**Information on Clinical Trial Protocol Template – please read before starting**

This protocol template has been designed primarily for Clinical Trials which are subject to the Medicines for Human use (Clinical Trials) Regulations 2004, and Amendments. It has been specifically adapted for non-commercially sponsored studies.

An algorithm is available to help you decide whether or not your trial is a Clinical Trial under the regulations. This is usually, but not always, sufficiently helpful, especially regarding studies involving Healthy Volunteers.

See <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/317952/Algothrim.pdf> If you remain unsure about your trial, RGEA or OUH R&D staff will be happy to advise you.

The template is available for use by all investigators who are carrying out clinical trials sponsored by the University of Oxford or Oxford University Hospital (OUH) NHS Foundation Trust if they so wish. However, there is no requirement to do so, 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/> or guidance available via the HRA protocol development tool at <https://www.hra.nhs.uk/planning-and-improving-research/research-planning/protocol/>

All advisory text and quotations from GCP are highlighted in yellow. These should all be deleted before finalising the document. All sample text is in ‘basic text’ style. This text of course will 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 trial processes. Instructional text for deletion/rearrangement is highlighted in blue.

For trials involving Dose Escalation (DE) the procedure for how DE will be conducted should be defined transparently in the protocol and /or a separate document (such as a standard operating procedure, charter, study specific plan etc.). This template protocol would need to be modified to detail the DE process, inserting new sections and subsections as needed.

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, contact either RGEA (University) or OUH R&D as early as possible in the planning stage:

https://researchsupport.admin.ox.ac.uk/contacts/rgea<https://www.ouh.nhs.uk/researchers/default.aspx>

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

**Short title:** This should be assigned by the Investigator/department (may be deleted if not required)

**Ethics Ref:** Insert

**IRAS Project ID:** Insert

**Note: The study should be registered on at least one of the following registries**

**CTIS Number:** Insert

**ISRCTN Ref:** Insert

**ClinicalTrials.gov Ref:** Insert

**Date and Version No**: Insert

|  |  |
| --- | --- |
| **Chief Investigator:** | Insert name and contact details, including institutional affiliations |
| **Investigators:** | Insert names of key collaborators, including institutional affiliations |
| **Statistician:** | Insert name and contact details, including institutional affiliations |
| **Sponsor:** | Oxford University Hospitals NHS Foundation Trust/University of Oxford Delete as appropriate  (Address of Sponsor) |
| **Sponsor Reference:** | Insert Sponsor PID |
| **Funder:** | Insert details of organisation(s) providing funding  (Address of Funder) |
| **Funder Reference** | Insert funder reference if available |
| **Chief Investigator Signature:**  **Date Signed** | The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol |
| **Statistician Signature:**  **Date Signed** |  |

Please declare any/no potential conflicts of interest of any investigator

Please refer to the University of Oxford Conflict of Interest policy (<https://compliance.admin.ox.ac.uk/conflicts-of-interest> and ). Any potential conflict of interest must be discussed with the departmental HAF and a conflict of management plan must be in place.

For Oxford University Hospitals NHS Foundation Trust, please discuss any concerns over potential conflicts with R&D.

**Confidentiality Statement**

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

**Optional page: Protocol signatures continued**

For multi-site trials, 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 (amend as appropriate):

**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 TRIAL CONTACTS

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

|  |  |
| --- | --- |
| **Chief Investigator** | Full contact details including phonenumber and email address. |
| **Sponsor** | Oxford University Hospitals NHS Foundation Trust/University of Oxford Delete as appropriate  Full contact details including phone number and email address. |
| **Funder(s)** | Names and contact details of all the organisations providing funding and /or support in kind for this trial. |
| **Clinical Trials Unit** | Full contact details including phone numbers and email address. A UKCRC accredited CTU is required for all Clinical Trials falling under UK Clinical Trials and Medical Devices regulations that are sponsored by the University of Oxford. or OUH NHS Foundation Trust. (If applicable) |
| **Statistician** | Full contact details including phone numbers and email addresses. |
| **Committees** | Head of committee  Full contact details including phone numbers and email addresses |

# LAY SUMMARY

It may be useful to include a copy of the lay summary from the IRAS form here. Suggested length is 300 words, as per question A.9 in IRAS Combined Review.

# SYNOPSIS

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

|  |  |  |  |
| --- | --- | --- | --- |
| Trial Title | Please ensure this is in accordance with the title page and the IRAS form | | |
| Internal ref. no. (or short title) | Please ensure this is in accordance with the title page and the IRAS form | | |
| Trial registration | Trial identifier, registry name, registration number and date of registration. If not yet registered, name of intended registry. | | |
| Sponsor | Oxford University Hospitals NHS Foundation Trust/University of Oxford Delete as appropriate  ( | | |
| Funder | Names and contact details of all the organisations providing funding and /or support in kind for this trial. If unsure of whether an organisation is a funder in-kind, contact your contracts specialist or RGEA/R&D.. | | |
| Clinical Phase |  | | |
| Trial Design |  | | |
| Trial Participants |  | | |
| Sample Size |  | | |
| Planned Trial Period | Include both the total length of the project (including analysis period) and the duration of an individual participant’s involvement (intervention phase and all follow up – including any long term follow up via medical records and registries etc.). | | |
| Planned Recruitment period | Indicate start and end dates for recruitment | | |
|  | Objectives | Outcome Measures | Timepoint(s) |
| Primary | List one primary objective. | List primary outcome measure(s) |  |
| Secondary |  |  |  |
| Intervention(s)   * IMP(s) * nIMP(s) * Other intervention(s) | Provide Formulation, Dose, Route of Administration for each named Investigational Medicinal Product(s)  Where applicable, provide details of non- Investigational Medicinal Product(s) used in the trial.  If there is an additional investigational intervention such as radiotherapy, surgery or device use provide the relevant details here in addition to the IMP details above. | | |
| Comparator | Provide Formulation, Dose, Route of Administration for each named comparator | | |

