**Clinical Trial of Investigational Medicinal Product**

**Protocol Template**

***(Version 4.0, 01Feb2021)***

**Guidance Notes for Protocol Template**

Please check the Joint Research Office (JRO) website <https://www.ucl.ac.uk/joint-research-office/resources-and-templates> to ensure you have the most up to date version of this template

This protocol template should be used to draft a protocol for a Clinical Trial of an Investigational Medicinal Product (CTIMP).

This Protocol template has been developed to reflect applicable UK regulations and guidelines, and should be adapted as required if international sites are planned.

**General notes on using the protocol template:**

The contents of the protocol template should be adapted to suit individual trial requirements. The protocol template includes sections of standard text and guidance notes.

Sections of the protocol template which are not relevant for a particular trial need to remain and ‘Not Applicable’ be added next to it.

The protocol must be consistent with the participant information sheet, consent form, IRAS form, Clinical Trial Authorisation (CTA) application, Investigator Brochure (IB)/Summary of Product Characteristics (SmPC) and any other relevant trial documentation, and should be cross checked prior to finalisation. The JRO will carry-out a review of the draft protocol and provide advice and guidance prior to approval.

1. **Text in blue is guidance and/or instruction and should be deleted once addressed**
2. **Suggested text given in red should be included/adapted/expanded/amended if appropriate for the trial (otherwise this can be deleted)**
3. **Some generic text is given in black and should be included (unless not applicable)**

**Guidance notes on Style and Formatting:**

1. Abbreviations should be written in full on first appearance and a list of abbreviations should be included in the protocol in section ii. LIST OF ABBREVIATIONS.
2. Ensure consistency:
	1. refer to trial ‘participants’ throughout the protocol (not patients, subjects or volunteers)
	2. refer to ‘trial’ throughout the protocol (we advise that you do not use the term study when referring to a CTIMP)
	3. refer to trial ‘sites’, not ‘centres’, for a participating institution
3. Use bullet point lists or tables where appropriate rather than long passages of prose

**Logos** - please ensure all appropriate and relevant logos are added to the front page, and that bodies represented have agreed to the use of their logo.

**This covering page should be deleted once the protocol has been drafted.**

# TITLE PAGE

**FULL/LONG TITLE OF THE TRIAL**

[Click here and type full descriptive trial title]

Aim: To identify the Trial to enable retrieval from literature or internet searches. It should be immediately evident what the trial is investigating and on whom to allow rapid judgment of relevance.

For intervention or exposure studies a structured title should contain:

* Information on participants (e.g. population, target disease)
* Intervention (exposure) (e.g. name of IMP)
* Comparison groups
* Outcomes
* Phase
* Trial design (e.g. randomised, placebo-controlled), single site/multi-site)

**SHORT TRIAL TITLE / ACRONYM**

[Click here and type short trial title]

Aim: To provide a summary of the long title. It is usually the title used on information sheets and consent forms for research participants or others giving consent or assent on their behalf. The full and short title must be the same on all trial documents.

The short title should be:

* Sufficiently detailed to make clear to participants what the research is about in simple English
* If acronyms are used the full title should explain them. The proposed acronym should not drive the long title

**PROTOCOL VERSION NUMBER AND DATE**

[Draft/Final]Version [Insert version number], [Insert Date]

Aim: To track changes to the document for trial conduct, review, and oversight so it is clear which is the most recent document.

Version control:

* All draft versions should be numbered 0.1, 0.2 etc.
* The final version for submission should be numbered 1.0
* A summary of changes made relative to the previous protocol version should be listed in the Protocol Version History table

**This protocol has regard for the HRA guidance and order of content.**

# RESEARCH REFERENCE NUMBERS

|  |  |
| --- | --- |
| **IRAS Number:** |  [Type IRAS No]The unique identifier generated by IRAS for the project. This will be the primary reference number used by REC, HRA and sites to identify the project and should be quoted in all project related correspondence. |
| **Clinical trials.gov Number:** | [Type Clinical trials.gov.uk No]This is a register of studies in the United States and around the world. All clinical trials of investigational medicinal products must be registered on the ClinicalTrials.gov database. |
| **EudraCT Number:** Delete if not applicable | [Type EudraCT No]This is to be allocated by JRO. All clinical trials of investigational medicinal products within the EU must be registered on the EudraCT database. |
| **ISRCTN Number / Other registries:** Delete if not applicable | [Type ISRCTN No] Accepted registers include: International Standard Randomised Controlled Trials Number (ISRCTN) Register. This register accepts registration of randomised controlled trials and any other research study designed to assess the efficacy of health interventions in the human population.  |
| **SPONSOR:** | University College London (UCL) |
| **LEGAL REPRESENTATIVE:**For trials with sites in EU only, delete if not applicable | UCL Research Limited70 Sir John Rogerson's QuayDublin 2D02 R296, Ireland |
| **SPONSOR Number:** | [Type Sponsor Protocol Number]Generated by the JRO.  |
| **FUNDER:** | [Type Name of Funder]If there are multiple funders please list all |
| **FUNDERS Number:** Delete if no funder reference number available | [Type Funder Reference Number]Generated by the funder. Enter if applicable |

# SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, the UK Policy Framework for Health and Social Care Research 3rd edition 2017 (as amended), GCP guidelines, the UK Data Protection Act (2018), the Sponsor’s (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

|  |
| --- |
| **Chief Investigator:** |
| Signature and Date:  |
|  |
| Name: (please print): |
|  |
|  |
|  |
| **For and on behalf of the Trial Sponsor:** |
| Signature and Date:  |
|  |
| Name (please print): |
|  |
| Position:  |
|  |

#

# PROTOCOL VERSION HISTORY

|  |  |  |  |
| --- | --- | --- | --- |
| **Version Number** | **Date** | **Protocol Update Finalised By**(insert name of person) | **Reasons for Update** |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

#  KEY TRIAL CONTACTS

Insert full details of the key trial contacts including the following, add/remove rows as applicable. It is not necessary to add Principal Investigators and Sites.

|  |  |
| --- | --- |
| **Chief Investigator** | [Full contact details including phone and email] |
| **Trial Co-ordinator** | [Full contact details including phone and email] |
| **Sponsor** | [insert SRA/ATIMP Manager]Joint Research Office, UCL4th Floor West, 250 Euston RoadLondon NW1 2PGTel:Email: |
| **Clinical Trials Unit / Contract Research Organisation** | [Full contact details including phone and email] (If applicable) |
| **Statistician**  | [Full contact details including phone and email] |
| **Add any additional central core services, i.e. laboratories, central pharmacy production units, medical and/or technical departments (e.g. imaging, radiology)** | [Full contact details including phone and email] |

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# LIST OF ABBREVIATIONS

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

AE Adverse Event

AR Adverse Reaction

CA Competent Authority

CI Chief Investigator

CRF Case Report Form

CRO Contract Research Organisation

CTA Clinical Trial Authorisation

CTIMP Clinical Trial of Investigational Medicinal Product

CTU Clinical Trials Unit

DMC Data Monitoring Committee

DSUR Development Safety Update Report

EC European Commission

EMA European Medicines Agency

EU European Union

EUCTD European Clinical Trials Directive

EudraCT European Clinical Trials Database

EudraVigilance European database for Pharmacovigilance

GAfREC Governance Arrangements for NHS Research Ethics

GCP Good Clinical Practice

GMO Genetically Modified Organisms

GMP Good Manufacturing Practice

HTA Human Tissue Authority

IB Investigator Brochure

ICF Informed Consent Form

ICH International Council on Harmonisation of technical requirements for registration of pharmaceuticals for human use

IDMC Independent Data Monitoring Committee

IMP Investigational Medicinal Product

IMPD Investigational Medicinal Product Dossier

ISF Investigator Site File (This forms part of the TMF)

ISRCTN International Standard Randomised Controlled Trials Number

MA Marketing Authorisation

MIA(IMP) Manufacturer’s Authorisation for IMP

MHRA Medicines and Healthcare products Regulatory Agency

MS Member State

NHS R&D National Health Service Research & Development

NIMP Non-Investigational Medicinal Product

PI Principal Investigator

PIC Participant Identification Centre

PIS Participant Information Sheet

PL Product License

QA Quality Assurance

QC Quality Control

QP Qualified Person

RCT Randomised Control Trial

REC Research Ethics Committee

RSI Reference Safety Information

SAE Serious Adverse Event

SAR Serious Adverse Reaction

SDV Source Data Verification

SOP Standard Operating Procedure

SmPC Summary of Product Characteristics

SSA Site Specific Assessment

SSI Site Specific Information

SUSAR Suspected Unexpected Serious Adverse Reaction

TMF Trial Master File

TMG Trial Management Group

TSC Trial Steering Committee

USM Urgent Safety Measure

WOCBP Women of childbearing potential

# TRIAL SUMMARY

It is useful to include a brief synopsis of the trial for quick reference. Complete information and, if required, add additional rows.

|  |  |
| --- | --- |
| **Trial Title** | [Add Full Trial Title] |
| **Short Title** | [Add Short Trial Title] |
| **Sponsor Protocol Number** | [Add Sponsor Protocol No] |
| **Clinical Phase**  | Phase [Insert Phase of Trial] |
| **Trial Design** | [Insert Brief Description of Trial Design]E.g. open/single-blind/double-blind, randomised, crossover/partial crossover/parallel group, single/multi-site trial. |
| **Trial Participants** | [Insert Brief Description of Trial Participants] E.g. age range, disease group, key inclusion/exclusion criteria |
| **Planned Sample Size** | [Insert Planned Sample Size] Include planned number to be enrolled for the whole trial. |
| **Treatment duration** | [Insert Treatment Duration]Include duration each participant is expected to receive trial treatment. |
| **Follow up duration** | [Insert Follow-up Duration]Include duration each participant will attend follow-up visits/contact with trial team after trial treatment has finished |
| **Planned Trial Period** | Include an estimate of trial period from commencement of recruitment to last participant last visit |
|  | **Objectives** | **Outcome Measures/Endpoints** |
| **Primary** | Add additional lines as required. |  |
| **Secondary** |  |  |
| **Investigational Medicinal Product(s)** | [Add Trial Medication / Comparators / Placebo, as applicable] |
| **Formulation, Dose, Route of Administration** | [Add Formulation, Dose, Route of Administration for Trial Medication / Comparators / Placebo, as applicable] |

# ROLE OF TRIAL SPONSOR AND FUNDER

Aim: To clarify the potential influence of sponsor and funders over the trial

The sponsor can be defined as the company, institution, or organisation assuming overall responsibility for the initiation and management of the trial, and is not necessarily the main funder. Identification of the trial sponsor provides transparency and accountability.

The protocol should explicitly outline the roles and responsibilities of the sponsor(s) and any funder(s) in trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. It is also important to state the obligation of the sponsor or funder in terms of the final decision regarding any of these aspects of the trial.

NB: in a CTIMP the sponsor has legal responsibilities that cannot be delegated.

Include the following statement:

University College London (UCL) will act as sponsor for this trial. As Sponsor, UCL will provide insurance for the clinical trial and undertake to ensure that the above trial is conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended), the UK Policy Framework for Health and Social Care Research 3rd edition 2017 (as amended) and all applicable regulatory requirements.

|  |  |
| --- | --- |
| KEY WORDS | [Insert relevant keywords to describe the trial; no more than 6 phrases]  |

# BACKGROUND

Aim: To place the trial in the context of available evidence.

The background should be supported by appropriate references to the published literature on the disease or condition, its treatment and the use of the trial drug for the indication and contain:-

* an up-to-date systematic review of relevant studies, new research should build on formal review of prior evidence
* a brief description of the proposed trial
* a description of the population to be studied
* the investigational product(s) and their mechanism of action
* relevant data from preclinical/non-clinical studies
* relevant data from previous clinical trials such as efficacy, safety, tolerability, pharmacokinetics & pharmacodynamics
* if no data is available, include a statement that there is no available clinical research data to date on the investigational product

It should be written so it is easy to read and understand by someone with a basic sense of the topic who may not necessarily be an expert in the area. Some explanation of terms and concepts is likely to be beneficial.

# RATIONALE

Aim: To explain why the research questions being asked are important and why closely related questions are not being covered.

This should include:

* a clear explanation of the research question/hypothesis and the justification of the trial i.e. why the question is worth asking and, through consultation with public and patient groups, why this is worthwhile to patients. Replication to check the validity of previous research is justified, but unnecessary duplication is unethical.
* the currently available treatment(s) and their limitations, why you think the IMP(s) might be an improvement on those treatments, why the treatment difference is clinically important to patients and if it is realistic. (The treatment difference is often referred to as the minimum clinically important difference or the difference we should not want to miss. A drug which reduces everyone’s systolic blood pressure by 2 mm of mercury may be genuinely effective, but the effect would not form the basis of a routine intervention)
* this justification is particularly important if the trial proposes to use the IMP:
	+ in children or in adults unable to consent for themselves
	+ in higher doses
	+ for longer duration
	+ in a participant population that might handle it differently (e.g. hepatic or renally impaired patients, children, elderly or immunocompromised individuals)
	+ it is being used in combination with another medicinal product
	+ the indication/ medical condition compromises the participant’s tolerance
	+ in healthy volunteers
* the rationale for the use of a placebo in the trial if one is being used
* justification for the choice of route of administration, dosage, dosage regimen, and treatment period(s)
* it should also include an explanation and justification as to the choice of control interventions/comparators especially if it involves withholding or delaying standard of care

## Assessment and management of risk

Aim: To describe a risk/benefit analysis plus risk management of all the medication involved in the trial (whether in or outside of licence).

The following should be described:

* the known and potential risks and benefits to human participants
* how high the risk is compared to normal standard practice
* frequency of risk
* how the risk will be minimised/managed

Consider the starting dose, dose increments, dose escalation, administration of doses, stopping rules and the resources required by site(s); particularly in terms of facilities and staff, procedures, type of participants, staff training required.

Please refer to the following documentation in preparing this section:

<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>

The table below summarises the risks, frequencies and mitigations of the Investigational Medicinal Products (IMP(s)) and Non-Investigational Medicinal Products (NIMP(s)) (delete NIMP if it is not applicable)

|  |  |  |  |
| --- | --- | --- | --- |
| **Name of IMP(s) / NIMP(s)** Delete NIMP if it is not applicable | **Potential risk**List below the main expected side effects as described in the SmPC /IB (NB each side effect should be listed on separate rows) | **Risk Frequency**In line with the SmPC/IB add whether the side effect is very common, common, infrequent or rare | **Risk Management**Describe how you will minimise or manage this risk. Consider if management requires dose adjustments, stopping drug treatment, any precautions or advice to be given to participants, or exclusions in the eligibility criteria, e.g. IDMC configured to mitigate participant safety and data integrity risks. |
|  |  |  |  |
|  |  |  |  |

The table below summarise the risks and mitigations of all tests and/or procedures above standard care that are being performed:

|  |  |  |
| --- | --- | --- |
| **Intervention** Add tests above standard care that are being performed (e.g. I.V drug administration, blood test, x-rays, ECG etc.) | **Potential risk**Describe the risks of the intervention or where applicable refer to a valid document that shows the risk. | **Risk Management**Describe how you will minimise the risk. Consider if management requires any precautions or advice needs to be given to participants, or exclusions in the eligibility criteria. |
|  |  |  |
|  |  |  |

This trial is categorised as: (delete as appropriate)

 • Type A = No higher than the risk of standard medical care

 • Type B = Somewhat higher than the risk of standard medical care

 • Type C = Markedly higher than the risk of standard medical care

# OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Aim: To define the primary research question, to address a specific hypothesis and to clearly define the secondary objectives

The objectives are generally phrased using neutral wording (e.g., “to compare the effect of intervention A versus intervention B on outcome X”) rather than in terms of a particular direction of effect.

