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| **logo -small use blk** |

**Interventional trial (non-CTIMP, non-device trial)**

**Protocol Template**

**Guidance Notes for Protocol Template**

Please check the Joint Research Office [website](mailto:CTIMPS@ucl.ac.uk) <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 an interventional trial.

**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’ (N/A) be added next to it.

The protocol must be consistent with the participant information sheet, consent form, IRAS form, 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.
2. Ensure consistency: refer to trial ‘participants’ throughout the protocol (not patients, subjects or volunteers), refer to ‘trial’ throughout the protocol, 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.
4. Logos: 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 logs as appropriate - trial specific logo, funders, collaborators, research networks

|  |  |
| --- | --- |
| **Full title of trial** |  |
| **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 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] |
| **ISRCTN / Clinicaltrials.gov no:** delete as applicable] | [Insert ISRCTN or Clinicaltrials.gov reference no] |
|  |  |
| **Intervention:** | [Insert trial intervention] |
| **Single site/multi-site:** | / |
| **Chief investigator:** | **Sponsor Representative**:  [insert name] [insert email address]  Joint Research Office, UCL, 1st Floor Maple House,  149 Tottenham Court Road,  London W1T 7NF  Postal address:  Joint Research Office, UCL  Gower 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, the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the current Research Governance Framework, the Sponsor’s SOPs, and other regulatory requirements as amended.

|  |  |  |
| --- | --- | --- |
| **Chief investigator** |  |  |
| UCL | Signature | Date |
| **Sponsor**  Sponsor representative |  |  |
| UCL | Signature | Date |
|  |  |  |

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|  |  |  |  |

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# List of abbreviations

Commonly used abbreviations – add or delete as applicable:

AE Adverse Event

CI Chief Investigator

CRF Case Report Form

CRO Contract Research Organisation

DMC Data Monitoring Committee

GAfREC Governance Arrangements for NHS Research Ethics

GCP Good Clinical Practice

HTA Human Tissue Authority

IB Investigator’s Brochure

ICF Informed Consent Form

IDMC Independent Data Monitoring Committee

IMP Investigational Medicinal Product

ISF Investigator Site File

ISRCTN International Standard Randomised Controlled Trial Number

NHS R&D National Health Service Research & Development

PI Principal Investigator

PIS Participant Information Sheet

QA Quality Assurance

QC Quality Control

RCT Randomised Controlled Trial

REC Research Ethics Committee

SAE Serious Adverse Event

SDV Source Document Verification

SOP Standard Operating Procedure

SPC Summary of Product Characteristics

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, 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: A randomised, single/multi-site trial in . |
| **Trial design and methods:** | Give brief summary of trial design 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. |
| **Total number of participants 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 intervention
* In summary, pertinent clinical and preclinical data

Summarise important trial relevant preclinical/non clinical studies.

Summarise previous trials conducted in support for this trial.

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

The current available treatment(s) and their limitations, and why you think the intervention might be an improvement on those treatments.

Justification should be provided to support that the intervention 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 intervention:

* + in children or in adults unable to consent for themselves
  + for longer duration
  + in a vulnerable population
  + the indication/ medical condition compromises the participant’s tolerance

Add rationale for:

* trial population 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
* combination of intervention and medical device (if applicable) to aid understanding of the effect of each individually and in combination.

# 3.1 Assessment and Management of Risk

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

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 is being performed (e.g. blood test, x-rays, ECG etc.) | Potential risk  Describe the risks of the intervention, or where applicable refer to a valid document that shows the risk. | Risk Management  Describe how you will minimise the risk. Consider if management requires any precautions or advice needs to be given to patients, or exclusions in the eligibility criteria. |
| Blood Test | Bruising, Pain, Bleeding and Infection | Performed by trained phelbometrist. Follow trust standard operational procedures. |

# Objectives

Please state the aims and objectives, not trial endpoints

Primary:

There should be only one primary objective

Secondary:

# Trial design

Include the following information:

* Clear description of the type of design (e.g. blind, cluster randomised)
* Schematic diagram(s) of overall trial design
* Description of the duration of intervention, participant participation and follow up if applicable.

# Selection of Participants

Please consider each criterion carefully, as there should be no deviations from it during the trial. You need to know which document you will use to assess compliance with the criteria. Where applicable, criteria must also be assessed against intervention manuals, SPCs, IBs and core data sheets.

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

# 6.1 Inclusion criteria

Consider:

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 [insert]
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.

