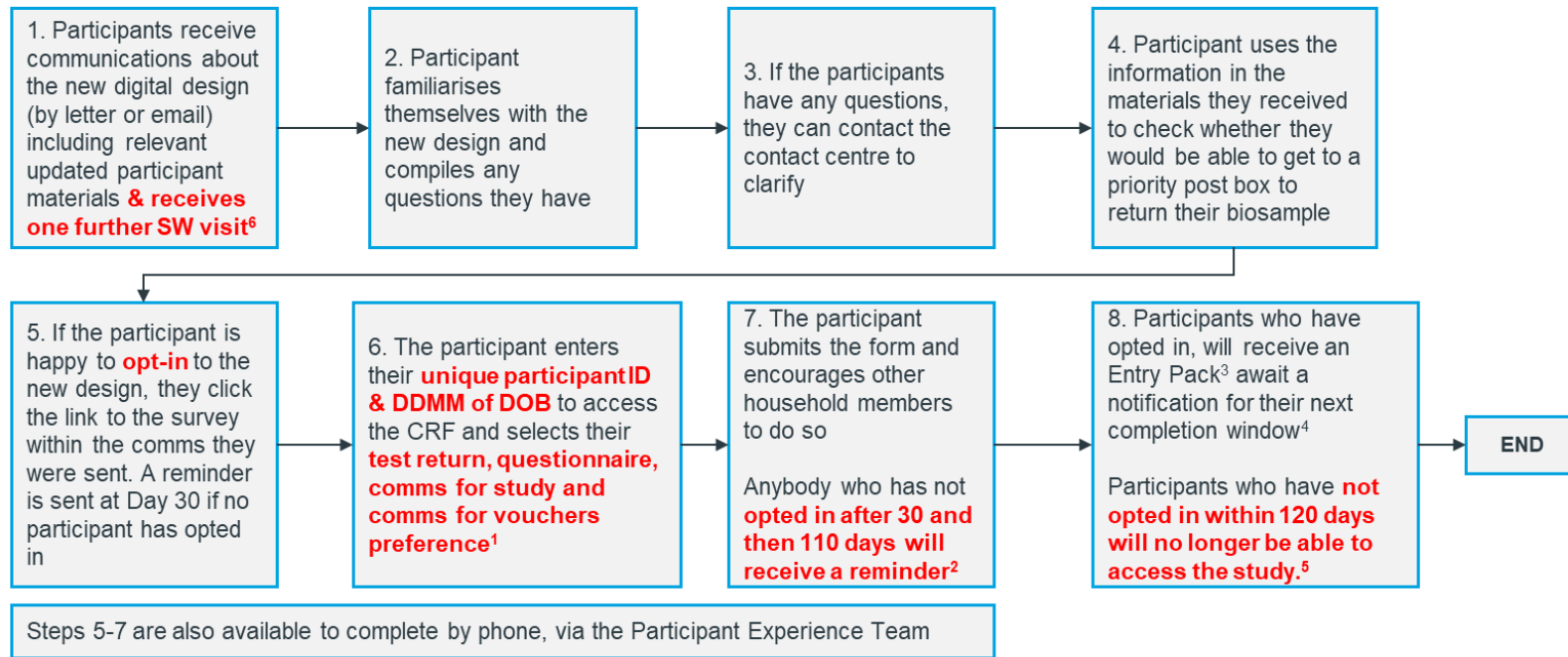
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Figure 15 Questionnaire completion flow



1. A parent/guardian completing the questionnaire on behalf of a dependent child, will need to complete the validation process on behalf of the child in a separate session.
 2. If barcode validation is failed (i.e. participant has used other participant’s assigned kit), please see [here](#) for barcode error process.

Figure 16 Existing participants – opt in



1. Individual participants within a household can each have differing questionnaire and comms preferences. We will encourage all members of a HH to have same test return method
2. Participants who opt-in later than other household members will join the next upcoming completion window
3. Entry Pack includes (1) participant ID, (2) survey storyboard tailored to stated preferences and, (3) detailed instructions for completing the test kits
4. Participants will not be able to influence when their first completion window occurs – this will occur ~9 days after the 1st participant of a household registers
5. No participants will be permitted to opt-in after the 120-day entry window is complete
6. From the start of Public Beta onwards, existing CIS participants will be invited to transition to CIS Digital between their penultimate and final study worker visit.