## Primary objective

Aim: To define the primary research question, to address a specific hypothesis

The protocol should define:

* the hypothesis which should be stated in quantifiable terms; e.g. “the experimental treatment will result in 12 months of additional survival compared to the control treatment”
* the null and the alternative hypotheses
* for multi-arm trials, the objectives should clarify the way in which all the intervention groups will be compared (e.g., A versus B; A versus C)

 A useful guide to use in the development of a specific research question are the PICOT criteria:

 P Population (patients) - What specific patient population are you interested in?

 I Intervention (for intervention studies only) - What is your investigational intervention?

 C Comparison group - What is the main alternative to compare with the intervention?

 O Outcome of interest - What do you intend to accomplish, measure, improve or affect?

 T Time - What is the appropriate follow-up time to assess outcome

## Secondary objectives

Aim: To clearly define the secondary objectives

The protocol should describe the secondary objectives which:

* may or may not be hypothesis-driven
* may include secondary outcomes
* may include more general non-experimental objectives (e.g., to develop a registry, to collect natural history data)

## Outcome measures/endpoints

Aim: To define primary and secondary endpoints/outcomes for the trial which usually appear in the objectives and sample size calculation.

An ideal endpoint/outcome is valid, reproducible, relevant to the target population, and responsive to changes in the health condition being studied. The COMET (Core Outcome Measures in Effectiveness Trials [www.comet-initiative.org](http://www.comet-initiative.org) ) provides a common set of key trial outcomes and it is beneficial to ascertain whether there is a core outcome set relevant to the trial. This does not preclude inclusion of additional relevant outcomes.

The protocol should define:

* the endpoint/outcome of main interest (primary outcome 3.4)
* the remaining endpoints/outcomes (secondary outcomes 3.5)
* whether the endpoint/outcome reflect efficacy (beneficial effect) or harm (adverse effect)
* the rationale for the choice of trial endpoint/outcome
* For each endpoint/outcome, the trial protocol should define four components:
* the specific measurement variable, which corresponds to the data collected directly from trial participants (e.g. all cause mortality);
* the participant-level analysis metric, which corresponds to the format of the outcome data that will be used from each trial participant for analysis (e.g., change from baseline, final value, time to event);
* the method of aggregation, which refers to the summary measure format for each trial group (e.g., mean, proportion with score > 2);
* the specific measurement time point of interest for analysis

## Primary endpoint/outcome

Aim: To identify a single response variable (primary endpoint/outcome) to answer the primary research question.

The primary endpoint/outcome should be a clear, unarguable, quantitative measure of effect that will be the focus of the primary analysis and will drive the choice of sample size. Less is more e.g. “The primary endpoint/outcome is 28 day survival.” It may be pertinent to list the time point at which endpoint/outcome will be measured if it is possible to be measured more than once during the trial. The protocol should describe any rules, references or programmes for calculation of derived values and describe what form it will take for analysis (e.g. continuous, categorical, ordinal)

Since there is only one choice of sample size, which may be based on the statistical power for the single primary analysis, there can only be one primary endpoint/outcome. The exception to this is in a trial that is comparing a new diagnostic or measurement technique to an existing standard. In which case, it is acceptable to have two co-primary endpoints: the old and the new technique.

## Secondary endpoints/outcomes

Aim: To identify a series of well established endpoints of clinical importance that in theory could be the primary endpoint in another trial

This should be a sequence of concise statements referring to observations that say nothing about the trial objectives or analysis. There can be any number of secondary measures, although they should all be relevant to the declared aims of the trial

## Exploratory endpoints/outcomes

Aim: To identify any other endpoints/outcomes which are not well established.

## Table of endpoints/outcomes

Aim: To give a clear and concise representation of all end/points/outcomes of the trial.

|  |  |  |
| --- | --- | --- |
| **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 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 7Example: Concentration of protein X in blood samples from participants on each treatment | 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 |  |
| **Tertiary Objectives**Please add if applicable, otherwise delete this row | As Above |  |

# TRIAL DESIGN

Aim: To describe the ideal design for the research question and what the trial is designed to show.

The framework of a trial refers to its overall objective to test:

* the superiority (treatment is superior to placebo or comparator treatment)
* non-inferiority (‘not worse than’ the comparator treatment)
* equivalence (treatment is similar to the comparator treatment ) of one intervention with another
* in the case of exploratory pilot trials, to gather preliminary information on the intervention (e.g. harm, pharmacokinetics, etc.) and the feasibility of conducting a full-scale trial

Common designs include:

* Parallel group design: each group of participants receives only one of the trial treatments.
* Cross-over design: each of the participants is given all the trial treatments in successive periods. The order in which the participants receive each treatment is determined at random.
* Factorial design: two or more treatments are evaluated separately and in combination against a control. For instance, in a factorial design to assess the effect of drug A and drug B for the treatment of pain, participants would receive drug A only, drug B only, a combination of drug A and B, or placebo.
* Cluster randomised controlled trials: the treatment is randomised to groups of participants (e.g. families) rather than individual participants.
* Groups sequential: outcomes are assessed in a group and sequential manner
* Multiple-armed design: trial with more than two arms. For example, a three-armed trial comparing a treatment with inactive control/placebo, and an alternative active treatment
* Pragmatic trial: reflects variations between patients that occur in real clinical practice and aims to inform choices between treatments. Although these are called pragmatic the same level of detail is required outlining the design as all other trials.

There is increasing interest in adaptive designs for clinical trials, defined as the use of accumulating data to decide how to modify aspects of a trial as it continues, without undermining the validity and integrity of the trial. Examples of potential adaptations include stopping the trial early, modifying the allocation ratio, re-estimating the sample size, and changing the eligibility criteria. The most valid adaptive designs are those in which the opportunity to make adaptations is based on pre-specified decision rules that are fully documented in the protocol.

## Trial Flow Chart

Aim: To give readers a schematic overview of the trial

A flow diagram should be included.

Flow diagrams are helpful tools to guide users of the protocol through the participant and trial pathway, for instance a participant pathway detailing intended fit of the screening and recruitment process with usual practice may be helpful for complex intervention trials and a schedule of events in table format is also recommended. The schedule of events can be included where most appropriate in the protocol or in an appendix at the end. An example table is provided in Appendix 1 - Schedule of Assessments (see also, section 7 TRIAL PROCEDURES).

Key information to convey includes the timing of all trial activity, starting from initial eligibility screening, each trial visit through to trial close-out and long term follow-up; time periods during which trial interventions will be administered; and the procedures and assessments performed at each visit (with reference to specific data collection forms, if relevant)

# TRIAL SETTING

Aim: To describe where the trial will be run and any site specific requirements

The protocol should include:

* if it is a multicentre or single centre trial
* if there are any site specific requirements to run the trial
* Whether there are different ‘types’ of site (e.g. recruiting, treating, continuing care, etc.) and what the specific requirements are for each
* if applicable, eligibility criteria for trial centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)
* consideration of the participant population and where they are found. What are the usual care pathways? Are patients with the condition of interest found in primary or secondary care? If using secondary care sites, will primary care Participant Identification Centres (PICs) be needed to recruit participants, or are patients found in secondary care?

# PARTICIPANT ELIGIBILITY CRITERIA

Aim: To define the trial population

This section should set out precise definitions of which participants are eligible for the trial, defining both inclusion and exclusion criteria.

The inclusion criteria should define the population the trial is aiming to include and indicate the generalisability of the trial findings. The exclusion criteria should exclude sub-groups of the population due to, for example, safety and other clinical risks or burden to the participant.

The eligibility criteria should be clear so they can be applied consistently through the trial and definitions for the timelines and flexibility of each eligibility criterion must be carefully considered to ensure that arbitrary or un-workable definitions are not used. The choice of criteria can affect recruitment and attrition to the trial as well as its generalisability.

The following wording must be included:

The Sponsor does NOT allow the use of “protocol waivers” or departures from the approved inclusion/exclusion criteria of the protocol. Occurrences of this nature may constitute a serious breach and be reportable to the MHRA.

## Inclusion Criteria

1. Participants capable of giving informed consent, or if appropriate, participants having an acceptable individual capable of giving consent on the participant’s behalf (e.g. parent or guardian of a child under 16 years of age)
2. Gender (if specifying) (Justification must be included in the rationale section if excluding)
3. Age (add upper and lower age limits as applicable)
4. Clinical parameters, compliance with EACH parameter for each participant will need to be clearly documented
5. Females of childbearing potential and males must be willing to use a highly effective (acceptable effective contraceptive measures are only acceptable for IMP’s with unlikely human teratogenicity / fetotoxicity in early pregnancy) method of contraception (hormonal or barrier method of birth control; abstinence). Contraceptive methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

• combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

 o oral

 o intravaginal

 o transdermal

• progestogen-only hormonal contraception associated with inhibition of ovulation

 o oral

 o injectable

 o implantable

• intrauterine device (IUD)

• intrauterine hormone-releasing system (IUS)

• bilateral tubal occlusion

• vasectomised partner

• sexual abstinence

Note - In order to specify the duration of the risk mitigation measures after discontinuation of treatment with the IMP, the risk assessment should include an estimation of the end of relevant systemic exposure (the time point where the IMP, including any active or major metabolites, has decreased to a concentration that is no longer considered relevant for human teratogenicity/fetotoxicity).

* If the SmPCs of the IMPs state that the IMPs are not teratogenic you might be able to state that this is Not Applicable for your trial]. Please note that the MHRA advise double contraception
* Note - A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.
* Women of childbearing potential (WOCBP) must have a negative pregnancy test within 7 days prior to treatment initiation). [If the SmPCs of the IMPs state that the IMPs are not teratogenic you might be able to state that this is Not Applicable for your trial]. NOTE: Participants are considered not of child bearing potential if they are surgically sterile (i.e. they have undergone a hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or they are postmenopausal.
* WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test, except for IMPs where an absence of risk of human teratogenicity/fetotoxicity in early pregnancy can be justified by human pregnancy data.
* Note - For advanced therapy medicinal products (ATMP) embryofetal risk assessment and the need for contraception and pregnancy testing recommendations should be considered on a case-by-case basis.
* Males - For genotoxic IMPs, the male participant should use condom during treatment and until the end of relevant systemic exposure in the male participant, plus a further 90-day period. For a non-pregnant WOCBP partner, contraception recommendations should also be considered.

Guidance on the acceptable contraception methods can be found here:

* <https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf>

## Exclusion Criteria

1. Females who are pregnant, planning pregnancy or breastfeeding
2. Consider contraindications to trial treatment (e.g. as listed in SmPC), incompatible concurrent treatments, recent involvement in other research.
3. Allergies to excipients of IMP and placebo
4. Significant medical history of a particular illness/disease. It is important to detail specifically how long you consider the history needs to be e.g. evidence of very early childhood asthma with no recurrence in adulthood is potentially not very significant in a participant aged 50.
5. Current or relevant history of a physical or psychiatric illness or any medical condition that in the opinion of the investigator could affect the participant’s safety or interfere with the study assessments

# TRIAL PROCEDURES

Aim: To provide a clear and concise timeline of the trial visits, enrolment process, interventions, and assessments performed on participants

The protocol should describe what the procedures/assessments are at each visit and where they will be undertaken i.e. hospital/ GP surgeries/ at home and if not at the trial site the timelines for notification of these results to the trial team, especially if they are outside of the range etc. A defined, appropriate, visit window should be established e.g. +-3 days.

Add schedule of procedures in Appendix 1, if appropriate

## Recruitment

Aim: to describe how participants are identified and recruited

This section should give details of the participant eligibility screening process for the project including information to be collected regarding participants who are screened and for participants who are not randomised / registered where data is being collated for Consolidated Standards of Reporting Trials (CONSORT) (<http://www.consort-statement.org/>) or other similar reasons for reporting the generalisability of the results. If a decision is made to not collect this information, the justification for this should be documented.

Anonymised information on participants who are not randomised / registered for CONSORT reporting should include:

* age,
* gender,
* ethnicity (if applicable),
* whether the participant is registered or not registered,
* the reason not eligible for trial participation, or if they are eligible but declined

### Participant Identification

The following should be described in the protocol:-

* who will identify participants
* what resources will be used
* will identification involve reviewing or screening the identifiable personal information of participants, service users or any other person (if so will this be undertaken by members of the normal clinical team or will Section 251 – <http://www.hra.nhs.uk/about-the-hra/our-committees/section-251/what-is-section-251/> - be applied for?)
* will any participants be recruited through PICs
* will any participants be recruited by publicity; posters, leaflets, adverts or websites
* details of the sources of identifiable personal information that will be used to identify potential participant. Normally only a member of the patient’s existing clinical care team should have access to patient records without explicit consent in order to identify potential participants, check whether they meet the inclusion criteria or make the initial approach to patients. If the research proposes to use someone outside the clinical care team to identify suitable participants or as first contact with the participant, the reason for this should be explained
* The arrangements for referral if the participants are to be identified by a separate research team
* If patient or disease registers are used to identify potential participants a brief description of the consent and confidentiality arrangements of the register should be included
* Certain studies, such as cluster trials, incorporate a separate screening process relevant to that trial design – in such cases it may be appropriate to collect more detailed information regarding screened participants.
* It should be clear who will confirm eligibility. NB: in a CTIMP this must be confirmed by a medical practitioner.

Please also include the following statement:

Participant recruitment at a site will only commence when the trial has:

1. Been initiated by the Sponsor (or it’s delegated representative), and
2. Issued with the ‘Open to Recruitment’ letter.

## Consent

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes the taking of informed consent of participants at their site. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent is acceptable then details should be provided.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are not part of standard routine care at the participating site (including the collection of identifiable participant data unless the trial has prior approval from the Confidentiality Advisory Group (CAG) and the Research Ethics Committee (REC)).

The right of a participant to refuse participation without giving reasons must be respected.

The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and must be provided with a contact point where he/she may obtain further information about the trial. Data and samples collected up to the point of withdrawal can only be used after withdrawal if the participant has consented for this. Any intention to utilise such data should be outlined in the consent literature.

Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner.

The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

Where the participant population is likely to include a significant proportion of participants who cannot read or write, require translators or have cognitive impairment, appropriate alternative methods for supporting the informed consent process should be employed. This may include allowing a witness to sign on a participant’s behalf (in the case of problems with reading or writing), or allowing someone to date the form on behalf of the participant, or providing Participant Information Sheets in other languages or in a format easily understood by the participant population (in the case of minors or cognitive impairment).

The protocol should specify what arrangements the sponsor considers to be appropriate at site(s) to support the consent process for these participants. For example, if translated written material is to be provided to participants, are these to be provided by the sponsor, or translated locally, and what arrangements are in place to confirm the accuracy of the translation, e.g. back translation; if age appropriate information for minors is to be provided, what age ranges is this divided into; if parent/guardian consent for a minor to participate is being sought, what are the acceptable relationships of the guardian to the minor?