# 6.2 Exclusion criteria

Consider:

1. Females who are pregnant, planning pregnancy or breastfeeding
2. Concurrent and/or recent involvement in other research that is likely to interfere with the intervention within [specify time period e.g. last 3 months] of study enrolment
3. Any clinical conditions which should be excluded.

# 6.3 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.

Please include the following statement for studies hosted at NHS sites/using NHS patients:

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

1. Been confirmed by the Sponsor (or it’s delegated representative), and
2. Been issued an ‘NHS permission letter’.

# 6.4 Informed consent

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 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 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 procedures. It is recommended you access the latest Health Research Authority guidance when completing PIS and consent documentation.

# 7 Product/Interventions

# 7.1 Name and description of intervention(s) under investigation

List full details of all interventions under investigation. For mechanistic studies, this should include the name of the drug/supplement, pharmaceutical form/strength, the status of this (licensed/non-licensed), and where this will be sourced.

# 7.2 Storage and handling of drug at site (if applicable)

All drug 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 drug(s).

Include the following details as required:

* Specify/describe storage requirements at site
* 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)
* 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)
* Include detailed instructions to ensure blinding of the trial is maintained where needed (e.g. where the person involved at the clinical site in the preparation of the drug cannot be blinded whilst the person responsible for the administration of the drug needs to be blinded)

# 7.3 Accountability of drug (if applicable)

This section needs to describe the procedures for the shipment to and receipt at trial site, dispensing, return, destruction or final transfer of the drug. If this is not applicable, justification should be provided (e.g. if the product involved is deemed to be low risk).

You may wish to produce a separate document where this is particularly complex:

Detailed instructions are contained in a separate summary of drug arrangements

# 7.4 Concomitant medication (if applicable)

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.

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

# 7.5 Dosages, modifications and method of administration (if applicable)

Add details of dosages of any drugs or supplements, and how it will be administered to participants and the duration.

# Trial procedures

# 8.1 Pre-intervention 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.

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:

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

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 the intervention) and indicate timing.

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

# 8.2 Registration/Randomisation Procedures (delete as appropriate) (if applicable)

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).

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

Describe the approach to be used to conceal allocation (e.g. sealed envelopes, telephone central allocation office, or 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 intervention by the central coordinating team/remote system.

# Intervention procedures

Include the schedule of procedures for the intervention, including:

* Details of how the intervention(s) will be delivered
* When/what intervals the intervention(s) will be delivered
* Where the intervention(s) will take place
* Who will deliver the intervention(s).

For mechanistic trials, you should give details here on route of administration, dosages, duration, and method of administration for any drug.

Include information on any medical devices to be used.

# 8.4 Subsequent assessments and procedures

Describe all 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 description of each of the assessments. Specify if they are clinic visits, inpatient visits, telephone assessments or home visits. Refer to Appendix 1 - schedule of assessments.

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

# Samples (if applicable)

# 8.5.1 Laboratory assessments

**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.

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 (if 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:

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

Consent will need to be sought and information provided in the Participant Information Sheet regarding this.

# 8.5.3 Sample storage and transfer

In the study, [Description of tissue samples to be inserted] will be collected from patients in accordance with the patient consent form and patient information sheet and shall include all tissue samples or other biological materials and any derivatives, portions, progeny or improvements as well as all patient information and documentation supplied in relation to them.

The [Description of tissue samples to be inserted] will be appropriately sent to [Full name and address of party handling the tissue samples to be inserted] for [Description of use/processing to be inserted].

[Full name and address of party handling the tissue samples to be inserted] will process, store and dispose of [Description of tissue samples to be inserted], in accordance with all applicable legal and regulatory requirements, including the Human Tissue Act 2004 and any amendments thereto.

The [Description of tissue samples to be inserted] will not be transferred to any party not identified in this protocol and are not to be processed and/or transferred other than in accordance with the patients’ consent.  After ethics approval for the study has expired, the [Description of tissue samples to be inserted] will be disposed of in accordance with the Human Tissue Act 2004 and any amendments thereto, or transferred to a licensed tissue bank.

# 8.6 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 intervention, assessments, follow-up and data collection.

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

* + disease progression whilst on therapy
  + intercurrent illness
  + patients withdrawing consent
  + persistent non-compliance to protocol requirements.

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

# 8.7 Definition of End of Trial

The protocol should define the end of the trial and state the expected trial duration.

