Study Protocol

Longer term impact of COVID 19 infection in people with diabetes

Trial/Study Acronym	**Diabetes Long COVID study**
Sponsor	**NHS Greater Glasgow and Clyde Health Board**
Sponsor Number	**GN20DI579_313445**
Public database registration	***ISRCTN to be added***
Funder	**Chief Scientists Office** **COV/LTE/20/28**
Grantholder	**University of Glasgow (UoG Ref 313445)** **Project Coordinator (ICAMS):** **Dr Chris Hinds** **College of Medical, Veterinary and Life Sciences** **Rm 443, BHF Glasgow Cardiovascular Research Centre** **University of Glasgow** **G12 8TA** **E-mail: Chris.Hinds@glasgow.ac.uk**
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REC Number	**Insert REC number before finalisation**
Version Number and Date	**Version 1.0, 24.03.2021**

PROTOCOL APPROVAL

Longer term impact of COVID 19 infection in people with diabetes

Signatures

The undersigned confirm that the following protocol has been agreed and approved by the Sponsor and that the Chief Investigator agrees to conduct the study in compliance with this approved protocol and will adhere to the principles of GCP, the Sponsor SOPs, and any other applicable regulatory requirements as may be amended from time to time.

Dr Robert Lindsay Chief Investigator	Signature	Date
[INSERT PI NAME] [INSERT HEALTH BOARD SITE NAME] Principal Investigator	Signature	Date

LIST OF ABBREVIATIONS

AE	Adverse Event
BG	Blood Glucose
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Indemnity Scheme
COVID-19	Coronavirus SARSCOV-2
CRF	Clinical Research Facility
DMS	Data Management System
GCP	Good Clinical Practice
ICF	Informed Consent Form
NHS GGC	NHS Greater Glasgow and Clyde
ISF	Investigator Site File
NRS	NHS Research Scotland
PI	Principal Investigator
REC	Research Ethics Committee
SDG	Scottish Diabetes Group
SOP	Standard Operating Procedures
SMF	Study Master File

SUMMARY/SYNOPSIS

Study Title	**Longer term impact of COVID 19 infection in people with diabetes (Short Title: Diabetes Long COVID study)**	
Study Design	Observational Case Cohort study with Nested Case Control study	
Study Population	Adults with Type 1 and Type 2 Diabetes in Scotland	
Sample Size	Total sample size in Nested Case Control study, as per IRAS form: 1000 participants (500 cases and 500 matched controls, with at least 200 people in each of the categories of Type 1 and Type 2 diabetes)	
Planned Study Period	May 2021 to approximately October 2022	
Follow up phase duration	1 year (cases only)	
Aims	To understand the proportion of people with diabetes who experience longer term symptoms or illness after covid-19 infection, the nature of these symptoms, and the potential health impact of that.	
Primary	Objective: Case Cohort: After COVID infection, what proportion of people with type 1 and type 2 diabetes experience symptoms in the longer term (up to 18-24 months after index infection)?	Outcome Measures: The prevalence of symptoms in the longer term in people with diabetes up to 2 years after COVID-19 infection using Wellcome questionnaire
Secondary	Nested Case Control: What is the impact of "long COVID" upon physical activity, diabetes control and outcomes?	incremental walking test, hand grip, HbA1c
Inclusion Criteria	**Case* Cohort study:** • Person with Diabetes (type 1 or type 2) • Aged 18 or over • Able to read and write in English *Cases additionally defined by self-reported COVID infection and or COVID test positive in clinical record **Nested Case Control study**:** **Cases defined by positive COVID test in the clinical record. Controls defined by no positive COVID test in clinical record or self-identified COVID infection.	
Exclusion Criteria	Nested Case Control study only: • Participating in the intervention phase of another clinical study	

1 INTRODUCTION

Severe, longstanding symptoms may be experienced after COVID-19 infection. This study will complete both a matched case cohort study (online questionnaires) and a nested case control study (CRF visit), recruiting people with diabetes who have had evidence of COVID-19 infection along with age, sex and ethnicity matched controls with diabetes. We will examine prevalence and correlates of long COVID symptoms with biomarkers of inflammation, cardiometabolic risk and body composition. Participants who are cases will have a repeat study visit at 12 months.

2 BACKGROUND & RATIONALE

The COVID-19 crisis has posed an unprecedented challenge to health services world-wide. Early in the pandemic it became apparent that symptoms, sometimes severe, could persist after the acute illness. In an Italian study it was found that 55% of patients, questioned on average two months after symptom onset, were still experiencing three or more symptoms including tiredness, breathlessness and chest pain (1). "Long COVID" might be considered to be analogous to syndromes described after other viral illnesses and has been variously defined as "not recovering [for] several weeks or months following the start of symptoms that were suggestive of COVID, whether you were tested or not" (2), and more recently by NICE and SIGN as "Signs and symptoms that develop during or following an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis". More recently an NIHR report suggested that there may be several overlapping post COVID syndromes underpinned potentially by direct effects on the heart, brain and indirect effects of prolonged hospitalisation (3).

