**Information on Clinical Research Study Protocol Template – please read before starting**

This template is available for use by all investigators who are carrying out clinical research studies to be reviewed by the Oxford Tropical Research Ethics Committee (OxTREC). However, there is no requirement to use this template, provided that an alternative GCP-compliant protocol is used. Other templates are available, for example, the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) protocol guidelines for minimum protocol content at <http://www.spirit-statement.org/spirit-statement/>

All advisory text is highlighted in yellow. This should be deleted before finalising the document. All sample text is in ‘basic text’ style. This text will of course be altered or deleted as required while you produce the draft. Where advisory text regarding <relevant possible options> is inserted into sample text, delete as needed.

Where a section is not relevant, this should be stated clearly, and the section header retained. There may be instances where rearrangement of the subsections within section 9 is appropriate, in order to match with the order of study processes. Instructional text for deletion/rearrangement is highlighted in blue.

Repetition of information throughout the protocol is not necessary; it may be useful to cross-reference other sections of the protocol to avoid repetition.

Should you require any assistance, please contact the OxTREC secretariat:

oxtrec@admin.ox.ac.uk

<https://researchsupport.admin.ox.ac.uk/governance/ethics/apply/oxtrec>

**Study Title:**  insert full title including brief reference to the design, disease or condition being studied, and primary objective

**Internal Reference Number / Short title:** This should be assigned by the investigator/department (may be deleted if not required)

**OxTREC Ref:** Insert

**Date and Version No:** Insert

|  |  |
| --- | --- |
| **Chief Investigator:** | Insert name and contact details, including institutional affiliation |
| **Investigators:**  | Insert names of key collaborators, including institutional affiliations |
| **Sponsor:**  | Insert name and address of Sponsor |
| **Funder:** | Insert details of organisation providing funding |
| **Chief Investigator Signature:**  | The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol |

**Statistician Signature:** For interventional studies provide statistician signature

Please declare any/no potential conflicts of interest.

**Confidentiality Statement**

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

**Optional page: Protocol signatures continued**

For multi-site research studies, the Principal Investigator at each site should sign below to document that the protocol has been read and understood before the protocol is filed in the site ISF. If the same PI covers more than 1 site both sites might appear here, but otherwise there is no requirement for signatures of multiple (or all) PI signatures to appear here together.

**Example**

**Trial Title:** insert full title

**Protocol Date and Version No**: insert

**Protocol signature page**

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |
| **Principal Investigator** (Please print name)  |  | **Signature** |  | **Site name or ID number**  |  | **Date** |

Following any amendments to the protocol, this page must be updated with the new protocol version number and date and re-signed by the site PI.

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# KEY CONTACTS

Insert full details of the key research project contacts including the following; please add/remove headings as necessary.

|  |  |
| --- | --- |
| **Chief Investigator** | Full contact details including phone, email and fax numbers |
| **Sponsor** | Name of, and full contact details including phone and email for, the organisation sponsoring this study  |
| **Funder(s)** | Names and contact details of all the organisations providing funding and /or support in kind for this study  |
| **Clinical Trials Unit** | Full contact details including phone, email and fax numbers (If applicable) |
| **Statistician** | Full contact details including phone, email and fax numbers |
| **Committees** | Name of each Committee Chair of each committeeFull contact details including phone, email and fax numbers for the Chair  |

# LAY SUMMARY

Include a lay summary here. Suggested length is approximately 300 words.

# SYNOPSIS

It may be useful to include a brief synopsis of the study for quick reference and/or to use as a standalone document. Complete information and, if required, add additional rows.

|  |  |
| --- | --- |
| Study Title |  |
| Internal ref. no. / short title |  |
| Study registration | Study identifier, registry name, registration number and date of registration. (Registration is encouraged for all studies but is mandatory for interventional studies. If the study will not be registered because it is non-interventional in nature state <<N/A non-interventional study>> here). See section 16.6: Transparency in Research.  |
| Sponsor  |  Name and address of Sponsor |
| Funder  | Names and contact details of all the organisations providing funding and /or support in kind for this study).  |
| Study Design |  |
| Study Participants |  |
| Sample Size | Where applicable include how many per arm / group |
| Planned Study Period | Include both the total length of the project and the duration of an individual participant’s involvement (intervention phase and all follow up – including any long term follow up via medical records etc.).  |
| Planned Recruitment period | Indicate start and end dates for recruitment |
|  | Objectives | Outcome Measures | Timepoint(s) |
| Primary |  |  |  |
| Secondary |  |  |  |
| Intervention(s) | Provide details of all investigational intervention(s) such as surgery, medicinal product that is not being tested, radiotherapy, investigational device or psychological therapy. |
| Comparator | Provide the relevant details of the comparator(s) here.  |