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

# 9.1 Definitions

|  |  |
| --- | --- |
| **Term** | **Definition** |
| Adverse Event (AE) | Any untoward medical occurrence in a patient or trial participant, which does not necessarily have a causal relationship with the intervention involved. |
| Serious Adverse Event (SAE). | Any adverse event 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. | |

# 9.2 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 further intervention; it causes slight discomfort |
| Moderate | The adverse event interferes with some aspects of the participant’s routine, or requires further 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 |

# 9.2.2 Causality

The assessment of relationship of adverse events to the intervention 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 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 procedure (specify e.g. surgery) / product failure / mandatory concomitant medications / device(s) (refer to section 9.17 for reporting requirements). 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 intervention). 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 intervention). 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. |
|  |  |

# 9.2.3 Expectedness

|  |  |
| --- | --- |
| Category | Definition |
| *Expected* | An adverse event which is consistent with the information about the intervention listed in the SPC, manual of Operation (amend as appropriate) **or clearly defined in this protocol.** |
| *Unexpected* | An adverse event which is not consistent with the information about the intervention listed in the SPC, manual of Operation (amend as appropriate)\* **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 Intervention is (add in SPC, Manual of Operation, core data sheet etc.) (include a reference document for each intervention).

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

# 9.3 Recording adverse events

You may wish to choose the most appropriate sentence(s):

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

AEs will not be collected in the CRFs for this trial(provide justification. However, all SERIOUS adverse reactions must be recorded in the CRF) or;

All Adverse events will be recorded in the CRF following consent.

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).

# Procedures for recording and reporting Serious Adverse Events

All serious adverse events 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 the JRO).

All SAEs (except those specified in section 9.5 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 within 5 working days of becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

Where the event is unexpected and thought to be related to the intervention, this must be reported by the Investigator to the Health Research Authority within 15 days.

Completed SAE forms must be sent within 5 working days of becoming aware of the event to the Sponsor

**Email forms to** [randd@uclh.nhs.uk](mailto:randd@uclh.nhs.uk)

**Managing serious adverse events in a multi-site trial (if applicable)**

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 to a central coordinating team (based with the CI or a CTU). Detail whether the CI will review the report first before it is notified to the sponsor and how safety information will be disseminated to all other PI sites if required.

SAEs will be reported to the sponsor until the end of the trial.

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)**

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

**Complete an SAE report form**

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

**Email forms to** [**randd@uclh.nhs.uk**](mailto:randd@uclh.nhs.uk)

No

Yes

Record in medical records,

And CRF in accordance with the protocol

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

Yes

Yes

Record in medical records and CRF (if applicable)

No

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

See section 9.5 for notifiable events which should also be reported as serious

No

**Was the event Serious?**

**AE occurs**

**Assign Severity Grade**

# 9.5 Serious Adverse Events that do not require reporting (if applicable)

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 or are related to the disease area of the participants. 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. Provide the rationale for doing so.

# 9.6 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 unblinding for the following situations, referring to trial specific SOPs where applicable:

**Emergency unblinding:**

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].

# Reporting Urgent Safety Measures

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 relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures.

# 9.8 Notification of reportable protocol violations

A reportable protocol violation 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 will be notified immediately of any case where the above definition applies during the trial conduct phase.

# 9.9 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 9.1 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 (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.

# 9.10 Trust Incidents and Near Misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.

b. It is contrary to specified or expected standard of patient care or service.

c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.

d. It puts the Trust in an adverse position with potential loss of reputation.

e. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them.

A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

1. It is an accident or other incident which results in injury or ill health.
2. It is contrary to specified or expected standard of patient care or service.
3. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
4. It puts the Trust in an adverse position with potential loss of reputation.
5. It puts Trust property or assets in an adverse position or at risk of loss or damage.

# Data management

# 10.1 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) 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.

# 10.2 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:

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

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. Consideration should be given to whether the original CRFs are to be sent via post to data management and a copy kept at site, or whether they are faxed with the original kept at site? Amend the wording below in line with the management of data for the trial.

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.

# 10.4 Data handling

In the study, [Description of type of patient data or reference to description of the patient data from a previous protocol section, to be inserted] will be collected from patients in accordance with the patient consent form, patient information sheet and sections [To be inserted] of this protocol.

The [Description of patient data to be inserted] will be appropriately sent to [Full name and address of party handling the patient data to be inserted] for [Description of use/processing to be inserted – e.g. for statistical analysis], and [To be inserted] will act as the data controller of such data for the study [NOTE: In most cases, it may be that UCL, as the study sponsor, is the data controller].

