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**Clinical Trial of Investigational Medicinal Product**

**Protocol Template**

**Guidance Notes for Protocol Template**

Please check the Joint Research Office website <http://www.ucl.ac.uk/jro/standingoperatingprocedures> 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.

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 non applicable (NA) be added next to it.

The protocol must be consistent with the participant information sheet, consent form, IRAS form, CTA application, IB/SPC 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 red is guidance and/or instruction and should be deleted once addressed**
2. **Suggested text given in blue 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 as appendix 1.
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**



**Include other logos as appropriate - trial specific logo, funders, collaborators, research networks**

|  |  |
| --- | --- |
| **Full title of trial**Title to include phase, design (e.g. double-blind, randomised, placebo-controlled), single-site/multi-site, name of IMP, target disease, and participant population. |  |
| **Short title**The full and short title must be the same on all trial documents e.g. participant information sheet. A Trial acronym is a useful short title.  |  |
| **Version and date of protocol**The protocol should be labelled draft until approved for submission to the MHRA and REC when draft should be deleted and it should become Version 1 | [Draft] Version ,   |
| **Sponsor:** | University College London (UCL) |
| **Sponsor protocol number** |  |
| **Funder (s):** | [Names of ALL organisations providing funding for this trial] |
| **EudraCT no** This is to be allocated by JRO. If this trial is part of a work programme where one trial leads onto the next, please link in trials from the same work package by listing the work packages and their EudraCT number. |  |
| **ISRCTN / Clinicaltrials.gov no:** delete as applicable] | [Insert ISRCTN or Clinicaltrials.gov reference no] |
|  |  |
| **ACTIVE IMP(s):** |  If Applicable |
| **PLACEBO IMP(s):** |  If Applicable  |
| **Phase of trial** | Phase  |
| **Sites(s)** | / Delete as appropriate, you should NOT add names of sites onto the protocol  |
| **Chief investigator:** | **Sponsor Representative**:Insert Name/ email address – JRO to AddJoint Research Office, UCL, 1st Floor Maple House,149 Tottenham Court Road,London W1T 7NFPostal address:Joint Research Office, UCLGower Street, London WC1E 6BT |

**Protocol Version History**

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

The Chief Investigator and the JRO have discussed this protocol. The investigator agrees to perform the investigations and to abide by this protocol

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the current Research Governance Framework, the GMO (Contained Use) Regulations 2000 (and subsequent amendments), the Sponsor’s SOPs, and other regulatory requirements as amended.

|  |  |  |
| --- | --- | --- |
| **Chief investigator** |  |  |
|  | Signature | Date |
| **Sponsor** JRO to Add  |  |  |
| UCL | Signature | Date |
|  |  |  |

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# List of abbreviations

Commonly used abbreviations – add or delete as applicable:

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

DI Designated Individual

DMC Data Monitoring Committee

DSUR Development Safety Update Report

EC European Commission

EMEA 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

GMP Good Manufacturing Practice

GMO Genetically Modified Organisms

HTA Human Tissue Authority

IB Investigator Brochure

ICF Informed Consent Form

IDMC Independent Data Monitoring Committee

IMP Investigational Medicinal Product

IMPD Investigational Medicinal Product Dossier

ISF Investigator Site File

ISRCTN International Standard Randomised

MA Marketing Authorisation

MHRA Medicines and Healthcare products Regulatory Agency

MS Member State

NHS R&D National Health Service Research & Development

PI Principal Investigator

PIS Participant Information Sheet

PL Product License

QA Quality Assurance

QC Quality Control

QP Qualified Person (for release of trial drug)

RCT Randomised Controlled Trial

REC Research Ethics Committee

SAR Serious Adverse Reaction

SAE Serious Adverse Event

SDV Source Document Verification

SOP Standard Operating Procedure

SPC Summary of Product Characteristics

SSA Site Specific Assessment

SUSAR Suspected Unexpected Serious Adverse Reaction

TMG Trial Management Group

TSC Trial Steering Committee

# Trial personnel

See protocol cover page for Chief Investigator and Sponsor contact details.

Statistician
e-mail:
tel: fax:

Central laboratories
e-mail:
tel: fax:

Add appropriate name (e.g. Head of Department) and address of any central core services i.e. laboratories, central pharmacy production units, medical and/or technical departments (e.g. imaging, radiology), and any external Contract Research Organisation (CRO) or Clinical Trials Unit (CTU) involved in the trial.

It is not necessary to list Principal Investigators and Sites.

# Summary

This summary should be 1–2 pages only. It should give the reader sufficient information to understand the rationale for the trial, its objectives and the methods that will be used to achieve these objectives.

|  |  |
| --- | --- |
| **Objectives:** | Summarise primary and secondary objectives. |
| **Type of trial:** | Example: Phase , open/single-blind/double-blind, randomised, crossover/partial crossover/parallel group, single/multi-site trial in . |
| **Trial design and methods:** | Give brief summary of trial design, including dosing regime and the assessments that will be made to achieve the primary and secondary objectives. |
| **Trial duration per participant:** | i.e., from consent to last trial assessment. |
| **Estimated total trial duration:** | i.e., from when first participant enrolled to last participant follow-up. |
| **Planned trial sites:** | Single-site or multi-site. If multi-site, include number of planned sites. |
| **Total number of participants planned:** | Include planned number to be enrolled for the whole trial. |
| **Main inclusion/exclusion criteria:** | Include the main disease/area to be investigated and the key inclusion/exclusion criteria. |
| **Statistical methodology and analysis:** | Briefly describe the statistical methodology to be used in the trial. |

# Background and Rationale

This section should describe:

* The disease to be studied in the trial, including its incidence
* Population being studied and why
* Background to development of the IMP to be used
* Justification of the dose(s) to be used
* In summary, pertinent clinical and preclinical data

Please summarise important trial relevant preclinical/non clinical studies. Please cross-refer to IMPD/IB/SPC (as applicable).

Please summarise previous clinical trials conducted/ or clinical use of the IMP(s) (or where relevant inference to a similar class of medicine) in support for this clinical trial.

Include the rationale or “problem statement” i.e. the research question (the hypothesis to be tested).

1. The current available treatment(s) and their limitations, and why you think the IMP(s) might be an improvement on those treatments (e.g. toxicity, cost):

Justification should be provided to support that the IMP could achieve clinical improvement over current practice (and indicate its relevance to healthcare practice).