# ABBREVIATIONS

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

|  |  |
| --- | --- |
| AE | Adverse event |
| AR | Adverse reaction |
| CI | Chief Investigator |
| CRA | Clinical Research Associate (Monitor) |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| CT | Clinical Trials |
| CTA | Clinical Trials Authorisation |
| CTIMP | Clinical Trial of an Investigational Medicinal Product |
| CTU | Clinical Trials Unit |
| CUREC | Central University Research Ethics Committee |
| DMC/DMSC | Data Monitoring Committee / Data Monitoring and Safety Committee |
| DSUR | Development Safety Update Report |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| HRA | Health Research Authority |
| IB | Investigators Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IMP | Investigational Medicinal Product |
| ISF | Investigator Site File |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| NHS | National Health Service |
| OUHFT | Oxford University Hospitals NHS Foundation Trust |
|  |  |
| PI | Principal Investigator |
| PIS | Participant/ Patient Information SheetSheet |
| PRN | ProReNata (taken as required) |
| PV | Pharmacovigilance |
| R&D | NHS Trust Research & Development Department |
|  |  |
| REC | Research Ethics Committee |
| RGEA | Research Governance, Ethics and Assurance |
| RSI | Reference Safety Information |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SDV | Source Data Verification |
| SMPC | Summary of Medicinal Product Characteristics |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMF | Trial Master File |
| TSG | Oxford University Hospitals NHS Foundation Trust / University of Oxford Trials Safety Group |
| USM | Urgent Safety Measure |

# 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. Include information on the current standard therapy with indication as to why a trial of a new intervention is needed.

Description of the population to be studied.

Name, description and characteristics of the investigational medicinal product(s) (may include mechanism of action). For CTIMPS, indicate whether or not the IMP has a marketing authorisation in the UK /or in a EU member.

Provide a brief summary of findings from non-clinical studies (if relevant) that potentially have clinical significance and from other clinical trials relevant to this trial.

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 trial with justification for the choice of the trial intervention/IMP(s), and the route of administration, dosage, dosage regimen, and treatment period. If applicable, include explanation for the choice of comparators also.

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

For early phase studies, clearly state the number of patients who have already received the IMP(s).

# OBJECTIVES AND OUTCOME MEASURES

There should be 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 trial 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 IRAS 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 trial.  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 trial. 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 9.  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 |  |
| **Exploratory Objectives** Please add if applicable, otherwise delete this row | As Above |  |

# TRIAL DESIGN

Briefly summarise the overall trial design by type of trial (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 trial settings (e.g., hospitals, GP surgeries, care homes, academic centres etc.) indicating whether multicentre or single centre, types of site (e.g., recruiting, providing intervention, continuing care etc.,) and, where there are non-UK sites 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.

For trials involving Dose Escalation (DE) define an absolute minimum for review in terms of numbers of participants and data to be reviewed. This should be its own section within the protocol. Note: It will be assumed that all participants in the cohort and all data at all the timepoints will be reviewed in the DE decision meeting, unless the protocol states otherwise.For guidance on GCP-compliant Dose Escalation plans see:

<https://mhrainspectorate.blog.gov.uk/2018/11/26/dose-escalation-is-it-gcp-compliant/> <https://www.ema.europa.eu/news/revised-guideline-first-human-clinical-trials>

# PARTICIPANT IDENTIFICATION

## Trial Participants

Give an overall description of the trial 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):

An individual may only enter the trial if all of the following apply:

* Willing and able to give informed consent for participation in the trial.
* Aged 18 years or above.
* ‘Male or FemaleAny sex’
* Diagnosed with required disease/severity/symptoms, any specific assessment criteria for these, or, if healthy volunteer trial: be in good health.
* (Alter as required) Stable dose of current regular medication (specify type if needed) for at least 4 weeks prior to trial entry. If healthy volunteer trial: have had no course of medication, whether prescribed or over-the-counter, in the four weeks before first trial dose and no individual doses in the final two weeks other than mild analgesia, vitamins and mineral supplements or, for females, oral contraceptives.
* Individuals of child bearing potential and males whose partner is of child bearing potential must be willing to ensure that they or their partner use effective contraception during the trial and for 3 months thereafter\*.
* Clinically acceptable laboratory and ECG results (specify any other additional assessments) within <insert duration> of enrolment.
* In the Investigator’s opinion, is able and willing to comply with all trial requirements.
* Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the trial.
* Additional trial specific criteria as required.

\* NOTE where the use of effective contraception is a protocol requirement a section on Contraception and Pregnancy should be added to the safety reporting section with corresponding information in the Participant Information Sheet.

## Exclusion Criteria

Example criteria only (amend as appropriate):

An individual may not enter the trial if ANY of the following apply:

* Pregnant, lactating or planning pregnancy during the course of the trial.
* Significant renal or hepatic impairment.
* Scheduled elective surgery or other procedures requiring general anaesthesia during the trial.
* Life expectancy of less than 6 months, or is inappropriate for placebo medication.
* Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the individual’s ability to participate in the trial.
* Participated in another research trial involving an investigational product in the past 12 weeks.
* Additional trial specific criteria as required. E.g. taking certain medications either regularly or ‘as required’ (see section 10.1.5: concomitant medications)

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 ‘Aged under 18’ among the example exclusion criteria above as this is already covered by the inclusion criterion ‘Aged 18 or above’.

# TRIAL PROCEDURES

Add a schedule of procedures either here or as an appendix.

## Trial Sites

Outline the different site types to be used (e.g. recruiting sites, PICs, Follow up centres, etc).

## Recruitment

.

Describe how, and by whom, potential participants will be identified andapproached, and if the staff approaching are considered part of the clinical care team. Note that if you are contacting individuals by electronic means (e.g. email, text, social media) to promote the trial and to recruit potential participants, this activity will be subject to the rules around Privacy and Electronic Communications Regulations (PECR) as well as UK data protection legislation. Guidance on steps for compliance can be found at: <https://compliance.admin.ox.ac.uk/mailing-lists>.

Describe if different approaches will be used for different settings and what these will be (e.g. approach via GP letter, or clinic lists, etc)

## Screening and Eligibility Assessment

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

State that protocol waivers are not permitted.