[Full name and address of party handling the patient data to be inserted] will process, store and dispose of [Description of patient data to be inserted] in accordance with all applicable legal and regulatory requirements, including the Data Protection Act 1998 and any amendments thereto. [More details regarding actual storage may be inserted here – e.g. patient data will be stored centrally at in a locked filing cabinet controlled by the Chief Investigator]

The [Description of patient data to be inserted] will not be transferred to any party not identified in this protocol and are not to be processed and/or transferred other than in accordance with the patients’ consent.

# 11 Statistical Considerations

# Primary Outcome

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).

# 11.2 Secondary outcome(s)

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

# 11.3 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, and 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 multisite 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.

# 11.4 Planned recruitment rate

Provide 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.

# 11.5 Randomisation methods

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

* participant / cluster randomised design (randomising individuals or groups (e.g. general practices, wards))
* type of randomisation to be used - simple, block, stratified, minimisation (block size should not be stated in the protocol to maintain blinding)
  + if using stratified randomisation or minimisation, include definition of stratification/minimisation variables (should only consider variables that are likely to be strongly prognostic of the outcome)
  + if using blocked randomisation consider varying block sizes.
* use of equal or unequal allocation between treatment arms.
* How and by whom random allocation lists/minimisation programs will be generated (e.g. using what software, by statistician or specialist company)

# Statistical analysis

# 11.6.1 Summary of baseline data and flow of participants

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

# Primary outcome analysis

Plans for statistical analyses of the primary outcome including:

* Summary measures to be reported
* Method of analysis (justified with consideration of form of the data, [assumptions](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/methods.cfm#assump) of the method and structure of the data (e.g. [unpaired, paired](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/methods.cfm#paired), [clustered](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/methods.cfm#hier)) etc.)
* Plans for handling multiple comparisons, missing data, non-compliers, spurious data and withdrawals in analysis
* Plans for 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 11.2 are addressed here.

# 11.6.4 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. 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.

# Record keeping and archiving

At the end of the trial, all essential documentation will be archived securely by the CI for a minimum of 20 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 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.

# 13.1 Trial Management Group (TMG)

State the composition and responsibilities of the group.

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, multisite trials).

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

# 13.2 Other committees

State if there is a TSC and list its responsibilities:

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 (if applicable) 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.

State if there is an IDMC/ DMC and list its responsibilities:

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 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, or as necessary to address any issues.

# Ethical requirements and patient and public involvement

**Ethics**

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 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 any NHS 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 9.6 for reporting urgent safety measures).

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 is 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 summary report of the trial, which will then be submitted to the REC within 1 year after the end of the trial.

**Patient and public involvement (PPI)**

Describe the involvement of Patients and Public in the research. This section should detail which aspects of the research process have actively involved, or will involve, patients, services users, and/or their carers or members of the public. In particular consider: design of the research, management of the research, undertaking the research, analysis of results and dissemination of findings.

Note that involvement as a participant of a trial is not considered patient and public involvement.

# Monitoring

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 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

University College London holds insurance against claims from participants for injury caused by their participation in the trial*.* Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the 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 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 trial shall provide 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.

# Intellectual property

All background intellectual property rights (including licences) and know-how used in connection with the study shall remain the property of the party introducing the same and the exercise of such rights for purposes of the study shall not infringe any third party’s rights.

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to UCLH.  Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights (“IPR”) to UCL and to disclose all such know-how to UCL.

Each participating site agrees to, at the request and expense of UCL execute all such documents and do all acts necessary to fully vest the IPR in UCL.

Nothing in this section X.Y shall be construed so as to prevent or hinder the participating site from using know-how gained during the performance of the study in the furtherance of its normal activities of providing or commissioning clinical services, teaching and research to the extent that such use does not result in the disclosure or misuse of confidential information or the infringement of an intellectual property right of UCL.  This does not permit the disclosure of any of the results of the study, all of which remain confidential.

# 20 Appendices

Include the schedule of assessments (appendix 1) and references.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Screening (Pre-treatment assessment)** | **Intervention 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 intervention, bloods/urine, ECGs, scans, c as applicable both trial specific and routine (include separate row for each assessment) |  |  |  |  |  |  |  |
| Randomisation | X |  |  |  |  |  |  |
| Adverse Events review | X | X | X | X | X | X | X |
| Concomitant Medication review (if applicable) | X | X | X | X | X | X | X |

# Appendix 1 - Schedule of assessments