Note that for studies involving sites in Wales, to comply with the Welsh Language Act 1993, the Participant Information Sheets and Consent forms must be translated into Welsh or provided bilingually where this is requested by a participant at a research site.

The protocol should fully describe the process which typically involves:

* discussion between the potential participant or his/her legally acceptable representative and an individual knowledgeable about the research about the nature and objectives of the trial and possible risks associated with their participation
* the presentation of written material (e.g., information leaflet and consent document which must be approved by the REC and be in compliance with GCP, local regulatory requirements and legal requirements
* the opportunity for potential participants to ask questions
* assessment of capacity. For consent to be ethical and valid in law, participants must be capable of giving consent for themselves. A capable person will:
	+ understand the purpose and nature of the research
	+ understand what the research involves, its benefits (or lack of benefits), risks and burdens
	+ understand the alternatives to taking part
	+ be able to retain the information long enough to make an effective decision.
	+ be able to make a free choice
	+ be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)
	+ where participants are capable of consenting for themselves but are particularly susceptible to coercion, it is important to explain how their interests will be protected

General good practice in research (and the basis of legal frameworks relating to both CTIMPs and non-CTIMPs) require that persons incapable of giving legal consent should be given special protection.

A person is assumed to have the mental capacity to make a decision unless it is shown to be absent. Mental capacity is considered to be lacking if, in a specific circumstance, a person is unable to make a decision for him or herself because of impairment or a disturbance in the functioning of their mind or brain. In practice for participants with mental incapacity this means that they should not be included in clinical trials if the same results can be obtained using persons capable of giving consent and should only be included where there are grounds for expecting that their taking part will be of direct benefit to that participant, thereby outweighing the risks. The Mental Capacity Act 2005 does not apply to CTIMPs.

The Clinical Trial Regulations define a child as a person under the age of 16 years of age. The legal framework and ethical considerations for involving young people (between the ages of 16 and 17) in research are set out in the Department of Health Reference Guide to Consent for Examination or Treatment (2009) and should be referred to for any trial including young people (between the ages of 16 and 17). In practice for young people and children this means that only medicinal products which are likely to be of significant value for young people and children are fully studied and the protection of participating children is fully considered.

For further details on the ethical considerations of including participants with mental incapacity or minors in research see the guidance notes available on the HRA website.

http://www.hra.nhs.uk/resources/before-you-apply/consent-and-participation/consent-and-participant-information/

Where the trial allows the inclusion of participants who lack the capacity to consent for themselves (for example, in cases where the research is related to the disease / illness causing mental incapacity), the full procedure for consent by a legal representative must be included in the protocol, along with appropriate information sheets and consent forms.

The issue of entry of incapacitated adults into CTIMPs is covered by The Medicines for Human Use (Clinical Trials) Regulations and the required procedures to be included in the trial protocol are detailed within these regulations. For studies involving Scottish research sites these Regulations supersede the Adults with Incapacity (Scotland) Act 2000 where any conflict arises. The specific schedules of the Regulations must be read and adhered to by the protocol authors.

Where a participant is able to consent for a CTIMP but later becomes incapacitated, the management of these participants must also be stipulated in the protocol; in all such cases the original consent given endures the loss of capacity, providing that the trial has not significantly altered (there may be clinical justification under such circumstances for cessation of any further clinical intervention while data collection for follow-up purposes continues).

Minimum suggested wording (update as required):

It is the responsibility of the Investigator, or a person delegated by the Investigator to obtain written informed consent from each participant prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial.

The person taking consent will be GCP trained, suitably qualified and experienced, and will have been delegated this duty by the Investigator on the Staff Signature and Delegation of Tasks Log.

**“Adequate time”** must be given for consideration by the participant before taking part. Consent will be sought at least 24 hours after being given the study documentation. [If the amount of time between the PIS being given and the date of consent is less than 24 hours, the PI needs to explain the rationale for this]. It must be recorded in the medical notes when the Participant Information Sheet (PIS) has been given to the participant.

The Investigator or designee will explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

No clinical trial procedures will be conducted prior to the participant giving consent by signing the Consent Form. Consent will not denote enrolment into the trial.

A copy of the signed informed consent form will be given to the participant. The original signed form will be retained in the Investigator Site File and a copy placed in the participant’s medical notes.

The PIS and consent form will be reviewed and updated if necessary throughout the trial (e.g. where new safety information becomes available) and participants will be re-consented as appropriate.

### Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Aim: to describe the consenting procedure for ancillary studies (if applicable)

The protocol should state:

* if data and/or biological specimens for ancillary studies will be acquired, transferred and stored during the trial (in line with section 7.12 - Storage and analysis of clinical samples).
* if the data and/or biological specimens will be used for a specified subset of studies or for submission to ethically approved research tissue banks for future specified or unspecified research
* what options participants will be given in respect to their participation in ancillary research including:
	+ whether participation in the ancillary research is required for participation in the trial or if participants may opt out but still participate in the main trial
	+ consent for the use of their data and specimens in specified protocols
	+ consent for use in future research unrelated to the clinical condition under trial
	+ consent for submission to an unrelated bio-bank
	+ consent to be contacted by trial investigators for further informational and consent-related purposes
* whether their withdrawal from the ancillary research is possible and what will happen to material provided up to that point:
	+ for example if the data and/or specimens will be coded and identifiable
	+ what withdrawal means in this context
	+ what information derived from the specimen related research will be provided to them, if any

## Screening

Aim: To list any screening requirements such as laboratory or diagnostic testing necessary to meet any noted inclusion or exclusion criteria such as:-

* physical examination
* medical history
* concomitant medication
* ECG
* laboratory tests
* biopsies and samples
* scans

Any assessments and or procedures performed as part of routine care which will be used to screen participants for eligibility will require defined timelines (e.g. x-rays within the last 6 months). Specify the maximum duration allowed between screening and recruitment (if applicable).

If applicable you may wish to define time period for overall screening e.g. screening has to be completed within 28 days of treatment commencing. Please consider this time window carefully to ensure it is workable (e.g. will results be available in time?) but also ensuring safety/eligibility of participants entered into the trial is not compromised.

Also, specify which assessments can be repeated if they fall outside the time window.

Screen failures i.e. patients who do not meet eligibility criteria at time of screening may be eligible for rescreening participant to acceptable parameters. If this is the case then the process needs to be clearly laid out.

If eligibility screening involves procedures that emit ionising radiation it is vital that the exposure is categorised correctly. The following guidance should be followed:

Ionising radiation exposures are considered to be ‘research exposures’ where the exposure is required as a specified part of, and for the purpose of, the research. For example:

* diagnostic procedures undertaken prospectively to confirm the eligibility of potential participants for the trial or to provide (qualitative or quantitative) data regarding disease status at baseline; or
* radiotherapy as part of a treatment strategy to which participants are assigned prospectively by the protocol, either as part of an experimental or control arm, and which will be evaluated by the trial; or
* diagnostic procedures scheduled at formal time-points within the trial protocol to assess disease status or response to treatment; or
* diagnostic imaging or image-guided procedures undertaken prospectively whilst the participant is enrolled in the trial

Exposures which meet any of these criteria are considered to be research exposures even where they would otherwise be part of normal clinical care for patients treated outside the research setting, and whether or not research participation will result in ‘additional’ exposure over and above routine care.

Suggested wording (update as required):

The following trial specific procedures will be carried out after consent to assess the participant’s eligibility:

Examples:

* Demographics recorded
* Medical History recorded
* Concomitant Medication recorded
* Physical Examination
* Height, weight and oral temperature
* Resting pulse and blood pressure (BP)
* Blood and Urine tests
* Pregnancy test (for women of child bearing potential) (if appropriately timed). Need to specify if this test will be a serum or urine pregnancy test.

The results from the following routine procedures may be used to assess the participant’s eligibility:

Examples:

* chest x-ray within 6 months of consent
* haematology blood test results (must include FBC) within 2 weeks of enrolment

Where routine results are not available, the procedure(s) will be carried out at screening after consent.

All pre-treatment procedures will be carried out as specified in the schedule of assessments (Appendix 1).

## The randomisation Procedures (if randomised trial) / Participant Registration (if non-randomised trial) [delete as appropriate]

**For non-randomised trials only**:

Aim: to provide an overview of the process of registering participants on the trial.

Coordinated registration and allocation of participant trial numbers will be required to enrol participants. You should describe the process, contacts and information required for registration of participants on the trial.

Please note consent and screening does not necessarily constitute enrolment.

Suggested wording:

Participant registration will be undertaken centrally by the coordinating trial team / remotely at sites using [insert name of system].

Following participant consent, and confirmation of eligibility (see section 7.3 - Screening) the registration procedure described below will be carried out.

Participants are considered to be enrolled into the trial following: consent, pre-treatment screening assessments (see section 7.3 - Screening), confirmation of eligibility, completion of the registration, and allocation of the participant trial number by the central coordinating team/remote system.

**For Randomised trials only:**

### Method of implementing the randomisation/allocation sequence

Aim: to describe how the randomisation / allocation sequence will be run in the trial. Protocol should describe details of the randomisation/registration procedure/method. Describe how participants will be allocated to trial treatments/groups. Please note that further information regarding thetype of randomisation used (e.g. simple, block, minimisation etc.) should be provided in section 10.4 - Randomisation Methods.

For example,

* the system to be used (e.g. a web based randomisation/treatment allocation system) and whether delegated to a third party provide,
	+ Telephone randomisation/ registration with email confirmation. If this is the case, include the telephone number and the ‘opening hours’ for randomisation/registration.
	+ Remote randomisation/ registration process (IXRS). If this is the case, include reference to training manual, location and site staff access to remote system. Give details of the randomisation/ registration procedure.

State who will receive new participant/randomisation alerts (preferably to include pharmacy), together with research nurse and/or investigator. Describe how these alerts will be received.

Studies that involve a trial-specific procedure prior to randomisation must include a registration phase prior to randomisation. Describe the procedure for registration and how it relates to subsequent randomisation e.g.

After registration, if a participant is eligible for randomisation do they get allocated a randomisation number to be used in conjunction with the registration number?

* Who will be informed of the participant registration and randomisation (if applicable) and how?
	+ Telephone randomisation/ registration with email confirmation. If this is the case, include the telephone number and the ‘opening hours’ for randomisation/registration.
	+ Remote randomisation/ registration process. If this is the case, include reference to training manual, location and site staff access to remote system. Give details of the randomisation/ registration procedure.

who will access this at each site

how the allocation will be documented e.g. will the system provide an immediate allocation with a confirmatory email

who else will be provided with a copy of the treatment allocation or randomisation number etc.

how will randomisation codes be accessed out-of-hours or in an emergency

## Blinding

Aim: to describe the blinding process to avoid bias in detail. If blinding is not to be used then justification should be provided. If a non-randomised trial then this section can be deleted.

The protocol should explicitly describe:

* who will be blinded to intervention groups including:
	+ trial participants
	+ care providers
	+ outcome assessors

A full description is essential and ambiguous terminology such as “single blind”, “masked” or “double blind” should not be used.

* the comparability of blinded interventions e.g. similarities in appearance, use of specific flavours to mask a distinctive taste
* the timing of final unblinding of all trial participants (e.g., after the creation of a locked analysis data set)
* any strategies to reduce the potential for unblinding such as pre-trial testing of blinding procedures.
* when blinding of trial participants and care providers is not possible because of obvious differences between the interventions, blinding of the outcome assessors can often still be implemented. It may also be possible to blind participants or trial personnel to the trial hypothesis in terms of which intervention is considered active.
* Special attention should be paid to situations where some members of the team are blinded and others unblinded . In this situation the protocol should be explicit in unblinding/masking strategies to ensure compliance.
* Management of sites/CROs etc. where both blind and unblind members of the research team may interact (e.g. pharmacist and nurse drawing up the dose are unblind vs the rest of the research team in order to protect the blind. Consider stating explicit strategies for management of this. Could also include other things which may reveal the treatment i.e. internal INR measurement vs sham outputs.

### Unblinding (if applicable)

We strongly advise that for double blind trials, you enlist the service of a CTU or a specialist company for unblinding (e.g. [www.sealedenvelope.co.uk](file:///C%3A/Users/rehbado/AppData/Local/AppData/Local/Microsoft/Windows/Temporary%20Internet%20Files/Content.IE5/Local%20Settings/Temporary%20Internet%20Files/Gemma%20Athorn/AppData/Local/Microsoft/Windows/Temporary%20Internet%20Files/Effective%20SOPs%20UNDER%20REVIEW/www.sealedenvelope.co.uk)). Any unblinding service procured/ proposed must be available 24 hours a day 7 days a week and have appropriate back up.

Specify the procedure(s) to be used for unblinding for the following situations, refer to trial specific SOPs where applicable.

### Emergency Unblinding

Aim: to provide a clear description of the conditions and procedures for unblinding. If the trial is not blinded then this section can be deleted.

Suggested wording:

The trial code should only be broken for valid medical or safety reasons e.g. in the case of a serious adverse event where it is necessary for the investigator or treating health care professional to know which treatment the participant is receiving before the participant can be treated. Subject to clinical need, where possible, members of the research team should remain blinded.

The protocol should provide a description of the code break method (e.g. code break envelopes, via randomisation list, via interactive voice/web response system). Where the sponsor requires code break to be managed by a particular department/ individuals, this should be explicitly described in the protocol including the rationale for the decision.

The protocol should outline that if the trial is single or double-blind it should give details of who is responsible for unblinding a participant in an emergency. Including full details of the procedure to be followed and by who. If an automated IXRS system is used give details of who and how sites will have access to the unblinding facility e.g. investigator/pharmacy. Bear in mind that an out of hours, an ‘on call pharmacist’ without specialist knowledge of clinical trials may be involved. Include details of any documentation which must be completed at the time of unblinding and by who.

It is essential that any unblinding mechanism does not unblind the whole trial, but only the individual concerned. The actual allocation must NOT be disclosed to the participant and/or other study personnel including other site personnel, monitors, sponsor or project office staff; nor should there be any written or verbal disclosure of the code in any of the corresponding participant documents.

The following information (or similar) should be inserted into the protocol:

* the code breaks for the trial are held [please add relevant department] and are the responsibility of [please add personnel]
* in the event a treatment allocation is required to be unblinded a formal request for unblinding will be made by the Investigator/treating health care professional
* if the person requiring the unblinding is a member of the Investigating team then a request to the holder of the code break envelope/list, or their delegate will be made and the unblinded information obtained
* if the person requiring the unblinding is not the Investigator then that health care professional will notify the Investigating team that an unblinding is required for a trial participant
* on receipt of the treatment allocation details the Investigator or treating health care professional will continue to deal with the participant’s medical emergency as appropriate
* the Investigator should document the breaking of the code and the reasons for doing so on the CRF/data collection tool, in the Investigator Site File and medical notes. It will also be documented at the end of the trial in any final trial report and/or statistical report
* the Investigator will notify the Sponsor in writing as soon as possible following the code break detailing the necessity of the code break
* The written information will be disseminated to the Data Safety Monitoring Committee for review in accordance with the DMC Charter (if applicable). The responsibility for which should be assigned and documented
* As investigator is responsible for the medical care of the individual trial participant (Declaration of Helsinki 3§ and ICH 4.3) the coding system in blinded trials should include a mechanism that permits rapid un-blinding (ICH GCP 5.13.4). The investigator cannot be required to discuss un-blinding with the sponsor if he or she feels that emergent unblinding is necessary.
* SUSARs are required to be reported unblinded (for more information see Section 9.4.3 - Unblinding for the submission of SUSAR reports)

For more information consult the following EMA GCP Q&A document: <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000016.jsp&mid=WC0b01ac05800296c5>

## Baseline Data

Aim: To clearly describe the baseline data that needs to be collected. NB: only data that forms part of the predefined data set essential for analysis should be collected.