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

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

If participants are first consented and then registered to the trial for screening purposes before randomisation (for example if screening procedures are specifically conducted to assess trial eligibility and therefore require prior consent), then place the screening and eligibility section between ‘Informed Consent’ and ‘Recruitment’. If applicable, provide details of how the enrolment procedure relates to the randomisation procedure.

Specify what data will be retained from individuals who do not enrol, and how this will be handled – for instance, if it will be treated the same as research data or not retained for similar periods. Include this information in the PIS as well.

## Informed Consent

Specify who will take Informed Consent, how, and when it will be taken. Informed Consent must be obtained prior to any trial 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.

Where e-consenting is used, include details of the electronic system being used, how the consent form will be stored (including details of remote servers and any third parties used to maintain them). Specify how participants will receive a copy of the consent form, referring to University guidance for handling confidential data <https://www.infosec.ox.ac.uk/handling-information#tab-1715161>.

For further guidance on e-consent, refer to the HRA/MHRA joint statement on econsent (<https://www.hra.nhs.uk/about-us/news-updates/hra-and-mhra-publish-joint-statement-seeking-and-documenting-consent-using-electronic-methods-econsent/)>

Note: Remote consent is not usually permitted under UK clinical trials regulations. If the study team wish to use new consenting models, please contact the sponsor for advice to ensure consenting procedures are compliant with UK regulations.

For further details on the ethical considerations of including persons who cannot consent for themselves see the guidance on the HRA website.

Example:

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

Written and verbal versions of the Participant Information and Informed Consent will be presented to the potential participants detailing no less than: the exact nature of the trial; 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 trial 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 potential participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. 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 obtains 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 trial site.

## Enrolment

Specify in this section when participants will be considered enrolled (e.g. at consent, registration or randomisation). Provide details of the trial registration and enrolment procedure here (e.g., web-based registration system), notification system and instructions for sites if required.

## Randomisation

If there is no randomisation in the trial please state that clearly and retain the section header.

If applicable, describe how randomisation is going to be carried out for the trial. 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 trial (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., pharmacy, independent organisation). 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., trial pharmacist at site, site PI, central trial manager) and provide details as to how this will be communicated to them.

## Blinding and code-breaking

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

In a blinded trial, 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 pharmacist access the randomisation schedule if required by the Investigator and supply the needed information? Cross reference to the ‘Safety Reporting’ section on SUSAR reporting and address steps to be taken to conceal the wider randomisation schedule after code-breaking for specific participants.

Note: “it is the opinion of the EMA GCP Inspectors Working Group (GCP IWG) and the Clinical Trial Facilitation Group (CTFG) that the responsibility to break the treatment code in emergency situations resides solely with the investigator. Consequently, the sponsor <or sponsor delegate> cannot require or insist on being involved in the decision to unblind, stall or delay in any way the unblinding of trial subject treatment in emergency situations.”

Please see number 6 on the following link for further information:

<http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000016.jsp&mid=WC0b01ac05800296c5>

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

## Baseline Assessments

Specify and describe all baseline assessments. They must reflect the objectives and outcome measures.

If there will only be one visit, this section should be renamed ‘Trial 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 and Follow up

Specify when participants will attend for visits/follow-up, and what assessments will be conducted. Specify if they are clinic visits, remote assessments, or home visits by the trial staff and how participants are contacted to arrange subsequent visits. Add visit numbers and window periods if applicable. **Clearly number these visits**.

For each visit, list appropriate assessment, and consider inclusion of the following, where appropriate. Refer to the trial schedule of procedures (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
* dispensing of trial drug (and of standard of care drugs, if applicable)
* assessment of compliance with trial intervention /trial drugs
* recording of concomitant medications
* high-sensitivity urine or serum pregnancy tests (particularly in first in human trials)

Detail passive follow up via notes or registers, data to be collected, and frequency of collection. Note that explicit consent will be required to access NHS England and other registers (see consent form template). Note also that duration of ethics approval must encompass planned period of follow up.

## Sample Handling

If not detailed previously, describe the samples that will be taken from each participant (e.g. blood, urine, tissue, etc.), the volume/size of samples, and the frequency of sampling. Clarify in this section 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 taken specifically for research under this protocol and/or ancillary studies. Research samples should be labelled with participant study ID, not any directly identifiable personal information. Consider using separate sections such as:

### 9.8.1 Sample handling for trial purposes (delete subsection header if not required)

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

### 9.8.3 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. Trial team only for this project, or will it be stored long-term for use in future ethically approved studies where there is consent to do so), and duration of storage (destroyed following local (NHS) analysis in accordance with local NHS Trust procedures; 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), including any separate information sheets and consent forms required by any biobanks receiving samples at the end of the trial.

Note: all laboratories processing human tissue samples for clinical trial purposes must be able to demonstrate compliance with GCP standards. Study teams should give consideration to how this may be assured for their particular trial. For further guidance on GCP training for laboratory staff see: https://mhrainspectorate.blog.gov.uk/2018/11/05/making-gcp-training-relevant-and-applicable-its-not-just-for-clinical-staff//<https://mhrainspectorate.blog.gov.uk/2018/11/05/making-gcp-training-relevant-and-applicable-its-not-just-for-clinical-staff/>

All Oxford University staff who are involved in collecting, receiving, using, storing or disposing of samples of human origin for research must comply with the Policy on the storage and use of human tissue for research ([MSD policy on storage and use of human samples for research APPROVED v1.0.docx (sharepoint.com)](https://unioxfordnexus.sharepoint.com/:w:/r/sites/ADMN-UASMosaicDocumentHub/_layouts/15/Doc.aspx?sourcedoc=%7B6C02CBBB-08A7-4745-B355-03432D5F80D5%7D&file=MSD%20policy%20on%20storage%20and%20use%20of%20human%20samples%20for%20research%20APPROVED%20v1.0.docx&action=default&mobileredirect=true&DefaultItemOpen=1&cid=53990f02-c8fb-4676-8a9c-c5ae7652de43). This means all members of staff who are involved in collecting, receiving, using, storing or disposing of samples of human origin for research must undertake the online Human Tissue Act training, information can be found here: [Training requirements for the Human Tissue Act 2004 | Research Support (ox.ac.uk)](https://researchsupport.admin.ox.ac.uk/governance/human-tissue/training)

More information can be found here: [Resources for human tissue governance | Research Support (ox.ac.uk)](https://researchsupport.admin.ox.ac.uk/governance/human-tissue/resources)

All OUH members of staff who are involved in collecting, receiving, using, storing or disposing of samples of human origin for research must undertake the online Human Tissue Act training, information can be found here: [Training requirements for the Human Tissue Act 2004 | Research Support (ox.ac.uk)](https://researchsupport.admin.ox.ac.uk/governance/human-tissue/training). Training must be undertaken prior to staff member commencing work on the study.

