NHS Tayside

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Academic and Clinical Central Office for Research and Development

NHS Lothian

University of Dundee

Study Protocol

(non-CTIMP)

Scottish COVID CAncer iMmunity Prevalence (SCCAMP) study

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LIST OF ABBREVIATIONS

Insert abbreviations as required

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
PI	Principal Investigator
QA	Quality Assurance
REC	Research Ethics Committee
SOP	Standard Operating Procedure

1 INTRODUCTION

1.1 BACKGROUND

COVID19, caused by the SARS-CoV2 virus, has infected around 50 million people worldwide (1). The true number is likely higher given the variable testing strategies around the world. Early studies suggested patients with cancer were at higher risk, in addition to risks extrapolated from previous SARS and Influenza outbreaks (2–4). To mitigate the risk, the cancer community responded with wide-reaching changes to cancer care (5). As a second wave of COVID19 emerges, it is clear cancer services cannot pause as they did before. Yet, we still know little of the prevalence and immune response of patients with cancer.

1.2 RATIONALE FOR STUDY

As part of the initial response to the COVID-19 pandemic, between March and August 2020, the Scottish Government identified cancer patients as a vulnerable group, recommending that patients on some cancer treatments should follow shielding advice. Cancer treatments and diagnostics were put on hold, with ramifications for morbidity and mortality (6,7). Registry-based evidence obtained during the first wave of COVID19 suggest the mortality risk to patients with cancer ranges from 13%-40.5% (8–11). Collectively, these suggest the risk to patients with cancer is highest in male, older patients with other comorbidities and poor performance status. Recent cancer therapy, including chemotherapy, has not emerged as a key risk factor. This surprising outcome underlines the need for a greater understanding of the true prevalence and immune response of patients with cancer, particularly given that the virus is likely to be endemic until a vaccine is approved.

In highly tested populations, a sizable proportion of asymptomatic individuals tested positive to COVID-19 either by PCR or antibody testing (12,13). It is not known whether this is also the case in patients with cancer, which, if true, would suggest the risk posed by COVID-19 is less than feared.

Since early 2020, testing of active infection has been by reverse transcription polymerase chain reaction (RT-PCR) via nasopharyngeal swab. Enzyme linked immunosorbent assay (ELISA) for the COVID-19 antibody allows confirmation of previous infection. Studies suggest an antibody ELISA can detect 100% of patients with COVID-19 15-39 days after a PCR-confirmed infection (14), with over 98% positive by day 14. Importantly, a study has demonstrated a decreasing titration of antibody levels in all but those with the highest titres of COVID-19 antibody (15). No equivalent study exists in a population of patients with cancer. Antibody testing is currently not used routinely in the NHS for screening of COVID-19, and as of 4th November 2020, the NHS in Scotland is using antibody testing for research and selected clinical situations only – it is not recommended for widespread use owing to uncertainties around the implications of a positive (or negative) result (16).

During the pandemic, cancer teams in NHS Lothian and NHS Tayside have created Biorepositories of blood samples from patients undergoing cancer care. Patients have provided blood samples during routine clinical visits for future use under BioResource approvals, including serum that can be tested for COVID-19 antibodies via ELISA.

The SCCAMP study aims to use a COVID-19 antibody test to assess the incidence and prevalence of COVID-19 infection in patients undergoing active cancer treatment at a regional cancer centre, and to comprehensively assess COVID-19 infection as proven by standard-care RT-PCR and track COVID-19 antibody levels in cancer patients receiving anti-cancer treatment.