# ABBREVIATIONS

Define all unusual or ‘technical’ terms related to the project. Add or delete as appropriate to your study. Maintain alphabetical order for ease of reference.

|  |  |
| --- | --- |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CTRG | Clinical Trials & Research Governance, University of Oxford |
| GCP | Good Clinical Practice |
| ICF | Informed Consent Form |
| OxTREC | Oxford Tropical Research Ethics Committee |
| PI | Principal Investigator |
| PIL | Participant/ Patient Information Leaflet |
| REC | Research Ethics Committee |
| SOP | Standard Operating Procedure |

# BACKGROUND AND RATIONALE

Include the following adding sub headings if needed:

Summarise briefly the main characteristics of the disease being studied and any possible opportunity for better treatment and/or diagnosis. If and as applicable, include information on the current standard therapy (or current diagnostic standard) with an indication as to why a study of a new intervention (or new diagnostic tool/method) is needed.

Description of the population to be studied & the population whom the results of the project might be generalised to.

Name, description and characteristics of the study intervention (or diagnostic tool/method) (if applicable).

Provide a brief summary of findings from previous studies (if relevant) that potentially have clinical significance. State any assumptions you are making, and any limitations to the project.

Summary of the known and potential risks and benefits, if any, to human participants with a cross reference to the fuller detail provided in the safety reporting section if required.

Brief description of the rationale for undertaking the study with justification for the choice of the study intervention/device/diagnostic tool, and (as applicable) the mode of operation, treatment regimen, treatment period. If applicable, include explanation for the choice of comparators also.

References to literature and data that are relevant to the study and that provide background for the study.

# OBJECTIVES AND OUTCOME MEASURES

There is usually only one primary objective, the rest are secondary objectives.

The wording of the objectives and outcomes provided below should be clear, unambiguous and as specific as possible – the study will be judged on how, and how well, the objectives were satisfied. The definitions should include specific measurement variables (e.g., systolic blood pressure or Incidence and severity of adverse events or Disability Rating Index etc.,) analysis metrics (e.g., change from baseline measurement or time to event etc.,) and, where relevant, the time point for each outcome measure. Additional more detailed descriptions and definitions of outcomes for all primary and secondary outcomes may also be provided elsewhere in the protocol (e.g., in the statistics section) with a cross reference to the summary information here.

Complete table below with all relevant information.

Please ensure these are in accordance with those stated in the synopsis above and on the ethics application form.

|  |  |  |
| --- | --- | --- |
| **Objectives** | **Outcome Measures**  | **Timepoint(s) of evaluation of this outcome measure (if applicable)** |
| **Primary Objective**Example: To compare the effect of treatment A versus treatment B on the levels of protein X in the blood | Describe the outcome measures and how/when they will be measured during the study.Outcome measures should reflect the objectives. It is important that only one primary outcome measure is selected as it will be used to decide the overall results or ‘success’ of the study. The primary outcome measure should be measurable, clinically relevant to participants and widely accepted by the scientific and medical community.Assessments of outcome measures should be described in detail in section 11.Example: Concentration of protein X in blood samples from participants on each treatment arm. | Example: Blood sampling at day 0 and day 28 post-treatment |
| **Secondary Objectives**Example: To assess the safety of treatment A in <insert condition/population> | As above. Note each secondary objective should have a clear outcome measure.  |  |
| **Exploratory Objectives**Please add if applicable, otherwise delete this row | As Above |  |

# STUDY DESIGN

Briefly summarise the overall study design by type of study (e.g. double-blind, placebo-controlled, parallel design, open labelled, observational) and framework (e.g. superiority, equivalence, non-inferiority, exploratory). Avoid repetition, as full details will be given in later sections.

Briefly summarise the study setting (e.g., hospitals, healthcare clinics, academic centres etc.) indicating number of study sites, types of site (e.g., recruiting, providing intervention, continuing care etc.,) and naming the countries where trial data will be collected.

