**UCL Sponsored Studies: Protocol Template for Interventional Studies**

**UCLH/UCL Research Office**

**(*Version 2.0, 06/01/2021)***

**Guidance**

*Please check the Joint Research Office* [*website*](mailto:CTIMPS@ucl.ac.uk)[*https://www.ucl.ac.uk/joint-research-office/resources-and-templates*](https://www.ucl.ac.uk/joint-research-office/resources-and-templates) *to ensure you have the most up to date version of this template.*

This protocol template is for use by **UCL investigators** to submit **interventional studies for UCL sponsorship** via the UCLH/UCL Joint Research Office (JRO).

***Interventional studies:***

*A clinical study in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions. These types of studies change the clinical care that the participant is receiving.*

Further information on which studies UCL will sponsor can be obtained from a JRO Sponsorship Officer.

This template should **not** be used for the following studies:

* deemed to be Clinical Studies of Investigational Medicinal Products (CTIMP)
* deemed to be Advanced Therapy Investigational Medicinal Products (ATIMP)
* involving new Medical Devices or Medical Devices being used for a new purpose
* managed via a UCL Clinical Trials Unit (CTU)
* using observational methodology
* Studies involving data only.

This template has been developed to include all relevant regulatory, ethics and local policy requirements. The template contains all sections recommended by the Health Research Authority (HRA) for regulatory review by the HRA and the Research Ethics Committees.

**Investigators may use other templates** but must ensure the sufficient level of detail is presented. Investigators wishing to do so are encouraged to read through this template. Text marked in **black** must be inserted into these protocols.

The JRO will review each protocol submitted to ensure key sections and details are included before Sponsorship is formally agreed.

**Instructions for use:**

**Please ensure the protocol template is written in third person.**

**Not all sections will be relevant for all studies.** 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 should be removed, following approval from the JRO Sponsorship Officer. Additional sections may be added in where appropriate.

Instructions and explanatory text are indicated in **red** and **blue** and should be removed or replaced in your protocol with the appropriate text.

**Post sponsorship approval;** any modification to the protocol should be written in the protocol version history table, or in an appendix. The annotation should note exact words that are changed, the location in the protocol, the date the modification was approved by the CI/relevant committee/parties, and the date it became effective.

The protocol must be consistent with the participant information sheet, consent form, IRAS form, SmPC and any other relevant trial documentation, and should be cross checked prior to finalisation. The JRO will carry out a review of the draft protocol and provide advice and guidance prior to approval.

**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 and JRO template header should be deleted once the protocol has been drafted**



Include other logos as appropriate – study specific logo, funders, collaborators, research networks

**Trial Protocol Front Page**

|  |  |
| --- | --- |
| **Full title of trial**  If this is a student project, ensure it is clearly identified as such here, and which UCL academic qualification it relates to. |  |
| **Short title**  The full and short title must be the same on the IRAS form and 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 [insert version number], [insert date DD/MM/YYYY] |
| **Sponsor:** | University College London (UCL) |
| **Sponsor reference number:**  **Funder (s):** | [Type EDGE number]  [Names of ALL organisations providing funding for this trial] |
| **IRAS Number:** | [insert IRAS no.] |
| **ISRCTN / Clinicaltrials.gov no:** delete as applicable] | [Insert ISRCTN or Clinicaltrials.gov reference no] |
|  |  |
| **UCL Data Protection Number:** | [Insert UCL Data Protection Number if only using identifiable or pseudonymised data. Remove if using anonymised date] |
| **Intervention:** | [Insert intervention, e.g. RCT] |
| **Chief investigator:**  [Insert name, title, address and contact details. Include details of Academic Supervisor (where applicable) if different from CI] | **Sponsor Representative**:  [insert name] [insert email address]  UCLH/UCL Joint Research Office,  4th Floor, West  250 Euston Road  London  NW1 2PG |