This justification is particularly important if the trial proposes to use the IMP:

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

Add rationale for:

* trial population, doses selected and the treatment schedule
* the type of design selected

If applicable Include detail for:

* level of blinding to be used – double-blind, single-blind or justification for open label design
* how blinding of investigator team and participant will be implemented (e.g. through use of active and matching placebo treatment)
* combination of IMP and medical device (if applicable) to aid understanding of the effect of each individually and in combination.
* the need for, the duration and nature of follow-up and objectives based on appropriate risk assessment including:
	+ the nature of the IMP
	+ current knowledge regarding the IMP
	1. the follow-up should be considered from the following aspects

– follow up for the protection of the participant i.e. clinical follow up;

– follow up for the purpose of collection of specific data (which might not involve all participants) i.e. safety follow up and efficacy follow up

## Assessment and management of risk

A discussion of additional risks posed by the experimental treatment and all test above standard care must be included and the mitigations of these risks should detailed in this section.

Consider drug interaction risks, hypersensitivity risks, any specific precautions and recommendations as documented in the SPC / IB and how these will be managed.

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

|  |  |  |  |
| --- | --- | --- | --- |
| Name of IMP(s) / NIMP (delete NIMP if it is not applicable) | Potential risk(list below the main expected side effects as described in the SPC /IB (NB each side effect should be listed on separate rows)) | Risk Frequency(In line with the SPC/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 patients, or exclusions in the eligibility criteria). e.g.. IDMC configured to mitigate patient safety and data integrity risks. |
|  |  |  |  |
|  |  |  |  |

The table below summarise the risks and mitigations of all test above standard care that are being performed in a table:

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

In accordance with the MRC/DH/MHRA Joint Project Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products, this trial is categorised as: (Choose one of the following types as appropriate for the trial)

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

Please state the aims and objectives not trial endpoints (see section 11.1)

*Primary: (there should be only one primary objective)*

*Secondary:*

# Trial design

## Overall design

This section of the protocol should include the following information:

1. Clear description of the type of design (e.g. open label, blind, parallel group, crossover, placebo-controlled, dose escalation, sequential, cluster randomised and equivalence)
2. SPC for a trial with a crossover design, information about possible carry over effects, detail of treatment ordering, washout (/in) periods
3. Schematic diagram(s) of overall trial design
4. Description of the duration of treatment, participant participation and trial follow-up

# Investigational Medicinal Products and Non-Investigational Medicinal Products

Please refer to the following guidance for classification of IMPs and NIMPs:

Guidance in chapter III of Eudralex website: <http://ec.europa.eu/health/documents/eudralex/vol-10/>

or Clinical trials, Directive 2001/20/EC, The rules governing medicinal products in the European union Volume 10 – guidance documents applying to clinical trials Guidance on investigational medicinal products (IMPS) and non investigational medicinal products (NIMPS) (REV. 1,MARCH 2011) and as updated.

## Name and description of IMP(s)

*The description of all the IMP(s) should be proportional to its development status (authorised or non-authorised), e.g. for marketed products reference to the authorized medicinal product with at least details of strength, dosage form, route of administration and marketing authorisation holder should be given, for new or modified products a full, although concise description should be given.*

Use of comparator or placebo should also be described. These are also defined as IMPs.

*Dosages should be included in section 8.4 so they do not need to be included here.*

If the trial uses a licensed drug, specify the generic name only, unless a specific brand must be used, for example as per an IMP supply agreement (e.g. if IMP is to be supplied free of charge by the manufacturer). Also, please add statement that any brand of the IMP can be used, if that is the case.

## Source of IMP, Manufacture, Distribution and Storage

If the IMPs to be used in the trial are being supplied, manufactured and/or imported by a company specifically for use in the trial please provide details of the arrangements. Insert the following statement:

The following IMP’s will be manufactured and QP released for use in the study by the holder of an MIA(IMP) licence

 Level of detail to be added in the protocol will depend on the development status of the IMP itself. If the IMP is novel, provide an overview of storage/transfer/distribution of the IMP prior to receipt at the trial site (if applicable).

If the IMP is based on a marketed product that will be modified describe briefly what the modification will be and who will be manufacture the modification.

If the IMP is marketed and provided by a company specifically for the trial briefly specify the details here.

If the IMPs are being sourced from hospital stock please insert the following statement, and list the IMPs as applicable:

The following IMPs will be sourced from routine hospital stock and their handling and management will be subject to standard procedures of the pharmacy: (list IMPs)

For multiple IMPs remember to include a statement for each.

Sourcing of the IMP(s) is also discussed in the Summary of Drug Arrangements/IMP management plan.

## Name and description of each NIMP (if applicable)

Please refer to the following guidance for requirements if using NIMPs:

http://ec.europa.eu/health/files/eudralex/vol-10/imp\_03-2011.pdf

The following drugs are standard treatment but all trial participants must be treated according to the following schedule in order to isolate the effects of the [name IMP(s)] or [name other trial treatment].

1. Drug x
2. Drug Y

These drugs are considered to be non-investigational medicinal products (NIMPs) in this Trial. Need to give justification why you consider this to be an NIMP.

Choose one of the paragraphs below to include, dependent on the licencing status of the NIMPs:

A similar system to that required for IMPs needs to be implemented if the NIMPS are unlicensed (i.e. come from another EU country or a country outside EEA).

Or in all other cases

Host sites are responsible for maintaining a system which allows adequate reconstruction of NIMP movements; there should be a procedure that permits recording which participants received which NIMPs during the trial with an evaluation of the compliance*.*

## Storage and handling of IMP(s) at site

All IMP aspects of the trial at participating sites are the responsibility of the PI, who may delegate this duty to the local pharmacist or other appropriately trained personnel. The delegation of duties must be recorded on the Staff Signature and Delegation of Tasks.

If there is no pharmacy involvement, include reference to applicable department(s), e.g. laboratories, and qualified members of staff who are delegated by the PI to be responsible for management of the IMP(s).

Storage and handling (e.g., reconstitution, labelling) of the IMP will be completed in accordance with the relevant SPC or Investigator Brochure and summary of drug arrangements.

Include the following details as required:

1. Specify/describe storage requirements at site
2. Technical modalities should be included if applicable (i.e. if the product is to be given in a syringe and is a powder and needs to be reconstituted)
3. Include instructions on any local preparation or reconstitution required. Include details of who will be responsible and where the activity will take place (e.g., will reconstitution take place in pharmacy or by other delegated individual at the bedside)
4. Include detailed instructions to ensure blinding of the trial where needed (e.g. where the person involved at the clinical site in the preparation of the IMP cannot be blinded whilst the person responsible for the administration of the IMP needs to be blinded)
5. For IMPs considered to be Genetically Modified Organisms, add details of any special requirements/containment/destruction required and/or reference specific procedures or SOPs which will be created (if known/applicable).

