Sections **MUST NOT** be deleted. If not relevant to a particular trial, please detail as “Not Applicable”. Sections should be adapted with trial specific details.

**Highlighted** text should be replaced with trial-specific details.

Text in **blue** is for guidance only and should be deleted prior to submission.

Study Protocol

**Full Title of Study**

**Short Title/Acronym**

|  |  |
| --- | --- |
| Co-Sponsors | The University of Edinburgh & Lothian Health Board ACCORD Usher Building, The University of Edinburgh  5-7 Little France Road  Edinburgh BioQuarter – Gate 3  Edinburgh  EH16 4UX |
| Funder | Insert name of funder. |
| Funding Reference Number | Insert funding reference  A copy of the grant award letter should also be submitted to the Co-Sponsors as part of the Sponsorship Review. |
| Chief Investigator | Insert name and title of CI. |
| Sponsor Reference | ACXXXX ACCORD will provide this number. |
| Registration Number | All CTIMPs must be registered on a publicly accessible database. This will generate a registration number e.g. ISRCTN or other appropriate registry.  The HRA automatically register clinical trials approved through [combined review](https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/combined-ways-working-pilot/)  with [ISRCTN registry](https://www.isrctn.com/). Automatic registration applies to both clinical trials of investigational medicinal products (CTIMP) and combined trials of investigational medicinal product and a medical device (IMP/device).  If a trial is registered with [ClinicalTrials.gov](https://www.clinicaltrials.gov/) you can request not to be registered on ISRCTN Registry. |
| REC Number | This will be provided at the time of REC submission |
| Version Number and Date | Version number and date should be entered here (and should correspond with header). Please refer to ACCORD SOP QA008 Document Version Control for more details. |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **KEY TRIAL CONTACTS** (**\*Protocol Authors** this information must be included for insurance purposes) | | | | |
| **Chief Investigator** | |  | **Lead Co-Sponsor Representative** | |
| **Name:** |  |  | **Name:** |  |
| **Address:** |  |  | **Address:** |  |
|  |  |  | **:** |  |
|  |  |  |  |  |
| **Email:** |  |  | **Email:** |  |
| **Trial Manager** | |  | **Trial Statistician** | |
| **Name:** | required for all multi-site trials |  | **Name:** | named statistician required for all CTIMPs |
| **Address:** |  |  | **Address:** |  |
| **:** |  |  | **:** |  |
|  |  |  |  |  |
| **Email:** |  |  | **Email:** |  |

PROTOCOL APPROVAL SIGNATURE PAGE

**Full Title of Study**

**Short Title/Acronym**

The undersigned accept the content of this protocol in accordance with the appropriate regulations and agree to adhere to it throughout the execution of the study.

|  |  |  |  |
| --- | --- | --- | --- |
| Name |  |  |  |
| **Chief Investigator** | **Signature** |  | **Date** |
| Name |  |  |  |
| **Trial Statistician** | **Signature** |  | **Date** |
| Name |  |  |  |
| **Lead Co-Sponsor**  **Representative** | **Signature** |  | **Date** |

For multi-site trials, the Principal Investigator must sign below to document that the protocol has been read and understood.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Name |  |  |  |  |  |
| **Principal**  **Investigator** | **Signature** |  | **Site** |  | **Date** |

Following any amendments to the protocol, this page must be re-signed.

A signed copy of the protocol is required for R&D submission

CONTENTS

To update the table of contents, highlight the existing table of contents, right click “Update Fields” and OK.