**PROTOCOL VERSION HISTORY**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Version Stage** | **Versions Number** | **Version Date** | **Protocol updated & finalised by;** | **Reasons for Update** |
| Current | [insert Version]  [Note: all draft versions should be numbered 0.1, 0.2, etc. the ‘final’ version to be submitted to HRA/REC should be numbered version 1.0] | [insert date] | [full name(s) & title(s)] | [include appendix no., if applicable]  NB: Appendix is to be attached to current version of the protocol |
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|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

**DECLARATIONS**

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the U.K. Policy Framework for Health and Social Care Research 2017 (3rd edition) (as amended thereafter), the EU General Data Protection Regulation (2016/679) and the UK Data Protection Act (2018), Sponsor SOPs and applicable Trust policies and legal frameworks.

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

I (investigator) agree to ensure that no research activity or recruitment will commence at participating research sites until the appropriate regulatory approvals and NHS confirmations of Capacity and Capability have been issued, and Sponsor green light confirmed.

I (investigator) also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given. Any deviations from the study as planned in this protocol will be explained and reported accordingly.

**Chief Investigator:**

**Signature: .................................................................................... Date....../....../.......**

**Print Name (in full): ......................................................................**

**Position: .........................................................................................**

**On behalf of the Study Sponsor:**

**Signature: ..................................................................................... Date....../....../.......**

**Print Name (in full): .......................................................................**

**Position: .......................................................................................**

**STUDY 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.

|  |  |
| --- | --- |
| IDENTIFIERS | |
| IRAS Number |  |
| REC Reference No. |  |
| Sponsor Reference No. |  |
| Other research reference number(s) (if applicable) | (e.g. UCL Data Protection number) |
| Full (Scientific) title |  |
| Health condition(s) or problem(s) studied |  |
| Study Type i.e. Cohort etc |  |
| Aim(s): | Summarise aim(s) of study. |
| Objectives: | Summarise primary and secondary objectives and their respective outcome measures |
| Type of trial: | Example: A randomised, single/multi-site trial in [insert study population]. |
| 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. |
| Key Study milestones | e.g. study submission, budget and contract to be finalised, first patient recruitment |
| Estimated total trial duration: | i.e., from when first participant enrolled to last participant follow-up. Include anticipated start date and end of study definition and date. Anticipated start date should be at least 3 months **after** the study has been granted Sponsorship Authorisation, to allow for regulatory and NHS reviews (where applicable). |
| 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. |
| FUNDING & OTHER | |
| Funding | Insert names and contact details of ALL organisations providing funding for this study |
| Other support | Insert details of the non-financial support given, and the names & contact details of all organisation providing the non-financial support. |
| STORAGE of SAMPLES / DATA (if applicable) | |
| Human tissue samples | Insert name and contact details for where samples will be transferred and/or analysed if external to the organisation. |
| Data collected / Storage | Insert name and contact details were the data will be transferred to for storage and analysis if external to the research group and institution. |
| KEY STUDY CONTACTS  Full contact details including phone, email and fax numbers | |
| Committees | Name(s) of committees, full contact details including, phone and email. E.g. study steering groups. For each committee/group, the protocol should state their roles and responsibilities and degree of independence from the Sponsor and Investigators. |
| Sub-contractors |  |
| Other relevant study personnel | (E.g. Data Custodian and Data Processors) |

**KEY ROLES AND RESPONSIBILITIES**

**SPONSOR:** The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also must be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

**FUNDER:** The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work. If further arrangements have been agreed with the funder, please refer to the funding agreement and insert.

**CHIEF INVESTIGATOR (CI):** The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than once site, the CI takes on the primary responsibility whether he/she is an investigator at any particular site.

The CI role is to complete and to ensure that all relevant regulatory approvals and confirmations of NHS Capacity and Capability are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the REC and JRO of the end of the study (including the reasons for premature termination, where applicable). Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC and JRO.