Give the expected duration of participant involvement providing concise details of the number of visits, including description of the sequence and duration of all trial periods e.g., screening, treatment, and post-treatment follow-up. Include a chart of the flow of the participant through the study (here, or as an appendix), if appropriate.

Briefly describe processes for collecting data, and why this method will be used, (e.g. type of equipment, questionnaire, interview schedule, observation schedule). Avoid repetition, as full details will be given in later sections.

Include a flowchart for the project as a whole (here, or as an appendix), if appropriate.

# PARTICIPANT IDENTIFICATION

## Study Participants

Give an overall description of the study participants.

Example:

Participants with <<medical condition>> of *xyz* severity and <<*other symptoms/disease specific criteria*> and/or healthy volunteers aged <<insert age>>.

## Inclusion Criteria

Example criteria only (amend as appropriate):

* Participant is willing and able to give informed consent for participation in the study.
* Male or Female, aged 18 years or above.
* Diagnosed with required disease/severity/symptoms, any specific assessment criteria for these, or, if healthy volunteer study: be in good health.
* Additional study specific criteria as required.

## Exclusion Criteria

Example criteria only (amend as appropriate):

The participant may not enter the study if ANY of the following apply:

* Specify any diseases/disorders/ conditions that would preclude entry into the study.
* Additional study specific criteria as required.
* Contraindication to MRI

Note: ensure each criterion is stated as either an inclusion or an exclusion criterion, but not as both. For example, it is not necessary to include ‘Male or female aged under 18’ among the example exclusion criteria above as this is already covered by the inclusion criterion ‘Male or female, aged 18 or above’.

# PROTOCOL PROCEDURES

Add a schedule of procedures and interventions (if applicable) including comparators (if applicable) here or as an appendix.

Describe all protocol procedures, non-clinical, clinical, and interventional (if applicable) and their comparators (if applicable) in detail in the designated sub-sections below. Change the order of sections as necessary updating the Table of Contents accordingly. Include visit numbers where appropriate (i.e., where there is more than 1 study visit).

## Recruitment

Describe how recruitment centres will be selected.

Describe how potential participants will be identified, approached, screened and recruited (registered and / or randomised).

## Screening and Eligibility Assessment

Specify the maximum duration allowed between screening and registration and/or randomisation (if applicable).

State that there will be no exceptions made regarding eligibility, i.e., that each participant must satisfy all the approved inclusion and exclusion criteria of the protocol. \* Note that changes to the approved inclusion and exclusion may be made by substantial amendment only.

Describe the screening procedures in detail, such as demographics, medical history, concomitant medication, physical examination, ECG, laboratory tests, biopsies and samples, scans.

Specify if rescreening will be permitted and any conditions or restrictions on this.

If any screening procedures require prior informed consent, (such as blood or urine sampling) then this screening section should be moved to between ‘Informed Consent’ and ‘Randomisation’. If participants are first consented and then registered to the study for screening purposes before being later randomised to a study arm, then place the screening and eligibility section between ‘Informed Consent’ and ‘Registration’. If applicable, provide details of how the registration procedure relates to the randomisation procedure.

## Informed Consent

You need to specify who will take informed consent, how and when it will be taken. Informed Consent must be obtained prior to any study related procedures being undertaken. In the example below participant\* can be substituted by parent/guardian or legally authorised representative, as appropriate, make sure that the term is consistent throughout the document.

Example:

The \*participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their healthcare provider or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant-dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

## Randomisation

If the study is not randomised, include a clear statement to that effect and change the section header to Registration or Enrolment as appropriate. Provide details of the study registration / enrolment procedure here (e.g., web-based registration system) notification system and instructions for sites if required.

If applicable, describe how randomisation is going to be carried out for the study. Specify the method for generating the randomisation schedule / allocation sequence (e.g., block allocation, simple computer generated random numbers, stratified randomisation) and include details of how this will be implemented for the study (sequentially numbered list, sealed envelopes, telephone or web-based randomisation system). Where computerised systems are used, will there be need for a paper-based back up randomisation procedure for use in emergencies?

Specify who will design the randomisation schedule (e.g., statistician, CRO) and who will hold the allocation code (e.g., named independent organisation or individual). Provide details on the timing for randomisation in terms of the participant’s study schedule. Will randomisation be done at the same visit as the baseline visit for example, or must participants return for a randomisation visit? Will there be a run-in period? State who will receive notification of a new participant/new randomisation, (e.g., CI, site PI, central trial manager) and provide details as to how this will be communicated to them.