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 trial a participant may choose to withdraw early from the trial at any time. This may happen for a number of reasons, including but not limited to:

* The occurrence of what the participant perceives as an intolerable AE.
* Inability to comply with trial 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 described here, as well as covered in the participant information sheet. Detail what data would be retained/destroyed in each scenario. It is expected that the default position for most studies would be to retain data collected up to the point of withdrawal in order to maintain data integrity. In some cases, study teams may decide that data may be destroyed at certain stages of the study without compromising integrity.

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

1. Participants may withdraw from active follow-up and further communication but allow the trial 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 or dose escalation decisions etc. should be explained here, as well as in the participant information sheet).

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

Example only (amend as appropriate):

* Pregnancy
* Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
* Significant protocol deviation
* Significant non-compliance with treatment regimen or trial requirements
* An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
* Disease progression which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures

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 wash out period) or that will continue to be required of all participants until the end of the trial; for example, would investigators be required to follow up SAEs until resolution or end of trial? Ensure that the appropriate information on these arrangements is included in the participant information sheet.

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

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.

If a participant is withdrawn from treatment due to pregnancy, the pregnancy will be followed-up to outcome. See the Safety Reporting section 11.6 .

## Definition of End of Trial

The definition of end of trial must be provided. In most cases the end of trial will be the date of completion of any follow-up monitoring and data collection for all participants, in accordance with the protocol. Where long term follow-up of participants is planned, the end of trial must include that follow-up period.

Note: Sample analysis is to be understood as part of data collection when defining end of study: “For studies involving human tissue, the analysis of the samples should be undertaken as part of the data collection before the end of study is declared” (<https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/> ).

This does not alter the 12-month grace period following end of study, during which researchers must make appropriate arrangements for their samples to be stored in compliance with the provisions of the Human Tissue Act.

Example:

The end of trial is the point at which all the data, including analysis of all samples collected during the study, has been entered and queries resolved.

# TRIAL INTERVENTIONS

The following sections may be adapted based on your trial classification. Please refer to the MHRA risk-adapted approach document for guidance

<https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf>

An investigational medicinal product (IMP) is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation, but used or assembled (formulated or packaged) in a way different from the authorised form, or when used at an unapproved dose or for an unauthorised indication, or when used to gain further information about the authorised form. (EU clinical trial directive 2001/20/EC).

## Investigational Medicinal Product(s) (IMP) Description

Name and describe the trial treatment(s) including comparator or placebo if used.

Confirm the marketing authorisation status of the IMP (and comparator(s) if applicable).

Briefly describe the comparator and indicate whether it is standard of care and describe how it will be administered.

Briefly describe the dosage, treatment duration and administration of trial medications.

Briefly describe the dosage form, packaging, and labelling of the trial medication(s) including Qualified Person (QP) release if applicable.

For labelling requirements, refer to Volume 4. Good Manufacturing Practices, Annex 13. Manufacture of investigational medicinal products, July 2010.

Where a medication is to be used in its normal indication and standard therapeutic dose, labelling exemptions may apply. Contact Sponsor for advice.

### 10.1.1. Blinding of IMPs

If not detailed elsewhere, describe how the IMP(s) and placebo will be packaged to achieve and maintain effective blinding. (Cross reference to section 9.5 *Blinding and code-breaking* above, if appropriate).

If there is no blinding of IMPs in the trial, please state that clearly and retain the section header.

### 10.1.2. Storage of IMP

Describe the storage arrangements and required storage conditions of the trial treatment. Will it be stored in the pharmacy? If not using the pharmacy, describe the conditions for storage and any procedures for checking that appropriate temperatures are maintained etc.

### 10.1.3. Compliance with Trial Treatment

Describe how compliance is assessed, and how it will be defined for the trial (e.g. 80% doses taken). Will you ask the participants to keep a diary, bring all unused or part-used medication/vials and packaging from used medication at each visit? You may want to define significant non-compliance and what procedures will be taken if there is significant non-compliance.

### 10.1.4. Accountability of the Trial Treatment

Describe how medication including placebo will be accounted for (Is full accountability required or will a risk adapted approach be employed?)

### 10.1.5. Concomitant Medication

List any contraindicated medications and check that they correspond with the exclusion and withdrawal criteria. Where a contraindicated medication is a PRN (ProReNata) i.e., a ‘taken when required’ medicine, e.g. medication for transient conditions such as migraine, state if the prescription of a PRN medication means a participant is automatically ineligible at screening or if it is the active use of the medication ‘taken as required’ while on the trial that will render them ineligible. If the latter, provide justification of their eligibility to participate in the trial and detail the trial mitigations in place to protect the safety of such a participant.

## Other Treatments (non-IMPS)

A non-investigational medicinal product is a product which is not the object of investigation (i.e., is not the tested product, the placebo or the active comparator) and is supplied to participants in a trial and used in accordance with the protocol. For classification of NIMPS see

[https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-10/imp\_03-2011.pdfhttps://health.ec.europa.eu/system/files/2016-11/imp\_03-2011\_0.pdf](https://health.ec.europa.eu/system/files/2016-11/imp_03-2011_0.pdf)

Name and describe each Non-IMP (NIMP) supplied to trial participants.

Briefly describe the dosage, treatment duration and administration of the NIMP trial medications.