The following should be considered for baseline data and subsequent trial assessments:

* the relevance of each baseline variable. Do not include a variable solely on the grounds that it is always recorded, if there is genuinely no interest in the variable
* if any of the procedures need to be undertaken in a certain order or in a certain way – i.e. sitting vs standing, left arm vs right arm, fasted state
* are explanations needed? E.g. if 3 measurements are to be taken and averaged that should be explained
* for particularly complex procedures or those that differ from routine standard practice, these should be detailed in full. E.g. if a 6 lead ECG is normal routine practice but the trial requires a 12 lead ECG this will need to be made clear to avoid potential errors
* if there are any translational aspects of the trial for example the collection of blood or tissue samples, this should be detailed in the relevant sections of the protocol (e.g., assessments section, analysis section, storage of samples section etc.)
* if specialist, non-standardised assessments are required, care should be taken to detail exactly what needs to happen during the assessment
* It is an offence under the data protection act to process data that is irrelevant or excessive for the purpose for which it was collected. CRFs must therefore collect only the information directly relevant to the objectives and outcome measures detailed in the protocol. Collecting additional data not so specified is not permissible.
* Specify any additional assessments for baseline measurements prior to treatment (these may all be taken during the same visit or at a different time prior to treatment) and indicate timing. Any additional assessments to be carried out immediately prior to dosing should be detailed here. Please specify for these additional pre-treatment assessments which results need to be back before the first dose of IMP, and which may not or will not be back.

## Trial Assessments

Aim: To clearly describe the trial assessments.

The protocol should describe:

* all trial procedures and assessments, including those that are part of routine care (if data will be captured from these routine assessments as part of the trial)
* the timing of the assessments should be detailed and broken down into visit numbers as appropriate, for example clearly defined visit window i.e. +-3 days
* the detail of any run-in or washout periods
* the time points for assessment data e.g. The following are to be recorded each month for the first 12 months and every three months afterwards:
* History and clinical examination
* Assessment of the toxicity of the previous course
* Weight
* Full blood count
* Biochemical series
* Chest X-ray
* Etc.
* how compliance will be checked if home dosing
* when diary cards should be checked
* any use of electronic participant reported outcome devices. In general, if third parties are involved in the provision of services related to the assessment or data collection then this should be detailed.
* assessment data required at the end of trial visit
* the methods and timing for assessing, recording and analysing efficacy parameters e.g.:
* the values/scores that will determine success or failure and how they will be assessed if appropriate
* Survival e.g.: These will be measured from the date of randomisation and will be reported for all deaths due to all causes. The cause of death is to be recorded in all instances
* Quality of life assessments if required

## Long term follow-up assessments

Aim: To clearly describe the long term follow-up assessments

If participants will be monitored after the active treatment phase has closed the protocol should describe:

* The frequency of follow-up visits
* duration of follow-up period
* assessments to be carried out
* how the follow up due to the research differs from standard of care
* retention strategies
* how participants will be identified as ‘lost to follow-up’
* measures taken to obtain the information if visits or data collection time-points are missed.
* which outcome data will be recorded from protocol non-adherers

Trial investigators should seek a balance between achieving a sufficiently long follow-up for a clinically relevant outcome measurement, and a sufficiently short follow-up to prevent missing data and avoid the associated complexities in both the trial analysis and interpretation.

## Qualitative Assessments (if applicable/delete if not applicable)

Aim: To describe any qualitative research that forms part of the trial

This section should detail any qualitative component to the trial and provide a rationale for the timing and tools for assessment, for example measuring the acceptability of the intervention or measuring reasons for non-adherence to trial medication. This section should also detail instructions for the timing and administration of measures and whether the nested qualitative component is optional or not. Timing should include the window around the time point for which each questionnaire/ focus group/interview should be completed, details regarding chasing of questionnaires and how participants with missing baseline measures will be followed-up. NB: Any data that contribute to the outcome/ endpoints of the trial should ideally be included in the case report form with a signature of the reviewer.

Further information on nested studies can be found in the Medical Research Council’s guidance on developing and evaluating complex interventions. [www.sphsu.mrc.ac.uk/Complex\_interventions\_guidance.pdf](file://ims.gov.uk/data/Users/GBEXPVD/EXPHOME14/WBowen/Data/Desktop/Protocol%20Template/Final%20CTIMPs/www.sphsu.mrc.ac.uk/Complex_interventions_guidance.pdf)

## Discontinuation / Withdrawal Criteria

Aim: To give a full description of the withdrawal criteria

It is always within the remit of the physician responsible for a patient to withdraw them from a trial (or certain aspects of the trial) for appropriate medical reasons, be they individual adverse events or new information gained about a treatment.

The protocol should therefore:

* Describe under what circumstances and how participants will be withdrawn from the trial / investigational product treatment – including whether the participant would continue to be part of the trial if IMP was withdrawn for specific reasons.
* Attention should be paid to what aspects of the trial the participant is withdrawing/ been withdrawn from. Are there certain aspects of the trial that you wish to continue? For example withdrawal from further treatment, withdrawal from translational aspect or complete withdrawal.
* Give details of documentation to be completed on participant withdrawal (including recording reasons for withdrawal and any follow-up information collected with timing)
* Whether and how participants are to be replaced (e.g. if a randomised trial, would the replacement be randomised to the same treatment as the participant they are replacing?)
* The follow up of participants that have withdrawn from the treatment / trial
* State under what circumstances the trial might be prematurely stopped.
* Include whether there is Withdrawal of Consent to Data Collection - ***this section must be consistent with the information contained in the PIS***
* If a participant explicitly states they do not wish to contribute further data to the trial their decision must be respected and recorded in the CRF and medical notes.
* If withdrawal or discontinuation is due to loss to follow-up
* If a participant moves from the area, every effort should be made for the participant to be followed up at another participating trial site and for this new site to take over the responsibility for the participant. (Delete this paragraph if trial is not a multisite trial.)
* If a participant is lost to follow-up at a site every effort should be made to contact the participant’s GP to obtain information on the participant’s status. ***(Include if applicable and in line with consent to contact GP in the PIS)***

## Stopping Rules

The trial may be stopped before completion for a number of reasons for example

* On the recommendation of the TSC or IDMC
* On the recommendation of the Sponsor and CI
* If a particular safety event or number of safety events are seen *(please describe)*

Provide explanation as to why the trial may be stopped.

## Storage and analysis of clinical samples (if details are provided in a laboratory/pathology manual there is no requirement to duplicate information in the protocol, but details of tests to be performed should be included so it is recommended to include a table as below if not covered in other sections)

Aim: To describe the procedure for dealing with biological samples

The protocol should describe the procedure for dealing with biological samples:

* the criteria for the collection, analysis, storage and destruction of biological samples
* the record keeping requirements for processing, transfer and storage should be clearly outlined
* the arrangements for sample collection
	+ sample type(s) e.g. whole blood, plasma, serum, saliva, urine, stool, fresh tissue biopsy, paraffin tissue block
	+ volume of sample(s) to be collected
	+ types of tubes, containers, swabs to be used for sample collection, and whether these will be provided by the sponsor or must be sourced locally by site(s)
	+ sample processing arrangements e.g. centrifugation (how soon after collection should samples be spun, how long for, at what speed, at what temperature)
* the arrangements for sample analysis
	+ whether samples will be tested/analysed locally or sent to a central facility
	+ which tests will be undertaken at local **and** central labs (example table can be used below)

|  |  |
| --- | --- |
| Laboratory test | Parameters |
| **BLOOD** |
| Haematology | leukocytes, erythrocytes, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), platelets, neutrophils, eosinophils, basophils, lymphocytes, monocytes;  |
| Serum chemistry | glutamate pyruvate transaminase (GPT / ALAT), glutamic-oxaloacetic transaminase (GOT / ASAT), gamma-glutamyl transferase (gamma-GT), alkaline phosphatase, total bilirubin, creatinine, chloride, potassium, sodium, total protein, albumin |
| Screening test | Hepatitis-B-virus surface antigen (HBsAg), anti-hepatitis C virus (anti-HCV) antibodies, immunodeficiency virus 1 an 2 (anti-HIV1/2) antibodies, Treponema pallidum haemagglutination *(*TPHA*)* test |
| **URINE** |
| Urinalysis (dip stick) | pH-value, urobilinogen, erythrocytes, total protein, ketone, bilirubin, nitrite, glucose |

* + how soon after collection should the samples be analysed or shipped
	+ if the samples are to be shipped, include details of the arrangements for this (e.g. on dry ice), indicate whether the sponsor or the site(s) will be responsible for arranging the courier to transport the samples
	+ what will happen to the samples after they have been analysed; will they be stored or destroyed (see below)
* the storage arrangements for samples
	+ how soon after collection should the samples be put under storage conditions
	+ how long will the samples be stored for, and what will be done with the samples after this time (e.g. destruction)
	+ where samples will be stored; locally at site(s) or sent to a central storage facility (and shipping arrangements if the latter)
	+ whether any samples will be held in long-term storage for future unspecified use, or held in an ethically approved tissue bank (in which case consent and Human Tissue Act need to be considered and addressed)
	+ what conditions should the samples be stored under (if samples are to be stored in specialist fridges or freezers e.g. a -80°C freezer, then it is beneficial to specify that samples will be stored at -80°C +/- 10°C (or the tolerance to which you specify), rather than to state -80°C. This will avoid numerous notifications of temperature deviations, when not really required)
* the destruction arrangements for samples
	+ when the samples will be destroyed; after analysis, after a set storage period?
	+ how the samples should be destroyed
	+ how destruction should be recorded
	+ that for any specialist sample handling, processing and or shipment, a lab manual will be available and to refer to the manual
* Reference to which SOPs and lab manual/sample management is being used
* The same information above will be required for the translation research samples being used if applicable

The following statement sets out the responsibilities of the trial site in regard to samples and can be included in the protocol if appropriate:

It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the Data Protection Act 2018. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

## End of trial

The protocol should define the end of the trial and expected trial duration. The safety and efficacy follow up involving active data collection (trial visits etc.) should form part of the clinical trial.

The sponsor must notify the MHRA of the end of a clinical trial within 90 days of its completion. It is usually the date of the last visit/data item of the last participant undergoing the trial. For the purpose of informing the MHRA “database lock” is not appropriate as a definition as it does not allow for early termination (see Section 10.6 - Interim analysis and criteria for the premature termination of the trial) to be reported within 15 days.

# TRIAL TREATMENTS

Aim: To provide a full description of the investigational drug(s) to be used plus any other non-investigational medicines, medical device, food supplement, radiation, surgery, behavioural interventions, etc. that forms part of the trial

According to the definition of the EU clinical trial directive 2001/20/EC, an investigational medicinal product 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 for an unauthorised indication, or when used to gain further information about the authorised form. Information about the comparator product/placebo should also be given in this section if they are not classed as IMPs. If the comparator/placebo is classed as an IMP it should be listed in section 8.1.

**It is recommended that expertise is sought from the JRO Regulatory Manager (pharmaceuticals) whilst developing this section.**

For this section of the protocol you might find the following document useful to read:

“Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials”

This document can be downloaded at:

<http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm>

## Name and description of investigational medicinal product(s)

Aim: To give a full description on the IMP and other medication to be used in the trial

Please refer to the following guidance for classification of IMPs and Non-Investigational Medicinal Products (NIMPs):

<http://ec.europa.eu/health/files/eudralex/vol-10/imp_03-2011.pdf>

The protocol should specify:

* For each IMP, specify its international non-proprietary name (or a unique reference code where the active ingredient is still under development), strength, formulation, and pack size.
* Where the IMP has been manufactured/packaged specifically for the trial (i.e. different to what is commercially available on the market), this should be clearly stated in the protocol, and the details of its presentation (i.e. contents, packaging and labelling) should be provided in a separate guide/manual for IMP handling and management (e.g. pharmacy manual).
* If the IMP is a product with marketing authorisation (i.e. UK-licensed and commercially available on the UK market), specify the brand name/manufacturer where a specific brand/manufacturer is required. Where the brand/manufacturer is not specified in the protocol, include a statement making clear that any brand/manufacturer of the IMP with a marketing authorisation in the UK can be used. (Seek further advice if the trial involves research sites outside of the European Economic Area)
* For IMPs under development or where commercially marketed products have been modified (e.g. over encapsulation), provide a description of the final dosage form including a summary of its chemical properties and excipient content (or reference can be made to an Investigational Medicinal Product Dossier (IMPD) for details).
* For CTIMPs using chemotherapy treatment the National Institute for Health Research, Clinical Research Network; Cancer Chemotherapy and Pharmacy Advisory Service (CPAS) Guidance should be referred to in drafting this section of the protocol
* For blinded clinical trials, provide details of how the IMP will be packaged to maintain blinding. For example:
	+ Drug X and Drug Y will be packaged in an identical manner. A unique pack ID will be used to identify each pack and its content.
	+ Drug X and placebo to look identical e.g. over-encapsulation or manufacturing of placebo to match Drug X
	+ Drug X and placebo will be packaged in a manner which is distinguishable to research sites so must be received by and handled only by unblinded personnel until distinguishing features are obliterated at the point of issue to blinded researchers or dispensing to the participant.

## Regulatory status of the drug

Aim: To define the regulatory status of the IMP

For each IMP, specify whether it has a marketing authorisation (MA) in the UK and whether or not it is being used in its marketed presentation and packaging bearing the MA number.

Where the IMP has a marketing authorisation in the UK but is further processed (e.g. repackaging and trial labelling) for the trial, specify the name and address of the organisation(s) performing such activities along with their manufacturing licensing details.

Where the IMP does not have a marketing authorisation in the UK, specify the name and address of the manufacturer(s), and importer where appropriate. (Seek further advice if the trial involves an IMP which is licensed in a country within the European Economic Area but not licensed in the UK).

## Drug storage and supply (if this is included in a pharmacy manual then there is no requirement to duplicate information in the protocol)

Aim: To describe the procedures for the ordering, shipment, receipt, distribution, return and destruction of the investigational medicinal products including placebo.

The protocol should include:

* For each IMP, specify the source of supply – For example:
	+ Free of charge and delivered from sponsor
	+ Discounted commercial supply ordered via trial specific arrangement (specify details of discount arrangement & source of supply)
	+ Sourced locally by the research site pharmacy at market price
* For each IMP, provide an overview of the initial order and re-ordering process. For example:
	+ Initial shipment: Supplied at site activation/ triggered by participant enrolment / manual ordering
	+ Re-ordering: Automatic triggered supply / manual ordering
* any special supply processes, e.g. a triggered release process or central supply to all sites from a 3rd party
* how the drug should be stored
* who will supply e.g. which site and how e.g. ‘upon receipt of a suitably signed trial specific prescription’
* any storage instructions once dispensed from pharmacy e.g. stored in a fridge at ##°C and used within 24 hours depending on the requirements of the product
* details of accountability and destruction/return, so that it can be verified who received what treatment and when
* any recall procedures stipulated by the sponsor
* Arrangements for post-trial access to IMP

For multicentre trials where supply details may vary between sites, this section should cover only aspects applicable to all sites.