1. INTRODUCTION 10

1.1 BACKGROUND 10

1.2 RATIONALE FOR STUDY 10

2. STUDY OBJECTIVES 10

2.1 OBJECTIVES 10

2.1.1 Primary Objective 10

2.1.2 Secondary Objectives 10

2.2 ENDPOINTS 10

2.2.1 Primary Endpoint 10

2.2.2 Secondary Endpoints 10

3. STUDY DESIGN 11

4. STUDY POPULATION 11

4.1 NUMBER OF PARTICIPANTS 11

4.2 INCLUSION CRITERIA 11

4.3 EXCLUSION CRITERIA 11

4.4 CO-ENROLMENT 11

5. PARTICIPANT SELECTION AND ENROLMENT 12

5.1 IDENTIFYING PARTICIPANTS 12

5.2 CONSENTING PARTICIPANTS 12

5.3 SCREENING FOR ELIGIBILITY 12

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS 12

5.5 RANDOMISATION 12

5.5.1 Randomisation Procedures 12

5.5.2 Treatment Allocation 12

5.5.3 Emergency Unblinding Procedures 12

5.6 WITHDRAWAL OF STUDY PARTICIPANTS 13

6. INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO 13

6.1 STUDY DRUG 13

6.1.1 Study Drug Identification 13

6.1.2 Study Drug Manufacturer 13

6.1.3 Marketing Authorisation Holder 13

6.1.4 Labelling and Packaging 13

6.1.5 Storage 14

6.1.6 Regulatory Release to Site 14

6.1.7 Destruction of Trial Drug 14

6.1.8 Summary of Product Characteristics (SPC) Booklet or Investigators Brochure 14

6.2 PLACEBO 14

6.2.1 Labelling and Packaging 14

6.2.2 Storage 14

6.3 DOSING REGIME 15

6.4 DOSE CHANGES 15

6.5 PARTICIPANT COMPLIANCE 15

6.6 OVERDOSE 15

6.7 OTHER MEDICATIONS 15

6.7.1 Non-Investigational Medicinal Products 15

6.7.2 Permitted Medications 15

6.7.3 Prohibited Medications 15

7. STUDY ASSESSMENTS 16

7.1 SAFETY ASSESSMENTS 16

7.2 STUDY ASSESSMENTS 16

7.3 COMPLIANCE ASSESSMENTS 16

7.4 LONG TERM FOLLOW UP ASSESSMENTS 16

7.5 STORAGE AND ANALYSIS OF SAMPLES 16

8. DATA COLLECTION 16

8.1 SOURCE DATA DOCUMENTATION 17

8.2 CASE REPORT FORMS 17

8.3 TRIAL DATABASE 17

9. DATA MANAGEMENT 18

9.1 Data Management Plan 18

9.2 Personal Data 18

9.3 Data Information Flow 18

9.4 Data Storage 18

9.5 Data Retention 18

9.6 Disposal of Data 19

9.7 External Transfer of Data 19

9.8 Data Controller 19

9.9 Data Breaches 19

10. STATISTICS AND DATA ANALYSIS 19

10.1 SAMPLE SIZE CALCULATION 19

10.2 PROPOSED ANALYSES 19

11. PHARMACOVIGILANCE 20

11.1 DEFINITIONS 20

11.2 IDENTIFYING AEs AND SAEs 20

11.3 RECORDING AEs AND SAEs 21

11.3.1 Pre-existing Medical Conditions 21

11.3.2 Worsening of the Underlying Condition during the Trial 21

11.4 ASSESSMENT OF AEs AND SAEs 21

11.4.1 Assessment of Seriousness 21

11.4.2 Assessment of Causality 21

11.4.3 Assessment of Expectedness 21

11.4.4 Assessment of Severity 22

11.5 RECORDING OF AEs 22

11.6 REPORTING OF SAEs/SARs/SUSARs 22

11.7 REGULATORY REPORTING REQUIREMENTS 22

11.8 FOLLOW UP PROCEDURES 23

11.9 PREGNANCY 23

12. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS 23

12.1 TRIAL MANAGEMENT GROUP 23

12.2 TRIAL STEERING COMMITTEE 23

12.3 DATA MONITORING COMMITTEE 23

12.4 INSPECTION OF RECORDS 23

12.5 RISK ASSESSMENT 24

12.6 STUDY MONITORING AND AUDIT 24

13. GOOD CLINICAL PRACTICE 24

13.1 ETHICAL CONDUCT 24

13.2 REGULATORY COMPLIANCE 24

13.3 INVESTIGATOR RESPONSIBILITIES 24

13.3.1 Informed Consent 24

13.3.2 Study Site Staff 25

13.3.3 Data Recording 25

13.3.4 Investigator Documentation 25

13.3.5 GCP Training 25

13.3.6 Data Protection Training 25

13.3.7 Information Security Training 25

13.3.8 Confidentiality 25

13.3.9 Data Protection 25

14. STUDY CONDUCT RESPONSIBILITIES 26

14.1 PROTOCOL AMENDMENTS 26

14.2 PROTOCOL NON COMPLIANCE 26

14.2.1 Definitions 26

14.2.2 Protocol Waivers 26

14.2.3 Management of Deviations and Violations 26

14.3 URGENT SAFETY MEASURES 26

14.4 SERIOUS BREACH REQUIREMENTS 26

14.5 STUDY RECORD RETENTION 27

14.6 END OF STUDY 27

14.7 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY 27

14.8 INSURANCE AND INDEMNITY 27

15. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS 28

15.1 AUTHORSHIP POLICY 28

15.2 PUBLICATION 28

15.3 DATA SHARING 28

15.4 PEER REVIEW 28

16. REFERENCES 28

APPENDIX 1: Trial Steering Committee 29

APPENDIX 2: Data Monitoring Committee 30

LIST OF ABBREVIATIONS

This is not an exhaustive list.

Any additional abbreviations used within the protocol must also be added here.

|  |  |
| --- | --- |
| **ACCORD** | Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board |
| **AE** | Adverse Event |
| **AR** | Adverse Reaction |
| **CI** | Chief Investigator |
| **CRF** | Case Report Form |
| **CSR** | Clinical Study Report |
| **CTA** | Clinical Trial Authorisation |
| **CTIMP** | Clinical Trial of Investigational Medicinal Product |
| **DMC** | Data Monitoring Committee |
| **DSUR** | Development Safety Update Report |
| **GCP** | Good Clinical Practice |
| **GMP** | Good Manufacturing Practice |
| **IB** | Investigator Brochure |
| **ICH** | International Conference on Harmonisation |
| **IMP** | Investigational Medicinal Product |
| **ISF** | Investigator Site File |
| **ISRCTN** | International Standard Randomised Controlled Trials Number |
| **MHRA** | Medicines and Healthcare products Regulatory Agency |
| **PI** | Principal Investigator |
| **NIMP** | Non-Investigational Medicinal Product |
| **QA** | Quality Assurance |
| **REC** | Research Ethics Committee |
| **SAE** | Serious Adverse Event |
| **SAR** | Serious Adverse Reaction |
| **SDV** | Source Data Verification |
| **SPC** | Summary of Product Characteristics |
| **SOP** | Standard Operating Procedure |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **TMF** | Trial Master File |
| **TMG** | Trial Management Group |
| **TSC** | Trial Steering Committee |

TRIAL SUMMARY

|  |  |
| --- | --- |
| Trial Title |  |
| Study Acronym |  |
| Clinical Phase |  |
| Trial Design |  |
| Trial Participants |  |
| Planned Number of Participants |  |
| Planned Number of Sites |  |
| Countries Anticipated to be Involved in Trial |  |
| Treatment Duration |  |
| Follow up Duration |  |
| Total Planned Trial Duration |  |
| Primary Objective |  |
| Secondary Objectives |  |
| Primary Endpoint |  |
| Secondary Endpoint |  |
| IMP(s) |  |
| IMP Route of Administration |  |
| NIMP(s) |  |
| Lay Summary of Trial |  |

# INTRODUCTION

## BACKGROUND

Text

Should include:

* Reviews of previous studies.
* Disease particulars.
* Disease incidence.
* Current treatment options.
* Risks and benefits.

## RATIONALE FOR STUDY

Text

A clear explanation of the research questions, hypothesis and justification of the trial is required here.

* An explanation of why the research is appropriate.
* Benefits to participants.
* Relevance to current policies.