As for IMPs, confirm the risk adapted arrangements for supply, storage, tracking of compliance and accountability or contraindicated medications

If there are no non-IMPs in the trial design, please state that clearly and retain the section header.

## Other Interventions

If there is an additional investigational intervention carried out as part of the research, including any diagnostic or therapeutic procedures, such as radiotherapy, surgery or device use provide the relevant details here in addition to the IMP details above.

Note: Interventions can also include non-invasive approaches such as surveys, education, and interviews.

If there are no additional interventions in the trial design, please state that clearly and retain the section header.

### 10.4. Post-trial Treatment

State if there will or will not be provision of the IMP beyond the trial period.

State what provisions of NIMP and/or other interventions will be made beyond the trial period

# SAFETY REPORTING

Please refer to the risk-adapted approach document as some of the following sections may be adapted based on your trial classification

<https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf>

Define the safety reporting window for the trial with a clearly stated starting point (e.g., from time of consent, from first administration of intervention etc.) and clearly stated end point (e.g. 30 days after last administration of the IMP, point that the participant completes the trial, end of trial, or where relevant, to point where the outcome of a pregnancy ongoing at trial end is known). Note the end point will depend on the nature and risks associated with the IMP. Advanced Therapy Medicinal Products, for example, have specific requirements over and above those for most trials and the MHRA and EMA websites should be consulted for their evolving guidance on ATMPs.

Confirm the limit of investigator follow up of AEs (e.g., follow up until event resolution or stabilisation, to participant completion of the trial, to trial end etc.). Confirm if the follow up requirement is the same for all AEs or differs for some events (e.g., follow up until event resolution required for related events only and / or for pregnancies that are ongoing at point of participant’s completion of trial or at point defined as End of trial at 9.10 above).

## Adverse Event Definitions

|  |  |
| --- | --- |
| Adverse Event (AE) | Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. |
| Adverse Event of Special Interest (AESI) | An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the product or programme under investigation, for which ongoing monitoring and rapid communication by the investigator to the sponsor, or delegate, could be appropriate. Such an event might require further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication to other parties (e.g., regulators) might also be warranted. |
| Adverse Reaction (AR) | An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.  The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.  All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. |
| Serious Adverse Event (SAE) | 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.  NOTE: Pregnancy is not, in itself an SAE. In the event that a participant or his/her partner becomes pregnant whilst taking part in a clinical trial or during a stage where the foetus could have been exposed to the medicinal product (in the case of the active substance or one of its metabolites having a long half-life) the pregnancy should be followed up by the investigator until delivery for congenital abnormality or birth defect, at which point it would fall within the definition of “serious”. |
| Serious Adverse Reaction (SAR) | An adverse event that is both serious and, in the opinion of the reporting Investigator, believed  to be an untoward and unintended response in a participant, which is related to an IMP. |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) | A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out:   * in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product * in the case of any other investigational medicinal product, in the approved investigator’s brochure (IB) relating to the trial in question. |

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

## Assessment results outside of normal parameters as AEs and SAEs

Confirm which trial assessments are relevant (e.g., only laboratory results or also others such as ECGs, chest x-rays or other scans). Specify any predefined criteria for ‘abnormality’ that signify that an out of range result is to be reported as serious (e.g., Grade ≥3 elevation of ALT or AST lasting 8 days or more). Consider providing tables of adverse event grading criteria for the relevant trial assessments (e.g., a Laboratory AE Grading Chart indicating the limits at which ‘out of range’ laboratory results are Grade 1, Grade 2, Grade 3, and the point they are reportable as SAEs etc.). Where relevant, confirm if the clinical significance of an abnormal result will be determined on a case by case basis by the medically qualified investigator.

## Assessment of Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual (i.e., a registered medically qualified doctor or a dentist - where appropriate) according to the following definitions:

Example:

**Related**: The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause.

**Not Related**: The adverse event is probably produced by the participant’s clinical state or by other modes of therapy administered to the participant.

Note: where the SAE form used for the trial employs additional options for expressing the probability of the causal relationship (e.g., definitely related, probably related, possibly related, probably not related and definitely not related) the binary definitions above may need to be supplemented and/or modified. If the SAE form includes the option ‘possibly related’ there should be a clear statement included in the protocol as to whether events reported as ‘possibly related’ will be managed as not related or as related i.e., may be assessed as a SUSAR.

## Procedures for Reporting Adverse Events

Note: it may be possible to adopt a risk adapted approach here; consider whether all non-serious AE’s need to be reported on the trial CRF, taking into account the safety profile of the IMP i.e. if the safety profile of the IMP is very well known then you may not need to report all or any non-serious AEs. If you decide not to report all non-serious AEs then state this and provide justification for not doing so.

If all (or, all related) non-serious AEs are to be reported on the trial CRF, consider adapting text below as appropriate:

<All/all related> AEs occurring during the safety window for the trial as defined above that are observed by the Investigator or reported by the participant, will be reported on the trial CRF, <whether or not attributed to trial medication>.

The following information will be reported on the CRF: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

Non-serious AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed up <either until resolution, or the event is considered stable>.

It will be left to the Investigator’s clinical judgment to decide whether or not an AE is of sufficient severity to require the participant’s removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must <Insert statement of requirements/conditions here (e.g., undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable)>. The statement should be consistent with information specified in section 9.9: Early Discontinuation/Withdrawal of Participants above, and outlined in the Participant Information Sheet.

## Reporting Procedures for Adverse Events of Special Interest

If AESIs are not included in this trial, remove this section.

The following adverse events are considered to be of special interest:

Insert all events considered AESIs

The procedure for reporting AESIs is as follows:

Describe the procedure for reporting AESIs, including which bodies (manufacturer, funder, CTU, Sponsor, etc) will receive reports and any associated timelines.

## Reporting Procedures for Serious Adverse Events

Note: it may be possible to adopt a risk adapted approach here taking into account the nature of the disease under study and the safety profile of the IMP; consider whether all adverse events meeting the criteria for seriousness above will be subject to immediate reporting. Note certain foreseeable and predefined SAEs do not need to be reported immediately, these should be clearly specified and the decision(s) justified.