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Figure 17 Existing participants – worked example of time from first opt in each household

		CISD Transition Window (120 days per HH)																																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30							
PERSON 1	Activity:	Scheduling & Entry Pack	Upcoming Completion Window Notification & Opt-Out Window				Kit Dispatch & Arrival			1st Monthly Completion Window																												
	Day:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	24	25	26	27	28	29	30														
PERSON 2	Activity:																													Scheduling & Entry Pack								
	Day:																													29	30							
		CISD Transition Window (120 days per HH)																																				
		31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60							
PERSON 1	Activity:			Upcoming Completion Window Notification & Opt-Out Window			Kit Dispatch & Arrival			2nd Monthly Completion Window																												
	Day:			33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53														
PERSON 2	Activity:			Upcoming Completion Window Notification & Opt-Out Window			Kit Dispatch & Arrival			1st Monthly Completion Window																												
	Day:			33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53														
		CISD Transition Window (120 days per HH)																																				
		61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90							
PERSON 1	Activity:			Upcoming Completion Window Notification & Opt-Out Window			Kit Dispatch & Arrival			3rd Monthly Completion Window																												
	Day:			63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83														
PERSON 2	Activity:			Upcoming Completion Window Notification & Opt-Out Window			Kit Dispatch & Arrival			2nd Monthly Completion Window																												
	Day:			63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83														

CIS Digital - Operating Model v5.0 - Feb 2022

Figure 18 Communications flow - existing participants

#	Name	Submitted to REC	Description	Timing	Audience	Format
1	Invitation	Opt in invitation Storyboard – opt in	Invitation to all participants of household to transition to CIS Digital, including any new information they require (e.g. participant ID) Includes storyboard detailing step-by-step guide to process of opting in	As required	Participant	Preferred ¹
2	Invite Reminder 1	Opt in reminder	Reminder notification to all participants who have not transitioned	30 days after Invitation	Participant	Preferred ¹
3	Invite Reminder 2	Opt in reminder	Reminder notification to all participants who have not transitioned, warning them that opt-in window closes after 120 days	110 days after invitation	Participant	Preferred ¹
4	Entry Pack	Information after opt in Storyboard	Communication to participant once they have opted in. Includes their unique Participant ID, test kit instructions & 'story-board' custom to preferences given ⁴	After registration	Participant	Preferred ¹
5	Upcoming Completion Window	Testing window notification	A notification to each participant advising them of their upcoming completion window	7 days prior to completion window	Participant	Preferred ³
6	Completion Window Reminder	Day 10 reminder	A reminder to each participant to complete their at-home test kit and associated survey, if not already done so. Not required if courier booked.	Day 10 of completion window for Monthly	Participant (monthly)	Email or N/A ²
7	Courier Confirmation		A notification to confirm courier collection date and time window	On day courier is booked	Non-Mobile Participant	Email or N/A ²
8	Test Result Notification	Results return	A notification to inform participant the result of their most recent swab and/or blood test	On day result is provided by lab	Participant	Preferred ¹
9	Cohort Change Request	Swab to blood Additional blood consent	A notification to participants, currently in the swab cohort, who test positive for COVID-19, asking them to move to the blood cohort	As follow-up to 7	Participant	Phone
10	Compensation Delivery		A delivery of a participants compensation voucher for completing their scheduled test and survey	Once eligible	Participant	Preferred ⁵

1. 'Preferred' means this will be determine by the participant's communication preference captured at registration
2. N/A applies to participants who have selected 'letter' as their preferred communication method at registration
3. Participants who prefer letters and have a completion starting on a Sunday, must receive this notification the day before (Saturday), so they do not lose opt-out time
4. Story board is a guide unique to that participant's chosen preferences (e.g. postal vs. courier process, online vs. telephone surveying)
5. Voucher delivery preference is de-coupled from notification/comms preference