Descriptions of the following should also be provided:

* Indication (diagnosis, incidence, current treatment(s) and their limitations).
* Treatment under investigation.

# STUDY OBJECTIVES & ENDPOINTS

## PRIMARY OBJECTIVES

### Primary Objective

Text

Detail the primary objective of the trial. Ensure this corresponds with the information provided in IRAS and the CTA.

### Primary Endpoint

Text

Detail the primary endpoint of the trial. Ensure this corresponds with the information provided in IRAS and the CTA.

## SECONDARY OBJECTIVES

### Secondary Objectives

Text

Detail the secondary objectives of the trial. Ensure this corresponds with the information provided in IRAS and the CTA.

### Secondary Endpoints

Text

Detail the secondary endpoint of the trial. Ensure this corresponds with the information provided in IRAS and the CTA.

# STUDY DESIGN

Text

* Type of trial (e.g. multi-centre, randomised, double-blind, placebo controlled etc.)
* Duration of trial.
* Duration of treatment phase.
* Duration of follow-up phase.
* Where trial visits will take place.
* Point in trial for measurement of outcomes.
* Duration of participant involvement.
* Any stopping rules for the trial.
* A schematic is recommended to summarise the measures/time points.

# STUDY POPULATION

## NUMBER OF PARTICIPANTS

Text

* Number of participants.
* Participant population.
* Length of recruitment period.

## INCLUSION CRITERIA

Text

* Detail participant inclusion criteria.
* Ensure this information is consistent with information provided on IRAS and CTA.

## EXCLUSION CRITERIA

Text

Detail participant exclusion criteria.

Ensure this information is consistent with information provided on IRAS and CTA.

Please ensure eligibility criteria include provision for appropriate contraception/pregnancy testing in line with the relevant [guidance](http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf). Methods of highly effective contraception, consistent with the CTFG document, need to be provided in the protocol rather than a reference to the CTFG document for the information.

## CO-ENROLMENT

Text

Please refer to ACCORD Co-enrolment Policy (POL008 Co-enrolment Policy).

Detail the policy towards co-enrolment and/or state that there will be compliance with the ACCORD Co-enrolment Policy POL008. Details of co-enrolment may entail identifying specific studies with which co-enrolment will be permitted. Alternatively, there may be situations where generic circumstances can be described. For example, co-enrolment could be permitted with studies that involve only the collection of data (e.g. questionnaires) or tissue samples (e.g. blood). Furthermore, details of how co-enrolment will be managed and recorded will be provided. If co-enrolment will not be allowed in any circumstances, this should be stated. Where co-enrolment is permitted, details of co-enrolment may entail identifying specific studies with which co-enrolment will be permitted. Alternatively, there may be situations where generic circumstances can be described. For example, co-enrolment could be permitted with studies that involve only the collection of data (e.g. questionnaires) or tissue samples (e.g. blood). In addition, when considering permitting co-enrolment, investigators should be mindful of the potential burden upon participants, their families and research staff.

## JUSTIFICATION FOR INCLUSION OF VULNERABLE POPULATIONS

Text

If any vulnerable populations will be involved (e.g. children, refugees, prisoners, individuals who are politically powerless) please provide justification for their involvement. Ethics committees should be assured that these populations will not be exposed to excess risk and that they will benefit from the research findings as a participant group or individually.

# PARTICIPANT SELECTION AND ENROLMENT

## IDENTIFYING PARTICIPANTS

Text

Describe how potential participants will be identified. This information must correspond with information provided on IRAS.

* Who will identify potential participants? Typically only a member of the participant’s direct care team can have access to their medical records prior to consent being given, to check if they meet inclusion criteria.
* How will first approach be made and by whom? If the study proposes to use individuals outside of the usual clinical care team to identify potential participants or make the first approach, the reason for this should be documented.

## CONSENTING PARTICIPANTS

Text

* How long will participants be permitted to consider the information sheet before participating in the trial (i.e. from the time the PIS is provided)?
* Who will be delegated to take informed consent from participants?
* Is e-consent intended to be used, if yes please specify the name of the system and vendor who manages it?

## SCREENING FOR ELIGIBILITY

Participant eligibility will be verified by a clinical trial physician after written informed consent has been obtained. Confirmation of eligibility will be recorded within the participants’ medical records.

* Detail any pre-randomisation assessments to be performed before a participant can formally enter the trial – including tests performed as part of routine care which will be used to confirm eligibility.
* Will a screening log be maintained? What information will be recorded and where e.g. screening log, eCRF/database?

## INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Text

Detail procedures for participants who are deemed ineligible or who are not randomised.

## RANDOMISATION

### Randomisation Procedures

Text

* If the trial is not randomised, please state here.
* Type of randomisation (e.g. simple, block, stratified, minimisation).
* Who will conduct randomisation.
* How will randomisation be performed (e.g. if web-based, please specify name of system).
* Use of equal or unequal allocation between treatment arms.
* If blinded, detail level of blinding.

### Treatment Allocation

Text

* Detail procedures for dispensing drug/placebo.
* Provide information on the instructions participants will receive.

### Emergency Unblinding Procedures

Text

* If the study is blinded, detail procedure for breaking the study blind.
* How will unblinding be performed (e.g. web-based, by telephone).
* Who can perform the unblinding?
* Who will be notified of the unblinding?
* Where will details of unblinding be recorded?
* In the event of a SUSAR, how will the Co-Sponsors unblind?

## WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study 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 record form if possible. The participant will have the option of withdrawal from:

1. study medication with continued study procedures and collection of clinical and safety data;
2. all aspects of the trial but continued use of data collected up to that point. To safeguard rights, the minimum personally identifiable information possible will be collected.
3. all aspects of the trial including data collected up to that point where it is possible to delete this data e.g. this data will not be used in the final data analysis. To safeguard rights, the minimum personally identifiable information possible will be retained e.g. consent form.

