**Guidance Notes for CIP/CPSP Template**

This protocol template is intended as a suggestion for the Clinical Investigation Plan (CIP) or Clinical Performance Study Protocol (CPSP) layout to be used for device studies that are sponsored or co-sponsored by the University of Edinburgh and/or Lothian Health Board. This is minimum criteria and extra information can be added in as necessary. It should contain the rationale, objectives, design and pre-specified analysis, methodology, organization, monitoring, conduct and record-keeping of the clinical investigation or performance.

This template is written in line with the minimum information stipulated ISO 14155 (Medical Devices) and ISO 20916 (*In vitro* diagnostics medical devices).

**General notes on using the CIP/CPSP template:**

Some sections may not be applicable, depending on the nature of the study. Please ensure that you remove any sections which are not relevant to your study unless there is an indication that the section is standard text and should remain unchanged.

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

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

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

Clinical Investigation Plan or Clinical Performance Study Protocol

**Full Title of Study**

|  |  |
| --- | --- |
| Co-Sponsors | The University of Edinburgh & Lothian Health BoardACCORD Usher Building, The University of Edinburgh 5-7 Little France Road Edinburgh BioQuarter – Gate 3 Edinburgh EH16 4UX |
| Local Representative | Certain national/regional regulations can require that if the sponsor is not resident in the country in which the clinical investigation is to be carried out, the name and address of a local representative who acts as the sponsor fulfilling responsibilities of the sponsor in that country is provided |
| Funder | Insert name of funder. |
| Funding Reference Number | Insert funding referenceA 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 Trials 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. The CIP/CPSP submitted to REC and/or MHRA should be V1.0 and date of submission |

|  |
| --- |
| **KEY TRIAL CONTACTS** (**\*Protocol Authors** this information must be included for insurance purposes) |
| **Chief Investigator1** |  | **Lead Co-Sponsor Representative** |
| **Name:** |  |  | **Name:** |  |
| **Position:** |  |  | **Address:** |  |
| **Address:** |  |  |  |  |
|  |  |  |  **Email:** |  |
|  **Email:** |  |  |  |  |
| **Trial Manager** |  | **Trial Statistician** |
| **Name:** | required for all multi-site trials |  | **Name:** | required named statistician  |
| **Address:** |  |  | **Address:** |  |
|  |  |  |  |  |
|  **Email:** |  |  |  **Email:** |  |

1 Add name, address, contact details and professional position of any principal investigator(s) and/or any coordinating investigator, if appointed.

Add appropriate name (e.g. Head of Department) and address of any external organisations, e.g. core laboratories, Contract Research Organisation (CRO) or Clinical Trials Unit (CTU), consultants or other contractors involved in the Clinical Investigation.

CLINICAL INVESTIGATION PLAN or CLINICAL PERFORMANCE STUDY PROTOCOL APPROVAL SIGNATURE PAGE

**Full Title of Study**

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

**Summary of Revision History**

|  |  |  |  |
| --- | --- | --- | --- |
| **Version no.** | **Date** | **Summary of revision(s)** | **Updated by**  |
| 1.0 | DDMMMYY | Initial Document Release | Name |
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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 |
| **ADE** | Adverse Device Effect |
| **AE** | Adverse Event |
| **CA** | Competent Authority |
| **CE** | *Conformité Européenne* |
| **CI** | Chief Investigator |
| **CIA** | Clinical Investigation Agreement |
| **CIP** | Clinical Investigation Plan |
| **CISR** | Clinical Investigation Study Report |
| **CPSR** | Clinical Performance Study Report |
| **CRF** | Case Report Form |
| **DD** | Device Deficiency  |
| **DMC** | Data Monitoring Committee |
| **EC** | European Commission  |
| **eCRF** | Electronic Case Report Form |
| **FDA** | Food & Drug Administration |
| **GCP** | Good Clinical Practice |
| **GMP** | Good Manufacturing Practice |
| **IB** | Investigator Brochure |
| **ICH** | International Conference on Harmonisation |
| **IFU** | Instructions for Use |
| **IMD** | Investigational Medical Device |
| **ISF** | Investigator Site File |
| **ISRCTN** | International Standard Randomised Controlled Trials Number |
| **IVD** | *In vitro* diagnostic |
| **MD** | Medical Device |
| **MHRA** | Medicines and Healthcare products Regulatory Agency |
| **PE** | Performance Evaluation |
| **CPSP** | Clinical Performance Study Protocol |
| **PI** | Principal Investigator |
| **POC** | Point of Care |
| **QA** | Quality Assurance |
| **REC** | Research Ethics Committee |
| **SADE** | Serious Adverse Device Effect |
| **SAE** | Serious Adverse Event |
| **SAR** | Serious Adverse Reaction |
| **SDV** | Source Data Verification |
| **SOP** | Standard Operating Procedure |
| **SPC** | Summary of Product Characteristics |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **TMF** | Trial Master File |
| **TMG** | Trial Management Group |
| **TSC** | Trial Steering Committee |
| **UKCA** | United Kingdom Conformity Assessed |
| **UKMDR** | The Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK medical devices regulations) |
| **USADE** | Unanticipated Serious Adverse Device Effect |