**PRINCIPLE INVESTIGATOR (PI):** Individually or as leader of the researchers at a site; ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.

**OTHER:**add other key personal/entity responsibilities where relevant to the study

**TRIAL PERSONNEL**

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

**Study Coordinator** Name: [insert name and address]  
E-mail:   
Tel: fax:

**Statistician** Name: [insert name and address]  
E-mail:   
Tel: fax:

**Central laboratories** Name: [insert name and email address]  
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. Include the name(s) of any committees, e.g. DMCs, TMGs, steering groups, etc. For each committee/group, the protocol should state their roles and responsibilities and degree of independence from the Sponsor and Investigators.

It is not necessary to list Principal Investigators and Sites.

**KEY WORDS**

Insert relevant key words to describe the study, no more than 6 phrases.

**LIST OF ABBREVIATIONS**

Commonly used abbreviations – insert a table of commonly used abbreviations here.

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***Ensure to click ‘update table’ prior to finalising the Protocol***

# **INTRODUCTION**

Overview of the study; it should be sufficient to guide the reader to the main purpose of the study, how it will be conducted, on which population(s) and its expected benefits. It should say how the results of the study would benefit in terms of clinical practice, policy or the NHS as whole. The introduction may include a study flowchart (recommended: allows users of the document to follow the participant and study pathway with ease, e.g. via a Gantt chart or timeline of activity), and should detail whether this project is being conducted in relation to an academic qualification (a student project), or is related to any previous research sponsored by UCL.

# **BACKGROUND AND RATIONALE**

This section should be written so it is easy to read and can be understood by someone with a basic sense of the topic who may not necessarily be an expert in the area. Some explanation of terms and concepts is likely to be beneficial. It 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). Also explain why the research questions being asked are important and why closely related questions are not covered.

The current available treatment(s) and their limitations, why you think the intervention might be an improvement on those treatments, why the treatment difference is clinically important to patients and if it is realistic.

Justification should be provided to support that the intervention could achieve clinical improvement over current practice (and indicate its relevance to healthcare practice), through consultation with public and patient groups, and why this is worthwhile to patients. Replication to check the validity of previous research is justified, but unnecessary duplication is unethical

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.

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

# **OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS**

Please state the aims and objectives, not trial endpoints. The objectives are generally phrased using neutral wording (e.g. “to compare the effect of intervention A versus intervention B on outcome X”) rather than in terms of a particular direction of effect.

# Primary Objective

There should be only one primary objective to address a specific hypothesis. A useful guide to use in the development of a specific research question is the PICOT criteria:

P *Population (participants)* – what specific participant population is this study focused on?

I *Intervention* – what is the investigational intervention?

C *Comparison group* – what is the main alternative to compare with the investigational   
 intervention?

O *Outcome of interest* – what will be measured?

T *Time* – what is the appropriate follow-up time to assess outcome?

# Secondary Objective(S)

The protocol should describe the secondary objectives which:

* May or may not be hypothesis-driven
* May include secondary outcomes

May include more general non-experimental objectives

# Outcome measures/endpoints

An ideal endpoint/outcome is valid, reproducible, relevant to the target population, and responsive to changes in the health condition being studied.

The primary endpoint/outcome should be a clear, unarguable, quantitative measure of effect that will be the focus of the primary analysis and will drive the choice of sample size. It may be pertinent to list the time point at which the endpoint/outcome will be measured and whether it will be measured more than once during the study.

Secondary endpoints/outcomes should be a sequence of concise statements that are relevant to the declared aims of the studies. There can be any number of secondary measures.

# **TRIAL DESIGN**

In this section, describe the ideal design for the research question and what the study is designed to show. Common designs include:

* Parallel group design: each group of participants receives only one of the study’s interventions
* Cross-over design: each participant is given all the study’s interventions in successive periods. The order in which the participants receive each intervention is determined at random.
* Factorial design: two or more interventions are evaluated separately and in combination against a control.