Detailed instructions are contained in the summary of drug arrangements.

## Accountability of IMP(s)

This section needs to describe the procedures for the shipment to and receipt at trial site, dispensing, return, destruction or final transfer of the IMP. Ideally the patient will be instructed to return used IMP packaging and/or unused IMP so that this can be accounted for by the sponsor/pharmacy to ensure adequate reconciliation of the product. If unused IMP will be transferred for non-clinical/research/other use, need to describe the procedure and how this will be documented.

Drug accountability allows the reconstruction of the trial such that it can be demonstrated that the medication was received by the participant, in the correct dose and form and what was returned to the Sponsor and/or destroyed. The level of record keeping should be sufficient to show this.

Choose one of the paragraphs below, dependent on whether IMP will be shipped to site or routine hospital stocks will be used.

For IMPs that will be shipped to site(s):

IMP shipping arrangement instructions for site will be described in the Summary of Drug Arrangements.

Usual procedures for monitoring of temperature and transport conditions of the IMP will apply and will be documented on the IMP shipping form. Upon receipt of the IMP, the site pharmacy will confirm receipt of the IMPs by posting/faxing back the accompanying shipping form to the supplier and copies retained at trial sites file. In cases where the IMP was damaged or not stored correctly this will warrant an urgent notification to the *manufacturer/supplier* (delete where appropriate) and a replacement will be arranged. *[Insert manufacturer/supplier details]* will be responsible for dispatching replacement IMPs to sites. Site pharmacy will be responsible for logging receipt of the IMPs on the site accountability log within the site pharmacy file. Site pharmacy will be responsible for storing the IMP in line with storage requirements as set out in this protocol. Site pharmacy will monitor temperature of IMP storage and report to the sponsor any temperature excursions that have occurred. Details of reporting temperature excursion are in the Summary of drug arrangements and in the SOP for IMP Management. Full IMP accountability will be conducted during the trial. All IMP dispensed by pharmacy will be logged on the site accountability log within the site pharmacy file.

Once the IMP is dispensed, the IMP will be administered to participants within *[insert number]* hours/days (delete where appropriate) of dispensing and the administration of the IMP will be documented in the source data and CRF.

All used/unused IMPs will be returned to site pharmacy, to be then updated in the drug accountability log in the pharmacy site file. Drug destruction will be conducted, once authorised by the sponsor and in accordance with local practice, and this will be documented in the drug destruction log in the hospital pharmacy file.

Or in the case of Hospital stocks being used:

The IMP Drug Accountability Log must be completed to record each dose of IMP dispensed for each trial participant. This log must be retained in the relevant section of the Pharmacy Site File, and a copy must be submitted to the sponsor upon request. It is the responsibility of the Pharmacy Lead to maintain drug accountability records.

All used/unused IMPs will be returned to site pharmacy, to be then updated in the drug accountability log in the pharmacy site file. Following authorisation by the sponsor, drug destruction will be conducted in accordance to local practice / *[insert alternative method if applicable]* , and this will be documented in the drug destruction log in the hospital pharmacy file.

Detailed instructions are contained in the summary of drug arrangements

## Concomitant medication

Medication(s)/treatment(s) permitted (if any) and/or not permitted before and/or during the trial (specify time restrictions). Refer to SPc as applicable.

Consider possible interactions or effects that could confound the results of the trial.

Please do not confuse con meds with NIMPs, refer to section 6.3 for further details

Concomitant medications will be recorded in the Participant’s medical records/CRF.

## Post-trial IMP arrangements

Describe what arrangements are in place should the IMP be provided to trial participants post trial participation. If there are no arrangements please state here.

# Selection of Participants

Please consider each criterion carefully as there must be NO deviations from it during the trial. You need to know which document you will use to assess compliance with the criteria.

These criteria need to be defined in such a way that a monitor/inspector can clearly identify from the CRF and medical notes that each participant meets the eligibility criteria. Therefore they should be as objective as possible.

Please add criteria as appropriate (for example, consider contra-indications to trial treatments, incompatible concurrent treatments, recent involvement in other research), and include points below if appropriate

## Eligibility of trial participants

#### Trial participant inclusion criteria

1. Age (add upper and lower age limits as applicable)
2. Gender (if specifying) (justification must be included in the trial rationale if excluding)
3. Clinical Parameters (including ranges if applicable).
4. Females of childbearing potential and males agree to use an effective method of contraception from the time consent is signed until X weeks after treatment discontinuation. Effective methods of contraception acceptable for this trial are ***PLEASE SPECIFY***. *Please refer to MHRA guidance document for contraceptive requirement in clinical trials* [*http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con2033037.pdf*](http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con2033037.pdf)
5. Females of childbearing potential have a negative pregnancy test within [specify e.g. 7 days] prior to being registered/randomised. 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
6. Willing and able to provide written informed consent

#### Trial participant exclusion criteria

1. Females who are pregnant, planning pregnancy or breastfeeding
2. Consider contraindications to trial treatment (e.g. as listed in SPC), incompatible concurrent treatments
3. Concurrent and/or recent involvement in other research or use of another experimental investigational medicinal product that is likely to interfere with the study medication within (specify time period e.g. last 3 months) of study enrolment
4. Known allergies to the IMP and excipients of IMP and placebo
5. Consider any clinical conditions which should be excluded

## Recruitment

Describe recruitment methods such as the use of adverts, websites, PICs (Participant Identification Centres) and the involvement of different sites. How will the participants be first approached? Are you considering posting participant information sheets, or calling potential participants? Details of any proposed recruitment methods should be detailed. Add details of recruitment stages (e.g. for dose escalation designs if an interim review is required).

Please 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.

## Informed consent procedure

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 CI/ PI on the Staff Signature and Delegation of Tasks.

**“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 trial.

A copy of the signed informed consent form will be given to the participant. The original signed form will be retained in the trial file at site and a copy placed in the 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.

If the trial is in children or adults unable to consent for themselves please include appropriate procedure. Refer to NRES website (<http://www.nres.npsa.nhs.uk/applications/guidance/>).

# Trial procedures

## Pre-treatment Assessments

You must list all the planned screening assessments, including physical examination, medical history and concomitant medication. 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). 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 fall outside time window.

Screening failures i.e. participants who do not meet eligibility criteria at time of screening may be eligible for rescreening subject to acceptable parameters. This will need to be described clearly in the protocol if applicable.

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

Examples:

* Demographics recorded
1. Medical History recorded
2. Concomitant Medication recorded
3. Physical Examination
4. Height, weight and oral temperature
5. Resting pulse and blood pressure (BP)
6. Blood and Urine tests
7. 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:

1. chest x-ray within 6 months of consent
2. 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.