People with diabetes are more likely to suffer severe adverse consequences of COVID-19 infection during the acute illness. In the Scottish population, people with diabetes are at considerably higher risk of having severe COVID-19 infection with odds ratio (OR) of fatal or critical care unit treated disease of 2.4 in type 1 diabetes and 1.4 in type 2 diabetes, with higher relative hazards in younger people with type 2 diabetes (4). Diabetes is also associated with an increased risk of in-hospital death following COVID in other populations (5). At this stage of the pandemic it is not clear whether there is also an increased susceptibility to longer term sequelae in people with diabetes. Risk scores have been developed to try to understand the likelihood of severe complications in acute illness both in diabetes (4) and the general population (6). Likelihood of longer term impact on health and economic factors will also be key in the public health response to COVID-19 and would ideally inform decisions as to the degree of shielding recommended for different groups of people in the population, including people with diabetes. Such information will also be key to the support of people with long-term consequences of COVID-19. Importantly however, chronic disease in general and diabetes and diabetes complications in particular, have well known effects on chronic wellbeing and association with depression, diabetes distress and related symptoms (7, 8). Understanding the effects of COVID in this population is therefore dependent on understanding the prevalence and architecture of symptoms in the *general* diabetes population.

In Scotland, information from clinical visits is held within the SCI Diabetes information system and, following additional data linkage to COVID-19 test results, this has allowed the detailed analysis of risks in the acute setting (4). We know that, to the end of July 2020, 2724 people with diabetes had had evidence of infection with COVID-19 (positive test, admission or death certificate) of whom 988 had unfortunately died. We expect therefore that conservatively there are at least 1736 people with diabetes in Scotland who may be living with the consequences of COVID-19. Understanding those consequences cannot be achieved with

routine electronic health record data and therefore this study will explore patient outcomes in people with diabetes compared to suitable controls. The study will use publicly available tools (Wellcome COVID questionnaire (9)) allowing cross comparison to other populations and to facilitate data sharing.

3 STUDY OBJECTIVES & OUTCOMES

To understand the proportion of people with diabetes who experience longer term symptoms or illness after COVID-19 infection, the nature of these symptoms, and the potential health impact of that.

The primary objectives of the study are:

After COVID infection, what proportion of people with type 1 and type 2 diabetes experience symptoms in the longer term (up to 18-24 months after index infection)?

The secondary objectives of the study are:

What is the impact of “long COVID” upon physical activity, diabetes control and outcomes?

4 STUDY DESIGN

4.1 INTERVENTION

This is a non-interventional study.

4.2 STUDY DESCRIPTION

We will recruit a large Case-Cohort of people with type 1 and type 2 diabetes in Scotland to assess the prevalence of symptoms after self-reported COVID infection. We will further recruit a nested case control study of those with positive COVID test in the clinical record (cases) and controls to examine physical measures, glycaemia and diabetes complications.

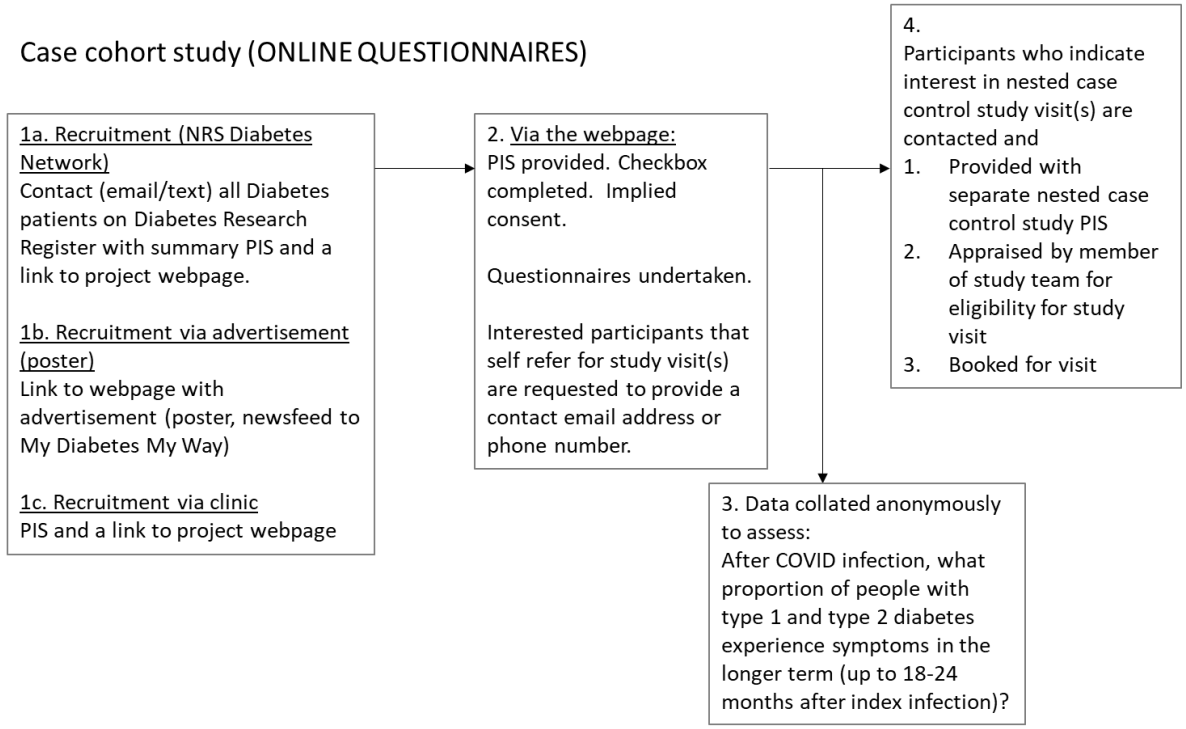
The cohort will be recruited predominantly from the NHS Research Scotland Diabetes Research Register with additional direct recruitment invited from clinic lists of those with previous evidence of COVID infection. This cohort will involve self-completed questionnaires and minimal personal information limited to contact details (e-mail, telephone) and not including patient identifiers such as name, address or CHI. The cohort will acknowledge “By ticking this box, you acknowledge that you have read the PIS and have had the opportunity to ask any and all questions to a research staff member" electronic checkbox prior to completion of demographic information and questionnaires.