CIS Digital - Operating Model v5.0 - Feb 2022

23. APPENDIX II: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
SA01	2.0	9 June 2020	Ann Sarah Walker	Title amended to include “COVID-19” at the request of the Research Ethics Committee, also Section 3 (Synopsis)
				P1: Jeremy Farrar formally named as clinical lead
				P2,6, Section 3: Additional in kind funding from the Devolved Administrations
				P7: additional key collaborator NatCen; resulting change of reference to IQVIA to ‘call centre’ to accommodate both organisations leading different parts of the fieldwork.
				Sections 2, 3, 5: amendment of recruitment in Phase I to ~5,000 households from England being approached per week and ~2,500 being enrolled rather than ~20,000/~10,000 per month for logistic reasons. In Phase II ~5,000 households from England, ~500 from Wales and ~500 from Northern Ireland will be approached per week, targeting ~2,500, 250 and 250 being enrolled respectively.
				Sections 3, 5, 9.3, 9.6.1, 11.2: clarification that results of tests for COVID-19 infection done within the NHS and held within Public Health England (PHE) and equivalent national test databases in Wales and Northern Ireland will also be linked into the study in order to accurately ascertain infection status outside of the study/study visits (was in the version 1.0 Participant Information Sheet).
				Sections 5, 6: clarification that neutralising antibodies will not now be done on all participants with blood drawn in the study (since this is highly labour intensive), but may be done on a subset to triangulate with results from the main high-throughput assay used. Correspondingly in section 6, neutralising antibodies also therefore moved to an “Other” exploratory outcome. Further, IgG will be assayed on all participants using a high-throughput version of the referenced assay, since IgM adds little information.
				Sections 5, 7: clarification that non-contact visits will be performed wherever possible to reduce risks to participants and study workers.
				Sections 5, 7, 9: addition of approach for consent for blood draw in any individual who tests positive for virus (new infection) during the study as quickly as possible after their positive test and then at monthly visits to contribute additional information to analyses of how immunity after infection changes over time

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
				Section 6: timepoints where outcome measures evaluated amended to weekly over calendar time, reflecting results as presented on https://www.ndm.ox.ac.uk/results . Objectives section reordered to clarify which timepoints go with which outcomes, but no changes (other than moving neutralising antibodies to an “other” exploratory outcome as described above).
				Section 7: clarification that in Phase II, between 10-20% of households will be randomly selected to be approached for consent for blood draws, targeting a minimum of 300 households enrolled per week undergoing blood draws (exact consent rate is unknown).
				Section 9.1, Table 1 (now Table 2): clarification that blood draws are done only in those within the blood sampling target, and that the telephone contact is made with the call centre (number provided on original invitation letter as two organisations will lead different parts of the fieldwork given the scale of Phase II).
				Section 9.1, 9.6.1: removal of participant suffix as a method for identifying participants, who are instead identified by a unique pseudonymised study number.
				Section 9.3: minor clarification to wording around scanning of the original paper copy of the consent form to obtain the research copy.
				Section 9.3: Added that a short summary of the study will be sent with invitation letter and the main Participant Information Sheet, and removed Informed Consent Form (included incorrectly here in v1.0 and was not consistent with Section 9.1).
				Section 9.6.1, 9.9.1, 12, 13, 16.4: At the suggestion of the REC we are actively in the process of setting up the ability to return results of nose and throat swabs directly to participants by text if they are happy to provide mobile phone numbers, as well as being returned to the GP by letter or email. Results of blood tests will be returned once the assay is approved by the MHRA (submission currently in preparation). We would like to seek approval to do this now so we can implement without delay when the system is finalised.
				Section 9.6.1: Minor changes to the questions being asked on the questionnaire, including adding domains about recent contacts outside the home. Section reordered into questions asked once at enrolment with only changes elicited at follow-up and questions asked explicitly at each follow-up.
				Section 9.6.1: clarified that swab and blood samples are primarily identified by a unique sample barcode linked to the participant’s unique study number on the database.