## Blinding and code-breaking

In a blinded study, specify who it is that is blinded to the allocation; e.g., the participant and/or the treating clinician; the central research team; the (independent) outcome assessors. Describe the steps taken to conceal the treatment/intervention allocation from the blinded parties. For example, it may be necessary that the full details of the method of randomisation not appear in the protocol document, that such information be held separately and confidentially.

If the clinical condition of a participant necessitates breaking the allocation code, describe the procedures for this (who will do this, and how). For example, will individual envelopes per participant per period be supplied so that the code may be broken for a single participant without unblinding the whole trial? Or will the protocol specified party access the randomisation schedule if required by the Investigator and supply the needed information?

If out of hours code-breaking will not be required due to the risk level of the study intervention, state this and justify the decision.

If there is no blinding in the study, and/or no code breaking procedure, please state that clearly and retain the section header.

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

N.B - Interventions are procedures that affect physiology or psychology and include, for example, administration of a drug, surgical procedures, or psychological therapy. Blood tests and biopsies are ‘invasive’ procedures but are not considered to be interventions.

If there is no study intervention and/or comparator, please state that clearly, retain the section header, and move to the description of study procedures.

### Description of study intervention(s)

Name and describe any study intervention(s) including details of study surgical procedure(s), investigational device(s), radiotherapies, psychological therapies etc., with indication of the schedule of interventions and/or treatment period(s).

Delete subsection header if not required.

### Description of comparator(s)

Name and describe any study comparator(s) including details of standard of care surgical procedure(s), comparator device(s), scanning techniques, diagnostic standards etc., with schedule of procedures and / or treatment period(s).

Delete subsection header if not required.

### Description of study procedure(s)

Describe any study clinical procedure(s) including name(s) of scanning techniques, biopsy types, physical examination, sample taking, questionnaires, investigational device, investigational assays etc.

Example: Investigational device.

If an investigational device is being studied, consider using the sub-headers (a) – (d) suggested below to provide the necessary information about the device either in the *Description of study procedure(s)* section, or the *Description of study intervention(s)* as appropriate to the intended purpose of the investigational device.

(a) *Device description*, including summary information (name of device, name of manufacturer etc.); intended purpose; materials and construction; mode of operation; manufacture of device; training needed before use.

(b) *Device safety*: risks to users and/or precautions required;

(c) *Maintenance and storage of device*: Description of any required storage conditions for the device. If applicable, describe how the device is cleaned / re-sterilised. Describe any maintenance issues for the device.

(d) Device accountability. Note: if the device is to be taken home by participants ensure the PIS is clear on whether the device must (or need not) be returned to the research team at the end of study participation. Consider including the return of the device as part of the description of the last study visit.

If no investigational device is used, please delete this example entirely.

Example: MRI procedure

Imaging procedure: Once contraindications to magnetic resonance imaging are excluded by use of the facility’s screening forms, the risks of undergoing a scan are minimal. A trained scanner operator or radiographer will go through a list of possible risks with the participant before scanning. The MRI scanner consists of a large powerful magnet. Magnetic resonance imaging uses no ionising radiation. There are, however, potential hazards associated with MRI and the scanning of participants including the presence of surgical implants, participants’ clothing, jewellery (such as body piercings) bodily habitus, or medical conditions. A comprehensive list of potential risks has been compiled, and the participant should be checked against this by the operator, prior to entering the controlled areas of the MRI scanners. During the actual scanning procedure, the scanner produces loud banging noises and the participant will be given suitable hearing protection (earplugs). There is a small mirror that will allow them to see out of the scanner. During the experiment, the participant will be able to communicate with the operator in the control room. In addition, they will be given a call button, which allows them to alert the operator at any time. People with a history of claustrophobia may be excluded from participation in the study. All participants will still be introduced carefully to the scanner and allowed to leave at any stage, should they wish to do so. Once in the scanner, participants will be able to indicate immediately if they wish the scanning to cease by pressing a call button in their hands.

If no MRI is used, please delete this example entirely.

## Baseline Assessments

Specify (and describe if not detailed above) all baseline assessments. They must reflect the objectives and outcome measures.