SYNOPSIS OF THE CLINICAL INVESTIGATION or CLINICAL PERFORMANCE

|  |  |
| --- | --- |
| Investigation Title |  |
| Study Acronym |  |
| Clinical Phase |  |
| Investigation Design |  |
| Investigation Participants |  |
| Planned Number of Participants |  |
| Planned Number of Sites |  |
| Countries Anticipated to be Involved |  |
| Investigation Duration |  |
| Follow up Duration |  |
| Total Planned Duration |  |
| Primary Objective |  |
| Secondary Objective |  |
| Primary Endpoint |  |
| Secondary Endpoint |  |
| Device(s) and Intended Purpose(s) |  |
| Main Inclusion/Exclusion Criteria |  |
| Regulatory Classification of the Device(s) |  |
| Lay Summary of Investigation |  |

# INTRODUCTION

## BACKGROUND

Text

Should include:

* Reviews of previous clinical trials conducted/ or clinical use of the device (or where relevant inference to similar devices) in support for this clinical trial.
* Disease particulars.
* Disease incidence.
* Current treatment options.
* Risks and benefits.
* Summary of important trial relevant preclinical/non clinical studies. Please cross-reference IB, as applicable.

##

## RATIONALE FOR CLINICAL INVESTIGATION/PERFORMANCE

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.
* The current available treatment(s) and their limitations, and why the device might be an improvement on those treatments (e.g. toxicity, cost).

Descriptions of the following should also be provided:

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

Justification should be provided to support that the device could achieve clinical improvement over current practice (and indicate its relevance to healthcare practice). Especially if the trial population is:

1. in children or in adults unable to consent for themselves for longer duration
2. in a participant population that might handle it differently (e.g. hepatic or renally impaired participants, children, elderly, immunocompromised)
3. it is being used in combination with another device or medicinal product
4. the indication/ medical condition compromises the participant’s tolerance

# OVERVIEW OF THE INVESTIGATIONAL DEVICE

Each sub-section below shall also provide available information for the comparator, if applicable.

## SUMMARY DESCRIPTION OF THE INVESTIGATIONAL DEVICE

Text

## MANUFACTURER OF THE DEVICE

Text

Include name, address, compliance to regulations and any certifications/standards achieved and details of a manufacturer representative. Please note some countries might require the contact details of a local authorised representative. Add who will provide sign off to release the devices to sites – this role is normally taken by the manufacturer of the device(s).

The lead ACCORD monitor for single centre trials or the Trial Manager for multi-centre trials will provide authorisation to ship the devices to sites using regulatory green light checklist (SOP CM001). Release cannot take place until required approvals are in place. Include information on the process to return the devices back to manufacturer or destruction at site and who will provide this authorisation and where it will be documented.

## DEVICE IDENTIFICATION

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Device name** | **Device Model** | **GMDN code** | **Classification** | **Regulation** |
| Blood gas analyser | BGA1 | 18853 | Class II | UK MDR 2002 |
|  |  |  |  |  |

Provide name or number of the model/type, including software version and accessories, if any, to permit full identification.

## TRACEABILITY

Text

Description as to how traceability shall be achieved during and after the clinical investigation, for example, by assignment of lot numbers, batch numbers, or serial numbers.