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.

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

## Registration / Randomisation Procedures (delete as appropriate)

Participant [specify registration or randomisation] 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 8.1 for pre-treatment assessments) the registration/randomisation procedure described below will be carried out.

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.

If participants will be randomised within the trial consider the following: Include information regarding how randomisation will be implemented (include who will be doing it, where and how including the procedure to be used out of hours if applicable). Specify who will hold the randomisation list.

Describe how participants will be assigned to treatment groups e.g. through consecutive allocation of subject numbers, and the use of a Trial Subject Enrolment Log. This section should not address the statistical aspects of randomisation (see section 11.3)

You should ensure you have a clear process on randomisation taking into consideration interaction between single site and/or multisite trials.

Describe the approach to be used to conceal allocation (e.g. sealed envelopes, telephone central allocation office, web-based system).

*We strongly advise that for double blind trials, you enlist the service of a CTU or a specialist company (e.g.* [*www.sealedenvelope.co.uk*](file://C:\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)*) to do randomisation. You should cost for this in your grant application.*

Please note consent and screening does not necessarily constitute enrolment.

Participants are considered to be enrolled into the trial following: consent, pre-treatment assessments (see section 8.1), confirmation of eligibility, completion of the registration/randomisation process, allocation of the participant trial number and treatment by the central coordinating team/remote system.

## Treatment Schedule

Include the treatment schedule to outline the order of events of IMP/NIMPs administered.

You should give details here on route of administration, dosages, duration, and method of administration for each IMP.

Remember to include dosage for all participants throughout the trial period, taking particular care to changes of dose as infants and children grow. You should include the frequency and timing of dose in each part and arm of the trial, methods for individualised doses, etc.

If chemotherapy, pre or post –standard treatment drugs will be administered to the participant this should be described here.

Include information on the application of the IMPs, detailing when this application may require specific concomitant therapy (these will be considered NIMPs) and/or may involve surgical procedures. Information on the standardisation and optimisation of the processes (especially where involving surgical procedures) should be included.

Include information on any medical devices to be used in the administration of treatment.

### Dose Modifications

You should give details here on required dose modifications if applicable, for example in the case of certain adverse events (specify the exact dose modifications and events), also include the maximum length of a treatment break, describe re-escalation of doses (if applicable) (see also stopping rules section 8.10).

## Subsequent assessments and procedures

### Visit schedule and assessments

Describe all trial procedures and assessments at each visit, including those that are part of routine care. **Breakdown into visit numbers/visit time points**. Ensure that assessments are included to answer all primary and secondary outcomes, if an assessment does not address an outcome (other than safety measures) consider if it is necessary. Provide a brief description of each of the assessments (e.g. venepuncture, 25 mls to be drawn for full blood count and biochemistry), use 8.5.3 for a detailed description of each assessment. Specify if they are clinic visits, inpatient visits, telephone assessments or home visits. Refer to Appendix 1 - schedule of assessments for visit window deviation parameters e.g., visits should occur +/- x days of the scheduled date.

Assessments/procedures to be considered at follow-up visits:

1. monitoring immediately after IMP administration (e.g. time-intervals for measurements of the participant’s temperature, blood pressure, pulse, respiratory rate and oxygen saturation level)
2. eligibility check (if applicable)
3. assessment of endpoints/outcome measures
4. assessments and recording of safety including general (e.g. physical examination), specific safety assessments (e.g. specific laboratory tests according to the applicable product information and/or population) and adverse event collection
5. dispensing of trial drugs
6. assessment of compliance with trial drugs (e.g. participant diary/collection of medication packaging)
7. recording of concomitant medications

A schedule of all trial assessments and procedures is set-out in Appendix 1.

### Laboratory Assessments and Procedures

**Local laboratories** (delete if not applicable)

Detail any laboratory measurements required, detailing any handling, storage and packaging instructions and/or refer to lab manual where required. Include details of the Lab conducting analysis.

Specify the parameters that are to be measured for efficacy/safety. If there are trial specific acceptable ranges for any of these parameters, please specify and the action to be taken if the result is outside the specified range (e.g. report as clinically significant, is it an abnormal lab value which requires expedited reporting?).

The following tests will be carried out at Local Laboratories:

Example Table (please add, amend or delete as required):

|  |  |
| --- | --- |
| 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 |

**Central laboratories** (delete if not applicable)

Detail any laboratory measurements required, detailing any handling, storage, packaging and shipping instructions and/or refer to lab manual where required. Include details of the Lab conducting analysis.

Laboratory x will be carrying out the following tests: (delete as appropriate)

Laboratory y will be carrying out the following tests: (delete as appropriate)

Add a reference to a lab manual/ sample management SOP if applicable

#  Translational Research Samples (delete if not applicable)

Add details of any research samples that are to be collected for research projects/future research projects which are not part of the trial, including:

1. whether this is an optional part of the trial
2. type of samples e.g. tissue, blood, urine etc, frequency and method of collection
3. how samples are to be processed at site, how samples will be stored, transported and where samples are to be sent
4. Add a reference to a lab manual/ sample management SOP if applicable.

### Clinical Procedures and Data Collection

Describe the methodology of all other procedures to assess the efficacy and safety of the product if not described in detail elsewhere. If any of the assessments must be carried out by a specific person (e.g. physician or blinded radiologist) this detail can be added here.

Examples (add/delete as required):

1. Medical examination: The following sites will be examined: head, neck, ears, nose, throat, eyes, chest, lungs, heart, abdomen, skin, and lymph nodes; and the following systems will be assessed: musculoskeletal and neurological
2. Spirometry: The forced expiratory volume in 1 second (FEV1), and forced vital capacity (FVC) will be measured
3. Clinical score questionnaires: The participant will be provided with a booklet incorporating all of the clinical scores. This includes VAS, VISA-A, MOXFQ and EQ5D questionnaires that will take approximately 20 minutes to complete
4. Concomitant Medication: All over-the-counter or prescription medication, vitamins, and/or herbal supplements will be recorded.

## Assessment of IMP/NIMP compliance

Define procedures for establishing compliance to IMP/NIMP schedule if applicable, e.g.:

* Monitoring (e.g. watching participant swallow pills and checking their mouth afterwards, getting participants to complete a diary card, package returns).
* Recording of participant compliance information (what will be recorded, when and where). Will participant diaries be kept?

Percentage of noncompliance equating to participant withdrawal should be described in the statistical section if applicable.

Note: IMP should be returned by Participants for Accountability and destruction (see section 6.5)

## Discontinuation/withdrawal of participants

The protocol should: describe under what circumstances and how subjects will be withdrawn from the trial.