If there will only be one study visit, this section should be renamed ‘Study Visit’ and full details of this visit be included. The next section ‘Subsequent Visits’ can be marked not applicable and the section header retained.

## Subsequent Visits

Specify when participants will be followed up and what assessments will be conducted. Specify if they are clinic visits, telephone assessments, or home visits by the study staff. Add visit numbers and window periods if applicable. **Clearly number these visits.** Ensure consistency with the PIS description of the study visits.

For each visit, list appropriate assessment, procedure and/or intervention (with comparator details if appropriate), and consider inclusion of the following, where appropriate. Refer to the study schedule (appendix):

* eligibility check
* assessment of outcome measures
* assessments of safety including general (e.g. physical examination), specific safety assessments (e.g. specific laboratory tests according to the applicable product information and/or population) and adverse event collection
* assessments of compliance with the study intervention (if applicable) and/or comparator (if applicable)
* recording of concomitant medications and/or psychological therapies (if applicable)

## Sample Handling

If not detailed previously, describe the samples that will be taken from each participant (e.g. blood, urine, tissue, etc.,) the volume of sample, and the frequency of sampling. It should be clear whether the samples referred to in the protocol are taken as part of a standard of care pathway with the results accessed by the research team or are research samples for analysis under this protocol and/or ancillary studies or are taken for future research. Consider using separate sections such as:

### 9.9.1 Sample handling for study purposes (delete subsection header if not required)

### 9.9.2 Sample handling for tissue bank (delete subsection header if not required)

### 9.9.3 Sample handling for standard of care (delete subsection header if not required)

In each applicable subsection provide brief details as to how the sample will be processed and stored once taken; who for example will have access to the samples (i.e. Study team only for this project, or will it be stored long-term for use in future ethically approved studies), and duration of storage (destroyed following local analysis; stored for 12 months following end of the study etc.). If the samples will be transferred to another organisation, state this clearly providing the name of the receiving institution and the country in which that organisation is situated. Provide an overview of the laboratory analyses that will be performed. Ensure that the appropriate information is included in the participant information sheet with corresponding clause(s) on the consent sheet(s). Note, if samples are being biobanked a separate information sheet and consent form for the biobank is required.

If no samples will be taken, please state that clearly and retain the main section header.

## Early Discontinuation/Withdrawal of Participants

Example:

During the course of the study a participant may choose to withdraw early from the study treatment at any time. This may happen for several reasons, including but not limited to:

* The occurrence of what the participant perceives as an intolerable AE.
* Inability to comply with study procedures
* Participant decision

Participants may choose to stop treatment and/or study assessments but may remain on study follow-up.

Participants may also withdraw their consent, meaning that they wish towithdraw from the study completely. In the case of withdrawal from both treatment and active follow up consider the following options for a tiered withdrawal from the study. Not all the options may be relevant to your study. The options elected for use in the study must be covered in the participant information sheet.

According to the design of the study, participants may have the following three options for withdrawal;

1. Participants may withdraw from active follow-up and further communication but allow the study team to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care; i.e., CT-Scans, blood results and disease progression data etc.
2. Participants can withdraw from the study but permit data and samples obtained up until the point of withdrawal to be retained for use in the study analysis. No further data or samples would be collected after withdrawal.
3. Participants can withdraw completely from the study and withdraw the data and samples collected up until the point of withdrawal. The data and samples already collected would not be used in the final study analysis. (Any limits to this type of withdrawal where, for example analysis of their data or samples has already been integrated into interim results, should be explained in the participant information sheet).

In addition, the Investigator may discontinue a participant from the study treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

delete/add as appropriate

* Pregnancy
* Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
* Significant protocol deviation
* Significant non-compliance with treatment regimen or study requirements
* Clinical decision

Specify what follow up of participants that have withdrawn from treatment will consist of.

Provide justification for any procedures and observations that will be required following a complete withdrawal (e.g., clinic visits during a safety follow up period) or that will continue to be required of all participants until the end of the study; for example, would investigators be required to follow up SAEs until resolution or end of study? Ensure that the appropriate information on these arrangements is included in the participant information sheet.

Wherever possible the data of randomised participants (or registered/enrolled participants in the case of non-randomised studies) should be analysed. State whether withdrawal from the study treatment will result in exclusion of the data for that participant from certain analyses. (Note that intention-to-treat analyses and analysis of all participants receiving the study treatment (e.g., most safety analyses) may require admission of data to analysis for participants that are withdrawn from treatment)

State whether or not withdrawn participants will be replaced and describe the conditions and limitations for this.