The Nested Case Control study will be conducted in person under written consent and include:

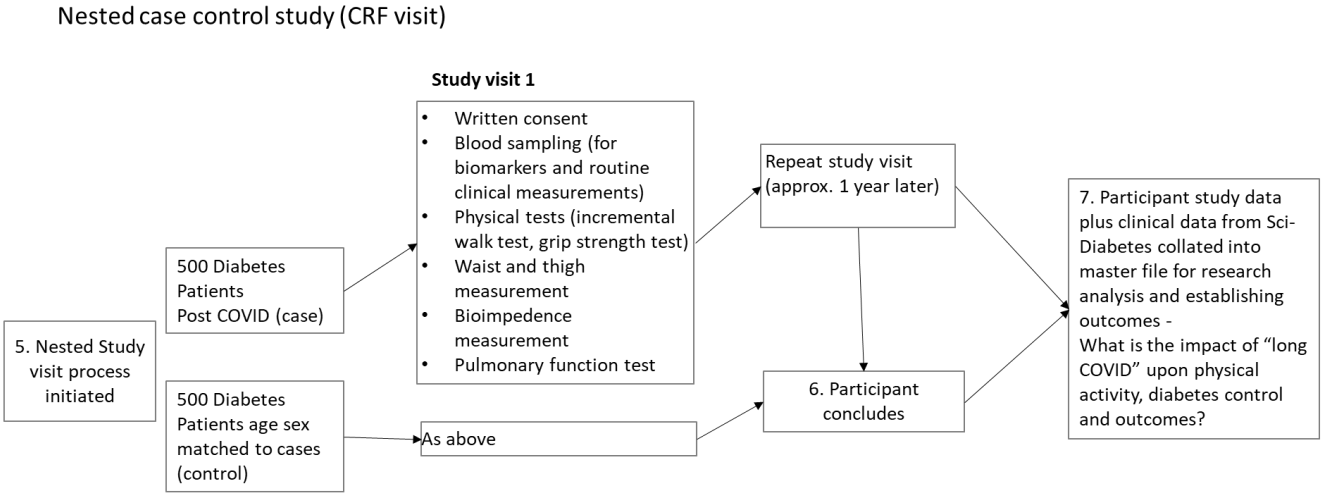
- Blood sampling (for biomarkers and routine clinical measurements)
- Physical tests (incremental walk test, grip strength test)
- Waist and thigh measurement
- Bioimpedence measurement
- Pulmonary function test

Cases will repeat the CRF study visit approximately 1 year from the baseline visit.

4.3 STUDY FLOWCHART



4. applies to COVID cases and selected, matched controls



4.4 STUDY MATRIX

The study matrix is shown below.

Case cohort study (online questionnaires):

Approximate Week	Anytime (cases and controls)
Interest to participate	X
Remote Implied Consent (online)	X
Demographic information (online)	X
Questionnaires (online)	X
Option to self-nominate for Nested case control study via provision of contact email and/or phone number (online)	X

Nested case control study (CRF visit):

Approximate Week	-4 to 0	0 (cases and controls)	1 year (40-64 weeks: cases only)
Interest to participate	X		
Inclusion and exclusion assessed by research nurse		X	
Consent (written)		X	
Questionnaires (if not done previously) or repeat of Wellcome section 1.3		X	X
Blood sample for labs (optional)		X	X
Blood sample for routine clinical measures*		X	X
Grip strength test		X	X
Incremental walk test		X	X
Waist and thigh measurement		X	X
Bioimpedence (optional)		X	X
Pulmonary function test** (optional)		X	X
Extract of routinely collected healthcare data from SCI Diabetes system		X	X

*HbA1c, LFTs, lipids, U&Es
**Spirometry/FEV1

4.5 STUDY ASSESSMENTS

Case-Cohort:
Self-completed, offered online (can be offered by phone/on paper for participants who request this).