In consenting to participate in the trial, participants are consenting to trial treatment, assessments, follow-up and data collection.

**Discontinuation of Trial Treatment for clinical reasons**

A participant may be withdrawn from trial treatment whenever continued participation is no longer in the participant’s best interests, but the reasons for doing so must be recorded. Reasons for discontinuing treatment may include (amend according to trial):

* 1. disease progression whilst on therapy
	2. unacceptable toxicity
	3. intercurrent illness which prevents further treatment
	4. patients withdrawing consent to further trial treatment
	5. Any alterations in the participant’s condition which justifies the discontinuation of treatment in the site investigator’s opinion
	6. Persistent non-compliance to protocol requirements

The decision to withdraw a participant from treatment must be recorded in the CRF and medical notes, and the sponsor when required should be notified in writing.

In these cases participants remain within the trial for the purposes of follow-up for safety and or data analysis according to the treatment option to which they have been allocated (randomised trials only delete if not applicable).

Participant withdrawal from trial treatment

If a participant expresses their wish to withdraw from trial treatment, sites should explain the importance of remaining on trial follow-up and seek permission to allow use of routine follow-up data to be used for trial purposes. The importance of safety follow-up should be emphasised to the participant in the Participant Information Sheet.

The decision of the participant to withdraw from treatment must be recorded in the CRF and medical notes.

The participant may withhold their reason for withdrawal however, if the participant gives a reason for their withdrawal, this should be recorded.

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.

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)***

## Replacements

State whether withdrawn participants would be replaced and how (e.g. if a randomised trial, would the replacement be randomised to the same treatment as the participant they are replacing).

## Stopping rules

Example text:

The trial may be stopped before completion for the following reasons:

1. On the recommendation of the TSC or IDMC (include as applicable)
2. On the recommendation of the sponsor and CI
3. Add other stopping rules as applicable

Individual participant stopping rules/discontinuation criteria can be included if applicable for the trial (cross reference section 8.4.1 dose modifications (if applicable) and section 9 adverse events).

Dose escalation trials may need stopping rules/criteria to be assessed prior to escalation to the next dose level. Please state these, along with when and how they will be assessed.

Describe what happens when a stopping rule is reached (e.g., if a stopping rule is reached safety data will be reviewed and a decision on continuation will be made by the TMG with input from the sponsor).

## Definition of End of Trial

The protocol should define the end of the trial and state the expected trial duration. The safety and efficacy follow up involving active data collection (trial visits etc.) should form part of the clinical trial whereas clinical follow up and passive data collection may take place after the end of the trial.

Example wording:

The expected duration of the trial is [**x** years] from recruitment of the first participant.

The end of trial is the date of the last visit/ telephone follow up/ home visit of the last participant (delete as appropriate).

# Recording and reporting of adverse events and reactions

**Collection, recording and reporting of adverse events (including serious and non-serious events and reactions) to the sponsor will be completed according to the sponsor’s SOP (INV/S05).**

## Definitions

|  |  |
| --- | --- |
| **Term** | **Definition** |
| Adverse Event (AE) | Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product 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 participant to whom an IMP or procedural intervention has been administered, including occurrences which are not necessarily caused by or related to that product.* |
| Adverse Reaction (AR) | Any untoward and unintended response in a participant to an investigational medicinal product which **is related** to any dose administered to that participant. *This includes medication errors, uses outside of protocol (including misuse and abuse of product)* |
| Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction  | Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:* results in death,
* is life-threatening\*,
* requires hospitalisation or prolongation of existing hospitalisation\*\*,
* results in persistent or significant disability or incapacity, or
* consists of a congenital anomaly or birth defect
 |
| \*A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.\*\* Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE. |
| Unexpected adverse reaction | An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out:(a) in the case of a product with a marketing authorization, in the summary of product characteristics for that product, (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question. |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) | An unexpected adverse reaction which is also categorised as serious. |
| Important Medical Event | These events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered ‘serious’. |

## Recording adverse events

Recording of AEs 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.

Choose most appropriate sentence:

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

Choose most appropriate sentence:

AEs will not be collected in the CRFs for this trial *(If you do not plan to record certain adverse events in the CRF (for example, in a phase IV trial of a licensed medication used within its license with a well-established safety profile) please state it here and provide justification. However, all SERIOUS adverse events must be recorded in the CRF. )*

Or

All Adverse events will be recorded in the CRF following consent/IMP administration (delete as appropriate).

All 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 until [insert as appropriate e.g. the participant completes the trial / 1 year after administration of the IMP].

## Assessments of Adverse Events

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

### Severity

The generic categories below are given for use as a guide. You may have a more specific scale that you want to use related to the disease (e.g. CTCAE criteria), amend as required.

|  |  |
| --- | --- |
| **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 is a clinical decision based on 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) (refer to section 9.17 for reporting requirements) (part of a combine product or used for the application of the product, please specify) - delete as appropriate. 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/AE Log and/or SAE form (amend as required).

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

|  |  |
| --- | --- |
| **Category** | **Definition** |
| Definitely: | There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. |
| Probably: | There is evidence to suggest a causal relationship, and the influence of other factors is unlikely |
| Possibly | There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant’s clinical condition, other concomitant events). |
| Unlikely | There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant’s clinical condition, other concomitant treatments). |
| Not related | There is no evidence of any causal relationship. |
| Not Assessable | Unable to assess on information available. |

### Expectedness

|  |  |
| --- | --- |
| Category | Definition |
| *Expected* | An adverse event which is consistent with the information about the IMP listed in the Investigator Brochure (or SPC if Licensed IMP) **or clearly defined in this protocol.** |
| *Unexpected* | An adverse event which is not consistent with the information about the IMP listed in the Investigator Brochure (or SPC if Licensed IMP) \* **or clearly defined in this protocol.** |

\* this includes listed events that are more frequently reported or more severe than previously reported

The reference document to be used to assess expectedness against the IMP is (add in either SPC/IB) (include a reference document for each IMP).

The following events listed below describe expected procedural/disease related AEs: List all expected procedural and or disease related events.

### Seriousness

All events are assessed for seriousness as defined for an SAE in section 9.1.

If specific adverse events have been specified as requiring expedited reporting as SAEs in section 9.3.5, refer to that section here as well.