## Preparation and labelling of Investigational Medicinal Product

Aim: To give a precise and complete description of the preparation and labelling of the IMP

The protocol should provide an overview of the method of IMP reconstitution/ dilution/ preparation for each IMP. Reference the guide/manual for IMP handling and management for further information on IMP preparation.

For each IMP, provide information on labelling status/ requirements. For example:

* IMP supplied by sponsor with annex 13 compliant labels
* Research site pharmacies to apply annex 13 compliant labels under Regulation 37 exemption.
* Exemptions to annex 13 labelling apply

Preparation and labelling of the investigational medicinal products should be completed in accordance with the relevant GMP guidelines.

<http://www.ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm>

## Dosage schedules

Aim: To give a precise and complete description of the dosage schedules

The dosing schedule for each drug should include:-

* description and justification of route of administration; oral, intravenous etc.
* frequency of administration
* details of dose adjustments e.g. dose escalation/de-escalation
* number of cycles/duration for chemotherapy
* timing of each dose
* dose capping
* information on what action would be taken if:
	+ a dose is missed i.e. is there a window within which a subject can take a missed dose e.g. within 6 hours of usual dosing time
	+ vomiting following a dose
* Dose-banding: State whether or not dose-banding of drugs is acceptable and indicate which drug(s), this applies to. (For further details on NHS England dose banding for chemotherapy drugs refer to https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b02/)
* if the drug is to be infused, it is important to detail how long the infusions will take – for example 5mg/kg (to a maximum of 250mg) infused over 8 hours. Include -/+ minutes or hours if permitted for infusion time, as appropriate.
* maximum dosage allowed each time the drug is given
* methods for monitoring cumulative dosing where required
* Where dosage is dependent on laboratory data, specify whether blood specimens must be taken on the day of dosing or specimens can be taken in advance in line with routine local procedure.
* methods for individualised doses, if calculations are required then state what specific calculation is to be used (if applicable)
* Where dosage is calculated using parameter(s) (e.g. body surface area, creatinine clearance) derived from specific equation(s), specify the equations(s) to be used or specify that routine local practice is acceptable. Any additional rules to be applied when using these equations should also be clearly stated.
* For weight based dosing, specify whether weight must be taken on the day of dosing or can be taken in advance (state time limits).
* maximum duration of treatment of a participant. The total amount of time the participant will be receiving the IMP. This is not necessarily the length of participant participation in the trial
* State whether dosage will be adjusted with weight change, and clearly detail any rules (e.g. participant should be weighed and if required, adjustment of dosage should only occur every 12 weeks at visit 3, 6, and 9)
* restarting treatment after temporary suspension.
* any blinding requirements for lines, giving sets, pumps etc.

## Dosage modifications

Aim: To give details here on required dose modifications (if applicable)

The protocol should detail:

* if the dose should be modified for example in the case of certain adverse events (specify the exact dose modifications and events and whether any specific dose calculations need to be performed by sites)
* the stopping rules (for individual participants and the trial as a whole)
* the restarting rules (for individual participants and the trial as a whole)
* treatment breaks/ drug-free holidays
* whether participants can increase the dose if they have previously been dose reduced for some reason. Also what about treatment breaks/ drug-free holidays
* whether the dosage will be modified in accordance with the participants results (e.g. lab results – and what the results should be) and whether this will be completed under controlled hospital conditions or whether the participant will be required to adjust their own dosages following medical guidance at home
* whether the dose can be modified due to participant request
* procedures in the event of toxicity reactions (if applicable) e.g. if it is possible to reduce the dosage of IMP or if any rescue medication may need to be administered
* when a dose modification will result in the participant having to withdraw from treatment

## Known drug reactions and interaction with other therapies

Aim: To identify any known drug reactions or interaction with other therapies or situations e.g. photosensitivity

The protocol should:

* cross-reference this with the section on safety reporting if applicable
* also cross reference this with the SmPC and/or IB
* list any prohibited concomitant medications or therapies in this section

## Concomitant Medication

Aim: To provide a full description of concomitant medication, it is important to consider topical medicine as well as oral and IV e.g. use of steroids – are topical steroids and inhaled steroids permitted but not systemic steroids? Use of other creams and emollients and timings for topical IMP trials

The protocol should:

* specify medication(s)/treatment(s) permitted and not permitted before, during and/or after the trial including their time restrictions
* consider possible interactions or effects that could confound the results and conclusions. Do not confuse these with Non-Investigational Medicinal Products (NIMPs)
* state wash out times from previous medication if applicable
* whether surgery/radiotherapy is allowed whilst on trial IMP

## Trial Restrictions

Aim: To provide a full description of trial restrictions

The protocol should specify:

* any contraindications whilst on the active phase of the trial including dietary requirements/restrictions
* whether contraception needs to be used and the duration for use. The list of approved contraception for the trial should be fairly extensive. For example: Women of childbearing potential are required to use adequate contraception for the duration of the trial and for ## weeks / months after the completion of the trial. This includes:
	+ Intrauterine Device (IUD)
	+ Hormonal based contraception (pill, contraceptive injection etc.)
	+ Double Barrier contraception (condom and occlusive cap e.g. diaphragm or cervical cap with spermicide)
	+ True abstinence
* also list any requirements for male participants

For further information on contraception and pregnancy testing consult the following guidance document: <https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf>

## Assessment of compliance with treatment

Aim: To describe how and by who compliance will be assessed

Define procedures for:

* monitoring (e.g. watching participant swallow pills and checking their mouth afterwards, getting participants to complete a diary card, package returns, weighing and measuring)
* deciding the percentage of IMP compliance acceptable for participant to continue on the trial
* recording of participant compliance information (what will be recorded, when and where and by who)
* how non-compliance to the protocol trial procedures will be documented by the investigator and reported to the Sponsor
* deciding when persistent non-compliance will lead the participant to be withdrawn from the trial e.g. percentage of non-compliance acceptable for participant to continue on the trial is <80% non-compliance equates to participant withdrawal (this includes compliance with IMP and trial procedures e.g.. visit window, refusal of trial specific assessments)
* following-up non-compliant participants
* improving compliance- ideally these should be strategies that can be easily implemented in clinical practice so that the level of compliance in the real world setting is comparable to that observed in the trial

## Name and description of each Non-Investigational Medicinal Product (NIMP)

Aim: To give a full description of each NIMP

The protocol should include some details about the NIMPs which are any products supplied to the trial participants according the protocol but are NOT under investigation.

They could be:

* challenge agents
* rescue or escape medication
* medicinal products used to assess end points
* any other product which is not under investigation that will be used in the trial, including any background medication(s) administered to all participants

Include details of the dosage, treatment duration and administration; if it is going to be provided by the sponsor and other details of storage and supply as appropriate.

Please refer to the following guidance for classification of NIMPs:

<http://ec.europa.eu/health/files/eudralex/vol-10/imp_03-2011.pdf>

A similar system to that required for IMPs needs to be implemented if the NIMPs are unlicensed (e.g. might come from another EU country or a country outside EEA) for further details see MHRA Guidance Note 14 ‘Supply of Unlicensed Medicinal Products (Specials)’: <https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/373505/The_supply_of_unlicensed_medicinal_products__specials_.pdf>

In all other cases host sites are responsible to maintain a system which allows adequate reconstruction of NIMP movements. There should be a procedure to record which participants received which NIMPs during the trial and an evaluation of the compliance.

# PHARMACOVIGILANCE

Suggested wording (update as required, if safety reporting has been delegated to a CTU/CRO add reference to appropriate SOP(s)):

Collection, recording and reporting of adverse events to the sponsor will be completed according to the sponsor’s SOP for the Recording, Management and Reporting of Adverse Events by Investigators (JRO/INV/S05).

## Definitions

|  |  |
| --- | --- |
| **Term** | **Definition** |
| **Adverse Event (AE)** | Any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment. *Therefore an AE can be any unfavourable or unintended change in the structure (signs), function (symptoms) or chemistry (laboratory data) in a subject to whom an IMP has been administered, including occurrences which are not necessarily caused by or related to that product.* |
| **Adverse Reaction (AR)** | A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function. *This definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.**This definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.* |
| **Serious Adverse Event (SAE)****or****Serious Adverse Reaction (SAR)** | Any adverse event or adverse reaction in a trial subject that:1. requires inpatient hospitalisation or prolongation of existing hospitalisation;

*Note: hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Therefore, participants do not need to be hospitalised overnight to meet the hospitalisation criteria. Hospitalisation (including hospitalisation for an elective procedure) for a pre-existing condition (prior to study entry) which has not worsened does not constitute a serious experience*1. results in persistent or significant disability or incapacity;

*Note: substantial disruption of one’s ability to conduct normal life functions*1. results in a congenital anomaly or birth defect;

*Note: in offspring of subjects or their partners taking the IMP regardless of time of diagnosis*1. is life threatening; or

*Note: places the subject, in the view of the investigator, at immediate risk of death from the experience as it occurred, this does not include an adverse experience that, had it occurred in a more severe form, might have caused death;* 1. results in death

Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such **important medical events** should also be considered as serious.The term “**severe**” is often used to describe the intensity of an event or reaction (e.g. mild, moderate or severe) and should not be confused or interchanged with the term “**serious**”. |
| **Suspected Unexpected Serious Adverse Reaction (SUSAR)** | A serious adverse reaction, the nature, severity or outcome of which is not consistent with the Reference Safety Information. |
| **Reference Safety Information (RSI)** | A list of medical events that defines which reactions are expected for the IMP being administered to clinical trial subjects, and so do not require expedited reporting to the Competent Authority. It is contained in a specific section in the Summary of product characteristics (SmPC) or the Investigator Brochure (IB). |

## Recording and Reporting Adverse Events

Aim: to provide operational information on recording and reporting adverse events

Recording of adverse events in the CRF normally occurs following IMP administration. However where trial specific interventions or NIMPs are administered prior to the IMP, adverse events occurring at this time point may be required to be recorded in the CRF.

The identification of adverse events that require reporting in the CRF will differ for individual trials and will be influenced by:

1. The nature of the intervention, for example:
* CTIMP with well known safety profile; using licensed drug(s) in licensed indication: in such trials it may be considered appropriate that certain AEs and ARs are not required to be reported, if they will not improve the knowledge regarding the safety profile of the drug and are not required for the trial analysis. Such adverse events should **still** be recorded in medical notes.
* CTIMP with less well known safety profile; using unlicensed drug(s) or licensed drug(s) outside of the licensed indication and where little class evidence is available. In such trials it would be considered appropriate that all AEs are required to be reported.
* Any reduced reporting must be justified and in-line with the documented risk assessment (see Section 2.1 - Assessment and management of risk) as per MHRA guidance.
1. The endpoints or design of the trial, for example:
* Where efficacy endpoints could also be (S)AEs or (S)ARs the integrity of the trial may be compromised by having such events reported through the safety monitoring / pharmacovigilance process. In such cases, the protocol can specify that deterioration of the existing condition or known side-effects recorded as primary or secondary endpoints are not reported as (S)AEs or (S)ARs but are recorded separately. For example, the protocol can specify that deterioration of the existing condition or known side-effects recorded as primary or secondary endpoints are not reported as adverse events.

In all cases AEs and / or laboratory abnormalities that are critical to the safety evaluation of the participant must be reported to the Sponsor; these may be volunteered by the participant, discovered by the investigator questioning or detected through physical examination, laboratory test or other investigation. Where certain AEs are not required to be reported to the Sponsor, these should still be recorded in the participant’s medical records.

Suggested wording (update as required):

All adverse events will be recorded in the participant’s medical records in the first instance.

Adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

All Adverse events will be recorded in the CRF following [insert as appropriate e.g. consent / IMP administration] until [insert as appropriate e.g. the participant completes the trial / 1 year after administration of the IMP].

Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the CRF.

If certain events are not to be recorded as AEs in the CRF include a list here, example text:

The following [events/episodes] in this patient population do not need recording in the CRF. These adverse events still need to be recorded in the participant’s medical record. However if the AE meets a serious criterion it must be reported as an SAE (see section 9.4).

*
*

## Assessing Adverse Events

Each adverse event will be assessed for severity, causality and seriousness as described below.

### Severity

Suggested wording:

The medical assessment of severity will be determined by using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version [add current version] regardless of causality at each assessment. For AEs that are not captured in the CTCAE, the intensity will be determined by using the following definitions:

|  |  |
| --- | --- |
| **Category** | **Definition** |
| **Mild** | The adverse event does not interfere with the participant’s daily routine, and does not require intervention; it causes slight discomfort. |
| **Moderate** | The adverse event interferes with some aspects of the participant’s routine, or requires intervention, but is not damaging to health; it causes moderate discomfort. |
| **Severe** | The adverse event results in alteration, discomfort or disability which is clearly damaging to health. |

### Causality

The assessment of relationship of adverse events to the administration of IMP must be made by the investigator (or delegated medically qualified person). It is based on clinical judgement using all available information at the time of the completion of the case report form.

If a differentiated causality assessment which includes other non-IMP factors in the trial is deemed appropriate, please add/amend the following wording to specify:

It is of particular importance in this trial to capture events related to [the product application procedure (specify e.g. surgery) / product failure / mandatory concomitant medications (specify e.g. conditioning chemotherapy) / the medical device(s) (part of a combine product or used for the application of the product, please specify)]. The assessment of relationship of an adverse event to [this/these] additional safety issue(s) will also be carried out as part of the trial.

The differentiated causality assessments will be captured in the trial specific CRF/SAE Recording Log and/or SAE Reporting Form (amend as required).

The following categories will be used to define the causality of the adverse event:

|  |  |
| --- | --- |
| **Category** | **Definition** |
| **Related**  | A causal relationship between an IMP/investigational treatment and an adverse event is at least a **reasonable possibility**, i.e., the relationship cannot be ruled out. |
| **Not Related**  | There is **no reasonable possibility** of a causal relationship between an IMP/investigational treatment and an adverse event. |

### Seriousness

All events are assessed for seriousness as defined for an SAE in Section 9.1 - Definitions.

## Recording and reporting of Serious Adverse Events

Aim: to describe the recording and reporting of SAEs, SARs and SUSARs

The period of time over which SAEs, SARs and SUSARs must be recorded and reported must be clearly stated in the protocol. The point where recording / reporting usually starts is IMP administration. However where trial specific interventions or NIMPs are administered prior to the IMP, adverse events occurring at this time point may be required to be recorded in the CRF.

The point where recording / reporting ends is based on the regulatory requirements, intervention and the trial design and the following should be considered in making this decision:

* The active monitoring period for (S)ARs should be defined based on the amount of information available regarding how long the IMP remains active in the participant, how long it may remain active / inactive in the participant and potentially be transferable to a foetus, how long it takes for (S)ARs to peak (e.g. is there an anticipated cumulative effect of dosing and when is this likely to occur), known late effects (e.g. secondary malignancies that will require active monitoring). It is not acceptable to simply state that SAEs will be actively monitored for 30 days post last treatment without justification.
* following the active monitoring period (when the participant has finished treatment and the active monitoring period has ended) investigators are still required to report any SARs or SUSARs that they become aware of.
* Safety reporting periods for SAEs and SARs must be equal across all arms of a randomised trial to prevent any bias in reporting.