1. Demographics
2. Questionnaires (in order of priority)
    a. Wellcome Trust COVID 19 questionnaire (Most up to date version in use at the time of the study): This is a comprehensive instrument covering physical, cognitive, and mental health domains and will also allow comparison to developing UK reference population data). Questions deemed to require additional support have been removed.
    b. Diabetes Related Quality of Life (DQOL)

   c. Diabetes-Specific Emotional Distress, DDS-1
   d. EQ5D

3. Option to self-nominate for nested case control study.

Nested Case Control (CRF visit):

1. Written consent
2. Questionnaires (if not done previously) or Update of symptoms score Wellcome questionnaire section 1.3
3. Blood sample (optional) for research labs (16ml total, 6ml purple top (EDTA), 6ml gold top (serum), 4ml blue top (citrate)) for non-routine bloods: inflammatory (e.g. CRP), vascular (t-PA, vWF) and cardiac (hs troponin, NT proBNP) biomarkers consistently predictive of long-term adverse outcomes.
4. Blood sample (8ml total, 3ml purple top (EDTA) and 5ml gold top (serum)) for routine clinical measures (HbA1c, LFTs, lipids, U&Es).
5. Physical measures
   a. Incremental walking test
   b. Grip strength
6. Waist and thigh measurement
7. Bioimpedence (optional if site does not have this equipment)
8. Pulmonary function test (optional if site does not have this equipment)

Cases will be invited to a repeat study visit 1 year (40 to 64 weeks) from the initial study visit.

SOPs (shared from other studies) will be used to standardise:

- Incremental walk test
- Grip strength test
- Blood sampling, storage and shipment
- Pulmonary function test

Clinical data: Baseline and follow up data from SCI-Diabetes including glucose control and blood pressure.

4.6 STUDY SAFETY ASSESSMENTS

There are no measures that will be used to evaluate or determine subject safety during the study.

Remote implied consent and Questionnaires: As these are participant facing questionnaires completed online or on paper at a time and place suitable for the participant, safety assessments are not required as there is no risk of harm to the participant.

Study visit attendees: As this is a non-interventional study with low risk of harm to participants, adverse events will not be recorded unless these relate specifically to study related tests or the study visit.

4.7 INCIDENTAL FINDINGS

Any incidental findings (previously undiagnosed condition) considered to be clinically significant will be reported to the participant's GP and/or consultant by the CI or Site PI, with the consent of the participant. However, it is not anticipated that any incidental findings will be found during the planned research.

4.8 STUDY POPULATION

The population being studied is patients with diabetes who live in Scotland and are part of the SCI Diabetes electronic medical record system.

4.9 NUMBER OF PARTICIPANTS

The total number of participants required to complete the study is 500 cases and 500 age and sex matched controls in the nested case control study. This total number may be smaller or larger, depending upon the number of COVID-19 infections which have occurred in the population with diabetes during the timeframe of the study. Reasonable efforts will be made to enrol a matched control for each case participant who is willing to attend. Multiple controls may be enrolled if the first assigned control fails to complete all aspects of the study or is re-assigned as a case.

4.10 INCLUSION CRITERIA

Case cohort study (online questionnaires):

- Person with Diabetes (Type 1 or Type 2)
- Aged 18 or over
- Able to read and write in English

Nested case control study (CRF visits):

- Cases defined by positive COVID test in the clinical record. Cases will be invited sequentially from the cohort but will be selected to include at least 200 people in each of the diabetes subgroups (type 1 diabetes or type 2 diabetes).
- Controls defined by no positive COVID test in clinical records and no reported infection by participant. Controls will be matched after matching of a limited demographic panel available from the panel (age in 5 year bands, ethnicity, sex, type of diabetes, SIMD quintile).

All participants attending a research facility must have completed a COVID safety check before attending in person, in line with local guidance. Cases will be post-COVID and at least 10 weeks post positive test result.

4.11 EXCLUSION CRITERIA

Nested case control study only:

- Participating in the intervention phase of another clinical study

Individuals will not be enrolled to the nested case control study if they are participating in the clinical phase of another interventional study or have done so within the last 30 days. Individuals who are participating in the follow-up phase of another interventional study, or who are enrolled in an observational study, will be co-enrolled where the CIs of each study agree that it is appropriate. Potential participants can choose to delay taking part until the other interventional study has been completed.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Case Cohort: To allow as wide participation as possible, study instruments (questionnaires) will by default be offered remotely using an online implied consent and completion. For this

reason, we will include only contact details (e mail and or telephone) and limited, broad demographics (age in 5 year categories, ethnicity, sex, type of diabetes, duration of diabetes in 5 year categories, first 4 characters of post code). To be inclusive we will offer support for completion of questionnaires if remote online completion by the participant is not possible.
Nested Case control: This will be with written consent and include CRF visit, physical measures and data linkage to the clinical record for evidence of diabetes complications (current and future).