## INTENDED PURPOSE

Text

## TARGET POPULATION(S) AND INDICATION(S) FOR USE

Text

## TECHNICAL DESCRIPTION OF THE INVESTIGATIONAL DEVICE

Text

Provide a description on how the device operates and its components, e.g. software, to achieve the intended purpose – this could include any images/photographs of the device. List any device components and/or accessories that are part of the device. Add the specification of the analyte or marker to be determined by the device.

### Materials and Active Ingredients

Text

Provide information on any biologically active substances, medical substances, human or animal tissues or their derivatives that are part of the device and reference compliance with the applicable national regulations.

### 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 components within a pack or pouch / a description of the label format.

Labels will be in the local language and comply with the legal requirements and the Medical Devices Regulations 2002 (Annex I, section 13), ISO 15223-1 and ISO 15223-2. They will include storage conditions for the device, but no information about the patient. The labelling should indicate that the Medical Device/IVD medical device under investigation is exclusively for use in a clinical investigation/performance study.

### Stability and Storage

Text

* What is the stability of the investigational devices? Could reference the IB instead.
* Where will the investigational devices be stored at site?
* What are the storage conditions (e.g. temperature)?
* Will temperature monitoring be in place at site?
* How will devices 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.

## TRAINING AND EXPERIENCE REQUIREMENTS

Text

Provide an overview of the user information, e.g. device used by lay users, by professionals, any specific training required to effectively use or operate the device – this training must be documented/logged.

## USER INFORMATION

Text

Description of the specific medical or surgical procedures involved in the use of the investigational device. Reference the Investigator Brochure (IB) and Instructions for Use (IFU) and any other supporting documents, e.g. brochures, training manuals.

# ANALYTICAL PERFORMANCE

Text

This will include all the pre-clinical testing of the device to demonstrate it is capable of performing under ideal and controlled conditions. It might include sensitivity, specificity, reading time, in-use stability, shelf-life, robustness etc. Please consider the points below in the justification.

• Evaluation of the results of the relevant pre-clinical testing/assessment and prior clinical investigations, if applicable, carried out to justify the use of the investigational device in human subjects.

• Evaluation of clinical data that are relevant to the proposed clinical investigation.

• Description of the clinical development stage, if appropriate.

# RISK MANAGEMENT

Text

Description of the Risk Management activities undertaken for the investigational device, clinical procedure and clinical investigation and its outcomes (see below points). Reference any supporting documentation, e.g. Risk Management Plan and Report that were conducted and any regulatory compliance.

* Anticipated clinical benefits.
* Anticipated adverse device effects.
* Risks associated with participation in the clinical investigation.
* Possible interactions with concomitant medical treatments as considered under the risk analysis.
* Steps that will be taken to control or mitigate the risks.
* Rationale for benefit-risk ratio.

# STUDY OBJECTIVES & ENDPOINTS

## PRIMARY OBJECTIVES

### Primary Objectives

Text

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

###

### Primary Endpoints

Text

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

Please include rationale for the selection and measurement of primary. If applicable, composite endpoints, with rationale for their selection and measurement. The primary endpoint shall be appropriate for the investigational device and should be clinically relevant.

## SECONDARY OBJECTIVES

Text

### Secondary Objectives

Text

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

### Secondary Endpoints

Text

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

# STUDY DESIGN

## GENERAL

Text

A schematic representation of the study is required to outline the study design and should include the outcome measures/time points and proposed analyses.

* The current study design and clinical performance should demonstrate with objective evidence how the device will perform in routine clinical practice. Please consider including the points below. Type of trial (e.g. randomized, blinded or open-label, parallel groups or crossover, multicentre, international etc.).
* Description of the measures to be taken to minimize or avoid bias, such as randomization, concealment of allocation, blinding/masking, and management of potential confounding factors. Any procedures for the replacement of participants (generally, not applicable to randomized clinical investigations).
* Control group (e.g. comparative claim and reversible treatment of a chronic state) and the comparator with rationale and justification for the choice (absence of control(s) shall be justified).
* Methods and timing for assessing, recording, and analysing variables.
* Equipment to be used for assessing the clinical investigation variables and arrangements for monitoring maintenance and calibration.
* Duration of trial.
* Investigation sites: number, location, and, if appropriate, differences in investigation site environment.
* 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.

## INVESTIGATIONAL DEVICE(S) AND COMPARATOR(S)

Text

* Include the description of the exposure to the investigational device(s) or comparator(s), if applicable.
* List of any other medical device or medication to be used during the clinical investigation if not already specified in the instructions for use.
* Number of investigational devices to be used, and a justification.