The type of withdrawal and reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for <follow-up visits or telephone calls until the adverse event has resolved or stabilised>.

## Definition of End of Study

The definition of end of study must be provided. In most cases the end of study will be the date of the last visit of the last participant. Where long term follow up of participants is planned, the end of study must include that follow-up period.

Example:

The end of study is the point at which all the study data has been entered and queries resolved.

# SAFETY REPORTING

Consider whether the study methodology, especially interventions or clinical investigations, could possibly be associated with any serious adverse events. If yes, then include (as a minimum) this section and sub-sections, otherwise make a clear statement here justifying why safety reporting is not applicable to the study and retain the main section header only (subsections 10.1 & 10.2 would be deleted in that circumstance).

Where safety reporting is applicable to the study, define the safety reporting window with a clearly defined starting point (e.g., from time of consent, from first administration of the study intervention etc.) and clearly defined end point (e.g. point that the participant completes the study, end of study overall).

Confirm the limit of investigator follow up of SAEs (e.g., follow up until event resolution or stabilisation, to participant completion of the study, to study end etc.). Confirm if the follow up requirement is the same for all SAEs or differs for some events (e.g., follow up until event resolution required for related events only).

## Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

* results in death
* is life-threatening
* requires inpatient hospitalisation or prolongation of existing hospitalisation
* results in persistent or significant disability/incapacity
* consists of a congenital anomaly or birth defect.

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

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

## Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the relevant local authorities following local reporting requirements and timelines <insert details> where in the opinion of the Chief Investigator the event was ‘related’ (resulted from administration of any of the research procedures) and ‘unexpected’ in relation to those procedures. Reports of related and unexpected SAEs should also be copied to OxTREC within 7 working days of the Chief Investigator becoming aware of the event.

# STATISTICS AND ANALYSIS

This section should be written by the statistician associated with the study.

State whether a Statistical Analysis Plan (SAP) is to be produced separately, and if it is then condense the most relevant information from the SAP sub sections at 11.1 below; otherwise provide full details below of the planned analyses. The sub-headings given below are suggestions. Sub-headings that are not applicable may be deleted entirely.

## Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan that will be available from the time <that the first participant is recruited>. The SAP will be finalised before <any analysis> takes place.

Or

The plan for the statistical analysis of the study are outlined below. There is not a separate SAP document in use for the trial.

(delete as appropriate)

## Description of the Statistical Methods

Describe the statistical methods to be employed for analysing primary and secondary outcomes. If not provided elsewhere detailed descriptions and definitions of outcomes for all primary and secondary outcomes should be provided here including specific measurement variables, analysis metrics and, where relevant, the time point for each outcome measure. If already described elsewhere, provide cross reference to the relevant protocol section.

## Sample Size Determination

State the estimated number of participants required to demonstrate the study objectives. (Note it is the primary outcome that determines the sample size needed).

Justify choice of sample size, i.e., how was it determined including reflections on (or calculations of) the power of the study, any statistical assumptions, or clinical justifications (where for e.g., the sample size was not arrived at statistically, due to rarity of the disease etc.).

Take into account any potential withdrawals.

## Analysis populations

Describe the selection of participants to be included in the analyses e.g. all participants as randomised / registered / enrolled (intention to treat); all participants who underwent the intervention (an adverse event analysis); all eligible participants (a per protocol analysis); all ‘evaluable’ participants (define ‘evaluability’) etc. If applicable, will data be included from participants who have been unblinded?

## Decision points

Provide details of any interim analysis, including schedule and description of why the interim analyses are to be performed at those time points (as the basis for specified dose / treatment escalating decisions or stopping decisions for example). Confirm who will have access to the results and who will make any decisions based on the results.

## Stopping rules

Describe any formal stopping rules for futility, efficacy or lack of power. Confirm who would make the final decision to terminate the trial.

## The Level of Statistical Significance

State the level of significance to be used.

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

Briefly describe the procedure(s) to be used for handling of spurious or missing or unused data (e.g. use of multiple imputation, random effects models or complete case analyses). Describe any possible biases these techniques may introduce. Cross refer to the Data Management Plan (if applicable).