### Other Notifiable Adverse Events (if applicable)

Include detail of any other specific events that would not necessarily fall under the definition of a ‘Serious’ event, but that the investigators think would benefit from expedited reporting including events related to known risk factors where applicable:

1. specific abnormal lab/assessment values
2. suspected or confirmed cases of infection
3. unexpected reactions (e.g., hypersensitivity, immunological, toxic)

adverse events related to medical devices which are used for application of the product (see section 9.17)

All safety events as described above will be treated as SAEs and reported in line with the procedures set-out in section 9.4 apart from regulatory reporting

## Procedures for recording and reporting Serious Adverse Events

All serious adverse events (SAEs/SARs/SUSARs) will be recorded in the medical records and the CRF, and the sponsor’s AE log (the sponsors AE log is used to collate SAEs and AEs 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, an AE log will not be required). The [include AE log or line-listing] of SAEs will be reported to the sponsor at least once or twice per year (amend as appropriate in liaison with JRO Pharmacovigilance Manager)

All SAEs will be recorded from XXXXXXXX until XXXXXX.

All SAEs (except those specified in section 9.4.1 as not requiring reporting to the Sponsor), must be recorded on a serious adverse event (SAE) form. The CI/PI or designated individual will complete the sponsor’s SAE form and the form will be preferably emailed to the Sponsor SAE@ucl.ac.uk and/or faxed on 020 3108 2312, within 24 h of his / her becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

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

**Email forms to** **SAE@ucl.ac.uk**

**and/or**

**Fax forms to 020 3108 2312**

* **Managing serious adverse events in a multi-site trial**

The protocol needs to have clear instructions for the reporting lines and timeframe for serious adverse events. These instructions will need to include where the investigator (PI) will send the reports: e.g. will the PI sends the report directly to the sponsor or to a central coordinating team. Detail whether the CI will review the report first before it is notified to the sponsor and how safety information (e.g. SUSARS, safety alerts) will be disseminated to all other PI sites.

Reporting to the sponsor will be completed as per the sponsor’s SOP and using the UCL SAE form (INV/S05) as amended for the trial.

This section of the protocol needs to specify how long after the last dose of IMP has been administered to the participants, that serious adverse events and reactions will be recorded and reported. Some suggested wording:

SAE’s will be reported to the sponsor until the end of the trial / 1 year post IMP treatment. SAR and SUSAR will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

This section also needs to describe the type and duration of follow-up care for participants. Some suggested wording:

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and/or trial follow-up if necessary.

Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to the JRO as further information becomes available.

**Flow Chart for SAE reporting (this simple flow chart is for single site trial, please amend in line with trial specific requirements)**

**Submit SAE form to Sponsor within 24 hours**

**Email forms to** **SAE@ucl.ac.uk**

 **Fax forms to 020 3108 2312**

**Was the event Serious?**

Criteria:

1. Results in death
2. Is life threatening
3. Results in persistent significant disability/incapacity
4. Results in a congenital anomaly or birth defect
5. Requires in-patient hospitalisation or prolongs existing hospitalisation
6. Is otherwise medically significant

Record in medical records and CRF (if applicable)

Record in medical records,

And CRF in accordance with the protocol

Record in medical records, CRF (and AE Log if required)

**Complete an SAE report form**

**AE occurs**

**Assign Severity Grade**

**Was the event an Other Notifiable event?**

See section 9.3.5 for notifiable events which should also be reported as serious

Yes

No

**Is the event specified as an adverse event which does not require immediate reporting as an SAE?**

Yes

Yes

No

No

### Serious Adverse Events which do not require immediate reporting (if applicable and in liaison with JRO)

You may choose not to report some particular SAEs to the sponsor for example if they are expected to occur on a regular basis and offer no further new information to your safety profile e.g. standard expected side effects of pre-conditioning chemotherapy as specified in the SPC 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, CRF and the AE log (if required), however you may state that you will not complete an SAE form and forward it to the sponsor. Please provide the rationale for doing so.

**Example of exception:**

SAEs anticipated from the surgical procedures (as listed below) will be RECORDED in the participants’ medical notes and in the CRF (if required). However, SAE forms will not be completed and sent to the sponsor.

SAEs which do not require immediate reporting: (specify)

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

### Notification of Deaths (if applicable)

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

Where there may be a variation to this, the protocol needs to be explicit as to whether, how and when the principal/chief investigator will notify deaths (expected or unexpected) to the sponsor. The following statements are examples of what could be stated in the protocol:

*“All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the IMP, or an unrelated event”.* This statement should be used for phase I/First in Human trials.

*“Only deaths that are assessed to be caused by the IMP will be reported to the sponsor. This report will be immediate”.*

*“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.

If there are any specific requirements around the management and notification of deaths in a trial (e.g., the need to obtain an autopsy reports) this should be described here.

### Reporting SUSARs

The sponsor will notify the main REC and MHRA of all SUSARs. SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days after the sponsor has learned of them. Other SUSARs must be reported to the REC and MHRA within 15 days after the sponsor has learned of them.

### Unblinding (if applicable)

We strongly advise that for double blind trials, you enlist the service of a CTU or a specialist company (e.g. [www.sealedenvelope.co.uk](file://C:\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)) for unblinding. 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 un-blinding for the following situations, refer to trial specific SOPs where applicable:

### Emergency Unblinding

Amend wording below as appropriate:

The trial code should only be broken for valid medical or safety reasons e.g. in the case of a severe 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 always to clinical need, where possible, members of the research team should remain blinded.

The code breaks for the trial are held [*add relevant department*] and are the responsibility of *[add personnel*].

In the event that unblinding is required a formal request will be made by the Investigator/treating health care professional to an individual authorised and delegated to perform code break.

If the person requiring the unblinded information is a member of the Investigating team then a request to the authorised individual to unblind will be made and the treatment allocation information obtained.

If the person requiring the unblinded information is not the CI/PI then that healthcare professional will contact the Investigating team to request the code break. Unblinding will take place if in the opinion of a treating physician a patient’s health is compromised. The authorised individual will break the code and immediately inform the treating healthcare professional of the participant’s treatment allocation. The treating physician has the ultimate decision and right to unblind the patient.

On receipt of the treatment allocation details the CI/PI or treating health care professional will treat the participant’s medical emergency as appropriate.

The CI/PI will document the breaking of the code and the reasons for doing so on the CRF and unblinding log and will file this, in the 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 CI/Investigating team will notify the JRO 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 DSMC Charter. [Delete as appropriate]

### Unblinding for the submission of SUSAR reports

Amend wording below as appropriate:

The following procedure will be used to unblind for the submission of a SUSAR report to the regulatory agencies.

1. A member of the JRO will contact the authorised individual for code break [please specify] via telephone in the first instance, to request unblinding information from the randomisation list.