SCCAMP therefore involves:

a) **Research on existing samples and clinical data in the Bioresource at NHS Lothian (SR1418) and NHS Tayside (Tayside Repository) for the SCCAMP study**
b) **Consenting patients prospectively to the SCCAMP study**

1.3 OBJECTIVES

1.3.1 Primary Objective

1. **To identify the incidence and prevalence of COVID-19 antibody in a population of cancer patients attending for cancer management**

1.3.2 Secondary Objectives

1. **To confirm if patients with previous PCR-confirmed COVID-19 infection or vaccination against SARS-Cov-2 have a measurable antibody response as tested by ELISA**
2. **To understand the duration of this immune response**
3. **To understand the risk of subsequent COVID-19 infection in cancer patients with demonstrated COVID-19 immunity or prior documented infection.**
4. **To identify whether age, tumour type, cancer burden, treatment type or comorbidities differ with prevalence of evidence of previous COVID-19 infection**
5. **To identify the impact of treatment modality on the duration of antibody response**

1.4 ENDPOINTS

1.4.1 Primary Endpoint

1. **Prevalence of positive SARS-CoV-2 antibody**

1.4.2 Secondary Endpoint

1. **Incidence of positive SARS-CoV-2 antibody**
2. **Durability of SARS-CoV-2 seroconversion**
3. **Rate of COVID-19 infection**
4. **Survival**
5. **Mean COVID19 antibody level**

2 STUDY DESIGN

As outlined above, SCCAMP consists of:

(a) Access to existing biological samples:

Samples are stored within existing biobanks - the Lothian NRS BioResource (Biobank SR1418)[1] and the Tayside Repository. Biobank SR1418, which commenced on 28th May 2020, has collected serial samples on 429 patients attending for routine care as of 3rd November 2020. Consented BioResource participants will be invited to re-consent to the SCCAMP Study for future sample collection in line with the timeline. If patients previously recruited to one of these Biorepositories declines participation with SCCAMP, they may continue to contribute samples to the Biorepository in line with their previous consent as part of routine clinical visits, and these samples would be available for serum COVID-19 antibody testing, but note no unscheduled visits or symptom checklist data can be requested from these patients. They should be offered the opportunity to withdraw from the Biorepository if they wish to do so, as per Biorepository protocols.

(b) Prospective recruitment

Whether patients are existing participants in a Biorepository or not, patients will be approached for the first time when they attend for cancer treatment in an outpatient setting. These are patients who have commenced or are commencing anti-cancer treatment, and therefore will have had a consultation under the care of a Consultant Oncologist to discuss their diagnosis and consent to treatment.

After consent, patients will be asked to provide blood samples at baseline (Timepoint 1 (T1)), T2+6 weeks (+- 2 weeks), T3+12 weeks (+- 2 weeks), T4+6months and T5+12 months. Dates will be scheduled by reviewing planned treatment dates on the chemotherapy prescribing system and the Electronic Health Record to diarise sample dates in line with scheduled visits as much as possible.
Where patients have previously consented to the respective Biorepository, the T1 Baseline timepoint will be taken as the date of first sample provided to the Biorepository. The protocol for processing serum and plasma samples can be found in the sample handling SOP. Samples will be stored at –80 degrees Celsius and transferred to liquid nitrogen (LN) for long-term storage.

Patient screening:

Screening to identify potential participants involves a review of the list of patients scheduled to attend the cancer treatment unit as part of routine clinical care by the clinical care team. To avoid multiple approaches to patients, the patient's name and CHI number will be used by the clinical care team to identify patients already consented to the Biorepository by cross-checking the name and CHI number with Biorepository record that is held on a secure NHS server (EDGE).

Patient data

Electronic healthcare records will be accessed for clinical data only after patients have consented to SCCAMP. In the case of patients who have provided clinical samples to the Biorepository prior to SCCAMP, the Baseline date will be taken as the date of the first sample provided to the Biorepository.