All SAEs <other than those defined in this protocol as not requiring reporting> must be reported on the SAE Reporting Form to the Sponsor, or delegate, immediately or within 24 hours of Site Study Team becoming aware of the event being defined as serious.

### 11.5.1. Events exempt from immediate reporting as SAEs

If relevant: specify if types of hospitalisation are not classed as SAEs: e.g., Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute a serious adverse event; e.g., Hospitalisation for procedures and treatments specified within the protocol, and standard supportive care for the disease under study are not SAEs, and do not require SAE reporting.

If relevant: specify if deaths due to the disease under study are exempt from reporting as SAEs (with instruction as to where in the trial CRF the information about this is captured).

If relevant: specify if disease progression/ relapse/ recurrence are exempt from reporting as SAEs (with instruction as to where in the trial CRF the information about this is captured).

If this section is not relevant to the trial, please state that clearly and retain the section header.

### 11.5.2. Procedure for immediate reporting of Serious Adverse Events

If the trial is multicentre, or if the single research site and the sponsor delegate’s office are separate, you need to consider the coordination of SAE reporting for the whole trial and outline the plan for that here.

Example (amend as needed):

* Site study team will complete an SAE report form for all reportable SAEs.
* Where the SAE requires immediate reporting, the SAE report form will be scanned and emailed to <insert the relevant name and contact details for the sponsor delegate i.e., for the coordinating centre/CRO/CTU > immediately i.e., within 24 hours of site study team becoming aware of the event.
* Site study team will provide additional, missing or follow up information in a timely fashion.

The processes for receipt, acknowledgement, and review of reported SAEs at the sponsor delegate’s office should also be outlined.

Specify who will review the SAE once reported to the sponsor delegate and the timelines for this. (e.g., pharmacovigilance officer, a local safety committee, nominated clinician, the trial DMC/DMSC). Review of SAEs must be timely, taking into account the reporting timeline for a potential SUSAR.

If the SAE is a SAR it must be assessed for expectedness. This is an assessment of whether the event is expected according to the version of the IMP Reference Safety Information that is Sponsor and Regulatory Agency approved *at the moment of occurrence of the event*. Clearly state in the protocol if the assessment of expectedness is to be completed at the reporting site by the local investigator or is made centrally by the sponsor delegate (e.g., PV officer, SAE Panel, Local safety Committee etc.). The design of the trial’s SAE form and any completion guidelines provided to site(s) should reflect this.

If needed, please contact your Sponsor (RGEA/OUH R&D) for further assistance.

***For OUH sponsored trials only***

***If the Joint Oxford University Hospitals NHS Foundation Trust / University of Oxford Trial Safety Group*** State the risk of Cytotoxicity / Fetotoxicity / Teratogenicity (if any) posed by the IMP(s). In line with the assessment state what (if any) contraceptive requirements there may be for trial participants, and for their partners (where relevant).

Clearly state acceptable contraceptive methods in accordance with applicable CTU SOPs and risks associated with specific IMP (e.g. possible exposure to pregnant partners of male participants). See Clinical Trials Facilitation Group recommendations related to contraception and pregnancy testing in clinical trials: http://www.hma.eu/fileadmin/dateien/Human\_Medicines/01-About\_HMA/Working\_Groups/CTFG/2014\_09\_HMA\_CTFG\_Contraception.pdf

It is possible that some participants may become pregnant and remain on the trial. Describe procedures to be followed in this situation. For example, treatment withdrawal but ongoing follow up to 3 months postnatally (see section 9.9: Early Discontinuation/Withdrawal).

On trials where pregnancy is an exclusion criterion, any pregnancy that occurs during IMP administration should be followed up by the investigator until delivery for congenital abnormality or birth defect, at which point it would fall within the definition of “serious” in section 11.1 above and should be reported as an SAE according to procedures described above. A process should be in place at trial start to ensure this follow up is possible. Pregnancies and outcomes should also be included in annually produced safety reports.

Clarify that any pregnancy follow up may affect end date if pregnancy continues after expected study end. Ensure consent for this is obtained in the PIS and consent form, or in a separate information sheet.

Ensure consideration is given to partners (who are of childbearing potential) of male participants and what contraceptive requirements and/or subsequent follow up of any pregnancies occurring during the male partner’s participation in the trial may be needed. Separate information sheet(s) and a consent form for pregnant partners of male participants may be needed.

## Expectedness

For SAEs that require reporting, expectedness of SARs will be determined according to the relevant RSI section (that is, section <N> of the Investigators’ Brochure/ section 4.8 of the Summary of Product Characteristics (complete /delete as appropriate, please note some trials may have both). The RSI used (within the IB/SmPC) will be the current Sponsor and MHRA approved version at the time of the event occurrence. For assessment of expectedness in the Development Safety Update Report, see section 11.8 below.

## SUSAR Reporting

All SUSARs will be reported by the sponsor delegate to the relevant Competent Authority and to the REC\* and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Treatment codes will be un-blinded for specific participants.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

\*Note: For trials that have been submitted and approved via the combined ways of working, there is now no requirement to separately notify the REC of SUSARs. See: [Safety and progress reports (CTIMPs) procedural table - Health Research Authority (hra.nhs.uk)](https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/safety-and-progress-reports-ctimps-procedural-table/)

## Development Safety Update Reports

Where appropriate, the IMP manufacturer may be encouraged to submit Development Safety Update Reports (DSURs). In such cases, this must be clearly covered by the relevant agreement.

**Either**

<Name of Company> will submit DSURs once a year throughout the clinical trial, or on request to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

**Or**

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee\*, HRA (where required), Host NHS Trust and Sponsor.

If there is more than one IMP, make it clear in the text of the protocol whether there will be one DSUR covering all of the trial’s IMPs, or multiple separate DSURs for the trial’s IMPs. For each DSUR make clear what the DSUR reporting period be determined by, i.e., the date of the MHRA’s CTA approval for the trial as a whole or by the Development International Birth Date(s) (DIBD) of the relevant IMP.