Case Cohort recruitment:

1. **From Diabetes Research Register:** We will utilise the NHS Research Scotland (NRS) Diabetes Research Network permission to contact research register of people with who have expressed a willingness to be involved in research. This register has a large cohort of people with diabetes (>14,000) who have given permission to be approached directly via email or letter or phone. People with diabetes in Scotland who are part of this system will be approached via email or letter or phone to take part. Remote participation does not require the R&D department permission of the Health Boards as no facility use is taking place. Within the data collected participants will be asked if they have had a positive COVID test or believe that they have had COVID infection.

2. **From diabetes clinic lists or database search (SCI Diabetes)**: To augment recruitment of COVID test positive participants we will also screen clinic lists and recruit directly. A member of the study team will screen diabetes clinic lists (eg trak or local clinical system, when possible SCI Diabetes) which routinely have a note of previous COVID infection. Name and CHI noted on screening log (excel spreadsheet held on NHS computer). If patient declines this is noted and no further action. If patient assents to contact then contact information taken (telephone and email – if neither possible postal address) and added to screening log. Electronic data collection link sent by preferred means. If electronic remote data collection not possible then paper questionnaires will be made available by post or study team will discuss over the phone. Cases identified to by SCI Diabetes search will be approached in writing with Caldicott Guardian approval in place within a Health Board (likely to be used in selected Health Boards only).

3. We will also advertise the study by leaflets and posters and via newsfeed to My Diabetes My Way, allowing self-referral to the study team.

NESTED CASE-CONTROL RECRUITMENT:

Cases, by definition, will have had a positive COVID test present on the clinical record. Potential cases will be selected from the cohort where a record of self-reported COVID infection is presented. Potential cases will be invited to CRF visit by telephone or email. Where assent is given by phone the clinical record will be checked to confirm positive COVID test, visit is arranged, and PIS sent. All other study procedures will take place only after face-to-face written consent is obtained at the CRF visit.

Controls will be selected from the pool of people who have completed the online questionnaire information and who have indicated that they have not had a **positive** COVID test and do not believe that they have had COVID infection. Those who had possible infection but subsequent test negative are included. Matching will be by age (5 year category),

ethnicity, sex, SIMD quintile and type of diabetes included in the participant completed questionnaire.

5.2 CONSENTING PARTICIPANTS

CASE COHORT

1. Electronic completion. It is expected that this will form the great majority of the study. From the link the patient will access a PIS on either personal computer or mobile phone using the RedCap platform and complete an electronic checkbox to confirm they have read the PIS and have had the opportunity to ask any questions before commencing the demographic questions and questionnaires.
2. Paper or phone completion - where the participant is not able to or does not wish to complete the online forma then questionnaires will be made available by other means according to the specific preferences of the participant. Verbal assent will be obtained and the data will be transferred to the online platform by a member of the research team.

NESTED CASE CONTROL: CONSENTED CRF VISIT

Participants that agree to attend a research facility in person will be consented in writing ahead of any study procedures taking place using the local process for research consent.

5.3 SCREENING FOR ELIGIBILITY

Participants will be consented to take part in the nested case control study and their SCI Diabetes records will be subsequently checked for eligibility. The research nurse will assess eligibility and will take a judgement on whether the participant is eligible at that time. It may become clear at a later date that the participant is not eligible eg. has difficulty reading questionnaires or providing written answers. Work arounds will be sought where possible (eg. verbally aid to support participation). However ineligible participants may have their data removed from the study, at the CI's discretion.

Participants assigned as controls who are subsequently found to be cases will be moved to the case arm of the study and a replacement control will be sought.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Participants who are not eligible will be informed and their details will be recorded on a screening log or within SCI Diabetes system. They will be thanked for their interest and no further data will be collected.

Ineligible participants may be removed from the dataset at the CI's discretion, if data and/or samples have been collected these will be removed/destroyed as applicable and this process will be documented.

5.5 RANDOMISATION

Randomisation is not used in this study.

5.6 REPLACEMENT OF DROP OUTS

Controls may be replaced if a participant does not complete all the required tests necessary for the nested case control study.

6 DATA COLLECTION & MANAGEMENT

6.1 DATA COLLECTION

The study will utilise the excellent data resource we have within Scotland for individuals with diabetes. Study relevant data from SCI Diabetes will be transferred into a data management system. Previous trials have used this methodology and we will use this expertise in this study. We will draw on the extensive expertise and knowledge of the SCI-diabetes and Scottish hospital admission datasets as well as cognate studies of the effects of COVID in this population. We also include a formal interim analysis after approximately the first six months of data collection (50 cases and approximately 50 controls) to allow examination of various aspects of recruitment.
As noted we are expecting that COVID status will be included in the SCI Diabetes record. Research participation is recorded in SCI Diabetes.