1. **Baseline Characteristics: The following baseline characteristics will be recorded on the study database against the Patient Study ID: Age, Gender, Cancer (ICD10 code), Treatment intent (Curative, Palliative, Type of anti-cancer treatment (ACT), Line of ACT, Cycle/fraction of ACT on day of sample collection, Date of last ACT, Date of surgery, Comorbidities (Charleson Score), Previous COVID-19+ve PCR?, If yes, date of first positive, Previous radiological diagnosis of COVID-19? If yes, imaging modality, date of imaging, Previous COVID19 vaccination? If yes, date of doses, name of vaccination**
2. **Recent symptom data (See Section 7 for details) will be reviewed from electronic healthcare records retrospectively. It should be noted that patients are screened for broad COVID-19 symptoms and for a fever before attending cancer centres, so patients are presumed to be asymptomatic at the point of serum testing.**

ELISA testing:

Samples will be analysed by enzyme-linked immunosorbent assay (ELISA). Serum samples will be stored until a validated ELISA is available for testing. A patient who was negative for the COVID-19 antibody would remain in the study until all samples had been taken.

Interval positive testing:

It may be that a patient tests positive for COVID-19 via PCR or antibody during the course of the study period. In this scenario, the duration of time in the study would remain as outlined in this protocol.

Informing patients about their COVID-19 antibody result

As outlined above, antibody testing is not routinely used for COVID-19 testing or screening as evidence is currently being generated, including by this study, around the implications of a positive or negative result. We acknowledge this is a rapidly evolving area. As such, patients will not be routinely updated about their COVID-19 antibody result, and this is highlighted clearly in the consent form. However, if government guidelines change, we will inform patients about their results via their clinical care teams to facilitate appropriate counselling. Patients are also directed to the study website: https://cancer-data.ecrc.ed.ac.uk/sccamp/ - this will be kept updated during the study.

3 STUDY POPULATION

3.1 NUMBER OF PARTICIPANTS

We plan to recruit 1500 patients, with the pre-planned sub-group analyses: age, tumour type, cancer burden (as per treatment intent), treatment type, comorbidities (Charleson score >2), previous COVID-19 infection, vaccination status. We would not expect any of these subgroups to influence the sensitivity and specificity of the ELISA, and as such, our sample size calculation would suggest >8 patients in each group will provide statistical confidence in the result.

Approximately 200-250 patients are seen for systemic cancer management each week in the treatment units at Edinburgh Cancer Centre (ECC) and Dundee Cancer Centre (DCC), suggesting recruit of 1500 patients will be feasible. In addition, both centres have commenced Biorepository sample collection, and samples from these Biorepositories will be used for COVID-19 antibody testing as outlined in this protocol.

3.2 INCLUSION CRITERIA

- **Patients over the age of 18**
- **Confirmed diagnosis of solid organ cancer, defined as cancer or metastasis in situ, and/or receiving cancer treatment (surgery, radiotherapy, hormone therapy, chemotherapy, targeted therapy, immunotherapy) in the last 12 months**
- **Attending for outpatient Cancer Centre Care**

3.3 EXCLUSION CRITERIA

- **Concurrent haematological malignancy**

3.4 CO-ENROLMENT

Patients are free to consent to any other study.

4 PARTICIPANT SELECTION AND ENROLMENT

4.1 IDENTIFYING PARTICIPANTS

Patients will be identified by the NHS clinical team who will screen patients to assess whether they meet the inclusion criteria. Patients will be approached when they attend on their day of treatment and invited to consent prior to venepuncture or cannulation.

4.2 CONSENTING PARTICIPANTS

Patients will be provided with the following forms: SCCAMP PIS, SCCAMP Consent form. A research nurse or tissue consent individual trained in the SCCAMP protocol will obtain written consent. Good Clinical Practice (GCP) (Section 4.8.7) outlines that written consent is valid if the patient feels they have had sufficient time to inquire about a study and ask questions, but does not specify a minimum timeframe. Therefore, if a patient feels they have had adequate time to read the information leaflet, and the consenter feels the patient is able to provide informed consent noting specifically that these samples will be held subsequently in an NHS Biobank, consent can be given. Alternatively, if the patient would prefer more time, or the trained individual taking consent feels more time would aid understanding, written consent can be sought at their next routine clinical encounter.