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
				Section 9.6.1: addition of option to be approached about further research if participant tests positive for COVID-19.
				Section 9.7: Clarified that the enrolment visit blood draw can be delayed if needed, at any time up to the first serial sampling visit (including its time window).
				Section 9.9: Clarification that residual material from blood samples are stored for consistency with the Participant Information Sheet and Informed Consent Form which referred to storing leftover blood sample.
				Section 11.2 Update to statistical analysis methods to reflect ongoing analysis results summarised on https://www.ndm.ox.ac.uk/results
				Section 11.5: Clarified that interim analyses will be conducted at least twice a month in order to inform the UK's response to the pandemic, in response to suggestion from the REC.
				Section 11.8: Clarified that regular checks for data quality will be run, in response to suggestion from REC
				Section 12: addition of NatCen as a second key collaborator and lead organisation, given the scale of Phase II and the need to conduct the study across the Devolved Administrations. Changes throughout this section to clarify data management with a second lead organisation.
				Section 12.1 Clarification that name is collected on the household CRF for the purposes of linkage, to make consistent with other parts of the protocol and the Participant Information Sheet
				Section 12.1: addition of mobile telephone numbers if participants wish to receive results by text, and of email addresses if they wish to receive vouchers by email (can be posted instead) and clarification that email addresses will be shared with the third parties named in 12.1 who provide the vouchers.
				Section 13: removed "GCP" from the first sentence for consistency with Section 13.2 which clearly states that no GCP monitoring will be performed.
				Section 16.8: Clarification that participants have the option of receiving vouchers more quickly if they provide an email address.
MA01 (non-notifiable)	2.1	17 June 2020	Ann Sarah Walker	Sections 7, 9, Table 1 (now Table 2): clarification that IQVIA will manage all households randomly allocated to be invited for blood draws and a proportion of households not randomly allocated to be invited for blood draws, for reasons of operational efficiency.

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
SA02	3.0	1 July 2020	Ann Sarah Walker	Synopsis, Sections 7, 8, 9.1, Figure 1; addition of random sampling from available databases of addresses given the larger sample numbers in Phase II, in order to ensure that the sample remains representative in terms of the country throughout its duration and also facilitate proportionate increases where there is evidence of increasing prevalence in Phase II (already included I protocol v0)
SA03	4.0	21 July 2020	Ann Sarah Walker	Sections 2, 3, 5, 6, 8, 11.3, Figure 1, new Table 1: Scale up of recruitment to achieve a target of ~150,000 individuals swabbed at least every fortnight in October in England, and ~15,000 in each of Wales and Northern Ireland in order to monitor for a potential second wave, and increase in percentage approached for blood sampling to 20%.
				Clarifications throughout that electronic record linkage includes the relevant databases from Devolved Administrations and that respondents to both previous ONS and NISRA surveys will be approached
				Section 2: justification for maintaining 2m distancing for study visits regardless of changes in government guidance for other activities
				Section 7, 9.3: clarification that only those present in the household at the enrolment visit are eligible for inclusion in the study (stated elsewhere)
				Section 9.1: clarification that the English NHS guidance quoted in this section is for the purpose of determining whether a visit where a blood draw is planned should be changed from a contact to a non-contact visit instead
				Section 9.9.1, 12: addition of the Glasgow Lighthouse Laboratory as well as the National Biosample Centre (Milton Keynes Lighthouse Laboratory as a testing centre)
				Section 9.9.2, 12: addition of automatic referral of positive swab tests results to the relevant public health bodies as required by law
				Section 9.9.2: clarification around the process of inviting individuals with positive swab tests in the study or elsewhere to undergo blood draws, and also their households
				Section 11.8: clarification regarding the definition of complete case analysis.
SA04	5.0	25 August	Ann Sarah Walker	Front material, Sections 3, 11.6, 17.1: Clarification that in-kind funding contribution is from the Northern Ireland Department of Health rather than the Northern Ireland Assembly, and that NISRA are also making an in-kind contribution

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
				Sections 2, 3, 5, 7: addition of Scotland to the survey, with the goal of achieving 15,000 individuals swabbed every fortnight by October. As recruitment will not start in Scotland until September, this requires a higher weekly recruitment rate than the other Devolved Administrations.
				Sections 2, 3, 5, 8.1, 11.3: clarification that the scale-up for October 2020 in Northern Ireland will be up to 900 households per week, given low current infection rates in the country and the smaller population size.
				Front material, Sections 7, 9, 9.3, 12: removal of NatCen as joint lead on fieldwork. This was planned earlier in the project and the protocol updated to reflect this. However, contract negotiations were prolonged and ultimately the funder has finally decided to remain with IQVIA as the sole lead. The protocol has therefore been updated to reflect this.
				Section 7, 9.1: option of either rescheduling a “contact” visit to later in the allowed window around a scheduled visit if anyone in the household is symptomatic, self-isolating or shielding if this is feasible, or conducting a “non-contact” visit instead.
				Section 8.2: clarification that inclusion criteria refer to participation in prior surveys conducted by ONS or NISRA as stated elsewhere in the protocol.
				Section 9.1: addition of a reminder postcard following the invitation letter.
				Section 9.1: updated text on duration of self-isolation to follow current guidance (10 days rather than 7 days self-isolation).
				Sections 9.3, 9.3.1, 9.9.2, 12, 13.1, 16.4: results of swab and blood tests will be returned directly to participants either by letter or via mobile message or email (in progress) rather than to the participant’s GP as both these tests are now widely available outside the study, through the NHS and through commercial companies.
				Section 9.3, 11.2, 12: removal of specific references to the Health and Social Care Board in Northern Ireland as a source of data at their request to align with wording for other Devolved Administrations.
				Section 9.6.1: addition of religion to the questions asked as well as ethnicity because of the importance of identifying particular communities within whom transmission may be greater or lesser than those not identifiable from ethnicity. Testing programmes in Pillar 1 and 2 collect both ethnicity and religion and we have been asked that the survey align with these programmes.