If a participant completes a questionnaire but later wishes to be withdrawn this will not be possible as the data will be anonymous.

6.2 DATA MANAGEMENT SYSTEM

We will use the RedCap data management system (DMS) hosted on a secure server at The University of Glasgow. This system will host all study information with the exception of screening logs and secure link between patient identifiers and study ID - both of which will be held separately on NHS computers. The RedCap platform allows for direct data entry by participants using either personal computer or smartphone.

Data held in NHS – on secure computer in CRF at each recruiting site:
Screening log for invitation to cohort from clinic lists – this will include patient identifiers restricted to CHI, name, telephone number, email address, as well as study process details (date contacted, consent given to send link for questionnaire data).
After written consent a separate file will be maintained with CHI and study ID.

Data held in RedCap (University of Glasgow)
All Cohort study information. This is entered by the participant and includes:

1. Panel of limited demographics (age in 5 year categories, ethnicity, sex, type of diabetes, duration of diabetes in 5 year categories, first 4 characters of post code to allow calculation of SIMD quintile)
2. Contact details (telephone, email address) – optional for participant
3. Study questionnaires (Wellcome, DQOL, DDS-1, EQ5D)

For nested case control study to this will be added:

1. Nested case control screening information recording interest in study/ willingness to attend CRF

After written consent at CRF the following will be added:

2. study ID
3. completed data from CRF visit (incremental walking, hand grip, pulmonary function, waist and thigh measurement, bioimpedence)
4. Participant information including (age to nearest year, ethnicity, sex, type of diabetes, diabetes duration), **e-mail address and/or contact telephone number**
5. Self filled questionnaire
6. Electronic pseudonymised linkage to variables in electronic clinical record being

a. Sci-diabetes with measures of glycaemia (HbA1c), nephropathy, retinopathy, foot disease
b. SMR01 with data on hospital admissions
c. Where possible COVID test data for positivity and cycle threshold (cT)

7.

The DMS will be based on the protocol and case report form for the study and individual requirements of the investigators. The case report form will collect only information that is required to meet the aims of the study and to ensure the eligibility and safety of the participant.

The database will be managed in line with all applicable principles of medical confidentiality and data laws. The Data Controller will be the University of Glasgow and the Data Custodian will be the CI.

7 STATISTICS AND DATA ANALYSIS

7.1 SAMPLE SIZE CALCULATION

The study will generate a large amount of continuous and categorical data. It is noted that some definitions (long covid, subgroups of post COVID syndromes) are in evolution at present therefore it is difficult to be definitive regarding this. We also note that as well as potential direct cardiovascular symptoms, symptoms of diabetes distress and indeed depression have increased prevalence in the population of people with diabetes (7, 8).

In general, sample size of 526 in each group allows 90% power (α=0.05) to detect sizes of 0.2 of a standard deviation (SD) and 85 allows power for differences of 0.5 SD. We plan for recruitment of 500 people after COVID infection with 500 controls and the opportunity to restudy cases (total recruitment 1500), expecting near complete data for questionnaire variables but allowing for reduced numbers of participants for biochemical measures (allowing for remote participation). A sample size of 500 per group would also allow detection of differences in highly prevalent symptoms from 50% to 40% (for example early estimates persistent symptoms after COVID 55% (1)) and for less prevalent symptoms from 20% to 12% (eg estimates of diabetes distress and depression often 10-20%).

7.2 PROPOSED ANALYSES

An analysis plan will be prepared for the University of Glasgow Research Data Management department before the study closes, to detail what analysis will be performed on the data.

Case cohort study:
This includes **participant completed questionnaires only.** We will not have access to clinical record for whole group (limited to those in nested study) and will rely on patient self-report of COVID testing and infection to create groups. Analysis will be in three groups:

a. Test positive COVID declared (**cohort A**)
b. no test but self-declared COVID (**cohort B**)
c. no COVID infection declared, including those with suspected infection but test negative **(control)**

Analysis of this data will include

1. **Frequency of COVID symptoms** (derived from question 1.3 Wellcome questionnaire: 28 domains answering yes/no for 0-28 score and by self-report at time of infection at 3 months and current (>3 months)).
    a. **Primary analysis**: current score cohort vs control with adjustment for limited demographic panel: age band, ethnicity, sex, type of diabetes
    b. Secondary analyses:
        i. within cohort comparison of time of infection vs 3 months vs current
        ii. comparison time of infection and 3 months vs current score of control (with adjustment)
2. **Other questionnaire data**: diabetes depression score, DQOL all of which are assessed currently only and will be assessed in cohort vs control.
3. Comparison of above end points in cohort B to cohort and controls.