## 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.

### Exclusion Criteria

Text

* Detail participant exclusion criteria.
* Ensure this information is consistent with information provided on IRAS.
* 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.

### 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. web-based).
* Use of equal or unequal allocation between treatment arms.
* If blinded, detail level of blinding.

## INFORMED CONSENT PROCESS

### 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.
* Total expected duration of the clinical investigation.
* Expected duration of each subject's participation.
* Number of subjects required to be included in the clinical investigation, and where needed, anticipated distribution of enrolment among the participating investigation sites.
* Relationship of investigation population to target population.
* Information on vulnerable, pregnant, and breastfeeding population, if applicable.

### 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.

### 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.

### 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.

### 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

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.

## PROCEDURES AND STUDY ASSESSMENTS

### Safety Assessments

Text

Detail and specific safety assessments required for the trial.

### 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 9.2

### 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 XXLab 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).***

### Monitoring Plan

Text

General outline of the monitoring plan to be followed, including access to source data and the extent of source data verification planned.

Note: It is possible to provide a detailed plan for monitoring arrangements separately from the CIP/CPSP.

During the initiation of the investigation site, the sponsor will ensure the investigators and the site study staff are trained on the device. The investigator is then responsible for ensuring that the investigation staff uses the device in the same way. All training will be documented in a Site Training Log.

The monitor will also ensure that the investigator and investigation site team have received and understood the requirements and content of:

* CIP or CPSP
* IB
* The informed consent forms
* eCRFs
* IFUs
* All written clinical investigation agreements as appropriate

# STATISTICAL DESIGN AND DATA ANALYSIS

## SAMPLE SIZE CALCULATION

Text

Sample size calculation and justification should take into account:

* + all relevant clinical data on outcome variable and effect size, if applicable;
	+ assumptions of expected outcomes across treatment groups, if applicable;
	+ adjustments due to any pre-planned interim analyses, if applicable;
	+ detectable effect size and non-inferiority margin, which shall be smaller than the detectable effect size and justified with reference to the effect of the comparator, if applicable;
	+ randomization allocation ratio (e.g. 1:1, 1:2), if applicable; expected drop-out rate, such as withdrawal, lost to follow-up, death (unless death is an endpoint).

All the statistical parameters and methods used to calculate sample size or the non-inferiority margin shall be clearly provided.

For exploratory and observational clinical investigations, in which the sample size is not required to be derived by calculation, the scientific rationale for the chosen sample size shall be provided.

Detail the sample size, precision or power calculation, dropout rates, relevant assumptions and justifications. Comment on an estimate of the recruitment period with justification that the required sample size will be achievable.

State if this information is detailed in a separate document.

## PROPOSED ANALYSES

Text

Description of and justification for statistical design and analysis of the clinical investigation shall cover the following.

* Descriptive statistics of baseline data, treatments, safety data and where applicable, primary and secondary endpoints.
* Analytical procedures including measures of precision such as confidence intervals, if applicable.
* The significance level and the power of primary endpoint(s) and the overall statistical testing strategy, if applicable.

If a hypothesis is tested, a significance level alpha 0,05 (two-sided) and 0,025 (one-sided) and powers between 0,8 and 1 minus alpha need no justification. Depending on the characteristics of the investigational medical device or the clinical investigation, higher or lower levels of significance can be used. Examples of justifications include but are not limited to: product standards, scientific reasons or discussion with regulatory authorities.

* The rationale for the number of procedures to be performed by a single user as part of the learning curve and how these data are to be analysed, if applicable.
* Pass/fail criteria to be applied to the results of the clinical investigation.
* The provision for an interim analysis, criteria for the termination of the clinical investigation on statistical grounds, where applicable.
* Management of bias and, when randomization, matching, or blinding are applied, plan for assessment of success thereof.
* Management of potential confounding factors (e.g. adjustment, stratification, or stratified randomization).
* Description of procedures for multiplicity control and adjustment of error probabilities, if applicable.
* The specification of subgroups for analysis, if applicable, or if response to treatment is expected to be different in these groups.
* Management, justification, and documentation of missing, unused or spurious data, including drop-outs.
* Exploratory analysis and sensitivity analysis (e.g. to explore robustness of results of primary and secondary analysis with respect to different methods used for handling missing data), if applicable.
* Procedures for reporting any deviation(s) from the original statistical analysis plan.
* For multicentre clinical investigations, a strategy for handling the potential imbalance of the numbers of subjects across investigation sites.
* A strategy for pooling data, if applicable.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:

# DATA COLLECTION AND MANAGEMENT

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.