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.

Describe where the study will be run and any site-specific requirements, such as whether the study will run at multiple sites of whether it is a single centre study. Consider the participant population and where they can be found e.g. usual care pathways.

# **SAMPLING METHODS**

This section should set out precise definitions of which participants are eligible for the study, defining both the inclusion and exclusion criteria. Inclusion criteria should define the population that the study is aiming to include and indicate the generalisability of the trial findings. Exclusion criteria should exclude sub-groups of the population due to, for example, safety and other clinical risks or burden to the participant. 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.

# 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.

Make sure this section is identical to A17-1 and A17-2 in your IRAS form.

If there are separate participant groups being used in the study, ensure separate inclusion and exclusion criteria are detailed (e.g. patients/staff).

# 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.

# 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 and by who? Are you considering posting participant information sheets, or calling potential participants? Details of any proposed recruitment methods should be detailed. Also describe details of the sources of identifiable personal information that will be used to identify potential participants. It should be clear who will confirm eligibility.

List any screening requirements such as laboratory or diagnostic testing necessary to meet any noted inclusion and exclusion criteria. Any assessments and or procedures performed as part of routine care which will be used to screen patients for eligibility will require defined timelines e.g. x-ray within the last 6 months. Specify the maximum duration allowed between screening and recruitment (if applicable).

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

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

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

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

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 with Confirmation of Capacity and Capability from each participating site (where applicable).

The protocol should also detail all intended payments to participants e.g. reasonable travel expenses for any visits additional to normal care. Please refer to HRA guidance for further information ([www.hra.nhs.uk](http://www.hra.nhs.uk)).

# 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.

The participant information sheet and informed consent form must contain the HRA’s GDPR recommended wording. This can be found on the HRA website: <https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/templates/template-wording-for-generic-information-document/>

**“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 will be recorded in the patient medical notes (or electronic health record system) when the participant information sheet (PIS) has been given to the participant.

The protocol should fully describe the informed consent process which typically involves:

* Discussion between the potential participant or his/her legally acceptable representative and an individual knowledgeable about the study
* The presentation of written material e.g. participant information sheet and consent form which must be approved by the REC and be in compliance with GCP, local regulatory requirements and legal requirements
* The opportunity for potential participants to ask questions
* Assessment of mental capacity: for consent to be ethical and valid in law, participants must be capable of giving consent for themselves. This includes:
  + Understanding the purpose and nature of the research, risks and benefits
  + Understanding the alternatives and being able to retain the information for long enough to make an effective decision.

General good practice in research requires that persons incapable of giving legal consent should be given special protection. Where the study allows the inclusion of participants who lack capacity to consent for themselves, the full procedure for consent by a legal representative must be included in the protocol, along with appropriate information sheets and consent forms. Additionally, the management of participants who lose capacity during the study must also be stipulated in the protocol. For further details on the ethical considerations of including persons with mental incapacity in research, please refer to the HRA’s guidance notes: <https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/mental-capacity-act/>

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 and without prejudicing his/her further treatment. Data and samples collected up to the point of withdrawal can only be used after withdrawal if the participant has consented for this. Any intention to utilise such data should be outlined in the consent form. Where a participant is required to re-consent or new information is required to be provided to a participant, it is the responsibility of the Investigator to ensure that this is done in a timely manner.

No trial procedures, including the collection of identifiable participant data (unless the study has prior approval from the Confidentiality Advisory Group (CAG) and the Research Ethics Committee (REC)), 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 Investigator Site File 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. The Investigator takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

Where the participant population is likely to include a significant proportion of participants who cannot read or write, require translators or have cognitive impairment, appropriate alternative methods for supporting the informed consent process should be utilised. The protocol should specify what arrangements the Sponsor considers to be appropriate at site(s) to support the consent process for these participants.