NESTED CASE CONTROL STUDY

For this data, consent will allow access to confirm that patient is COVID test positive in the clinical record. Definitions and comparison will therefore be between:
Cases - COVID test positive in clinical record
Control - no previous clinical COVID infection reported by patient, no record positive COVID test.

Case vs control (First visit)

1. **Frequency of COVID symptoms** (derived from question 1.3 Wellcome questionnaire: 28 domains answering yes/no for 0-28 score and by self-report at time of infection at 3 months and current (>3 months)).
    a. **Primary analysis**: current score case vs control with adjustment for age, sex, ethnicity, sex, type of diabetes, SIMD
    b. Secondary analyses:
        i. within cohort comparison of time of infection vs 3 months vs current
        ii. comparison time of infection and 3 months vs current score of control (with adjustment)
        iii. relationship of cycle threshold to symptom scores
2. **Other questionnaire data**: diabetes depression score, DQOL all of which are assessed currently only and will be assessed in cohort vs control
3. **Walk test**
4. **Hand grip**
5. **Pulmonary function measures eg. FEV1**

Comparison of cases vs COVID positive cohort for demographics and main study measures.

Case vs control (First and second visit data)

1. **Frequency of COVID symptoms** (derived from question 1.3 Wellcome questionnaire: 28 domains answering yes/no for 0-28 score and by self-report at time of infection at 3 month, at time of first questionnaire, first visit and at second visit).
    a. **Primary analysis**: second visit score case vs control (first visit) with adjustment for age, sex, ethnicity, sex, type of diabetes, SIMD
    b. Secondary analyses:
        i. within cohort comparison of time of infection vs all time points
        ii. comparison time of infection and 3 months vs current score of control (with adjustment)
2. **Other questionnaire data**: diabetes depression score, DQOL all of which are assessed first and second visit cohort vs control (first visit)

3. **Walk test** first and second visit cohort vs control (first visit)
4. **Hand grip** first and second visit cohort vs control (first visit)
   Pulmonary function measures eg. FEV1 first and second visit cohort vs control (first visit)

B. Screening log. As above contain patient identifiers, will be held on NHS computers. Output - acceptance rate for study
C. Study data - will be held within Redcaps platform. Outputs: process data on completion of the different modules of the study, final study dataset.

Key aspects will be
a. Record of consent and electronic consent
b. Ability to enter data to personal computer/ smartphone by participant
c. Ability to enter separate data under same study ID for study visit
d. Cloud exportable to SAS/ SPSS/ R

Analyses will be carried out by the study team using the statistical support offered by the University of Glasgow.

Output will include locked data set, written report, manuscript, presentation of findings to Scottish Diabetes Group (SDG) and widespread dissemination of results via the existing infrastructures within the Scottish diabetes community. In addition, given the use of resources such as the Wellcome COVID questionnaire we would expect to contribute to shared data analysis more widely. Long term data storage will be with the University of Glasgow Enlighten system and access to bona fide researchers to data stripped of contact details and identifiers.

7.3 MISSING DATA

The online questionnaires will flag incomplete data and will ensure all questions are answered. The questionnaires that are completed on paper or by phone contact may have incomplete sections.

7.4 TRANSFER OF DATA

Data transfer outside of The University of Glasgow/NHS GGC is planned. The study uses the shared Wellcome questionnaire and therefore comparison to other datasets may be desired. Information transfer will be via NHS or University computers only and data will primarily be accessed using the local safe haven.

8 STUDY MANAGEMENT AND OVERSIGHT ARRANGEMENTS

8.1 STUDY MANAGEMENT GROUP

The study will be co-ordinated by the Chief Investigator (CI), and Principal Investigators (PI) with support from NHS Research Scotland Diabetes Network.

8.2 STUDY STEERING COMMITTEE

A study steering committee comprising the PIs for the project, clinical collaborators, NHS Research Scotland Diabetes Network Manager and University of Glasgow funding project manager will convene on a regular basis during the timeframe for the planned research.

8.3 DATA MONITORING COMMITTEE

Not applicable.

8.4 INSPECTION OF RECORDS

The CI, PIs and all institutions involved in the study will permit study related monitoring, audits, and REC review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

9 GOOD CLINICAL PRACTICE

9.1 ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the principles of good clinical practice (GCP).

In addition to Sponsorship approval, a favourable ethical opinion will be obtained from the appropriate REC and appropriate NHS R&D approval(s) will be obtained prior to commencement of the study.

9.2 CONFIDENTIALITY AND DATA PROTECTION

The CI and study staff will comply with all applicable medical confidentiality and data protection principles and laws with regard to the collection, storage, processing and disclosure of personal data.

The CI and study staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or equivalent.

All study records and personal data will be managed in a manner designed to maintain participant confidentiality. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate trial staff only. Computers used to collate personal data will have limited access measures via user names and passwords.

Personal data concerning health will not be released except as necessary for research purposes including monitoring and auditing by the Sponsor, its designee or regulatory authorities providing that suitable and specific measures to safeguard the rights and interests of participants are in place.