A note will be added to the patient's electronic care record in keeping with local guidelines indicating if a patient is participating in the study, or explicitly if the patient has declined inclusion to avoid repeated approaches.

4.2.1 Withdrawal of Study Participants

Participants are free to withdraw from the study or biobank at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if possible. The participant will have the option of withdrawal from:

- **(i) all aspects of the study but continued use of data, including clinical data, collected up to that point, and permission to allow access to prior samples and future medical records. To safeguard rights, the minimum personally-identifiable information possible will be collected.**
- **(ii) all aspects of the study including samples and data collected up to that point will be discarded, and samples destroyed. Patients will be advised at the point of consent that samples may have already been analysed.**

5 STUDY ASSESSMENTS

5.1 STUDY ASSESSMENTS

Study assessments are outlined in the table. Sample collections should only occur during routine visits for the first three samples (Day 1, Day 42, Day 84) when the prevalence of COVID-19 is likely to be at its highest, and therefore it would not be appropriate to ask shielding patients to attend a hospital environment. If this remains the case for the final two time points, this will be reviewed by amendment.

Assessment	Pre-Screening	Day 1 baseline	Day 42 +- 14 days	Day 84 +- 14 days	6 months +- 30 days	1 year +- 30 days
Assessment of Eligibility Criteria	X	X				
Written informed consent		X				
Demographic data, contact details		X				
Blood sample		X	X	X	X	X
Symptom record (clinical notes)		X	X	X	X	X

We acknowledge that some samples collected in the BioResource SR1418 will not map exactly to the dates outlined above, or that patients may actively decline to make an additional journey to provide a sample within the timeframe outlined above. As such, the above remains a guide for planning, with the over-arching aim to obtain five separate blood samples from patients over the course of a year, with a minimum of two weeks between each blood sample.

5.2 LONG TERM FOLLOW UP ASSESSMENTS

Follow up assessments are as per 6.1.

5.3 STORAGE AND ANALYSIS OF SAMPLES

For samples currently being held in existing Biobanks:

- **Serum samples from the existing Lothian NRS BioResource (Biobank SR1418) and from NHS Tayside Repository will be transferred for COVID-19 testing in the Blood Sciences Department, Ninewells Hospital, Dundee DD1 9SY.). Any leftover samples after COVID-19 testing will be destroyed in line with local protocols.**

For prospectively collected SCCAMP samples:

- **Samples from NHS Lothian will be stored in the Edinburgh Experimental Cancer Medicine Centre (ECMC) in the Lothian NRS BioResource (Biobank SR1418), and those from NHS Tayside in the Tayside Repository. All samples will be labelled with a Biorepository Patient ID and not patient identifiers.**

Samples for COVID-19 antibody testing will be sent for storage and COVID-19 testing in the Blood Sciences Department, Ninewells Hospital, Dundee DD1 9SY.
. Any leftover samples after COVID-19 testing will be destroyed in line with local protocols.

6 DATA COLLECTION

The patient's BioResource ID will be used as their SCCAMP study ID in the interest of continuity and anonymity. Data will be obtained from the NHS clinical record[1], including (but not limited to) as a minimum dataset:

On Day 0 (Baseline)

- **Age, Gender, Cancer diagnosis (ICD10 code), Treatment intent (Curative, Palliative) Type of anti-cancer treatment (ACT), Line of ACT, Cycle/fraction of ACT on day of sample collection, Date of last ACT, Date of surgery, Comorbidities (Charlson Score), prescribed medications, socioeconomic status, rurality (by postcode), Health Board of residence, previous COVID-19+ve PCR?, If yes, date of first positive, previous radiological diagnosis of COVID-19? If yes, imaging modality, date of imaging**
- **Any of the following in the period leading up to treatment (17): Ageuisa (loss of taste) /Anorexia/Anosmia (loss of smell)/Arthralgia/Chills /Corzyal symptoms/Cough /Diarrhoea /Fatigue /Fever (>37.5) Haemoptysis / Headache /Myalgia /Nausea and/or vomiting/Shortness of breath/Skin Rash/Sore throat.**
- **Vaccine status – dates of vaccination, vaccine received**