**Electronic consenting**

* it is recommended that PPI groups are consulted to advise if electronic consenting/data collection is appropriate and feasible for your target population and study design. Please ensure the rationale for including this method is documented in your protocol, and traditional means of consenting (paper, in person informed consenting) are available for participants as an alternative, and clarified in all patient documents.
* Considerations for using electronic methods of consent and data collection should always be considered and documented, particularly in preparation for potential pandemics or lockdown measures (e.g. COVID-19).

UCL sponsored studies or Chief Investigators with UCL contracts may use REDCAP free of charge, UCL’s Research Data Collection Service. This may be used for eConsent and data collection, either for collection of all source data, or as an alternative to paper methods. Refer here for further information: <https://www.ucl.ac.uk/isd/it-for-slms/redcap-research-data-collection-service>. The Safe Haven version should always be used for research projects.

If consent is not applicable, describe why, the type of data that is being collected and from where, and what regulatory approvals will be made. Decisions on whether an application to process patient information without consent should be made locally and ultimately decided by those who hold the requested data. The following sets out some key considerations to assist these local decisions on whether an application to the Confidentiality Advisory Group (CAG), to avoid a breach of the common law duty of confidentiality, is advised.

If there are consent exemptions, justify here, and discuss with Sponsorship Officer if an application to CAG is also required. Insert details here if applicable.

# Additional consent provisions for collection and use of participant data and human tissue in ancillary studies (if applicable)

Please use this section to describe the consenting procedure for ancillary studies, if applicable. The following details should be included:

* If the data and/or biological specimens for ancillary studies will be acquired, transferred and stored during the study
* If the data and/or biological specimens will be used for a specified subset of studies or for submission to ethically approved research tissue banks for future specified or unspecified research
* What options participants will be given regarding their participation in ancillary research including:
  + Whether participants can opt out of ancillary research but still participate in the main study
  + Consent for use of their data/specimens and/or submission to an unrelated biobank.

# **PRODUCT/INTERVENTIONS**

# Name and description of intervention 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.

# Storage and handling of drugs 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 another 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).

# 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.

# 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.

The protocol should specify:

* Which specific medication(s)/treatment(s) are permitted and not permitted before, during and/or after the study including their time restrictions
* Possible interactions or effects that could confound the results and conclusions of the study
* Wash out times from previous medication, if applicable
* Whether surgery/radiotherapy can continue whilst the participant is taking part in the study

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

# Dosages, modifications, and methods of administration (if applicable)

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

The dosing schedule for any drugs or supplements used should include:

* Description and justification for the route of administration e.g. oral, intravenous etc. If the drug is infused, it would be important to detail how long the infusion will take
* The frequency of administration
* Details of increments, adjustments and/or dose capping
* The number of cycles/durations
* The timing of each dose
* Information regarding what actions would be taken if:
  + A dose is missed by the participant
  + Vomiting following dose administration
* For weight-based dosing, specify whether weight must be taken on the day of dosing or whether it can be measured in advance (state time limits)
* Where dosage is dependent on laboratory data, specify whether blood specimens must be taken on the day of dosing or specimens can be taken in advance in line with routine local procedure
* Dosage modifications:
  + In the event of certain adverse events, specify whether the dose should be modified or if any rescue medication may need to be administered
  + Specify when a dose modification will result in the participant having to withdraw from treatment.

# **TRIAL PROCEDURES**

# 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 childbearing 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).

# 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. Also consider who will be informed of the patient’s registration and how they will be informed.

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 Envelope, telephone central allocation office, or web-based system). Also state who will receive new patient/randomisation alerts and describe how these alerts will be received.

If blinding will be used, the following should be considered and included in the protocol:

* Who will be blinded to intervention groups: participants, care providers, outcome assessors etc. A full description is essential and ambiguous terminology such as “single blind”, “masked” or “double blind” should not be used.
* The timing of final unblinding of all study participants
* Any strategies for reducing the potential for unnecessary unblinding

If blinding is not used, then justification should be provided.