The CI and study staff will not disclose or use for any purpose other than performance of the trial, any personal data, record, or other unpublished, confidential information disclosed by those individuals for the purpose of the trial. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated personal data relating to participants will be restricted to the CI and appropriate delegated study staff.

Where personal data requires to be transferred, an appropriate Data Transfer Agreement will be put in place.

Published results will not contain any personal data that could allow identification of individual participants.

9.3 INSURANCE AND INDEMNITY

NHS GGC is sponsoring the study.

Insurance – NHS GGC will obtain and hold a policy of Public Liability Insurance for legal liabilities arising from the study.

NHS GGC Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme ("CNORIS") which covers the legal liability of Health Boards in relation to the study

Where the study involves University staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with their local NHS Health Board which means they will have cover under their local Health Board's membership of the CNORIS scheme.

Indemnity – The Sponsors do not provide study participants with indemnity in relation to participation in the Study but have insurance for legal liability as described above.

10 ADVERSE EVENTS

Remote participation: Adverse events are not anticipated and participants will complete the consent form and questionnaires in their own time in home, work or other environment (this will be decided by the participant).

Attending a research facility: Adverse events will not be collected in the interval between attending the facility on the first occasion and attending on the second occasion. Adverse events are only recorded if these occur during the study visit and were not present prior to the study visit. Worsening of existing symptoms will also be recorded.

Anticipated adverse events will not be reported but will be recorded in the case report form.

Participants who take part in the case cohort study (online questionnaires) will carry out this activity in an environment of their choosing. Adverse events are not anticipated and the risks are minimal - no different from the risks experienced by anyone making use of the internet from their own device. Questions which we have deemed to require additional support have been removed from the Wellcome questionnaire.

Participants who attend the research facility for the nested case control study visit may experience some risks from the blood sampling procedure - these include bruising, infection at the needle site, inflammation of the area around the needle entry, and in rare instances individuals can experience loss of consciousness. This is unlikely however, as patients with diabetes deal with finger prick sampling on a routine basis and generally cope well with needles. To support the participant, a research staff member will stop the procedure if the patient faints or experiences distress. There are some risks from the incremental walk test such as tripping, falling, exhaustion and fatigue. A research staff member will be present to offer one:one support and the walk test will be carried out in a wide corridor free of trip hazards and obstructions. Participants will be able to use a walking aid if he/she routinely uses this. Participants will be asked to stop the test if they experience difficulty. Pulmonary function tests (spirometry) require the use of a mouthpiece connected to the device which poses a risk of infection. To minimise risk, mouthpiece plastic is single use and participants will be shown how to carry out the test correctly.

Risks associated with COVID will be minimised by use of appropriate PPE for research staff and participants and by operating local procedures for COVID checks the day in advance of a planned nested case control study visit. We anticipate that the majority of participants will have received a COVID vaccination before this study commences due to their priority status.

Unanticipated adverse events (those not listed above) occurring during the study visit will be reported and recorded following local SOPs.

If onward referral to support the healthcare of the participant is deemed to be required by the study team member, a letter will be sent to the participant's GP. Data will be recorded but not reported on the incidence of this "alert reporting".

Routinely collected health data will be extracted from SCI Diabetes and added to the study dataset. Adverse events arising from this healthcare data will have been addressed by diabetes care services. Health records of the participants will not be checked in real time during the study so awareness of adverse events will be minimal unless the participant self-reports or misses a planned study visit.

11 ANNUAL REPORTING REQUIREMENTS

Annual reporting will be conducted in compliance with local SOPs, as a condition of sponsorship and as a condition of a favourable opinion from a REC. An HRA Annual Progress Report for NCTIMPs will be prepared and submitted by the CI to the REC, and copied to the Sponsor, on the anniversary date of the REC favourable opinion.

12 STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS, DEVIATIONS AND BREACHES

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHS R&D Office(s). Amendments to the protocol or other study docs will not be implemented without these approvals.

In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the SMF, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

In the event that a serious breach of GCP or protocol is suspected, this will be reported to the Sponsor Governance Office immediately.

12.2 STUDY RECORD RETENTION

Archiving of study documents will be for five years after the end of study.

12.3 END OF STUDY

The end of study is defined as reaching the number of completed cases and controls that the CI or delegate deems adequate for analysis, with a minimum sample size of 100 participants in the case arm part of the study.

The Sponsor, CI and/or the PI have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a study report will be prepared.

13.2 PUBLICATION

The study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

13.3 PEER REVIEW

The study has been reviewed by the PI group, members of the research team and by NHS Research Scotland Diabetes Network staff.

14 REFERENCES

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8. Rawlings AM, Sharrett AR, Golden SH, Windham BG, Selvin E. Prevalence and correlates of depressive symptoms in older adults across the glycaemic spectrum: the Atherosclerosis Risk in Communities (ARIC) study. Diabet Med. 2018;35(5):583-7.
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