On subsequent visits (since previous visit)

- **Ageuisa (loss of taste) /Anorexia/Anosmia (loss of smell)/Arthralgia Chills /Corzyal symptoms/Cough /Diarrhoea /Fatigue /Fever (>37.5) Haemoptysis / Headache /Myalgia /Nausea and/or vomiting/Shortness of breath/Skin Rash/Sore throat.**
- **Vaccine status – dates of vaccination, vaccine received**

6.1 Source Data Documentation

Contemporaneously obtained data will be documented directly on the study database under that patient's study ID.

7 DATA MANAGEMENT

7.1.1 Personal Data

The following personal data will be collected as part of the research: Name, CHI number, postcode, sex, ethnicity

Personal data will be stored by the research team on an NHS database (EDGE – hosted by University of Southampton and approved for use in the NHS – www.edge.nhs.uk), and this will be the only data storage location linking name, CHI/date of birth and postcode, to the study ID. This will be accessible by the research team assigning the SCCAMP patient ID. Consent will include key break if required for urgent medical care (e.g. if data emerge regarding COVID-19 antibody status that subsequently are required in a patient's urgent care). Consent will state that patients will not be routinely informed of their antibody result unless this becomes standard of care.

Personal data will be stored in line with ACCORD data storage guidance.

7.1.2 Data Information Flow

- **Collection: Research nurse/tissue consenter**
  - **Personal data on NHS database (EDGE) linking Personal data to SCCAMP Patient ID, held at the host NHS Board (NHS Lothian or NHS Tayside)**
- **Study database hosted at the University of Edinburgh: Data manager**
  - **SCCAMP Patient ID and baseline data**

[1] Within NHS Lothian this is the NRS Bioresource SR1418 study ID, or equivalent study ID at other sites.

- **Sample dates and symptoms as recorded in patient clinical record**

Access: Only research staff trained in SCCAMP and on the delegation log for the study will have access to patient data.

Extraction: Data extraction for the Study Database will be performed by a Data Manager as outlined in 7.1.2.

Use: Only data outlined in this protocol will be extracted and stored as outlined in 7.1.2. These data will be used only for the purpose of this study, and only anonymised data will be analysed. The proposed analyses are outlined in Section 8.2.

7.1.3 Transfer of Data

Data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s).

7.1.4 Data Controller

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site)

7.1.5 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

8 STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

Antibody levels will be measured as chemiluminescence values divided by the cutoff (S/CO). The cutoff value of this test is defined by receiver operating characteristic curves based on positive control. Existing data suggest median values of approximately 10 (IQR approx 5) and 0.8 in a positive and negative population respectively (18). Antibody levels will be transformed in accordance with best practice at the time of analysis, to provide a normal distribution (e.g. log2) as log2(S/CO + 1) and to be consistent with literature. Using positive controls, we will estimate the coefficient of variation (CV) to evaluate the precision of the serology assays.

As the main analysis is a cross-sectional study our main comparison of interest is the study cohort of cancer patients compared to reference populations tested for COVID-19 serology. The current population prevalence based on RT-PCR testing in the regions covered by NHS Lothian and Tayside as of 31st October 2020 is 11.7/1000 persons (19). (COVID-19 positive cases = 14,029, population size covered by NHS Lothian and Tayside = 1.2 million) = 11.7/1000 individuals).

Given known issues in testing of asymptomatic/symptomatic but non-critical patients we expect the rate to be at least double, hence estimate at least 22-23 patients to be COVID-19 positive based on antibody testing that were not previously reported.

If other regions in Scotland are recruited to SCCAMP, patients from these sites will contribute to the 1500 patient target.