\*Note: For trials that have been submitted and approved via the combined ways of working, there is now no requirement to separately notify the REC of DSURs. See: [Safety and progress reports (CTIMPs) procedural table - Health Research Authority (hra.nhs.uk)](https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/safety-and-progress-reports-ctimps-procedural-table/)

***For clinical trials which are not part of a multi-study development programme and are authorised under the Notification Scheme (Type A trials), please include the following 2 sentences*** (otherwise delete):

If approved under the notification scheme, the HRA Annual Progress Report (APR) form should be used as a template for the DSUR, and should include a list of all SARs in Section 6. The cover letter must state that this is an APR in lieu of a full DSUR, and include any registry number and CTA reference number.

For assessment of SARs in the DSUR, the RSI that was approved at **the start of the safety reporting period** will be used. When there has been approved changes to the RSI by substantial amendment during the reporting period, the RSI used for the DSUR will differ to the RSI used to assess expectedness at the time of SAR occurrence for SARs which require expedited reporting.

Note a substantial amendment is *always* required to be submitted if there are changes to the RSI. The timing of this amendment should be considered with regards to the DSUR reporting window. For further details see the answers to Questions 11 and 12 in the Clinical Trials Facilitation Group (CTFG) guidance for RSI for a clinical trial below. The MHRA recommends full compliance with the Q&A from 1 January 2019.

<http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf>

# STATISTICS

This section should be written by the study statistician.

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 12.1 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)

Example: Either

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 trial is outlined below. A separate SAP document is not in use for the trial.

(delete as appropriate)

## Description of 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 trial, 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 dosed participants (adverse event analysis); all eligible participants (per protocol analysis); all ‘evaluable’ participants (define ‘evaluability’) etc. Will you include data 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 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

A detailed Data Management Plan should be developed in tandem with the protocol. A template DMP is available from the MRC @ *https://mrc.ukri.org/documents/doc/data-management-plan-template/*

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 trial. A justification for not developing a separate detailed DMP must be provided here. This will be considered by your sponsor during the sponsor review process.

(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.

Give clear details of what this includes for the trial. Examples may be:, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical charts, laboratory and pharmacy records, diaries, radiographs, and correspondence, CRFs where the CRF is the site of the original recording (e.g. there is no other written or electronic record of data).

Give details of how source data will be held throughout the trial.

Include the following statement: All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code.

## Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

## 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*>>. Specify who (role) will undertake this. Note that ICH 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.

Where there is not a separate Data Monitoring Plan providing this detail, describe databases to be used, where they are hosted, and who has access.

Describe where, and for how long, data will be retained, distinguishing between different data as necessary (i.e., contact details will not be held as long as research data)

If only pseudonymised 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* *for CONFIDENTIAL data* @ https://www.infosec.ox.ac.uk/handling-information#tab-1715161

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 UK 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.

If third parties will be involved in handling data, whether as a service (transcription) or provision of an online platform or in any other way, a security of assessment of that provider may be required. See <https://www.infosec.ox.ac.uk/working-third-parties#tab-279866>

Refer to <https://unioxfordnexus.sharepoint.com/sites/ADMN-InformationSecurity/Lists/Third%20Party%20Risk%20Register/AllItems.aspx> to determine if the provider has already been assessed for the activity intended.

Ensure compliance with the relevant Sponsor organisation’s data policy. For University of Oxford sponsored trials 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

## Risk assessment

Provide details of how data monitoring and other quality control measures will be performed in the light of risk adaptive approach based on the formal risk assessment.

Example:

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

## Monitoring

Describe arrangements for GCP monitoring.

Note: In some cases, regular on-site monitoring may not be necessary. In this case the below text should be removed and replaced with justification and plans for central monitoring. Contact the Sponsoring organisation for advice on whether this should be the case for individual studies.

Example, where on site monitoring has been determined necessary by the Risk Assessment, delete as appropriate:

Regular monitoring will be performed according to the trial 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 trial specific Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical trial 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 documents.

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.

## Trial committees

Provide a separate subsection below for each committee in place for the trial (e.g., Trial Management Group, Trial Steering Committee (or equivalent), Independent Data (Safety) Monitoring Committee, (or the *University of Oxford /OUH Trial Safety Group* if being used), and describe the role(s), frequency of meetings and composition of the committee here. Where applicable, cross refer to the charter document governing the relevant committee for further details.

### 14.3.1 Safety Monitoring Committee

If a trial specific safety monitoring committee / DSMC is to be used, describe arrangements here.

Or

If the Joint Oxford University Hospitals NHS Foundation Trust / University of Oxford Trials Safety Group will have oversight of safety reporting in the trial via independent review of SAEs then the following text should be adapted as appropriate. Note for University of Oxford sponsored trials, the appropriateness of such oversight by the TSG will be assessed during sponsorship review.

***For OUH sponsored trials only, use the following wording (otherwise delete):***

The Oxford University Hospitals NHS Foundation Trust / University of Oxford Trials Safety Group (TSG) will conduct a review of all SAEs for the trial reported during the quarter and cumulatively. Note: the TSG Committee has oversight of cumulative SAE data for trials that have reported at least one SAE in the time period reviewed at their meetings. The aims of this committee review include:

* To pick up any trends, such as increases in un/expected events, and take appropriate action
* To seek additional advice or information from investigators where required
* To evaluate the risk of the trial continuing and take appropriate action where necessary

# URGENT SAFETY MEASURES

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) to protect trial participants from any immediate hazard to their health or safety. USMs may be taken without prior authorisation but they should be reported immediately, and not later than 3 days, to the Sponsor, REC and MHRA. This should be followed by submission of a substantial amendment specifically covering the USM related changes.

A standard operating procedure should be in place describing the procedure for identifying and implementing USMs appropriately, as well as reporting lines from investigators to CTU and from CTU to Sponsor, REC and MHRA.

# PROTOCOL DEVIATIONS

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process or IMP administration) 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 trial 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

# DATA BREACHES

For University of Oxford sponsored studies only:

According to the Information Commissioner’s office (ICO), “there will be a personal data breach whenever any personal data is accidentally lost, destroyed, corrupted or disclosed; if someone accesses the data or passes it on without proper authorisation; or if the data is made unavailable and this unavailability has a significant negative effect on individuals.