Where a participant withdraws consent for further processing of data, this does not preclude the reporting of SARs and SUSARs which are required to continue being reported according to the protocol for regulatory purposes.

In all cases SAEs should be reported to the Sponsor, although it is acceptable to specify that certain SAEs do not require immediate reporting, e.g. in trials using a drug with a well-known safety profile based on a documented risk assessment. Assessment of seriousness, causality and expectedness for trials involving IMPs must be made by the sponsor or designated authority e.g. investigator. If an authorised doctor from the reporting site is unavailable, initial reports without medical assessment should be submitted to the Sponsor by a healthcare professional within 24hours of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter.

Suggested wording:

All **Serious Adverse Reactions (SAEs)** occurring from the time of [insert as appropriate e.g. written informed consent / randomisation / start of trial treatment]until [insert as appropriate e.g. XXX days post cessation of trial treatment / last trial visit] must be recorded in the medical records, the CRF, [insert if applicable: the SAE Recording Log / SAE and AE Recording Log] and Sponsor SAE Reporting Form and reported to the Sponsor **within 24 hours** of the research staff becoming aware of the event.

The Investigator or designated individual will complete the Sponsor’s trial specific SAE Reporting Form and email it to the Sponsor at **SAE@ucl.ac.uk**. The Investigator will respond to any SAE queries raised by the Sponsor as soon as possible.

Completed SAE Reporting Forms must be sent to the Sponsor within 24 hours of becoming aware of the event

**Email SAE Forms to:** **SAE@ucl.ac.uk**

Any change of condition or other follow-up information should be emailed to the Sponsor, on an SAE Reporting Form (clearly marked as follow-up) as soon as it is available or at least within 24 hours of the information becoming available.

Events will be followed up until the event has resolved or a final outcome has been reached. SAE follow-up should continue after completion of protocol treatment and/or trial follow-up if necessary. Any SAR will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred until resolved.

In addition, the sponsor’s SAE log is used to collate SAEs so that the CI can review all in one place for trend analysis. If this data will be collated on a database throughout the trial, from which a line listing of the SAEs can be extracted for review, a separate SAE log will not be required. Please note for some higher risk trials such as Phase I trials this log/listing would also include AEs. For multi-site trials there must be instructions as to how and when the CI will be informed of SAEs at all trial sites. It is recommended that SAE Recording Logs and SAE Reporting Forms are sent to the CI using a trial specific email address in addition to reporting them to the Sponsor.

Suggested wording:

The [insert as applicable: SAE Recording Log / SAE and AE Recording Log / SAE line listing] will be reported from each site to the Sponsor [and Chief Investigator, if appropriate] [monthly / quarterly / once a year] or upon request.

### Serious Adverse Events which do not require reporting to Sponsor

You may choose not to report some particular SAEs to the sponsor on a SAE Reporting Form. Exceptions can include certain hospitalisations (e.g. routine, general care, outpatient), or SAEs anticipated to occur on a regular basis and offer no further new information to your safety profile e.g. deterioration of the existing condition, known expected side effects as specified in the SmPC or an anticipated adverse event related to a surgical procedure. It should be specified that where the frequency or severity of these events is unusual they must be reported. These events must continue to be recorded in the medical records in the first instance, and in the CRF and SAE Recording Log if deemed appropriate. However you may state that you will not complete an SAE Reporting Form and forward it to the sponsor within 24 hours. Please provide the rationale for doing so.

**Example of exception wording**:

The following events do not require immediate reporting to the sponsor as SAEs, however they will be still be recorded in the participant’s medical records.

Hospitalisation for:

* Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
* Any admission to hospital or other institution for general care where there was no deterioration in condition.
* Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

Include the below wording if applicable for your study and after discussion with the JRO.

The following SAEs anticipated from [surgical procedures / common side effects of IMP administration / deterioration in condition under study (*delete as applicable*)], as listed below do not required expedited reporting to the Sponsor on an SAE reporting Form. The SAEs will still be recorded in the participant’s medical record, CRF and SAE Recording Log:

* *Please specify*

Please provide rationale for including these anticipated events that do not need expedited reporting to the Sponsor.

If the frequency or severity of these events is not consistent with the [SmPC / IB / disease under study *(delete as applicable)*], the event must be reported to the sponsor as an SAE in the normal way.

### SUSAR Reporting

Suggested wording:

All SAEs assigned by the PI or delegate as suspected to be related to IMP-treatment (SARs) will be assessed for expectedness against the current approved Reference Safety Information (RSI) for the trial by the Sponsor.

The following categories will be used to define the expectedness of the SAR:

|  |  |
| --- | --- |
| Category | Definition |
| *Expected* | An adverse event which is consistent with the information about the IMP listed in the current approved Reference Safety Information (RSI) for the trial.  |
| *Unexpected* | An adverse event which is not consistent with the information about the IMP listed in the current approved Reference Safety Information (RSI) for the trial.  |

All SARs assessed as unexpected will be classified as SUSARs and will be subject to expedited reporting to the MHRA and REC.

When determining the anticipated nature of ARs and SARs, appropriate Reference Safety Information (RSI) must be used, for instance an IB for the IMP must be used where the IMP is unlicensed (i.e. it does not have a marketing authorisation). Where the IMP being used is licensed, but is being used outside of its licensed indication, an IB should be used where available and should be supplied from the collaborating pharmaceutical company, if they are supplying the drug. There may be certain situations where it is acceptable to use the latest SmPC, but consultation with the Sponsor will be required. Where a generic IMP is to be used one comprehensive SmPC should be chosen at time of request for a CTA for use in the trial for the purposes of pharmacovigilance monitoring only; for any other information regarding a generic IMP, the site should be instructed to refer to the relevant manufacturer’s SmPC and ensure that a copy of this is saved in the Investigator Site File.

The Reference Safety Information (RSI) that is used for pharmacovigilance purposes is used to assess the expectedness of events and will be checked by the sponsor for changes on the anniversary of the issue date of the reference safety information. A statement should be included in the protocol describing which document is approved for use within the trial for pharmacovigilance monitoring (it is best not to include the IB / SmPC as an appendix to the protocol, as a protocol amendment would be required if the IB / SmPC is updated).

Add details of the RSI to be submitted with the CTA, either SmPC / Investigator Brochure, including the section containing the list of ‘expected’ event terms.

The RSI to be used to assess expectedness against the IMP is:

Examples wording provided:

* SmPC for Ketalar (ketamine hydrochloride) 10mg/ml Injection (Pfizer Ltd) - Section 4.8: Undesirable Effects **or;**
* IB for ketamine hydrochloride (UCL) – Section 6.11: Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions

The sponsor will inform the MHRA and REC within the required expedited reporting timescales. SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days after sponsor awareness. Other SUSARs must be reported to the REC and MHRA within 15 days after sponsor awareness.

### Unblinding for the submission of SUSAR reports *(include this section if applicable)*

Routinely breaking the blind in double blind trials could compromise the integrity of the trial. It is important to separate out emergency unblinding (section 7.5) and unblinding for expedited reporting to authorities. For this reason the protocol should state that breaking the blind will only take place where information about the participant’s trial treatment is clearly necessary for the appropriate medical management of the participant. In all cases the Investigator and sponsor would be anticipated to evaluate the causality and expectedness of SAEs as though the participant was receiving the active medication.

Suggested wording:

A representative of the Sponsor will be authorised to access the code break system [please specify the system used] for the purposes of unbinding for the submission of a SUSAR. If the participant has received active treatment, the sponsor will submit the SUSAR report to the MHRA and REC.

SUSAR information will be disseminated to Investigators at site(s) and will remain blinded, regardless of whether the participant received active treatment or not. The unblinded information will not be forwarded to the trial team and will be kept in the JRO sponsor file.

### Flow Chart for Adverse Event Recording [to be modified as required for each trial by Sponsor]

**Adverse Event Noted**

**Adverse Event (AE)**

**Serious Adverse Event (SAE)**

**Unrelated to IMP**

**Related to IMP**

**Unrelated to IMP**

**Related to IMP**

**Adverse Event (AE)**

**Adverse Reaction (AR)**

**Serious Adverse Event (SAE)**

**Serious Adverse Reaction (SAR)**

**Seriousness**

**Causality**

**Expectedness**

**Expected SAR**

**Unexpected SAR**

**SUSAR**

**Record in:**

* **Medical Record**
* **CRF**
* **SAE Recording Log**
* **SAE Reporting Form**

**Report to JRO: sae@ucl.ac.uk**

**within 24 hrs**

**Record in:**

* **Medical Record**
* **CRF**

**JRO submit SUSAR to MHRA and REC**

## Notification of deaths (include this section if applicable)

If all SAEs will be reported to the sponsor for the duration of the trial this section is not required, because all deaths will be reported within 24 hours as SAEs.

Aim: to describe the procedure for notification of death if not all SAEs are reported to sponsor.

The protocol should state whether, how and when the investigator will notify deaths to the sponsor.

Example wording:

* All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the IMP, or an unrelated event, *or;*
* Only deaths that are assessed to be caused by the IMP will be reported to the sponsor. This report will be immediate, *or;*
* All deaths, including deaths deemed unrelated to the IMP, if they occur earlier than expected will be reported to the sponsor.

The protocol needs to specify the timelines of such reports.

## Pregnancy Reporting

Aim: to describe the procedure for notification of pregnancy (where applicable)

The protocol needs to state:

* All pregnancies within the trial (either the trial participant or the participant’s partner, with participants consent) should be reported to the Chief Investigator and the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification
* Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE
* follow-up of pregnant participant: Describe in detail the process for monitoring and managing a pregnancy
* follow-up of child born to a pregnant trial participant, or to the partner of a male trial participant. (How long will follow-up be for?)

**Suggested wording**:

If a female participant [or the female partner of a male participant] becomes pregnant at any point during the trial, a completed trial specific Pregnancy Reporting Form will be emailed to the Sponsor at **SAE@ucl.ac.uk**, within 24 hours of the Investigator becoming aware of the event in line with the Sponsors SOP (JRO/INV/S05). The Chief or Principal Investigator will respond to any queries raised by the sponsor as soon as possible.

Completed Pregnancy Reporting Forms must be sent to the Sponsor within 24 hours of becoming aware of the event

**Email Pregnancy Forms to:** **SAE@ucl.ac.uk**

The Sponsor must be kept informed of any new developments involving the pregnancy through the completion of a follow-up Pregnancy Reporting Form. Any pregnancy that occurs in a female trial subject during a clinical trial should be followed to termination or to term.

Consent to report information regarding the pregnancy [include follow-up of a child born if applicable] must be obtained from the pregnant participant [include partner if applicable]. A trial-specific pregnancy monitoring information sheet and informed consent form for trial participants [include the partners of trial participants if applicable] must be used for this purpose.

With consent additional information regarding the pregnancy will be collected and reported to the Sponsor, the Sponsor will advise on the length of follow up of the pregnancy / child on a case by case basis.

## Overdose

Aim: to describe the procedure for notification of overdose

The protocol should describe:

* The definition of an overdose
* How to record and notify overdoses to the sponsor (this information should be placed on the deviation log)
* Where overdoses can be observed from (pill counts, diary cards, drug charts or participant comment)
* How will it affect final analysis e.g. will participants be withdrawn from the trial? (Consider what will constitute an overdose that warrants trial discontinuation)
* If an SAE is associated with the overdose ensure the overdose is fully described in the SAE report form

## Reporting Urgent Safety Measures

Please refer to the following website for details on clinical trials safety reporting: <http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARSandASRs/index.htm>

If any urgent safety measures (USMs) are taken the CI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA, the relevant REC and the Sponsor of the measures taken and the circumstances giving rise to those measures.

## Development Safety Update Reports

The Sponsor will provide the MHRA and REC with Development Safety Update Reports (DSUR) which will be written by the Sponsor’s office in conjunction with the trial team. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

## Responsibilities

Aim: To define responsibilities

This section should detail the responsibilities for reporting and reviewing toxicity and safety information arising from the trial and any timeline associated with these. Responsibilities for the PI, CI, Sponsor, Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) should always be included. Depending on the trial, if a pharmaceutical company is involved, their responsibilities will also need to be included, for example the company may take on the function of delegated sponsor review.

A process must be in place to review individual SAEs, AEs, ARs and trends in events and reactions will be independently reviewed in addition to usual trial safety monitoring procedures. The decision regarding the frequency of review of individual and cumulative SAEs will be based on the trial design, risk assessment and advice from the Sponsor / TSC / DMC but may include:

* Clinical review of a line listing of all life threatening or SAEs resulting in death within 1 week of their occurrence (for lower risk trial).
* Clinical review of a line listing of all other SAEs on a monthly basis (for lower risk trial).
* Clinical review in real time of each SAE as it occurs (for higher risk trial).
* Cumulative review of all safety information by the DMC on a 3 or 6 monthly basis.
* Total numbers of SAEs per month sent to the DMC Chair – in order to expedite a safety review if more SAEs are being seen than would be expected.

Indicate any activities that the sponsor is delegating to a third party and any expectations of the third party when working with the research site(s). Highlight any activities that the sponsor is delegating to the research site(s) and identify any specific requirements that the research site(s) will need to meet to carry out the delegated activities.

NB: in a CTIMP the sponsor has legal responsibilities that cannot be delegated.

**Suggested wording:**

Principal Investigator (PI) / delegate:

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness and causality.
2. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 3 working days of initial reporting.
3. Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / delegate:

All of the above responsibilities of a PI, and in addition:

1. Clinical oversight of the safety of participants participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness and causality where it has not been possible to obtain local medical assessment.
3. Review of all SUSARs.
4. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.
5. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC), *delete as appropriate*))
6. Reviewing and contributing to the annual Development Safety Update Report (DSUR).

Sponsor:

1. Data collection and verification of SAEs, SARs and SUSARs according to the trial protocol onto a database.
2. Reporting safety information to the CI or delegate for the ongoing assessment of the risk / benefit.
3. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
4. Notifying Investigators of SUSARs that occur within the trial.
5. The unblinding of a participant for the purpose of expedited SUSAR reporting *(Include for double blind trials only)*.
6. Checking for and notifying PIs of updates to the Reference Safety Information for the trial.
7. Preparing the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC (within 60 calendar days).

Trial Steering Committee (TSC) *(if applicable)*:

*Amend the following wording as required:*

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC) *(if applicable)*:

In accordance with the Trial Terms of Reference for the DMC, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

# STATISTICS AND DATA ANALYSIS

This section should be written or reviewed by the statistician.

The sub-headings given below are suggestions. If a Statistical Analysis Plan (SAP) is produced please state here, and condense information in this section that is also included in the SAP. It should be noted that the sample size section should be completed in full in the protocol.

## Outcomes

### Primary Outcomes

A full description of the primary outcome; its definition, when it is measured, any rules, references or programs for calculation of derived values and what form it will take for analysis (e.g. categorical, continuous ordinal)

### Secondary Outcomes

Detail as above for secondary outcomes

## Sample size justification

Aim: To define how the planned number of participants was derived

This section should detail the approach taken for the determination of the target sample size and must include references to tables, equations or statistical software used to carry out calculations, and sources of any estimates or information used in the justification/calculation.