8.1.1 Outcome measure definitions

- **Positive antibody status is defined as… (sensitivity analysis will be conducted on the positive definition)**

- **Prevalence of positive SARS-CoV-2 antibody status is cross sectional, where the cross-section is taken over defined time periods by calendar. The initial cross section will be over 3 months from first study sample. Analysis by simple proportions, adjustment using logit model.**

- **Incidence of positive SARS-CoV-2 antibody status is longitudinal – taking the study cohort from day of registration as timepoint one, this represent the incidence rate per time-unit and cumulative incidence over the study follow-up period. Analysis by Kaplan-Meier function, with adjustment by Cox model.**

- **Durability of SARS-CoV-2 seroconversion is measured longitudinally in the population with positive SARS-CoV-2 antibody status as time-to antibody negative status. Analysis by Kaplan-Meier function, with adjustment by Cox model.**

- **COVID-19 infection, longitudinal, by initial antibody status. Analysis by Kaplan-Meier function, with adjustment by Cox model.**
  - **Definition 1 = PCR confirmed COVID-19 infection**
  - **Definition 2 = PCR confirmed COVID-19 infection, documented clinically suspected COVID-19 infection, death certificate identified COVID-19 infection.**
  - **Definition 3 = PCR confirmed COVID-19 infection, development of new positive SARS-CoV-2 antibody status, documented clinically suspected COVID-19 infection, death certificate identified COVID-19 infection.**

- **Severe COVID-19 infection – WHO standard definition. Analysis by Kaplan-Meier function, with adjustment by Cox model.**

8.2 PROPOSED ANALYSES

Primary outcome analyses

1. **Incidence and prevalence of COVID19 antibody in 1500 patients with cancer as per the quantitative cut-off for an ELISA antibody test**
2. **Mean COVID19 antibody level (+- standard deviation) in patients with positive and negative COVID19 antibody results as per the antibody titre**

Secondary outcome analyses

1. **Incidence and prevalence of COVID19 seroconversion in patients subgrouped by age, tumour type, cancer burden, vaccination status, treatment type or comorbidities as per the quantitative cut-off for an ELISA antibody test**
2. **Mean COVID19 antibody level trend (+- standard deviation) in patients with a positive COVID19 antibody level, and proportion that subsequently develop negative antibody titre following anti-cancer treatment.**

We anticipate due to the size and duration of the study that patients may be lost to follow up due to patient withdrawal, non-compliance or patient illness/death. As such we will continue to recruit beyond 1500 patients and will review the intended scope when 1500 patients is reached.

An interim analysis will be performed within three months with all available samples give the importance of sharing emerging trends with the cancer community. These will explore all primary and secondary analysis highlighted above.

9 ADVERSE EVENTS

Venepuncture is a low risk procedure, but there is a risk of failure, infection (local or systemic) and thrombus. Local procedures for managing complications of venepuncture will be followed, and venepuncture will only be formed by individuals trained to perform the procedure.

10 OVERSIGHT ARRANGEMENTS

10.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

10.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

11 GOOD CLINICAL PRACTICE

11.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

11.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

11.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

11.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

11.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

11.2.4 Investigator Documentation

- **The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.**

11.2.5 GCP Training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all investigators should be indicated in their respective CVs.

11.2.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study.. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place

STUDY CONDUCT RESPONSIBILITIES

11.3 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

11.4 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

11.5 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

11.6 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

11.7 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators or the co-sponsor(s) 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 REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot

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

11.8 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

Detail if intervention will be continued to be provided following the end of the study. If not provide justification

11.9 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- **The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.**
- **Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.**
- **Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.**
- **Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.**

12 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

12.1 AUTHORSHIP POLICY

Authorship of academic publications will include the protocol authors and study team, where the definition of authorship is met in accordance with the International Committee of Medical Journal Editors http://www.icmje.org.

Ownership of the data arising from this study resides with the study team.

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