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?
* 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 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 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](https://www.ed.ac.uk/information-services/research-support/research-data-service/after/datavault/why-use-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) and NHS Lothian (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.

# 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

The PI or designee, will record the non-compliance using the MHRA Deviation Log template. Details about the nature of the non-compliance, when it occurred, where it occurred, and any proposed corrective and preventative actions should be provided. The PI, or designee (e.g. Trial Manager, Research Nurse), will send the log to the Sponsor (QA@accord.scot) and MHRA (info@mhra.gov.uk) as soon as they have been made aware. New non-compliances will be added to the deviation log as they occur. 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) (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) 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.

* Outline the retention period and the reason for the length of time for the CIP/CPSP
* Please also refer to funders for any funding stipulations associated with retention of records.

All study documentation, e.g. CIP/CPSP, IB, CRF and clinical investigation report, will be kept for a minimum of 5 years from the protocol defined end of study point. The documentation should be incorporated into the device technical documentation under the quality management system of the manufacturer. 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.

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

The MHRA should be provided with a copy of the final clinical investigation/performance report within 1 year of the end of the clinical investigation or clinical performance. Please email the end of study report to CI-applications@mhra.gov.uk and copy the Sponsor(s) (QA@accord.scot).

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.

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).

##

## CONTINUATION OF DEVICE FOLLOWING THE END OF STUDY

Text

Detail arrangements for continuation of use of investigational device beyond the end of the trial. If none, provide justification.

# DEVICE ACCOUNTABILITY

Text

In this section there should be a description of the procedures for the accountability of investigational devices and the procedures and particular materials and instructions for the safe return of investigational devices, including those that are potentially hazardous.

Please note that the principal investigator or an authorized designee shall keep records documenting the following:

* name(s) of person(s) who received, used, returned, or disposed of the device;
* the date of receipt, identification, and quantity of each investigational device (batch number/serial number or unique code);
* ﻿﻿the expiry date, if applicable;
* the date or dates of use;
* subject identification;
* date on which the investigational device was returned/explanted from subject, if applicable;
* the date of return of unused, expired, or malfunctioning investigational devices, if applicable;
* the date and documentation of disposal of the investigational devices as per instructions of the sponsor, if applicable.

Written procedures shall be established for the entire process of device accountability.

# CLINICAL INVESTIGATION COMPLIANCE

Text

This section should include the following statements.

* Statement specifying that the clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.
* Statement specifying compliance with this document and any regional or national regulations, as appropriate.
* Statement specifying that the clinical investigation shall not begin until the required approval/favourable opinion from the Ethics Committee and Regulatory Authority have been obtained, if appropriate.
* Statement specifying that any additional requirements imposed by the Ethics Committee or Regulatory Authority shall be followed, if appropriate.

##

## 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 the device has accepted limited liability related to the manufacturing and original packaging of the study device 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 device, but not where there is any modification to the study device (including without limitation re-packaging and blinding).

# ADVERSE EVENTS, ADVERSE DEVICE EFFECTS, AND DEVICE DEFICIENCIES

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 risks and side effects that have been reported following use of the device can be found in the relevant Investigator’s Brochure (IB) and/or Instructions for Use (IFU).

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 participation in the trial 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 medical device (IMD).

A **serious adverse event** (SAE):

* 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.

An **Adverse Device Effect** (ADE) is an adverse event related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

An ADE includes any event that is a result of a use error or intentional misuse. Use error refers to an act or omission of an act that results in a different device response than intended by the manufacturer or expected by the user. An unexpected physiological response of the subject does not in itself constitute a use error.

**Serious Adverse Device Effect** (SADE) is an adverse device effect that has resulted in any of the characteristics of a SAE. This includes device deficiencies that might have led to a SAE if;

* suitable action had not been taken
* intervention had not been made
* if circumstances had been less fortunate

**Unanticipated Serious Adverse Device Effect** (USADE) is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the Investigator’s Brochure (IB).