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

Detail procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

## Health Economics Analysis

If a health economics analysis is to be undertaken, include the rationale for inclusion of the economic investigation and means of assessment here. (To be written by the health economist).

# DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

Or

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

(Delete as appropriate)

## Source Data

Define what will comprise source documents

Example:

Source documents are where data are first recorded, and from which participants’ CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

## Access to Data

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

## Data Recording and Record Keeping

Describe method(s) of data collection, entry and management, including details of data management tools, for example CRF software, etc.

Example:

All trial data will be entered on <to paper CRFs and/or a <<*quote software and validation procedure*>>. Note that GCP (Section 5.5) requires that electronic data entry systems are validated and that Standard Operating Procedures are maintained.

The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

Describe where, and for how long, data will be retained

If no identifiable, personal data will be retained centrally (i.e. by the sponsoring organisation), but rather this will be held at individual sites **only**, please state this explicitly.

If identifiable personal data may be transferred during or after the study please be aware that under GDPR, it is necessary to assure against the risks that are presented by this processing, i.e., risks of accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to the personal data transferred and stored or otherwise processed by the recipient. This is true for paper based and electronic data transfers. Recommendation: when transferring personal data particularly sensitive personal data, use an appropriately secure communications procedure. University of Oxford Researchers: For detailed practical guidance see the University of Oxford’s *Information Security Handling Rules* @ <https://www.infosec.ox.ac.uk/asset-management>

If your study will collect samples and intends to make further use of these beyond the study, please be aware that the consent form will need to be retained for the life of the sample to meet HTA traceability requirements.

If participants are given the option to be approached for future research, please be aware that under GDPR, it is necessary to retain the consent form as the basis for retention of details and future approach. Those contact details should be held securely, separately from the research data, and kept updated.

Ensure compliance with the relevant Sponsor organisation’s policy. For University of Oxford sponsored studies please refer in particular to the University of Oxford’s:

Data Protection Checklist <https://researchsupport.admin.ox.ac.uk/policy/data/checklist>

Practical Considerations <https://researchsupport.admin.ox.ac.uk/policy/data/practical>

Cross refer to the Data Management Plan (if applicable).

# QUALITY ASSURANCE PROCEDURES

Provide details of how data monitoring and other quality control measures will be performed, and who will undertake these activities.

Example

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

In addition, depending on the complexity, scale and risks inherent to the research study the quality assurance procedures may include a risk adaptive approach based on a formal risk assessment, planned monitoring activities (onsite and / or central monitoring) and the involvement of a number of study oversight committees. If there are alternative provisions to those in the subsections below provide the details in further dedicated sub-sections.

## Risk assessment

Example:

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

For University of Oxford sponsored studies: if no formal risk assessment will be will be undertaken, please state that clearly providing the justification for this. Delete the example text and retain the sub-section header.

## Study monitoring

Describe arrangements for GCP monitoring

Example:

Regular monitoring will be performed according to the study specific Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the study specific Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. Cross refer to the trial Risk Assessment and Monitoring Plan document.

Where the primary or secondary endpoints are associated with data requiring expert analysis and/or interpretation, e.g., pathology slides, image analysis, the verification of those key data points by independent expert, committee or a monitor with the appropriate expertise should be addressed in the risk assessment, monitoring plan and where applicable the protocol.

If no GCP monitoring will be undertaken, please state that clearly, providing justification for this. Delete the example text and retain the sub-section header.

## Study Committees

Provide a separate subsection below for each committee in place for the study, for example the Study Management Group, Safety Committee, Data Monitoring Committee, Steering Committee etc. Not all of these committees may be required where the study is smaller, logistically simple and low risk. Describe the role(s), frequency of meetings and composition of the study committee(s) in place for the study. If there are no oversight committees, please state that clearly, providing justification for this. Retain the sub-section header.

# PROTOCOL DEVIATIONS

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

A standard operating procedure should be in place describing the procedure for identifying non-compliances, escalation to the central team and assessment of whether a non-compliance /deviation may be a potential Serious Breach.

# SERIOUS BREACHES

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

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

(b) the scientific value of the research.

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

# ETHICAL AND REGULATORY CONSIDERATIONS

## Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki. NB. The 2008 Declaration of Helsinki provides detail on what must be included in a protocol: funding, sponsorship, affiliations and potential conflicts of interest, incentives to participate and compensation for harm.