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, confirmation of eligibility, completion of the registration/randomisation process, allocation of the participant trial number and intervention by the central coordinating team/remote system.

# Baseline and Intervention Procedures

# Baseline data

Clearly describe the baseline data that needs to be collected. Consider including the following in the protocol:

* The relevance of each baseline variable
* Whether any of the procedures need to be undertaken in a certain order or in a certain way
* For any particularly complex procedures or for those that differ from routine standard practice, these should be detailed in full
* If specialist, non-standardized assessments are required, care should be taken to detail exactly what needs to be happen during the assessment.

# 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)
* The time points for assessment data e.g. weight will be recorded each month
* How compliance will be reviewed if the participant is self-dosing at home
* When diary cards should be checked
* Any use of electronic patient reported outcome devices
* Quality of life assessments, if required

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.

# 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.

If participants will be monitored after the active intervention phase has closed, then the protocol should describe:

* The frequency of follow-up visits
* The duration of the follow-up period
* How participants will be identified as ‘lost to follow-up’
* Retention strategies

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

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

# Samples (if applicable)

# 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.

# 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.

Detail relating to jurisdictions where samples will be transferred.

Technical aspects of storage equipment – temperatures, transport methodologies etc.

# 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.

It is always within the remit of the physician responsible for a patient to withdraw the patient from a trial (or certain aspects of the trial) for appropriate medical reasons, adverse events or new information gained about an intervention. 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/electronic health record system. 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. Any inclusion of collected data needs to be used in accordance with GDPR and HRA guidance.

# 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).

# **FINANCE AND SUPPLY OF EQUIPMENT**

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. At a minimum, disclosure should reflect:

* Ownership interests that may be related to products, services or interventions considered for use in the study that may be significantly affected by the study
* Commercial ties requiring disclosure such as a technology company
* Any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion

The oversight groups should determine what is appropriate to report. At the time of writing the protocol not all sites/personnel may have been identified. In such instances, the protocol should state that this information will be collected and where it will be documented.

The research costs for the study have been supported by (add funder, including funding amount and date of award).

This section should contain (where applicable) an outline of the funding arrangements to support external sub-contractors and additional sites. It should also provide details of excess treatment costs or the supply of equipment or other resource from third parties where this is applicable.

Also include the details of specific equipment to be used and their intended use, department where they will be used, and whether these are to be provide by an external body.

If external collaborators are being used, e.g. the study will be managed by an external Clinical Trial Unit (hosted by another university/NHS Trust), detail what the arrangements are, what will they be responsible for and how this will be different from Sponsor responsibilities (and consequently detail in relevant sections in the protocol). Discuss with Sponsor Officer for guidance if required.

Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, shareholding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest? Insert details here.

# **DATA MANAGEMENT**

# Confidentiality

The study is compliant with the requirements of the General Data Protection Regulation (2016/679) and the UK Data Protection Act (2018). All Investigators and study site staff will comply with the requirements of the General Data Protection Regulation (2016/679) with regards to the collection, storage, processing and disclosure of personal information, and will uphold the Act’s core principles. UCL is the data controller; the UCL Data Protection Officer is [insert DPO generic email address/name and contact details of UCL DPO]. The data processors are [insert details]. The study will be collecting the following personal data:

This section may include:

* Where data is coming from (e.g. directly from participants, medical records, NHS Digital, etc.)
* Data collection procedures: What personal data is being collected, and whether it’s identifiable, pseudo-anonymised, or anonymised (and whether the extent to which it can be identified changes throughout duration of study). If data will be depersonalised, what will participant’s personal data be replaced with?
* Where data will be recorded (source data, e.g. medical notes)
* Where electronic and hard copy data will be stored
* Who is the data custodian?
* Who in the research team will have access to data? Mention if you will be limiting access to the minimum number of individuals necessary for quality control, audit and analysis.
* Data security: E.g. secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media.
* Details of where, how and to who the data will be transferred to, and how confidentiality of data will be preserved during this process (what are the issues and arrangements in place to maintain participant confidentiality?).
* If data will be maintained outside the study unit/office/organisation:
* Which institution will maintain the data, specifically how the data will get there
* The purpose for its transfer over to other institutions, and who will view/custodian of the data at the other institution
* Data monitoring committees (if applicable)
* How long will data be stored for, and what are the destruction arrangements (if applicable)?