**Device Deficiency** is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labelling.

## IDENTIFYING AEs, ADEs, SAEs AND SADEs

All AEs, ADEs, SAEs, SADEs and USADEs will be recorded in the participants medical records from the time a participant signs the consent form to take part in the study until the end of the follow-up period. Participants will be asked to contact their Investigator at any time after consenting to join the trial if any symptoms develop.

Participants will be asked about the occurrence of AEs/SAEs and SAE/SADEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE and SAE/SADEs 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 in the medical records. AE/ADEs and SAE/SADEs may also be identified via information from support departments e.g., laboratories, device software. In the case of an AE/ADE, the Investigator should initiate the appropriate treatment according to their medical judgment.

## RECORDING AEs, ADEs, SAEs AND SADEs

When an AE/ADE/SAE/SADE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital notes, laboratory, and diagnostic reports) related to the event. The Investigator or delegate will then record all relevant information in the SAE form (if the AE/ADE meets the criteria of serious). SAEs/SADES will be followed up until resolution or death of the clinical investigation participant. All AEs, ADEs, SAEs, SADEs and USADEs will be recorded in the participant's medical records. All AEs that are endpoints and all SAEs will also be recorded in the CRF.

Information to be collected includes 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, ADEs, SADEs AND USADEs

Seriousness, causality, severity and expectedness will be assessed by the Principal Investigator or another suitably qualified physician in the research team who has been delegated this role.

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

### Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 12.1.

### Assessment of Causality

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

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

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 ADE the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the IB – mention here the appropriate section of the document where the info can be found.

The event may be classed as either:

* **Expected**:the ADE is consistent with the effects of the device listed in the IB.
* **Unexpected**:the ADE is not consistent with the effects in the IB.

Anticipated potential risks are documented in relevant Technical File/Risk Assessment – section X. The risk analysis report can be found in section X (Risk Analysis) of the appropriate Investigators Brochure/Technical File/Device Risk Assessment.

In this section clearly mention the section of the IB/Technical File/other document where the potential risk is mentioned.

### Assessment of Severity

The Investigator will make an assessment of severity for each AE/ADE/SAE/SADE and record this on the CRF or SAE/SADE 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 SAEs/SADEs/USADEs

All adverse events for each participant will be recorded on the AE/SAE/USADE log. Additionally, it will be assigned the appropriate MedDRA Systems Organ Class (SOC)code *–* delete if investigation/performance does not require MHRA authorisation. Confirm who in the trial team will perform the MedDRA coding if it needs to be done

## REPORTING OF SAEs/SADEs/USADEs

Once the Investigator becomes aware that an SAE, SADE or USADE has occurred in a study participant, the information will be reported to ACCORD within 24 hours using Template report CR012-T01 SAE (Devices) Form.

SAE reports must provide an assessment of causality and expectedness (if required) at the time of initial reporting to ACCORD. Initial reports will be submitted within 24 hours of the investigator becoming aware of the event. If the Investigator does not have all information regarding an SAE or SADEs they should not wait for this additional information before notifying ACCORD. The SAE/SADE report form can be updated when the additional information is received. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

The SAE/SADE form will be transmitted by email to safety@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. To ensure patient confidentiality, SAE, SADE, and device deficiency reports will detail the trial participant number only.

Are there any onward reporting requirements for SAEs/SAEs/USADEs (e.g. to trial manager/device 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 device has a well-defined risks and effects will these events be captured as AEs? If some SAEs were mentioned as not to be reported in section 12.3.2 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).

Please include the following if reporting to MHRA is required:

ACCORD is responsible for reporting without delay to MHRA, all the following:

1. any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible
2. any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate

(c)  any new findings in relation to any event referred to in points (a) and (b)

A cumulative SAE reporting form will be used.

The research team are responsible for submitting a cumulative, quarterly SAE report to the MHRA ([Quarterly Summary Reports template](https://assets.publishing.service.gov.uk/media/66cda25bb0bac21caec708ed/QSR_Template_Guidance_v2.pdf)) providing an update on the latest overall safety profile of the device. This report should be reconciled with the Sponsor vigilance database prior to submission.

In addition, ACCORD is responsible for reporting any SAE that is related and unexpected (USADE) to the REC within 15 calendar days of the Sponsor becoming aware of the event. For medical devices this means the USADEs should be reported.