For trials that involve a formal sample size calculation, the target sample size must ensure adequate power or precision for the planned analysis of the primary outcome. It may also be worthwhile to consider power/precision that will be achievable (given the proposed sample size) for other important outcomes or analyses because trials are often underpowered to detect harms or subgroup effects.

Sufficient information should be provided so that sample size calculations can be reproduced and rationale fully understood, including detail of:

* Null Hypothesis: A clear statement of the hypothesis, in terms of numerical values, of the treatment being ineffective. For example: an absolute difference in response rates between arms of zero.
* Treatment Effect: this is the smallest size of effect that would be of clinical interest
* Power (typically 90%): this is the probability of detecting a true effect of a given magnitude, should it exist.
* Significance level (typically 5%): this is the probability of concluding the treatment is effective, when in reality the treatment is ineffective.
* Other estimates: e.g. for continuous outcomes the standard deviation of the primary outcome and correlation coefficient between baseline and outcome measurement; for time to event outcomes the median survival; where relevant, dropout, non-compliance and response rates
* Assumptions made (e.g. assumptions of normality, proportional hazards)
* Allowance for planned interim analysis(es) , any inflation of sample size to account for multiple testing.
* Allowance for planned subgroup analyses
* Allowance for clustering effects
* Methods/formulae/software used (with references)

All estimates used in the calculations should be appropriately justified, for example based on previous studies or pilot work (with references) or clinical arguments.

If the planned sample size is not derived statistically, then this should be explicitly stated along with a rationale for the intended sample size (e.g. exploratory nature of pilot studies; pragmatic considerations for trials in rare diseases).

NB: an appropriate level of statistical advice should be sought to ensure trial validity, in most cases the trial statistician should be consulted for calculation/justification of sample size.

## Planned Recruitment Rate

Aim: to estimate the planned recruitment rate

Realistic estimates of expected accrual rate and duration of participant entry based on estimated sample size should be provided. Justification that the required sample size will be attainable in practice should be included. This section may also include information such as the number of recruiting centres, the size / percentage of the population that is captured by the eligibility criteria, the expected consent rate, and the expected screen failure rate. This information will help sites to determine whether they are likely to be able to recruit their target number of participants. Pilot work or surveys can help to give a realistic idea of the likely recruitment rates.

## Randomisation Methods

Aim: to provide an overview of the process of how treatments will be allocated between participants in enough detail to theoretically enable a full reproduction of the process.

Successful randomisation in practice depends on two interrelated aspects:

 1) generation of an unpredictable allocation sequence and

 2) concealment of that sequence until assignment irreversibly occurs

The protocol should describe:

* The method of randomisation and justification for choice of method e.g.:
* simple randomisation based solely on a single, constant allocation ratio is known as simple randomisation. Simple randomisation with a 1:1 allocation ratio is analogous to a coin toss.
* restricted randomisation which includes any randomised approach that is not simple randomisation including:-
	+ Blocked randomisation
	+ Biased coin and urn randomisation
	+ Stratified randomisation (including stratification factors)
	+ Minimisation (including minimisation factors): Minimisation assures similar distribution of selected participant factors between trial groups. The first participant is truly randomly allocated; for each subsequent participant, the treatment allocation that minimises the imbalance on the selected factors between groups at that time is selected. That allocation may then be used, or a choice may be made at random with a heavy weighting in favour of the intervention that would minimise imbalance (for example, with a probability of 0.8).
* if an un-equal treatment allocation will be used and a justification for its use
* if the allocation ratio will adaptively evolve over the course of the trial and a short overview statement to that effect with a reference to the full description in the “Interim Analysis” section
* include information regarding participant / cluster randomised design (randomising individuals or groups (e.g. general practices, wards))
* if using stratified randomisation or minimisation, include definition of stratification/minimisation variables (should only consider variables that are likely to be strongly prognostic of the outcome)
* if using blocked randomisation consider varying block sizes.

Full details of a restricted randomisation procedure (including minimisation) should not be included in the trial protocol as knowledge of these details (for example block size) might undermine randomisation by facilitating deciphering of the allocation sequence. Instead, this specific information should be provided in a separate document with restricted access to protect the trial from selection/allocation bias.

## Statistical Analysis Plan

Aim: to provide an overview of the statistical analysis plan

Please note that a more detailed statistical analysis plan should be produced as a separate document at some point prior to the final analysis (as recommended by the ICHE9 guidelines). In this document, a more technical and detailed elaboration of the principal features stated in the protocol should be included. The plan may include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. The plan should be reviewed and possibly updated as a result of the blind review of the data and should be finalised before breaking the blind. Formal records should be kept of when the statistical analysis plan was finalised as well as when the blind was subsequently broken.

### Summary of baseline data and flow of participants

* list variables to be used to assess baseline comparability of the randomised groups including for each factor: a definition, any rules, references or programmes for calculation of derived values, what form it will take for analysis (e.g. continuous, categorical, ordinal) and how it will be reported (e.g. means, standard deviations, medians, proportions)
* plans to produce a consort flow diagram (<http://www.consort-statement.org/>)

### Primary Outcome Analysis

Plans for statistical analyses of the primary outcome including:

* summary measures to be reported
* method of analysis (justified with consideration of form of the data , [assumptions](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/methods.cfm#assump) of the method and structure of the data (e.g. [unpaired, paired](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/methods.cfm#paired), [clustered](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/methods.cfm#hier)) etc.)
* plans for handling multiple comparisons, missing data, non-compliers, spurious data and withdrawals in analysis
* plans for analyses which adjust for predefined baseline characteristics (if it is not clear in advance which these should be then the objective criteria to be used to select variables should be pre-specified)
* plans for predefined subgroup analyses
* statement regarding use of [intention to treat](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/methods.cfm#intent) (ITT) analysis
* description of any non-statistical methods that might be used (e.g. qualitative methods)

In describing analyses of the primary outcome it should be made clear what constitutes the main analysis and which are supportive/sensitivity/secondary analyses.

### Secondary Outcome Analysis

Plans for statistical analysis of each secondary outcome. In general the use of hypothesis tests may not be appropriate if the trial has not been powered to address these and use of estimates with confidence intervals is preferred. Secondary analyses should be considered as hypothesis generating rather than providing firm conclusions.

## Interim analysis and criteria for the premature termination of the trial

Aim: to describe any interim analysis and criteria for stopping the trial.

The protocol should describe:

* any interim analysis plan, even if it is only to be performed at the request of an oversight body (e.g., DMC)
* include the statistical methods
* who will perform the analyses
* when they will be conducted (timing and indications)
* the decision criteria—statistical or other—that will be adopted to judge the interim results as part of a guideline for early stopping or other adaptations.
* who will see the outcome data while the trial is ongoing
* whether these individuals will remain blinded (masked) to trial groups
* how the integrity of the trial implementation will be protected (e.g. maintaining blinding) when any adaptations to the trial are made
* who has the ultimate authority to stop or modify the trial e.g. the Chief Investigator, trial steering committee, or Sponsor
* the stopping guidelines
	+ Criteria for stopping for harm are often different from those for benefit and might not employ a formal statistical criterion
	+ Stopping for futility occurs in instances where, if the trial were to continue, it is unlikely that an important effect would be seen (i.e. low chance of rejecting null hypothesis)
		- if pre-specified interim analyses are to be used for other trial adaptations such as sample size re-estimation, alteration to the proportion of participants allocated to each trial group, and changes to eligibility criteria.

NB: in CTIMPs recommendations made by the DMC must be expedited to the MHRA where they are deemed relevant for the safety of participants participating within the trial (refer to the EU Guidance Document ‘Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use – CT-3’: <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2011:172:0001:0013:EN:PDF> ).

## Participant Population

Aim: to describe the participant populations whose data will be subjected to the trial analysis.

Protocols should describe:

* the participant populations whose data will be subjected to the trial analysis – both for the primary analysis and any applicable secondary analyses e.g.
* All-randomised population: Any participant randomised into the trial, regardless of whether they received trial drug
* All-treated population: Any participant randomised into the trial that received at least one dose of trial drug
* Protocol-compliant population: Any participant who was randomised and received the protocol required trial drug exposure and required protocol processing
* if the participants to be included in the analysis will vary by outcome e.g. analysis of harms (adverse events) is sometimes restricted to participants who received the intervention, so that absence or occurrence of harm is not attributed to a treatment that was never received.

To avoid:

* selection bias, an “as randomised” analysis retains participants in the group to which they were originally allocated
* attrition bias, outcome data obtained from all participants are included in the data analysis, regardless of protocol adherence

These two conditions (i.e., all participants, as randomised) define an “intention to treat” analysis, which is widely recommended as the preferred analysis strategy.

## Procedure(s) to account for missing or spurious data

Aim: to describe how missing data will be dealt with

The protocol should describe:

* the strategies to maximise follow-up and prevent missing data
* how recording of reasons for missing data will be undertaken
* how missing data will be handled in the analysis and detail any planned methods to impute (estimate) missing outcome data, including which variables will be used in the imputation process (if applicable). Sensitivity analyses are highly recommended to assess the robustness of trial results under different methods of handling missing data.

## Other Statistical Considerations.

Aim: to describe any other statistical consideration pertinent to the trial.

The protocol should describe:

* procedures for reporting any deviation(s) from the original statistical plan
* any other statistical considerations e.g. if there is a requirement for an economic analysis plan in which case it should be included in this section

## Economic Evaluation

If economic evaluation is to be undertaken this section should include the rationale for inclusion of the economic investigation and means of assessment.

NB: it should be written by the health economic investigator

# DATA MANAGEMENT

## Data collection tools and source document identification

Aim: to describe procedures for data collection, recording and handling

**Source Data**

ICH E6 section 1.51, defines source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

The basic concept of source data is that it permits not only reporting and analysis but also verification at various steps in the process for the purposes of confirmation, quality control, audit or inspection. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are:

* Accurate
* Legible
* Contemporaneous
* Original
* Attributable
* Complete
* Consistent
* Enduring
* Available when needed

**Source Documents**

ICH E6 1.52, defines source documents as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

A source document list will be implemented prior to the start of the trial to identify:

* which data is to be recorded directly onto the CRF;
* which data is recorded firstly into source documents, such as medical notes, and then transcribed into the CRF; and
* which data is not to be recorded in the CRF but only recorded in source documents, e.g., participant questionnaires and diary cards.

**Case report forms**

A case report form (CRF) is a form on which individual participant data required by the trial protocol are recorded. It may be a printed or electronic document (eCRF). The CRF data is used to perform statistical analysis for the trial. Design of individual CRFs will vary from trial to trial, but it is essential that the design ensures that:

* adequate collection of data has been performed
* proper audit trails can be kept to demonstrate the validity of the trial (both during and after the trial)
* only the data required by the protocol are captured in the CRF (using the CRF to capture secondary data not required for the trial may be a criminal beach of the Data Protection Act (2018), makes the CRF unnecessarily complicated, and can make it more difficult to extract the primary data for analysis)

**CRFs as Source Documents**

If the protocol allows data to be entered directly onto the case report forms (CRF), the CRF would then be considered a source document. If the CRF is then transmitted to the Sponsor, it is necessary for the trial site to retain a copy to ensure that the PI has an independent account from the Sponsor as to what has occurred during the trial at his/her site. Additional information can be found in ICH E6, section 6.4.9.

Guidance can be found here: <http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/08/WC500095754.pdf>

The protocol should:

* specify whether the data are from a standardised tool (e.g. McGill pain score) or involves a procedure (in which case full details should be supplied)
* specify if a non-standard tool is to be used, giving detail on its [reliability and validity](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/describe.cfm#valrel)
* describe the methods used to maximise completeness of data e.g. telephoning participants who have not returned postal questionnaires
* specify that the investigator /institutions should keep records of all participating patients (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages
* Detail what happens to the CRFs once complete. If trial is multisite, need to describe how CRFs will be sent to a coordinating site/data manager for review and data processing, where they are to be sent and specify timelines. Need to consider if the original CRFs be sent in the post to data management and a copy kept at site, or will they be sent electronically with the original kept at site?
* Ensure wording in this section is consistent with the data management SOP.

**Include following wording:**

All CRFs must be completed [and signed*, if paper CRF*] by staff that are listed on the site staff delegation log and authorised by the Investigator to perform this duty. The Investigator is responsible for the accuracy of all data reported in the CRF.

## Data handling and record keeping

GCP requires that sponsors operating such systems validate the system, maintain SOPs for the use of the system, maintain an audit trail of data changes ensuring that there is no deletion of entered data, maintain a security system to protect against unauthorised access, maintain a list of the individuals authorised to make data changes, maintain adequate backup of the data, safeguard the blinding of the trial and archiving of any source data (i.e. hard copy and electronic). If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data. The sponsor should use an unambiguous participant identification code that allows identification of all the data reported for each participant. Sponsors are responsible for ensuring compliance with the requirements outlined above when tasks are subcontracted. There should be no loss of quality when an electronic system is used in place of a paper system.

Specific principles can be found here: <http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/08/WC500095754.pdf>

If this information is included in a trial specific data management SOP then add summary detail about how data will be handled and refer to the data management SOP for further details. You could briefly describe the data query process and how sites will be contacted to address any data issues.

Suggested wording:

A trial specific data management SOP will be in place for the trial. This will contain details of the software to be used for the database, the process of database design, *[add coding if applicable]*, database validation, data entry, data quality checks, data queries, data security, database lock *[add data transfer if applicable]*.

Where data are transferred electronically this will be in accordance with the UK Data Protection Act 2018 as well as UCL Information Security Policy and Trust Information Governance Policy. There will be a documented record of data transfer and measures in place for the recovery of original information after transfer.

## Access to Data

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to the source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

## Archiving

Aim: to describe the process for archiving the trial documentation at the end of the trial

The protocol should state:

* archiving will be authorised by the Sponsor following submission of the end of trial report
* which trial documents the sponsor will be responsible for archiving and which trial documents the site(s) will be responsible for archiving
* the location and duration of record retention for:
* essential documents
* the trial database
* include the process for transferring the final trial dataset to UCL if the trial database is managed by another party (e.g. non UCL CTU).
* all essential documents will be archived by the trial site and CI for a minimum of 25 years after completion of the trial.
* Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of Good Clinical Practice and all applicable regulatory requirements.
* destruction of essential documents will require authorisation from the Sponsor

Suggested minimum wording:

At the end of the trial, all essential documentation will be archived securely by the CI and the trial sites for a minimum of 25 years from the declaration of end of trial.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of Good Clinical Practice and all applicable regulatory requirements.

The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

# OVERSIGHT COMMITTEES

Aim: To outline the various committees or groups involved in trial coordination and conduct.

There are three main trial management groups which may be involved in the set up and management of a clinical trial, depending on the trial size, design, number of sites and documented risk assessment of the trial. For each committee/group the protocol should state their roles and responsibilities and degree of independence from Sponsor and Investigators.

The terms of reference for these committees will need to be provided in separate documents.

For guidance on Data Monitoring Committee Charters follow this link

<http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003635.pdf>

## Trial Management Group (TMG)

The Trial Management Group should meet regularly to ensure all practical details of the trial are progressing well and working well and everyone within the trial understands them. All trials should have a TMG. State the composition and responsibilities.