Randomised patients who wish to be withdrawn from the study before they have undertaken any study related procedures will be withdrawn from the study and another participant will be recruited to replace them. Data on the original participant will be kept on the CRF/database if the participant agrees to this.

* Detail reasons and procedures for a trial participant stopping early (i.e. stopping rules and discontinuation criteria).
* State whether withdrawn participants will be replaced.

# INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

## STUDY DRUG

### Study Drug Identification

Text

* Full name/generic name /UK trade name of trial drug.
* Form (e.g. tablet, capsule).

### Study Drug Manufacturer

Text

Detail the name and address of the company responsible for supplying the trial drug.

### Marketing Authorisation Holder

Text

Detail the name address and MA number of the company manufacturing the trial drug.

### Labelling and Packaging

Text

* Name and address of the party responsible for any additional packaging and/or labelling.
* Any specifics such as the number of tablets in a bottle to be dispensed to participants / a description of the label format.

Medication labels will be in the local language and comply with the legal requirements of Annex 13 of the European Union’s Good Manufacturing Practice (GMP).

### Storage

Text

* Where will drugs be stored at site?
* What are the storage conditions (e.g. temperature)
* Will temperature monitoring be in place at site?
* How will drugs be transported (e.g. between manufacturer and site, or between site and participant homes) – will conditions be monitored during transit?
* Consider whether any risk adaption for temperature monitoring is possible, taking into account stability of product and storage conditions required

### Regulatory Release to Site

Text

* Who will provide sign off? Routinely this is the lead ACCORD monitor for single centre trials or the Trial Manager for multi-centre trials using regulatory green light checklist (SOP CM001).
* If QP services are required, use of a contract QP can be discussed with ISG/HTAF. Products shipped to sites outside Great Britain may require separate QP release in those territories.
* Release cannot take place until required approvals are in place.

### Destruction of Trial Drug

Text

* If required, how will trial drug be destroyed? (Consider destruction of drug dispensed to participants and of unused/expired drug e.g. at the end of the trial. If participant returns at the end of the treatment course will not be required please justify this here)
* Who will be responsible for this?
* Who will provide authorisation to destroy the trial drug?
* How will this be documented (typically the Certificate of Destruction will be retained within the pharmacy file).

### Summary of Product Characteristics (SPC) Booklet or Investigators Brochure

The drug name Summary of Product Characteristics (SPC) (date of SPC) is provided in a separate document with a cover sheet and signature page (signed and verified by the CI and Co-Sponsors) and is filed in the TMF.

Please refer to drug name Investigator’s Brochure (IB edition and date).

## PLACEBO

Text

Detail the placebo form and composition.

### Labelling and Packaging

Text

* Name and address of the party responsible for any additional packaging and/or labelling of placebo.
* Any specifics such as the number of tablets in a bottle to be dispensed to participants/a description of the label format.

Medication labels will be in the local language and comply with the legal requirements of Annex 13 of the European Union’s Good Manufacturing Practice (GMP). They will include storage conditions for the drug, but no information about the patient.

### Storage

Text

* Where will placebo be stored at site?
* What are the storage conditions (e.g. temperature)
* Will temperature monitoring be in place at site?
* How will the placebo be transported (e.g., between manufacturer and site) – will conditions be monitored during transit?

## DOSING REGIME

Text

* Dosage (including duration of treatment and location of dosing).
* When drug/placebo will be dispensed.
* Route of administration.
* Timing of each dose.
* Maximum dosage allowed.

## DOSE CHANGES

Text

Detail if any changes in dose will be implemented and in what circumstances.

## PARTICIPANT COMPLIANCE

Text

Detail any potential issues in relation to compliance and detail the methods by which compliance will be verified. In addition, detail how non-compliance will be recorded and accounted for. If applicable, state the threshold for non-compliance.

## OVERDOSE

Text

Detail any expected effects of overdose (based on available study drug information) and what action is to be taken in the event of overdose.

## OTHER MEDICATIONS

### Non-Investigational Medicinal Products

Text

Products which are not the object of investigation but will be used in accordance with study procedures will be described here including details of proposed use.

For example, support or rescue/escape medications used to ensure that adequate medical care is provided to study participants. Another example is a product used to induce a physiological response. The quality of such products must be verified by the Co-Sponsors. Such products without a Manufacturing Authorisation (MA) should be manufactured to GMP standards – please consult the Co-Sponsors in this scenario.

Please note, for trials involving NIMPS, a **NIMP dossier** must be submitted to the MHRA as part of the CTA application.

### Permitted Medications

Text

Detail drug/medications that may be taken during the trial.

Consider recording of concomitant medications – will all concomitant medications be recorded in the CRF or is there scope for risk adaption? If only certain concomitant medications will be recorded please detail and justify why this is acceptable.

### Prohibited Medications

Text

Detail other drugs that are not allowed during the study due to e.g. interaction with the study drug, an effect on study outcome etc. Provide a specific list of prohibited drugs for clarity. Also comment on what will happen if a prohibited medication is taken during the study.

# STUDY ASSESSMENTS

## SAFETY ASSESSMENTS

Text

Detail and specific safety assessments required for the trial drug.

## STUDY ASSESSMENTS

Text

Describe all study procedures and assessments. Indicate the time points of all assessments and ensure that they are broken down as per visit number if appropriate for clarity. A table of assessments would be useful here. Consider an acceptable range of variation in the timing of visits, i.e. +/- windows around the stated timepoint.

## COMPLIANCE ASSESSMENTS

Text

Detail any potential issues in relation to compliance and detail the methods by which compliance will be verified. In addition, detail how non-compliance will be recorded and accounted for. If applicable, state the threshold for non-compliance.

## LONG TERM FOLLOW UP ASSESSMENTS

Text

If participants will be monitored after the active treatment phase has finished, the protocol should describe the long term follow up period including the frequency of follow up visits, duration of follow up period and any assessments that will be carried out. Include a description, where possible, of the method and number of attempts to contact participants, to collect follow-up data in accordance with the schedule, before exhaustion is reached and a participant is considered lost to follow-up. Consider whether non-collection of follow-up data in a lost to follow-up scenario should be exempted from deviation reporting, as detailed in protocol section 14.2.