Suspected personal data breaches must be reported immediately to the University of Oxford’s Data Breach Team [data.breach@admin.ox.ac.uk](mailto:data.breach@admin.ox.ac.uk)

IT security related incidents e.g. malware, hacks to be reported to the Information Security Team(IST): [oxcert@it.ox.ac.uk](mailto:oxcert@it.ox.ac.uk) (ext. 82222).

Sites may have reporting obligations within their own organisation as well.

# SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

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

(b) the scientific value of the trial”.

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 REC committee, Regulatory authority and the relevant NHS host organisation within seven calendar days.

# ETHICAL AND REGULATORY CONSIDERATIONS

## Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

Note: The 2013 Declaration of Helsinki provides detail on what must be included in a protocol: funding, sponsorship, affiliations and potential conflicts of interest, incentives to participate, compensation for harm and post-trial access to drugs and care: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

## Guidelines for Good Clinical Practice

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

## Approvals

Consider the following example text:

Following Sponsor approval the protocol, informed consent form, participant information sheet <and any proposed advertising material> will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) 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 or trial-specific ethical considerations, e.g. use of placebo, involvement of vulnerable participants.

## Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

## Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database. The trial details on this database will be maintained and regularly updated throughout the lifetime of the trial

Results will be uploaded to the [insert registry] Database within 12 months of the date stated on the end of trial declaration (6 months for paediatric trials\*) by the Sponsor, or delegate.

\*Exceptionally this can be extended to within 12 months after the end of a paediatric trial if justification is included here and OU or OUH are not the marketing authorisation holder for the involved IMP(s)

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.

## Participant Confidentiality

Example:

The study will comply with UK General Data Protection Regulation (UK GDPR) and Data Protection Act 2018, which require data to be anonymised 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 trials 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>

For OUH sponsored trials please refer to the OUH’s:

Information Governance Policy: <http://ouh.oxnet.nhs.uk/InformationGovernance/Document%20Library/Policies%20and%20Procedures/Information%20Governance%20Policy/Information%20Governance%20Policy%20v9.2%20FULL.pdf>

Privacy Notice: <https://www.ouh.nhs.uk/privacy/default.aspx>

## 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. FINANCE AND INSURANCE

## Funding

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

For advice on whether support is considered a funder in-kind please contact your contracts associate or manager.

## Insurance

Describe insurance arrangements.

**Either** *for OUH sponsored studies:*NHS bodies are legally liable for the negligent acts and omissions of their employees. If participants are harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the trial team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University NHS Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

**Or** *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). NHS indemnity operates in respect of the clinical treatment that is provided.

The section in red is only to be included if there is an NHS clinical procedure taking place during the trial.

## Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.   
Refer to <https://www.infosec.ox.ac.uk/working-third-parties> for guidance on information compliance aspects of these arrangements.

Ensure all details are also provided in IRAS and are consistent across documents.

# 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. Consider describing how trial results may be disseminated to trial participants.

Ensure that the publication policy stated here is consistent with any contract applicable to the trial.

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

Note: these statements are determined by the Sponsor Office and are not subject to modification by study teams. Please contact your contracts specialist or manager to discuss further requirements for IP or contractual issues.

**Either** *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.

***Or*** *for OUH sponsored studies:*

Ownership of IP generated by employees of the OUH vests in OUH.  The protection and exploitation of any new IP is managed by the IP and Research Contracts Team at OUH unless it is generated in collaboration with the University of Oxford in which case this is led by the University’s technology transfer office, Oxford University Innovations.

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

# ARCHIVING

Documents need to be stored in a way that preserves their accuracy, integrity and legibility, and restricts access to authorised individuals only. The medium of storage should consider the ability to retrieve in light of developing technologies replacing obsolete systems. The data, both paper and electronic, should be archived appropriately (consider space, security, fire protection without water sprinkler systems, water protection, humid conditions, pests, etc). If appropriate a professional external archive site may be utilised with appropriate checks and contracts in place.

## Minimum archiving period

State what the minimum archiving period is in years and clearly specify the point at which the period begins. Describe the location(s) of the archive(s). These details (duration and location of storage) should correspond with those provided in the participant information sheet.

Note: The TMF including all essential documents, as well as any non-trial-specific records (e.g. SOPs, training records and equipment records), must be archived for at least 5 years after the completion of study-related activities, see [Medicines for Human Use (Clinical Trial) 2006 (and amendments) Regulation 31A (7) & (8)](https://www.legislation.gov.uk/uksi/2006/1928/regulation/18/made) or longer where required, e.g. in the case of genetic studies or if the clinical research involves minors under 18 years old.

Note: Where minors are involved, essential documents should be archived until 3 years after the youngest subject reaches 18 years old, or for 5 years, whichever is longer.

## Trial Master File

For University of Oxford sponsored studies, all paper and electronic data including the Trial Master File and trial database will be retained and archived in accordance with <University of Oxford CORE SOP 005 and the named CTU or OUH> standard operating procedures which are compliant with the UK GDPR.

For Oxford University Hospitals NHS Foundation Trust sponsored studies, all paper and electronic data including the Trial Master File and trial database will be retained and archived in accordance with Trust SOPs.

## Investigator Site File and participant medical records

The Investigator Site Files will be archived at the participating sites in accordance with the site agreements, and with site local procedures. Where applicable, the medical records of trial participants are not archived and must be retained at the site for the minimum archiving period above and in accordance with requirements of the host healthcare provider (where that is the longer retention period).

# REFERENCES

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

# APPENDIX A: TRIAL FLOW CHART

Optional

# APPENDIX B: EXAMPLE SCHEDULE OF PROCEDURES

Alter as required, delete from here if the schedule appears in the procedures section above instead.

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

# APPENDIX C: SAE REPORTING FLOW CHART

# APPENDIX D: 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 / MHRA / HRA submission.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee, HRA (where required) or MHRA.