## Guidelines for Good Clinical Practice

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

## Approvals

Consider the following text:

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to the appropriate Research Ethics Committees (RECs), regulatory authorities, and host institutions for written approval.

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

## Other Ethical Considerations

Include any other general and study-specific ethical considerations, e.g. involvement of vulnerable participants, or participants who are unable to consent for themselves.

For studies involving imaging technologies, such as MRI, CT scans etc., consider adding:

In the unlikely event of seeing any structural abnormalities on a scan, the scan will be checked by a clinical specialist. If the specialist feels that the abnormality was medically important, they will discuss the implications with the participant and arrange for further investigations as necessary. Participants will not be informed unless the doctor considers the finding has clear implications for their current or future health. It is important to note that scans are not carried out for diagnostic purposes, and therefore the scans are not a substitute for a clinical appointment. Rather, the scans are intended for research purposes only.

## Reporting

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

## Transparency in Research

For interventional trials\* a statement of registration and undertaking to keep trial data up to date and results publicly available is required.

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

\*Note the WHO definition of a clinical trial is “*For the purposes of registration, a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc”.*

For other types of clinical research, registration is also encouraged wherever possible. Non-interventional studies may use the template text above if they wish to report their voluntary registrations and undertakings to make the results of their research public, or they may mark the section non-applicable.

If the section is not applicable, state ‘not applicable the research is non-interventional’ and retain the section header

## Participant Confidentiality

Example:

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), <with the exception of the CRF, where participant initials may be added>.  All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants’ personal data.

For University of Oxford sponsored studies please refer in particular to the University of Oxford’s:
Data Protection Checklist <https://researchsupport.admin.ox.ac.uk/policy/data/checklist>

Practical Considerations <https://researchsupport.admin.ox.ac.uk/policy/data/practical>

## Expenses and Benefits

Detail all intended payments to participants and any other benefits (Declaration of Helsinki requirement).

Example:

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

# FINANCE AND INSURANCE

## Funding

Describe financing arrangements, including all the organisations providing finance and /or support in kind for this trial.

## Insurance

Describe insurance arrangements

*For University of Oxford sponsored studies:*

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

If the study is sponsored by an organisation other than the University of Oxford, please provide details of the insurance arrangements put in place by that organisation.

## Contractual arrangements

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

# PUBLICATION POLICY

The publication policy should cover authorship, acknowledgements, and review procedures for scientific publications. If there is a department or institution policy, or agreement, the protocol can refer to it.

Ensure that the publication policy stated here is consistent with any contract applicable to the study. Consider describing how study results may be disseminated to study participants.

Example:

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by <insert name>. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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

*For University of Oxford sponsored studies:*

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

If the section is not applicable state ‘not applicable’ and retain the section header.

# ARCHIVING

Describe the arrangements for archiving the study including location and duration of storage. These details should correspond with those provided in the participant information sheet.

# REFERENCES

Insert references used in text (preferably numbered, or in alphabetical order of first author).

# APPENDIX A: STUDY FLOW CHART

Optional

# APPENDIX B: SCHEDULE OF STUDY PROCEDURES

*Optional* Alter as required, delete if not wanted

|  |  |
| --- | --- |
| **Procedures** | **Visits (insert visit numbers as appropriate)** |
| **Visit timing****e.g. Day 0** | **e.g. Day 7** |  |  |  |
| **Screening** | **Baseline** |  |  |  |
| Informed consent |  |  |  |  |  |
| Demographics |  |  |  |  |  |
| Medical history |  |  |  |  |  |
| Physical examination |  |  |  |  |  |
| ECG |  |  |  |  |  |
| Laboratory tests |  |  |  |  |  |
| Eligibility assessment |  |  |  |  |  |
| Randomisation |  |  |  |  |  |
| Assessment 1 (*describe*) |  |  |  |  |  |
| Assessment 2 (*describe*) |  |  |  |  |  |
| Assessment 3 (*describe*) |  |  |  |  |  |
| Assessment 4 (*describe*) |  |  |  |  |  |
| Adverse event assessments  |  |  |  |  |  |

# APPENDIX C: AMENDMENT HISTORY

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Amendment No.** | **Protocol Version No.** | **Date issued** | **Author(s) of changes** | **Details of Changes made** |
|  |  |  |  |  |

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC submission.