## STORAGE AND ANALYSIS OF SAMPLES

Text

This section should describe the procedure for dealing with biological samples, if applicable to the study. The section should include:

* Sample types.
* Volume of samples.
* Arrangements for storage (including location) and analysis (e.g. where are samples going to be analysed).
* Will samples be shipped from site?
* For international study settings: Will samples be shipped from local site to a 3rd party, or to other institution/laboratory/company, or to a UK-based institution?
* Will samples be destroyed at the end of the trial?
* Will consent be sought for long term storage of samples?
* Whether the sample analysis is critical to the conduct of the trial, i.e. is necessary to determine eligibility and/or relates to primary/secondary endpoint data and objectives (e.g. specific mutations associated with eligibility assessments).
* Whether the sample analysis is not critical to the conduct of the trial, i.e. relates to tertiary/exploratory endpoint data and objectives.

This information must also be detailed within the PIS/Consent form.

DNA/genome/exome wide analysis must be explicitly consented for by participants.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Sample** | **Sample Type** | **Analysis** | **Location of Lab** | **Endpoint** | **Documentation** |
| 4.9mL Serum Tube | Research Blood | High sensitivity liver injury markers (keratin-18, microRNA-122, GLDH) | Mass Spectrometry Core in the Queens Medical Research Institute, Edinburgh BioQuarter | Primary  (explicitly detail which endpoint relates to) | SOP XX  Lab Manual |
| 2.8mL EDTA Tube | Clinical Blood | Liver Function test (LFT) | NHS Lothian Laboratory Medicine | Secondary (explicitly detail which endpoint relates to) | Standard of Care |
|  |  |  |  |  |  |

\*The above table is an illustrative example of how to present analysis of samples.

Please specify sample type: standard tests performed by local NHS labs **(clinical)** or non-standard research tests either in NHS labs or external labs **(research).**

# DATA COLLECTION

Text

The UK General Data Protection Regulation (GDPR) requires appropriate technical and organisational measures to be in place to implement the data protection principles effectively and safeguard individual rights. This is ‘data protection by design and by default’. In essence, this means you have to integrate or ‘bake in’ data protection into your processing activities and business practices, from the design stage right through the lifecycle.

Detail data to be collected, including:

* Time points for collection (e.g. baseline, during treatment, follow up).
* Who will collect the data.
* Details of any standardised tools to be used (e.g. pain score, questionnaires).
* Describe any methods to maximise completeness of data (e.g. telephoning participants who have not returned questionnaires).
* How will data be recorded? eCRF (detailing system pCRF?
* Consider identifying key data which is essential for study design/analysis to allow for risk adaption in data QC and completion.
* Describe the use of any transcription services.
* Describe any audio / video recordings and where these will be stored

## SOURCE DATA DOCUMENTATION

Source data is defined as all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Source documents are original documents, data and records where source data are recorded for the first time.

Text

* The source must be detailed here.
* Where the case report form is a source document, source data captured in the CRF must be detailed within this section. Alternatively this can be detailed in a separate source data plan which should be referenced here e.g. source data captured directly in the CRF will be detailed in a source data plan (CR004-T01).
* Where external data is supplied by a third-party, and the third-party stipulate conditions for the security and management of data on the infrastructure to be used, confirmation of the infrastructure to be used and how it meets the third-party conditions should be detailed here and detailed in a contract as appropriate.

## CASE REPORT FORMS

This section should provide information regarding the case report forms to be used during the trial, including the type of case report forms (i.e. paper and/or electronic). If electronic case report forms are to be used with personal data, this section must show how the eCRF will provide data protection by design and default, including encryption of data while it is being stored (at rest) and encryption while it is being entered or transferred into the eCRF. Please specify the name of the electronic CRF system and where it is hosted.

Text

All case report forms must be reviewed and approved by the ACCORD Monitor prior to use (see ACCORD SOP CR013 CRF Design and Implementation).

NOTE: All electronic case report forms are subject to Co-Sponsor approval (see section 8.3).

## TRIAL DATABASE

Text

* Will a trial database be used? What is the name of the system? Is it bespoke for the trial?
* Who (e.g. CTU, research group) will provide and be responsible for the database? The servers of which organisation (country) will host the database?
* How will the database provide data protection by design and default, including encryption of data while it is being stored (at rest) and encryption while it is being entered or transferred into the database?
* Who will enter data?
* What will happen to data at the end of the trial / how long will data be retained for / where will it be archived?
* NOTE: All databases are subject to Co-Sponsor approval and may be subject to NHS Lothian Information Governance/IT Security risk assessment [see ACCORD SOP GS008 Personal Information Caldicott Approval and Information Governance Review]

## STUDY DOCUMENT TRANSLATIONS

## If the study plans to use a 3rd party provider for translating the study documents, please include details of this service here. Otherwise, please specify who will be responsible for providing the study document translations.

# DATA MANAGEMENT

## DATA MANAGEMENT PLAN

All aspects of data collection, data processing (entry/uploading, cleaning, and query management), and the production of the final dataset ready for analysis and/or archiving will be detailed in a separate Data Management Plan (DMP).

For studies subject to a combined risk assessment (GS002), all data management activities should be detailed in a separate data management plan (DMP). Where data management tasks have been delegated to a specialist function group, the vendor DMP template can be used, if applicable. Otherwise the ACCORD DMP template (POL011-T01) will be used.

## PERSONAL DATA

Describe how the data will meet the ‘data protection by design and default’ principles of the UK GDPR legislation at every stage of the Data Information Flow. This may require explanation of the infrastructure and systems that will be used to manage the data, and how they are secured at each stage of the flow.