The request will be documented in an email from the Sponsor to the authorised individual detailing the protocol number and trial name, name of the requester, reason for unblinding, participant initials subject number and timeline to receive the unblinded information.

1. On receipt of the treatment allocation, The Sponsor will provide the unblinded information on the e-SUSAR website form.
2. SUSAR reports will be disseminated to Investigators at site(s) and will be manually blinded.
3. The authorised individual should not reveal details of the participant’s treatment allocation to other, blinded members of the trial team.
4. The unblinded information will not be forwarded to the trial team and will be kept in the JRO sponsor file until the trial has ended and the data locked.

OR (if an online system such as [www.sealedenvelope.com](http://www.sealedenvelope.com) is in use)

1. A representative of the Sponsor will be authorised to access the code break system [please specify] for the purposes of unbinding for the submission of a SUSAR
2. On receipt of the treatment allocation, the Sponsor will provide the unblinded information on the e-SUSAR website form. SUSAR reports will be disseminated to Investigators at site(s) and will remain blinded.
3. The unblinded information will not be forwarded to the trial team and will be kept in the JRO sponsor file.

## Development Safety Update Reports

The sponsor will provide the main REC and the MHRA with Development Safety Update Reports (DSUR) which will be written in conjunction with the trial team and the Sponsor’s office. 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.

## Pregnancy (If applicable)

Describe any specific risk that there may be during pregnancy and detail any evidence to support whether there is, or is not a risk to the partner of a male participant during pregnancy.

Describe the procedure in place to:

1. record and notify pregnancies to the sponsor (use sponsor’s SOP)
2. follow-up of pregnant participant: Describe in detail the process for monitoring and managing a pregnancy (if required)
3. follow-up (include length of time) of child born to a pregnant trial participant, including male trial participant who is the partner of the pregnant woman (if required)
4. Please consider type of f/u for your particular IMP, active follow-up or passive follow-up, consent requirements and length of f/u required

Suggested wording to be amended as required:

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 preferably emailed to the Sponsor **SAE@ucl.ac.uk** and/or faxed on **020 3108 2312,** within 24 hours of his / her 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 within **24 hours** of becoming aware of the event to the Sponsor

**Email forms to** **SAE@ucl.ac.uk**

**and/or**

**Fax forms to 020 3108 2312**

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

Describe the procedure in place to:

1. record and notify overdoses to the sponsor (this information should be placed on the deviation log)
2. where can overdoses be observed from (pill counts, diary cards, drug charts or participant comment)
3. How will it affect the final analysis. Will participants be taken withdrawn from the trial? Consider what will constitute an overdose that warrants trial discontinuation
4. if an SAE is associated with the overdose ensure the overdose if fully described in the SAE report form
5. How will participants be followed up? E.g. resultant symptoms will be treated as per routine clinical care.

## Reporting Urgent Safety Measures and other safety events

If any urgent safety measures are taken the CI/ PI 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 Sponsor of the measures taken and the circumstances giving rise to those measures.

## Notification of Serious Breaches to GCP and/or the protocol (SPON/S15)

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

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

(b) the scientific value of the trial.

The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of –

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

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor’s SOP on the ‘Notification of violations, urgent safety measures and serious breaches’ will be followed.

## Reporting incidents involving a medical device(s) (if applicable)

Any adverse incident involving a medical device should be reported to the manufacturer of the device.

This is especially important where the incident has led to or, was it to occur again could lead to an event classified as serious (see section 9.2 for definition of SAE). Other minor safety or quality problems should be reported along with incidents that appear to be caused by human error.

For multisite trials detail the process for reporting to the manufacturer or MHRA if applicable (e.g. sites to report to central trial coordinator who submits reports to manufacturer).

All adverse incidents must be reported to [add contact details of the device manufacturer for reporting purposes].

Incidents should be reported as soon as possible (usually within 24 hours). Specify any additional timelines which have may have been agreed with the manufacturer for reporting.

Incidents should be reported to the manufacturer using the [Specify if a particular report format is required by the manufacturer] form provided.

It may be required for events to be reported directly to the MHRA as well as or instead of the manufacturer (this should be discussed with the manufacturer). In this case the following information can be included:

Adverse incidents related to a medical device can be reported directly to the MHRA via the online system ([www.mhra.gov.uk](http://www.mhra.gov.uk)). Alternative contact details: Medicines & Healthcare products Regulatory Agency Adverse Incident Centre (Tel: 020 7084 3080; Fax 020 7084 3109).

Local trust reporting procedures may also need to be followed. It is the responsibility of the PI and trial site team to ensure they are aware of any specific local requirements for reporting device incidents.

# Data management and quality assurance

## Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998.

The Case Report Forms (CRFs) will not bear the participant’s name or other personal identifiable data. The participant’s initials, date of birth and trial identification number, will be used for identification and this will be clearly explained to the patient in the Patient information sheet. Patient consent for this will be sought.

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.

## Data collection tools and source document identification

Data will be collected from sites on Trial specific case report forms (CRFs) or data collection tools such as electronic CRFs.

Source data are contained in source documents and must be accurately transcribed on to the CRF. Examples of source documents are medical records which include laboratory and other clinical reports etc.

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

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

The methods used to maximise completeness of data should be described (e.g. telephoning participants who have not returned postal questionnaires).

It is the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

## Completing Case Report Forms

All CRFs must be completed and signed by staff that are listed on the site staff delegation log and authorised by the CI/ PI to perform this duty. The CI/ PI is responsible for the accuracy of all data reported in the CRF.

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 faxed with the original kept at site? Amend the wording below in line with the management of data for the trial. Ensure this is consistent with the data management SOP.

Once completed the original CRFs must be sent to [specify where CRFs should be sent] and a copy kept at site. The CRFs must be returned within [xx days/weeks] of the participant visit (add further detail where there are different timeframes for different forms). Source data verification of a CRF page should be completed and all data queries answered prior to submission where possible.

## Data handling and analysis

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.

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], 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 1998 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.

# Statistical Considerations

## 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. continuous, categorical, ordinal).

### Secondary outcomes

For each secondary outcome, detail as for primary outcome above.

## Sample size and recruitment

### Sample size calculation

Details of the precision or power calculation used to estimate the required sample size (for analysis of the primary outcome), should contain all information required to reproduce the sample size calculation including:

* [estimates used](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/size.cfm#info) (e.g. Standard deviation, size of the [clinically important effect](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/size.cfm#effect) to be detected, correlations, dropout and noncompliance rates) with relevant justifications in the form of appropriate references, pilot data or clinical arguments.
* assumptions made (e.g. assumptions of Normality, proportional hazards)
* allowance for planned subgroup and interim analysis and clustering effects
* chosen levels of [significance](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/size.cfm#sig) and [power](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/size.cfm#power)
* methods / formula / software used with reference

For international multi-site trials only, if the power of the trial is based on the UK sites only, you must insert the following statement:

‘The power of the trial based on the UK sites alone is [add value] %.’