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				Section 9.6.1: clarification that date of birth and postcode will be available from the original NISRA (rather than ONS) survey for some participants (in Northern Ireland).
				Sections 9.6.1, 9.9.2, 12, 13.1: antibody (blood) results will be returned to participants in the same way as swab results, since a large-scale evaluation has shown the test used in the study to have very high performance, comparable to the best of 4 commercially available assays tested on >1500 samples.
				Sections 9.6.1, 12.3, 16.6, 16.8: provision of study updates and study results through email, as well as the option to receive test results through email as well as mobile text message (also in the Participant Information Sheet).
				Sections 9.7 and 9.8: extension of the windows around scheduled monthly visits from 10 to 14 days, and extension of the initial window for enrolment blood draw from 10 to 14 days to maximise the number of blood samples obtained.
				Section 9.9.1: clarification that couriering of blood samples to the University of Oxford will happen within 24 hours rather than overnight.
				Sections 9.9.1, 12: addition of the Alderley Park Lighthouse Laboratory at Liverpool as well as the National Biosample Centre (Milton Keynes) and Glasgow Lighthouse Laboratories as testing centres
				Section 9.9.1: Clarification that residual material (sera and spun cells) will be stored by the University of Oxford in secure storage facilities, rather than at the University of Oxford.
				Section 9.9.3: correction of the name of the contact tracing programme in Northern Ireland to "Test, Trace, Protect".
				Sections 12, 20; additional clarifications regarding data capture and storage by IQVIA.
SA05	6.0	20 November 2020	Ann Sarah Walker	Title page, and Sections 3 and 16.6: addition of ISCRTN number (also a condition of NIHR granting the survey Urgent Public Health status)
				Contacts: updated ONS representatives
				Contacts: added details of Study Clinical Experts
				Contacts and Section 13.3: addition of a representative of the Devolved Administrations and an independent Chair to the Study Management Group (the latter as a condition of NIHR granting the survey Urgent Public Health status).

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				Sections 6, 11.2: update of timing of analyses and statistical methods to reflect the fact that models assessing a continuous relationship between positivity and incidence and calendar time are used as the primary analysis, with models based on categorising time a secondary analysis.
				Sections 7, 9.3, 9.9.2: For households invited to provide nose and throat swabs only, additional optional consent will be sought at enrolment for additional blood samples if anyone in their household tests positive on a nose and throat swab (in order to avoid reconsenting them later on – information about this already in the participant information sheet).
				Section 9.1: clarification that a single “nudge” telephone call may be made to addresses where a telephone number is available through either participation in previous surveys or the address list via which households were sampled.
				Section 9.1: addition of a website hosting translated participant materials.
				Section 9.3: extension of optional consent for other research studies to other programmes approved by DHSC (or equivalent in Devolved Administrations) (e.g. convalescent plasma).
				Section 9.6.1: addition of questions around long COVID
				Section 9.7: addition of phone call to elicit missing participant data.
				Section 9.8: clarification around visit windows being equidistant.
				Sections 9.9.2, 12: amendment of methods for returning results to participants given changes to the Public Health Regulations (2010) in England (in process for Devolved Administrations) to require all results (positive/negative/void) of any laboratory test (swab or blood) to be returned to public health bodies, not just positive tests. Until these regulations are in place, only positive swab results will be passed onto public health bodies in the relevant nations as per protocol v5.0 and all results will continue to be provided to participants by letter. Once regulations are in place, notification of swab test results will be via the national reporting systems linked to national tracing programmes.
				Section 9.10: clarification of different options around withdrawal from the study.
SA06	7.0	1 February 2021	Ann Sarah Walker	Sections 2, 6: clarification that survey remains important to monitor infection rates as increasing numbers of people get vaccinated and that vaccination is an important participant characteristic to be considered in analyses.
				Sections 2, 3, 5: removal of plans to rapidly decrease recruitment in the absence of a “second wave” of infection in October 2020