Example wording:

The TMG will include the Chief Investigator and trial staff. The TMG will be responsible for overseeing the trial. The group will meet regularly [*state approximate number of times per year*] and will send updates to PIs *(if applicable, multi-site trials)*.

The TMG will review recruitment figures, SAEs and substantial amendments to the protocol prior to submission to the REC and/or MHRA. All PIs will be kept informed of substantial amendments through their nominated responsible individuals *(if applicable, multi-site trials).*

Mention TMG charter *(if applicable*).

## Trial Steering Committee (TSC)

The TSC must have a majority independent representation, including the Chair, meet regularly and send reports to the sponsor. Lay members or patient representatives are desirable. State if there is a TSC and describe the responsibilities.

Example wording:

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the (Independent) Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder(s) and Sponsor.

Mention TSC charter *(if applicable*).

## Independent Data Monitoring Committee (IDMC) or Data Monitoring Committee (DMC)

Independence is a key characteristic of a Data Monitoring Committee where the committee members are completely uninvolved in the running of the trial and who cannot be unfairly influenced (either directly or indirectly) by people, or institutions, involved in the trial. State if there is a DMC and describe the responsibilities. **Please note** for phase I trials, it is expected that an IDMC will be in place unless justified.

Example wording:

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held [*state timeframe*] to review interim analyses *[cross check with the Interim Analysis section]*, or as necessary to address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

*or*

The role of the DMC is to provide advice on data and safety aspects of the trial but where not all members are independent. Meetings of the Committee will be held [*state timeframe*] to review interim analyses *[cross check with the Interim Analysis section]*, or as necessary to address any issues.

Mention IDMC/DMC charter (*if applicable*).

# MONITORING, AUDIT & INSPECTION

Aim: to describe the procedures for monitoring audit and inspection (if this information is supplied as part of a monitoring plan then this section should reference it and not duplicate its detail)

Suggested minimum wording (update as required):

The sponsor will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

The degree of monitoring will be proportionate to the objectives, purpose, phase, design, size, complexity, blinding, endpoints and risks associated with the trial.

A trial specific oversight and monitoring plan will be established and the trial will be monitored in accordance with this agreed plan.

# ETHICAL AND REGULATORY CONSIDERATIONS

## Research Ethics Committee (REC) / MHRA review & reports

Aim: to demonstrate that the trial will receive both regulatory and ethical review & approval

Include the following wording as a minimum:

The Sponsor will ensure that the trial protocol and associated documents have been approved by the appropriate regulatory body (MHRA in the UK).

Before the start of the trial, approval will be sought from a REC for the trial protocol and other relevant documents e.g. Participant information sheet, advertisements and GP information letters.

Prior to site recruitment the Chief Investigator/Principal Investigator or designee must receive NHS permission in writing from the Trust Research & Development (R&D) known as confirmation of capability and capacity.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial (note that amendments may also need to be reviewed and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at sites).

All correspondence with the REC / MHRA will be retained in the Trial Master File.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the Chief Investigator’s responsibility to produce the annual reports as required.

The Chief Investigator or Sponsor will notify the REC and MHRA of the end of the trial within 90 days. If the trial is ended prematurely the notification of end of trial will made within 15 days.

At the end of the trial the CI will supply the Sponsor with a clinical trial report and upload the trial results to all applicable trial registries within 12 months of the end of trial declaration date (6 months for paediatric trials). A copy of this report must also be submitted to the REC and MHRA.

## Peer Review

Aim: to descibe the peer review process for the trial which should be instigated or approved by the Sponsor

The protocol should provide details on who reviewed this trial protocol e.g. the funder or an internal Trust department/committee, but not include individual names unless the person in question gives their express permission.

As sponsor two peer reviews are required as part of the sponsorship process. Please refer to the UCL policy on peer reviews.

The NIHR CRN provide the following standard for peer review for studies to be included on their portfolio:

**High quality peer review**

Peer review must be independent, expert, and proportionate:

1. **Independent**: At least two individual experts should have reviewed the trial. The definition of independent used here is that the reviewers must be external to the investigators’ host institution and not involved in the trial in any way. Reviewers do not need to be anonymous.
2. **Expert**: Reviewers should have knowledge of the relevant discipline to consider the clinical and/or service based aspects of the protocol, and/or have the expertise to assess the methodological and statistical aspects of the trial.
3. **Proportionate**: Peer review should be commensurate with the size and complexity of the trial. Large multicentre studies should have higher level (more reviewers with broader expertise and often independent review committee or board), and potentially international peer review.

## Public and Patient Involvement

Aim: to describe the involvement of Patients and Public in the research

This section of the protocol should detail which aspects of the research process have actively involved, or will involve, patients, service users, and/or their carers, or members of the public in particular;

* Design of the research
* Management of the research
* Undertaking the research
* Analysis of results
* Dissemination of findings

Guidance on involving patients and the public in research can be found on the INVOLVE website. <http://www.invo.org.uk/>

## Regulatory Compliance

Aim: to demonstrate that the trial will comply with regulations

Minimum suggested wording (update as required):

Thetrial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA and Favourable REC opinion. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Other considerations:

* For trials *using ionising radiation the protocol should state that:*
	+ the procedures are compliant with the Ionising Radiation (Medical Exposure) Regulations, and appropriate review by a Medical Physics Expert and Clinical Radiation Expert has been undertaken, and
	+ Where a trial involves the administration of radioactive substances the protocol should clearly identify that a current Administration of Radioactive Substances Advisory Committee (ARSAC) certificate will be required for each site and, where exposures are additional to normal standard of care, a research ARSAC certificate will be required for each site

NB: Ionising radiation includes:

* X-rays, CT scans, DXA scans
* Radiotherapy (including brachytherapy and radionuclide therapy, using unsealed sources)
* Radionuclide studies (including nuclear medicine imaging, PET-CT and in vitro measurements)
* Administration of a radioactive substance

Neither MRI nor ultrasound involve ionising radiation.

There is a legal and ethical need to justify the use of ionising radiation in research protocols.  Be aware that the Ionising Radiation (Medical Exposure) Regulations relate to any research exposure, not only to those additional to routine clinical care.

Procedures involving administration of radioactive material to participants, which differ from standard of care, must be covered by an appropriate ARSAC certificate. Procedures might include:

* Radionucleotide imaging
* MUGA scans
* Brachytherapy

ARSAC certificates are specific to the site, procedure and purpose (diagnosis, treatment, or research) of the administration. Under the current ARSAC arrangements, a research ARSAC certificate is only needed at a site where the administration required by a research protocol is additional to that which participants would receive under routine clinical care at that site (routine procedures will be covered by existing diagnostic or treatment ARSAC certificates held by a certificate holder at the site). Currently research ARSAC certificates are trial specific, so each site will need to apply for a research ARSAC certificate for each trial that involves administration additional to routine clinical care.

Special consideration should be given to potential variation in procedure at sites; what might be routine at one site could be additional to routine care at another site. Also, care should be taken where the protocol gives sites an option on the testing method, for example heart function may be determined either by echocardiogram or MUGA scan. Sites may intend to use echocardiograms, so not apply for a research ARSAC certificate to cover the MUGA scans, but this would leave them in a difficult position if, due to practical reasons, they were unable to use echocardiograms (e.g. equipment failure, scheduling issues) to perform the tests required by the protocol.

All imaging technologies have the potential to uncover previously unknown pathology. You should always consider how likely such a discovery may be, and how best to handle this discovery when developing research protocols that involve any imaging techniques.

The protocol should state that:

* Before any site can enrol participants into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance. Different arrangements for NHS and non NHS sites are described as [relevant](http://www.hra.nhs.uk/resources/hra-approval-guidance-for-sponsorschief-investigators-working-collaboratively-with-nhs-organisations-in-england/#3).
* For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as [amended](http://www.hra.nhs.uk/resources/after-you-apply/amendments/).

**For trials where the IMP is a genetically modified organism (GMO-IMP), the wording below should be amended for inclusion.**

* If the product is classed as a GMO, generally it will fall under the contained use regulations in the UK and the following paragraphs should be included for UK trials:
* The [name product] is classified as a genetically modified organism under the Genetically Modified Organisms (Contained Use) Regulations 2014.
* Each UK clinical trial site administering the GMO-IMP must be notified to the Health and Safety Executive (HSE) for first use of premises for genetic modification activities before commencement of activities at site. A risk assessment of the activities must be carried out and reviewed by the local/central (delete as applicable) Genetic Modification Safety Committee or the individual with expertise in risk assessment relating to contained use, allocated to review GMO risk assessments on behalf of the trial site (individual is allowed for class 1 products only).
* Local approval to allow the GMO activities to commence must be in place before the site will be opened to recruitment.

If the GMO-IMP is considered Class 2 or higher product, further notifications to/consents from the HSE would be required, after an initial notification of premises for first use. The JRO will advise on the assessment route of such a product and the additional requirements. These discussions should happen as early as possible to consider whether it will be possible to implement a clinical trial with the additional risk and/or what mitigations may be needed.

## Protocol Compliance

Aim: to demonstrate how protocol compliance will be managed and documented

Protocol non-compliances are departures from the approved protocol.

Include the following wording:

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately, as per Sponsor SOP for the Recording & Reporting of Deviations, Violations, Potential Serious breaches, Serious breaches and Urgent Safety Measures (SPON/S15).

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

## Notification of Serious Breaches to GCP and/or the protocol

Aim: to demonstrate how serious breaches will be managed

Include the following wording:

A “serious breach” is a breach which is likely to effect to a significant degree –

* 1. the safety or physical or mental integrity of the participants of the trial; or
	2. the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase as per the Sponsor SOP for the Recording & Reporting of Deviations, Violations, Potential Serious breaches, Serious breaches and Urgent Safety Measures (SPON/S15). The sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of

1. the conditions and principles of GCP in connection with that trial; or
2. the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

## Data Protection and Participant Confidentiality

Aim: To describe how participant confidentiality will be maintained and how the trial is compliant with the requirements of the Data Protection Act 2018.

The protocol should state that all investigators and trial site staff must comply with the requirements of the Data Protection Act (2018) with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles.

 The protocol should describe:

* the means whereby personal information is collected, kept secure, and maintained. In general, this involves:
	+ the creation of coded, depersonalised data where the participant’s identifying information is replaced by an unrelated sequence of characters
	+ secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media
	+ limiting access to the minimum number of individuals necessary for quality control, audit, and analysis
* how the confidentiality of data will be preserved when the data are transmitted to sponsor and co-investigators
* how long the data will be stored for
* who is the data custodian

Include the following wording as a minimum:

All data will be handled in accordance with the Data Protection Act (2018).

The Case Report Forms (CRFs) will not bear the participant’s name or other personal identifiable data.

If for any reason paperwork leaving the hospital (e.g. to go to the Manufacturer) or labelling of the IMP product contains participant identifiers this should be specified and justified here, and the wording above amended in line with this. This will also need to be clearly described in the Participant Information Sheet and Consent Form.

## Financial and other competing interests for the Chief Investigator & PIs at each site

Aim: to identify and disclose any competing interests that might influence trial design, conduct, or reporting

At a minimum, disclosure should reflect:

* a statement of finance for the trial such as details of the funding body
* ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial
* commercial ties requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company
* any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.

At the time of writing the protocol not all sites/personnel may have been identified. When this is the case then the protocol should state that this information will be collected and where it will be documented.

## Insurance and Indemnity

Aim: to fully describe indemnity arrangements for the trial

Include the following wording as a minimum:

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial*.* Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital’s duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor’s Insurers, via the Sponsor’s office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

The following areas should also addressed in the protocol:

What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research? Note that if the trial involves sites that are not covered by the NHS indemnity scheme (e.g. GP surgeries in primary care) these investigators/collaborators will need to ensure that their activity on the trial is covered under their own professional indemnity.

##  Access to the final trial dataset

Aim: to describe who will have access to the final dataset

The protocol should:

* identify the individuals involved in the trial who will have access to the full dataset
* explicitly describe any restrictions in access for trial investigators e.g. for some multicentre trials, only the steering group has access to the full trial dataset in order to ensure that the overall results are not disclosed by an individual trial site prior to the main publication
* state if the trial will allow site investigators to access the full dataset if a formal request describing their plans is approved by the steering group

# DISSEMINATION POLICY

Aim: to describe the dissemination policy for the trial

It is highly recommended that the Consort Guidelines and checklist are reviewed prior to generating any publications for the trial to ensure they meet the standards required for submission to high quality peer reviewed journals etc. <http://www.consort-statement.org/>

The protocol should state

* who owns the data arising from the trial (this will be UCL as Sponsor in most cases)
* that on completion of the trial, the data will be analysed and tabulated and a Final Trial Report prepared
* where the full trial report can be accessed
* if any of the participating investigators will have rights to publish any of the trial data
* if there are any time limits or review requirements on the publications
* whether any funding or supporting body needs to be acknowledged within the publications and whether they have review and publication rights of the data from the trial
* whether there are any plans to notify the participants of the outcome of the trial, either by provision of the publication, or via a specifically designed newsletter etc.
* if it is possible for the participant to specifically request results from their PI and when would this information be provided e.g. after the Final Trial Report has been compiled or after the results have been published
* whether the trial protocol, full trial report, anonymised participant level dataset, and statistical code for generating the results will be made publicly available; and if so, describe where, the timeframe and any other conditions for access.

## Authorship eligibility guidelines and any intended use of professional writers

Aim: to describe who will be granted authorship on the final trial report

The protocol should detail:

* guidelines on authorship on the final trial report
* criteria for individually named authors or group authorship (The International Committee of Medical Journal Editors has defined authorship criteria for manuscripts submitted for publication)
* if professional medical writers are going to be hired and how their employment and funding will be acknowledged in trial reports

# REFERENCES

List the literature and data that are relevant to the trial, and that provide background for the trial. Please ensure the text contains appropriate cross references to this list.

# APPENDICES

## Appendix 1 - Schedule of Assessments

|  |  |
| --- | --- |
| **Procedures** | **Visits (insert visit numbers as appropriate)** |
| **Screening** | **Baseline** | **Treatment Phase** | **Follow Up** |
| **Visit window**  |  |  | **+/- x days** | **+/- x days** |
| Informed consent |  |  |  |  |  |
| Demographics |  |  |  |  |  |
| Medical history |  |  |  |  |  |
| Physical examination |  |  |  |  |  |
| Vital signs |  |  |  |  |  |
| Add ALL Protocol Assessments including bloods/urine etc. as applicable both trial specific and routine |  |  |  |  |  |
| Concomitant medications |  |  |  |  |  |
| ECG |  |  |  |  |  |
| Laboratory tests |  |  |  |  |  |
| Eligibility assessment |  |  |  |  |  |
| Randomisation |  |  |  |  |  |
| Dispensing/administration of trial drugs |  |  |  |  |  |
| Compliance |  |  |  |  |  |
| Assessment 1 (describe) |  |  |  |  |  |
| Assessment 2 (describe) |  |  |  |  |  |
| Assessment 3 (describe) |  |  |  |  |  |
| Assessment 4 (describe) |  |  |  |  |  |
| Adverse event assessments  |  |  |  |  |  |
| Physician’s Withdrawal Checklist |  |  |  |  |  |