If x<80%, the following statement should be added as well:

Therefore only descriptive analyses will be performed using the UK data. Tests of efficacy of the intervention will only be performed after combining the data with those from the other international sites.

### Planned recruitment rate

An estimate of the recruitment period for the trial (calculated based on the expected number of eligible and recruited participants available per month/year) with justification that the [required sample size](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/trials.cfm#achieving) will be attainable in practice.

## Randomisation methods

Include detail for each of the following (Please do not repeat section 8.2 here):

1. participant / cluster randomised design (randomising individuals or groups (e.g. general practices, wards))
2. type of randomisation to be used - simple, block, stratified, minimisation (block size should not be stated in the protocol to maintain blinding)
	1. 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)
	2. if using blocked randomisation consider varying block sizes.
3. use of equal or unequal allocation between treatment arms

## Statistical analysis plan

### Summary of baseline data and flow of participants

1. List variables to be used to assess baseline comparability of the randomised groups including for each factor: a definition, any rules, references or programs 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).
2. 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 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)
* If economic evaluation is a measure consider measures to capture and report this.

### Secondary outcome analysis

Plans for statistical analysis of each secondary outcome. Note that 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. Ensure all secondary outcomes listed in 11.1.2 are addressed here.

### Sensitivity and other planned analyses

A description of plans for sensitivity and other analyses. For example sensitivity to missing data or non-compliance.

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.

## Interim analysis

Detail of approach for interim analyses (e.g. timing and statistical methods) and criteria for early termination of the trial

Stopping / discontinuation rules and breaking of randomisation code:

* define completion and premature discontinuation of the trial
* describe procedure regarding decisions on discontinuation of the trial (e.g. [interim analyses, role of data monitoring committee](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/trials.cfm#monit))
1. state documentation to be completed if part / all of the trial is discontinued
2. Describe circumstances under which the randomisation codes may need to be broken and the procedure for this.

## Other statistical considerations

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

# Record keeping and archiving

At the end of the trial, all essential documentation will be archived securely by the CI and 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

Please insert any applicable committees and their remits.

Describe which of the three committees will be in place for the trial: Trial Management Group (TMG) (*all trials should have a TMG*), Independent Data Monitoring Committee (IDMC) and Trial Steering Group (TSC). The terms of reference for these committees will need to be provided in separate documents.

**Please note for phase I trials,** it is expected that an IDMC will be in place unless justified.

## Trial Management Group (TMG)

*State the composition and responsibilities of the group. E.g.*

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)

*State if there is a TSC and list its responsibilities. E.g.*

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)

*State if there is an IDMC/ DMC and list its responsibilities. E.g.*

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 11.5), 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 11.5), or as necessary to address any issues.

*Mention IDMC/DMC charter (if applicable)*

# Direct Access to Source Data/Documents

Include the following statement:

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

# Ethics and regulatory requirements

The sponsor will ensure that the trial protocol, participant information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory body (MHRA in UK) and an appropriate research ethics committee, prior to any participant recruitment. The protocol, all other supporting documents including and agreed amendments, will be documented and submitted for ethical and regulatory approval as required. Amendments will not be implemented prior to receipt of the required approval(s).

If the trial involves the use of radiation, document here if an Administration of Radioactive Substances Advisory Committee (ARSAC) licence is needed.

Before the site may be opened to recruit participants, the Chief Investigator/Principal Investigator or designee must receive NHS permission in writing from the Trust Research & Development (R&D). It is the responsibility of the CI/ PI or designee at each site to ensure that all subsequent amendments gain the necessary approvals, including NHS Permission (where required) at the site. This does not affect the individual clinician’s responsibility to take immediate action if thought necessary to protect the health and interest of individual participants (see section 9.9 for reporting urgent safety measures).

**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 2000](http://www.legislation.gov.uk/uksi/2010/2840/contents/made).

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 / as part of a connected programme of work (delete as applicable) 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.

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 a Class 2, 3 or 4 product further notifications will be required and the JRO will advise.

Include the following for all trials:

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. The chief investigator will prepare the APR.

Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a report of the clinical trial which complies with the format as defined by the EMA. This will then be uploaded to EudraCT for availability to the MHRA and a copy of the report will be submitted to the main REC, within 1 year after the end of the trial.

# Monitoring requirement for the trial

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 objective, purpose, phase, design, size, complexity, blinding, endpoints and risks associated with the trial.

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

# Finance

A statement of the finance for the trial such as details of funding body. Include a statement to address if there are financial interests by CI, PIs or trial management members.

# Insurance

The following must be included for all trials:

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.

If a medical device is to be used in the trial, there must also be indemnity arrangements in place, with the manufacturer, to cover the malfunction and breakdown of the device.

# Publication policy

Please include details as required of: Authorship guidelines, any details of publication restrictions and a process and timeframe for approving and submitting reports for dissemination. If contractual obligations regarding publication and/or review of publication are in place these could be detailed here.

All proposed publications will be discussed with and reviewed by the Sponsor prior to publishing other than those presented at scientific forums/meetings. Please refer to UCL publication policy.

# References

List of 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

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Screening (Pre-treatment assessment)** | **Treatment Phase** | **Final visit** |
| Visit No: | 1 | 2 | 3 | 4 | 5 | 6 | 8 |
|  | Day – X to Day -X | Day 1 | Day 7 | Day 14 | Day 21 | Day 28 | Day 42/ Early Discontinuation visit |
| Window of flexibility for timing of visits: |  |  | e.g. +/- 2 days | e.g.+/- 2 days | E.g..+/- 3 days | e.g.+/- 3 days | e.g.+/- 3 days |
| Informed Consent | X |  |  |  |  |  |  |
| Medical History | X |  |  |  |  |  |  |
| Physical Examination |  |  |  |  |  |  |  |
| Vital Signs |  |  |  |  |  |  |  |
| Eligibility confirmation | X | X |  |  |  |  |  |
| Add ALL Protocol Assessments including bloods/urine, ECGs, scans, c as applicable both trial specific and routine (include separate row for each assessment) |  |  |  |  |  |  |  |
| Randomisation  | X |  |  |  |  |  |  |
| IMP administration |  | X | X | X | X | X |  |
| Adverse Events review | X | X | X | X | X | X | X |
| Concomitant Medication review | X | X | X | X | X | X | X |

# Appendix 1 - Schedule of assessments