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				Sections 2, 5, 7, 8, 9, 11, 16: approach for consent from individuals from enrolled households currently providing swabs only to provide optional blood samples at monthly visits and for monthly visits to be extended to April 2022, in order to monitor vaccine rollout. Approach for optional consent for individuals from households already providing blood samples to extend follow-up to April 2022 (because the original consent form specified a 12 month study participation). The target is to achieve up to ~125,000 people giving blood samples every month in England, and up to ~7,500, ~5,500 and ~12,000 per month in Wales, Northern Ireland and Scotland (~150,000 in total across the UK) through to April 2022.
				Sections 2, 5, 7, 9, 10, 11.8, 13.1: addition of the option for blood to be obtained from participant fingerprick (capillary) rather than only venous blood draw, to avoid the need to rely on trained HCP who may be needed in other parts of the NHS and to allow the ability to obtain blood if individuals in the house are symptomatic, self-isolating or shielding.
				Sections 5, 6, 9.6, 9.9.1: extension of the antibody assays to measure antibodies against both S (spike) and N (nucleocapsid) proteins on the same sample within the same automated workflow. Only anti-S results will be returned to participants (as in previous protocol versions) since both natural infection and vaccination produce these antibodies.
				Section 9.6.1: clarification that questions about vaccination include both the offer and receipt, and also the type of vaccine, number of doses and dates if vaccinated.
				Section 11: updates to statistical analysis since the survey has now reached sufficient size that spatiotemporal models can be fitted (originally presented as a future aspiration in Phase I).
				Section 12.3: addition of possibility of data processing by IQVIA outside the EEA as they are a worldwide organisation. This had always been in the participant information sheet, but had been omitted from the protocol in error.
MA02	7.0	05 April 2021	Ann Sarah Walker	Updates to the instruction sheet for participants for capillary blood which will be sent ahead of the visit.
MA03	8.0	9 April 2021	Ann Sarah Walker	Lay summary, Synopsis, Sections 5, 7, 8.1: Extension of recruitment from 23 April 2021 to 31 July 2021 and study duration to 31 July 2023. We will continue to invite new households to join the study in order to maintain the stated targets for swab results per fortnight and blood results per month.

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SA08	9.0	29 April 2021	Ann Sarah Walker	Lay summary, Synopsis, Sections 5, 7, 8.1, 9.4.2, 16: From April 2021 onwards, we will maintain both the targets for swab results per fortnight and blood results per month above through to April 2022 by <ul style="list-style-type: none"> • inviting everyone who is currently active in the study to remain on monthly follow-up visits until April 2022 (additional consent) • inviting additional households who are only giving swabs at their monthly visits to additionally give blood by fingerprick at these visits until April 2022 (additional consent) • continuing to invite new households until January 2022 to join the study in order to replace participants who stop follow-up and to supplement current numbers in order to meet targets despite possible missed visits.
				Sections 7, 9, 11, 13: phasing out of venous blood draws so that blood is only taken from fingerprick tests, meaning that study workers never enter participants' homes. Participants on venous blood draws will receive the option of moving to capillary blood draws or only taking swabs for the rest of their study visits.
				Section 11: clarification of targets for swabs and bloods, and addition of reference to the Methods article on the ONS website.
MA04	9.1	12 May 2021	Ann Sarah Walker	Section 12: Change from Serco to Capita to help resource the call centre from July 2021.
SA09	10.0	22 July 2021	Ann Sarah Walker	Section 9.9.2, 12: removal of text option for returning study test results, removal of results return through NPEX (which is being phased out of the national testing programme processes) and transitioned to the NHS Business Services Authority) and implementation of results return via email, with letters remaining for those who do not have or do not wish to provide an email to receive test results (and clarification of sub-contracting arrangements to enable this).
				Sections 9.6.1, 11.2: clarification that case record forms collect sex rather than gender. Removal of religion (no longer collected).
				Section 10: addition of standard further detail for safety reporting.
SA10	11.0	13 September 2021	Ann Sarah Walker	Sections 2, 3, 5, 7, 8.1: Amendment of country-level adult blood targets for England, Northern Ireland and Scotland to reflect the Barnett formula (same overall target of 150,000 antibody test results per month) and clarification that, as per sample size section, all targets relate to test results being obtained.
				Sections 2, 3, 5, 7, 8.1: Addition of targets for blood test results in those aged 5-15 years (~5,500 antibody test results per month).