Where personal identifiable data is being processed, justify why this data is required, whether it will be uploaded to the eCRF/database or if the personal identifiable data will be retained in the NHS. Where possible, personal identifiable data should not leave the NHS.

The following personal identifiable data will be collected as part of the research:

Text

Here you should detail what personal identifiable data (e.g. name, CHI number, other unique numeric identifiers, location data, online identifiers (including IP address, cookies), one or more specific identifiers relating to the physical, physiological, genetic, biometric, mental, economic, cultural or social identity of a participant.

## DATA INFORMATION FLOW

Text

Describe the collection, use and deletion of personal data here. It could be useful to provide a list of the IT to be used, how data is secured and insert a flow diagram here.

## DATA STORAGE

Text

Describe where the data will be stored e.g. paper/electronic (if electronic, name organisation and country where data will be hosted). You should distinguish between personal identifiable data and pseudonymised data

Refer to [guidance](https://www.ed.ac.uk/information-services/research-support/research-data-service/guidance) from the UoE Research Data Service, in particular [Quick Guide 3: Data Storage](https://libraryblogs.is.ed.ac.uk/datablog/files/2019/10/Quick-Guide-3-DATA-STORAGE-OPTIONS-v1.4.pdf) and the [flowchart](https://www.ed.ac.uk/files/atoms/files/rds_flowchart_-_20170608_-_dmd_-_v7.pdf) for data management before, during and after your research.

Personal data (pseudonymised) will be physically stored by the research team at detail location of data storage, who will have access to personal data and where the code break/key will be kept.

Personal identifiable data will be physically stored by the research team at detail location of data storage, who will have access to personal data and where the code break/key will be kept.

Personal data (pseudonymised) will be digitally stored by the research team using detail location (organisation, country) of all systems involved in the collection, transfer and storage of personal data, and who will have access to it for which purposes.

Personal identifiable data will be digitally stored by the research team using detail location (organisation, country) of all systems involved in the collection, transfer and storage of personal data, and who will have access to it for which purposes.

## DATA RETENTION

Outline the retention period and the reason for the length of time.

Refer to [guidance](https://www.ed.ac.uk/information-services/research-support/research-data-service/guidance) from the UoE Research Data Service and the [flowchart](https://www.ed.ac.uk/files/atoms/files/rds_flowchart_-_20170608_-_dmd_-_v7.pdf) for data management before, during and after your research.

Typically, personal data should be stored in a suitable repository e.g. DataStore/DataVault. Costs for this should be considered during the funding application stage.

Personal data (pseudonymised) will be stored for detail duration of personal data retention.

Personal identifiable data will be stored for detail duration of personal data retention.

## DISPOSAL OF DATA

Text

How will the data be deleted or made anonymous once the retention period is over?

Refer to [guidance](https://www.ed.ac.uk/information-services/research-support/research-data-service/guidance) from the UoE Research Data Service.

## EXTERNAL TRANSFER OF DATA

Please detail here if there is an intention for any personal identifiable data to be transferred/stored out with NHS Lothian, e.g. for transcription services, eCRF/database. An NHS Lothian IT security risk assessment for securely transferring personal identifiable data outside of NHS Lothian will be required by NHS Lothian Information Governance. This may also be required if pseudonymised personal data is be shared with organisations out with the UK/EU depending on GDPR adequacy arrangements i.e. transfer of any personal data out with NHS Lothian should be described in the protocol and the PIS

Data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside the sponsoring organisation(s) without participant consent, appropriate approvals (where applicable) and a data sharing agreement.

Where it is known that data will be shared, this should be explicit in the PIS e.g. what data, with whom (organisation, country).

## DATA CONTROLLER

A data controller is an organisation that determines the purposes for which, and the manner in which, any personal data are processed.

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, or collaborating institution in the local country where the study is being conducted).

## DATA BREACHES

Any data breaches will be reported to the University of Edinburgh ([dpo@ed.ac.uk](mailto:dpo@ed.ac.uk)) and NHS Lothian ([Loth.DPO@nhs.scot](mailto:Loth.DPO@nhs.scot)). Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required. **For non-UK study settings only:** Please insert here details of any relevant Data Protection Officer/Committee in the local setting who must also be notified of data breaches.

# STATISTICS AND DATA ANALYSIS

## SAMPLE SIZE CALCULATION

Text

## PROPOSED ANALYSES

Text

Detail the variables to be used for assessment and how these will be reported (e.g. means, standard deviations, medians etc.). Write detailed plans for analyses of primary and secondary outcomes including:

* Summary measures to be reported.
* Method of analysis.
* Plans for handling missing, unused and spurious data, non-compliers and withdrawals.
* Plans for pre-defined subgroup analyses.
* Statement regarding use of intention to treat analysis.
* Details of any interim analysis.

# PHARMACOVIGILANCE

This section may be amended in consultation with the Co-Sponsor Representative(s) (e.g. if a third party is delegated the responsibility for safety reporting).

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SPC) Booklet/Investigator’s Brochure (IB).

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AE) that occur after informed consent until [enter a time period to specify how long after the last dose of IMP AEs will be recorded for] must be recorded in the Case Report Form (CRF) or AE log. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment.

## DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

* results in death of the clinical trial participant;
* is life threatening\*;
* requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
* results in persistent or significant disability or incapacity;
* consists of a congenital anomaly or birth defect;
* results in any other significant medical event not meeting the criteria above.

\*Life-threatening in the definition of an SAE or SAR refers to an event where 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.

^Any hospitalisation that was planned prior to enrolment will not meet SAE criteria. Any hospitalisation that is planned post enrolment will meet the SAE criteria.

**A suspected unexpected serious adverse reaction** (SUSAR) is any AR that is classified as serious and is suspected to be related to the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SPC) booklet or Investigators Brochure.

## IDENTIFYING AEs AND SAEs

Participants will be asked about the occurrence of AEs/SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified via information from support departments e.g. laboratories.

## RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator, or another suitably qualified physician in the research team who is delegated to record and report AEs/SAEs, to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF/AE log and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

### Pre-existing Medical Conditions

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as adverse events if medically judged to have worsened during the study.

### Worsening of the Underlying Condition during the Trial

Medical occurrences or symptoms of deterioration that are expected due to the participant’s underlying condition should be recorded in the patient’s medical notes and only be recorded as AEs on the AE log if medically judged to have unexpectedly worsened during the study. Events that are consistent with the expected progression of the underlying disease should not be recorded as AEs.

In this section you can mention what are the underlying condition expected due to the trial population or the other treatment this population has to take (e.g.: chemotherapy)

This can be presented in a list, make sure the list is exhaustive. If events are not to be recorded as AEs please indicate where those will be recorded. Also indicate if the events are serious, will they be reported as SAE or not?

## ASSESSMENT OF AEs AND SAEs

Each AE must be assessed for seriousness, causality, severity and ARs must be assessed for expectedness by the Principal Investigator or another suitably qualified physician in the research team who has been delegated this role.

For randomised double blind studies, AEs will be assessed as though the participant is taking active IMP. SUSARs will be unblinded by ACCORD before they are reported to REC and CA (by ACCORD).

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

### Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 11.1.

### Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

* Unrelated: where an event is not considered to be related to the IMP.
* Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug.

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

### Assessment of Expectedness

If the event is an AR the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SPC Booklet/IB. – mention here the appropriate section of the document where the info can be found.The event may be classed as either:

* **Expected**:the AR is consistent with the toxicity of the IMP listed in the SPC Booklet/IB.
* **Unexpected**:the AR is not consistent with the toxicity in the SPC Booklet/IB.

Fatal and life threatening SARs should usually be considered unexpected. Fatal SARs can only be expected for IMPs with an MA in the EU, when it is clearly stated in the list of ARs of the SPC (Section 4.8) that the IMP causes fatal SARs.

### Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE/SAR/SUSAR and record this on the CRF/AE log or SAE form according to one of the following categories:

* **Mild**: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.
* **Moderate**: an event that is sufficiently discomforting to interfere with normal everyday activities.
* **Severe**: an event that prevents normal everyday activities.

Note: the term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

## RECORDING OF AEs

All adverse events for each participant will be recorded on the AE log and will be assigned the appropriate MedDRA Systems Organ Class (SOC) code.

Please note that the MedDRA SOC Coding of all AEs is mandatory for trials registered with EudraCT only. Amend this part if necessary. MedDRA SOC coding is not mandatory for trials registered with ISRCT but please speak to statisticians or other person of interest before amending this part to confirm if MedDRA coding will need to be performed or not and at what level.

Confirm who in the trial team will perform the MedDRA coding if it needs to be done

## REPORTING OF SAEs/SARs/SUSARs

*Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance* ***within 24 hours****. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.*

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 11.4.2, Assessment of Causality and 11.4.3, Assessment of Expectedness.

The SAE form will be transmitted via email to [safety@accord.scot](mailto:safety@accord.scot). Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

Are there any onward reporting requirements for SAEs/SARs/SUSARs (e.g. to trial manager/IMP manufacturer)? If so, details should be provided here and reflected in the relevant agreement(s).

All reports sent to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

If any SAEs are not to be reported to the Co-Sponsors, they should be listed here. Consider possibilities for risk adaption e.g. where SAEs will be captured as endpoint data or where the IMP has a well-defined safety profile of side effects will these events be captured as AEs? If some SAEs were mentioned as not to be reported in section 11.3.2 you should also list those here. Make sure the list is exhaustive.

## REGULATORY REPORTING REQUIREMENTS

ACCORD is responsible for pharmacovigilance reporting on behalf of the Co-Sponsors (The University of Edinburgh and NHS Lothian).

ACCORD has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial) of SUSARS. Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD (or delegate) will inform Investigators at participating sites of all SUSARs and any other arising safety information.

ACCORD will be responsible for providing safety line listings and assistance; however, it is the responsibility of the Investigator to prepare the Development Safety Update Report. This annual report lists all SARs and SUSARs reported during that time period. The responsibility of submitting the Development Safety Update Report to the regulatory authority and RECs, lies with ACCORD.

Are there any DSUR onward reporting requirements (e.g. to IMP manufacturer)? If so, details should be provided here and reflected in the relevant agreement(s).

## FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported as necessary. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the CRF or AE log or additional information section of SAE form.

## PREGNANCY

Although pregnancy is not considered an AE or SAE; as a matter of safety, the Investigator will be required to record any female participant’s pregnancy or any pregnancy of a female partner of a male participant, who became pregnant while participating in the study. The Investigator will need to record the information on a Pregnancy Notification Form and submit this to the ACCORD office within 14 days of being made aware of the pregnancy.

All pregnant female participants and pregnant partners of male participants will be followed up until the outcome of the pregnancy.

# TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

## TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), A Trial Manager and coordinating nurse.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

## TRIAL STEERING COMMITTEE

If no Trial Steering Committee is to be established, justification must be provided here.

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the Trial Steering Committee, the draft template for reporting and the names and contact details are detailed in CR015 DMC & TSC Charters.

## DATA MONITORING COMMITTEE

If no Data Monitoring Committee is to be established, justification must be provided here.

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The terms of reference of the Data Monitoring Committee and the names and contact details are detailed in CR0015 DMC & TSC Charters.

The DMC Charter will be signed by the appropriate individuals prior to the trial commencing.

## INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the Co-Sponsors, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the Co-Sponsors 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.

## RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the Co-Sponsors, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions could be incorporated into to trial design.

## STUDY MONITORING AND AUDIT

ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including 3rd parties) audits as necessary (delete where not required).

# GOOD CLINICAL PRACTICE

## 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 necessary approvals will be obtained and any conditions of approvals will be met.

## REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

## 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.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

### Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any study 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 Co-Sponsors.