If only reporting to REC (e.g. medical devices that are UKCA/CE/CE UKNI marked for the purpose that is under investigation) include the following:

ACCORD is responsible for reporting any SAE that is related and unexpected (USADE) to the REC within 15 calendar days of the Sponsor becoming aware of the event. For medical devices this means the USADEs should be reported.

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

## DEVICE DEFICIENCIES

### Definition

**Device Deficiency** is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. Device deficiencies include malfunctions, use errors and inadequate labelling.

### Reporting of Device Deficiencies

All device deficiencies will be documented on the ACCORD CR012-T02 Medical Device Deficiency Form. Reports will be emailed as a .pdf file to Safety@ACCORD.scot within 7 days of being made aware of the Device Deficiency for Device Deficiencies that are not linked to a potential SAE and within 24h for Device Deficiencies linked to a potential SAE. Reports will be complete as far as possible and will be signed and dated by the Investigator.

On receipt of device deficiency reports, the Pharmacovigilance Officer, or designee, will assess the report to ensure the correct assessment has been made.

The Pharmacovigilance Officer, or designee, will send an email to confirm receipt of the Device deficiency report within 1 working day. If this email is not received within 1 working day of sending the report to ACCORD, the Investigator must email ACCORD to check that the report has been received by ACCORD

The Investigator is responsible for reporting device deficiencies to the relevant NHS Medical Physics department, if applicable.

Device deficiency reports emailed to ACCORD and any follow-up information and correspondence will be kept by the Investigator in the Investigator ISF and by the Sponsor in the Sponsor File or TMF.

### Device Quarantine

If the event is defined as serious i.e. a SAE or device deficiency that could have led to SADE or USADE the Investigator must quarantine the device as soon as possible e.g. segregating the device from other equipment and labelling as not for use with contact details attached.

Until the MHRA (if applicable) and Sponsor have been given the opportunity to carry out an investigation, all items (together with relevant packaging materials) should be quarantined. They should not be repaired, or discarded or returned to the manufacturer without agreement from the sponsor.

Medical devices should not be sent to the MHRA unless this has been specifically requested. Investigators should contact the manufacturer to obtain information relating to the procedure for returning the device, where considered appropriate.

The device should be cleaned, securely packaged, and clearly labelled, including the manufacturer reference number and CI details. Documentation regarding shipment and receipt of the device, where available, will be retained in the ISF.

## FOLLOW UP PROCEDURES

After initially recording an AE/ADE or recording and reporting an SAE/SADE, 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/SADE 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 log or additional information section of SAE/SADE 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).

# VULNERABLE POPULATION

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.

Include the description of:

* vulnerable population to be included in the clinical investigation.
* screening process to identify and protect the vulnerable population.
* specific informed consent process.
* Ethics Committee specific responsibility.
* what medical care, if any, will be provided for subjects after the clinical investigation has been completed.

# SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

Text

Include the following information.

* Criteria and arrangements for suspension or premature termination of the whole clinical investigation or of the clinical investigation in one or more investigation sites.
* Criteria for access to and breaking the blinding/masking code in the case of suspension or premature termination of the clinical investigation, if the clinical investigation involves a blinding/masking technique.
* Requirements for subject follow-up and continued care.

# 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) and according to ISO 14155 Clinical investigation of medical devices for human subjects – Good clinical practice and/or ISO 20916 IVD Clinical performance studies using specimens from human subjects – Good study practice.

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 non-objection is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the The Medical Devices Regulations 2002, as amended.

## NHS LOTHIAN MEDICAL PHYSICS

NHS Lothian Medical Physics (NHSLMP) Department are independent NHS physicists and engineers who facilitate the introduction of new clinical technology into healthcare, ensuring their safe and effective use. Medical physics experts will review the technical documentation for the medical devices involved in this study and perform physical inspection of the devices where required. The study will not begin until authorisation has been received from NHSLMP.

## 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 device, 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 device, 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 particular 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 usernames and passwords.

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

# 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 Clinical Investigation/Performance Study Report (CISR/CPSR) will be submitted to the Co-Sponsors and REC within 1 year of the end of the study. The Chief Investigator will provide the Report to ACCORD, for review, prior to finalization. The clinical investigation/performance 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 European clinical trials database within 1 year of the end of the study.

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