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				Section 7, 9.3: clarification that the choice of participating once at enrolment, weekly for the first month, or weekly for the first month and then monthly will be made at the enrolment visit; participants will not be offered the option to extend if they initially choose weekly visits for one month only.
				Section 9.4.3, 16.8 (plus brief statement in other sections where fingerprick testing is mentioned): Addition of optional fingerprick blood tests for antibody levels to those aged 5-16 years; implementation starting with a pilot including collection of a small number of questions relating to parent/carer experience either on the main study database (depending on time needed to develop this) or on a separate survey tool, Smart Survey. If Smart Survey is used, only pseudonymised identifiers (household identifier, age in years, sex) would identify child participants. Participating children would receive a sticker as a thank you.
				Section 9.6.1: Addition of questions about flu vaccination and other respiratory virus related symptoms to the questionnaire.
				Section 9.9.1: Clarification regarding use of stored serum samples.
				Section 12: details regarding the Smart Survey tool and its certification and assurance.
SA11	12.0	7 October 2021	Ann Sarah Walker	Section 6: clarification regarding the different types of characteristics that will be investigated for associations with positive swab and/blood tests, and that an exploratory objective is to investigate long COVID using available survey data
				Section 9.4: Addition of reminder letters or emails where participants are being approached for consent to continue follow-up to the end of the survey.
SA12	13.0	12 November 2021	Ann Sarah Walker	Throughout: alignment of the recruitment period to 31 January 2022 and that this means enrolling new households through to this date (rather than sending letter invites to this date which may not be acted on for several weeks).
				Sections 2, 3, 5, 7, 8.1, 9.4.3: Antibody testing in under 16s restricted to those aged 8-15 years and monthly based on results of the pilot phase and feedback from parents/carers, with targets amended to ~3,600 antibody test results per month to reflect this.
				Section 8.5: clarification that co-enrolment is allowed.
				Section 12: clarification that the mechanism by which linkage to NHS health records will occur is to link the personal information provided by the participant (name, address, date of birth, sex) to their NHS number through the Personal Demographics Service, and then use the NHS number to link the relevant health records. NHS number would not be returned to the study dataset, but used only for linkage.

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				Section 16.8: removal of stickers for children and young people attempting the fingerprick blood test based on feedback in the initial phase that this was not useful or wanted, and change in age to 8 to 15 years.
	13.1	24 November 2021	Ann Sarah Walker	Section 9.4.3: Rationale for the change in blood sampling target for 8 to 15 year olds after results of the initial pilot phase.
				Section 11.3: additional justification of the blood sampling target for 8 to 15 year olds
SA13	14.0	21 December 2021	Ann Sarah Walker	Sections 3, 5, 6, 7, 9.3: extension of linking of NHS health data from 1 year to 15 years after the end of study participation to enable analyses of the impact of SARS-CoV-2 infection on development of multiple long-term conditions over the long-term, because of the unique ability to accurately assess groups who have and have not been infected with SARS-CoV-2, including asymptotically, in the survey. Inclusion of data back to January 2016 to capture pre-existing health conditions to adjust for these in analyses. Clarification that linkage will be happening throughout the course of the study as well as after the end of the study.
				Section 9.6.1: addition of extra symptoms for all symptom questions to cover symptoms associated with "long COVID".
				Section 9.6.1: clarification that S antibody results will be returned as positive or negative in line with the MHRA approval for the test (already in results return letter).
				Section 9.8, 13.2: Addition of a small random number of telephone calls to participants after visits in order to ensure quality control of study procedures and data quality.
				Throughout: replace Public Health England with UK Health Security Agency
SA14	15.0	9 February 2021	Ann Sarah Walker	Sections 5, 8.4, 7: clarification that those testing positive on a nose and throat swab, and their household members, would be approached to give blood if this does not lead to targets for blood sampling being exceeded by >5% (which impacts the capacity of the laboratory to conduct all the required tests).
				Section 9.6.1, 9.9.2: return of antibody results at both the current standard threshold, and a higher threshold reflecting protection from new infection in those vaccinated who have not had COVID-19 before.
				Throughout: typographical errors and edits to match previously approved versions which had been missed.