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 original will be signed in the Investigator Site File (ISF). The participant will receive a copy of the signed consent form and a copy will be filed in the participant’s medical notes.

### Study Site Staff

The Investigator must be familiar with the IMP, 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 IMP, protocol and their trial related duties.

### Data Recording

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

### Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

* An original signed Investigator’s Declaration (as part of the Clinical Trial Agreement documents);
* Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.
* ACCORD will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) or Sponsor File, where required. The Principal Investigator will ensure that the required documentation is available in local Investigator Site files (ISFs). Under certain circumstances the TMF responsibilities may be delegated to the research team by ACCORD.

### GCP Training

All study staff must hold evidence of appropriate GCP training.

### Data Protection Training

Research staff are responsible for completing mandatory data protection training in accordance with local policy.

### Information Security Training

All University of Edinburgh employed researchers, students and study staff will complete the [Information Security Essentials modules](https://www.ed.ac.uk/information-services/help-consultancy/is-skills/catalogue/capability-wellbeing/info-security-essentials)  and will have read the [minimum and required reading](https://www.ed.ac.uk/infosec/information-protection-policies/information-security-required-reading) setting out ground rules to be complied with.

NHS Lothian employed researchers and study staff will comply with NHS Lothian mandatory Information Governance IT Security training. .

Non-NHS Lothian staff that have access to NHS Lothian systems will familiarise themselves and abide by all NHS Lothian IT policies, as well as employer policies

### 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 Co-Sponsors or its designee must be obtained for the disclosure of any said confidential information to other parties.

### Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including where applicable the UK General Data Protection Regulation legislation 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 that could allow identification of individual participants.

# STUDY CONDUCT RESPONSIBILITIES

## 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.

Proposed amendments will be submitted to the Co-Sponsors for classification and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to implementation.

## PROTOCOL NON-COMPLIANCE

### Definitions

* **Deviation** - Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subjects rights, safety, or well-being, or study outcomes.
* **Violation** - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject’s rights, safety, or well-being.

### Protocol Waivers

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the Co-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, Regulatory Authority and local R&D for review and approval if appropriate.

### Management of Deviations and Violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the Co-Sponsors every 3 months. Each protocol violation will be reported to the Co-Sponsors within 3 days of becoming aware of the violation.

Deviation logs/violation forms will be transmitted via email to [QA@accord.scot](mailto:QA@accord.scot). Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

## URGENT SAFETY MEASURES

The Investigator may implement a deviation from or change to the protocol to eliminate an **immediate hazard** to trial participants without prior approval from the REC and the MHRA. This is defined as an urgent safety measure and the investigator must contact the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately (+44 (0) 20 3080 6456).

The Investigator will then notify the MHRA ([clintrialhelpline@mhra.gsi.gov.uk](mailto:clintrialhelpline@mhra.gsi.gov.uk)) (or other Regulatory Authority where relevant), the REC and ACCORD, in writing of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment.

## 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 ([QA@accord.scot](mailto:QA@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 regulatory authorities and research ethics committees as necessary.

## STUDY RECORD RETENTION

This section should describe the duration for which paper and electronic trial records will be retained following the end of the trial.

* The minimum period is 15 years for CTIMPs collecting data to be used in a Manufacturing Authorisation application.
* Please also refer to funders for any funding stipulations associated with retention of records.

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will be destroyed with permission from the Co-Sponsors.

## END OF STUDY

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

The Investigators and/or the trial steering committee and/or the Co-Sponsors 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, Regulatory Authority, 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](mailto:resgov@accord.scot).

In accordance with ACCORD SOP CR011, a Research Study Report will be provided to the Co-Sponsors ([QA@accord.scot](mailto:QA@accord.scot)) and REC within 1 year of the end of the study. [Note for paediatric trials this timeline is 6 months].

Within one year of the end of trial, the Investigator will publish summary results on the publicly accessible database that the trial was registered with, on behalf of the Co-Sponsors.

The Investigator will submit a short confirmatory e-mail to the MHRA ([CT.Submission@mhra.gsi.gov.uk](mailto:CT.Submission@mhra.gsi.gov.uk)) once the result-related information has been uploaded to the public registry. The subject line of the email notification must state:‘End of trial: result-related information: EudraCT XXXX-XXXXXX-XX and/or IRAS ID XXXXXXX’. The Co-Sponsor(s) will be copied in this e-mail ([QA@accord.scot](mailto:QA@accord.scot)). It should be noted that you will not get an acknowledgment e-mail or letter from the MHRA.

If your clinical trial is not on a public register or the results will not be published in the register (for example an adult phase I study), summary results should be submitted via MHRA Submissions. Only trials with sites in the EU will require EudraCT registration.

For clinical trials being conducted in a non-UK setting, End of trial summary results will be submitted to the relevant Regulatory Authority and individual Ethics Committees in the local setting, and in accordance with relevant local Regulatory Authority/Ethics Committee timelines. The sponsor will be copied in to this email ([QA@accord.scot](mailto:QA@accord.scot)).

## CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

Text

Detail arrangements for continuation of trial drug beyond the end of the trial. If none, provide justification.

## 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 authored 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 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.
* The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

# REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

## AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the Co-Sponsors although the study team will be responsible for retaining data, publishing findings and submitting necessary reports derived from the data. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

## PUBLICATION

The study report will be submitted to the Co-Sponsors and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the study report. The Chief Investigator will provide the study report to ACCORD, for review, prior to finalization, where applicable. The study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. The results of the study, together with other mandated information, will be uploaded to the publicly accessible database that the trial was registered with, on behalf of the Co-Sponsors, within 1 year of the end of the study. [Note for paediatric trials this timeline is 6 months].

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

## DATA SHARING

Text

Detail procedures for data sharing (if any) – these may be funder specific.

## PEER REVIEW

Text

Detail procedures for peer review – these may be funder specific or involve an internal department.

# REFERENCES

# APPENDIX 1: Trial Steering Committee

# APPENDIX 2: Data Monitoring Committee