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SA17	16.0	8 March 2022	Ann Sarah Walker	<p>Throughout: extension of funding to 31 March 2023 in England only with reduction in sample size. From April 2022, the swab targets will be reduced by 25% and the blood targets by 10% (i.e. retaining a greater percentage of those giving blood in order to maintain precision to monitor declines in antibodies), to achieve the following:</p> <ul style="list-style-type: none"> Swab target: up to ~112,500 individuals with swab test results every fortnight in England, ~6,700 in Wales, ~3,700 in Northern Ireland and ~11,200 in Scotland (~134,200 total across the UK) Blood target 16 years and older: up to ~104,000 adults 16 years and older with blood test results every 28 days in England, and ~6,200, ~3,700 and ~10,400 per month in Wales, Northern Ireland and Scotland (~124,200 in total across the UK) Blood target 8-15 years: up to ~1,800 older children/adolescents with blood test results every 28 days across the UK.
				Sections 2, 3, 5, 7, 8, 9, 11.8: transition from assessments being done by a study worker visiting participants' homes, to sample kits being posted and questionnaires completed online or via the telephone.
				Section 5, 6: removal of anti-N antibody assay for all participants giving blood (may still be used in a subset, depending on capacity and funding)
				Section 9.9.1: swabs will be tested in one of the government accredited testing laboratories (Glasgow Lighthouse or Rosalind Franklin Laboratories) using endpoint or reverse transcriptase polymerase chain reaction.
				Section 11: clarifications regarding statistical methods.
				Throughout: removal of information about contact home visits and venous blood draws which are no longer used.
SA18	17.0	12 April 2022	Ann Sarah Walker	<p>Throughout: 1. Clarification that targets relate to samples taken rather than results obtained, because test failures are still a cost within the budget. Test failures are expected to remain relatively low and this has been added to the sample size justification. Amendment of targets to reflect further changes to the funding envelope, so that reductions are proportionately less in Wales and Northern Ireland in order to maintain power within these countries, and proportionately more in England to meet the overall reductions, and clarification that blood targets are across all age groups. Specifically the targets are now</p> <ul style="list-style-type: none"> Swab target: up to ~227,300 swab samples taken from individuals 2 years and older every 28 days in England, ~15,650 in Wales, ~10,050 in Northern Ireland and ~23,200

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				<p>in Scotland (~276,200 total across the UK every 28 days, ~300,000 swab samples in total across the UK per month)</p> <ul style="list-style-type: none"> Blood target: up to ~90,850 blood samples taken from individuals 8 years and older every 28 days in England, ~6,300 in Wales, ~4,150 in Northern Ireland and ~9,200 in Scotland (~110,500 in total across the UK every 28 days, ~120,000 blood samples in total across the UK per month)
				Section 9.1.2: inclusion of a short summary of key information with sample kits.
				Section 9, 9.4.4: Monthly visits will initially be implemented as 31 days apart, but given substantial uncertainty in the percentage of testing windows that will be completed under the new approach, this schedule may be extended by up to 5 days (to 36 days) or shortened by up to 3 days (to 28 days) in order to achieve the overall sample targets with the (unknown) number of participants who choose to opt in to the new approach. This does not impact analysis as the key objectives relate to rates over calendar time.
				Section 9.4.4: reduction of the time participants have to opt in to the new delivery approach from 120 days to 90 days from the invitation being sent (with final reminder at 80 days rather than 110 days, still 10 days before the end of the opt in period).
SA19	18.0	21 May 2022	Ann Sarah Walker	Section 9.4.4: second reminder to be sent 60-80 days after the initial opt-in invitation, informed by response rates to Stage 1 invites; participants may opt-in at any time after their initial invitation to improve accessibility. Second reminder will be by letter where possible dependent on funding. Study workers can provide a leaflet to help participants understand the action needed to stay in the survey if they wish at study worker visits in June and July 2022.
				Section 13.2: clarification that quality monitoring will including telephone calls for the new approach as well as for study worker visits.
SA20	19.0	13 June 2022	Ann Sarah Walker	Section 9.3: clarification of process for inviting those turning 16 years old in the study to formally consent for themselves under the new approach