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.

# 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.

# 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 2018 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.

Direct access to the data will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections, in line with participant consent.

Include data flow diagram here to map out the organisational relationship and flow of anonymised, pseudonymised and identifiable data between the different organisations and collaborators.

# Personal Data breaches

In some instances, despite risk management and mitigations, personal data breaches may occur throughout the duration of the study. GDPR broadly defines personal data breaches as a security incident that has affected the confidentiality, integrity or availability of personal data. In short, there will be a personal data breach whenever any personal data is lost, destroyed, corrupted or disclosed; if someone accesses the data or passes it on without proper authorisation; or if the data is made unavailable, for example, when it has been encrypted by ransomware, or accidentally lost or destroyed.

* If there is a data breach/breach of confidentiality (as per GDPR definitions), how will this be handled by each site, and how will this be reported to Sponsor and Data Controller?
* If there is a CTU involved in the management of this study, detail what their responsibilities are in investigating/managing data breaches, and reporting these to the Sponsor and Data Protection Officer.

Personal data breaches will be immediately reported to the UCL Information Security Group (ISG) and the UCL Data Protection Officer [insert name and contact email], and to the Sponsor via the [UCL JRO research incident reporting form](https://redcap.slms.ucl.ac.uk/surveys/?s=NE5dypTdFo) (as per form and guidance: <https://www.ucl.ac.uk/legal-services/guidance/reporting-loss-personal-data>). The following information will be provided: full details as to the nature of the breach, an indication as to the volume of material involved, and the sensitivity of the breach (and any timeframes that apply). Sites will additionally follow their Trust incident reporting mechanisms, and will document this within their TMF/ISFs.

# **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).

# Secondary outcome(s)

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

# 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 studies that involve a formal sample size calculation, the main principle is that the planned sample size should be large enough to have a high probability (power) of detecting a true effect of a given magnitude, should it exist. It is important that an appropriate level of statistical advice is sought to ensure trial validity.

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.

# 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. This section may also include information such as the number of recruiting centres, the size/percentage of the population that is captured by the eligibility criteria, the expected consent rate and the expected screen failure rate. This will help sites to determine if they are likely to be able to recruit the target number of participants.

Mention Loss to Follow-up considerations if appropriate.

# Randomisation methods

Include detail for each of the following (Please do not repeat previous randomisation sections 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

# 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 10.2 Secondary Outcomes 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. 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.

Subgroup analyses: Explore whether estimated intervention effects vary significantly between subcategories or study participants. As these data can help tailor healthcare decisions to individual patients, a modest number of pre-specified subgroup analyses can be useful.

Adjusted analyses: The protocol should if there is an intention to consider adjusted analyses, any known variables for adjustment, how continuous variables will be handled, and what the main analysis is if unadjusted and adjusted analyses are intended

The protocol should also include and plans for interim analysis and the criteria for premature termination of the study. The following should be considered:

* Any interim analysis plan, even if it is only performed at the request of an oversight body e.g. DMC
* The statistical methods that will be used
* Who will perform the analyses?
* When the analyses will be conducted (timing and indications)
* The decision criteria – statistical or other – that will be used to judge the interim results as part of a guideline for early stopping or other adaptations
* Who will see the outcome data while the study is ongoing?
* Whether these individuals will remain blinded to the trial groups
* How the integrity of the trial implementation will be protected (e.g. maintaining blinding) when any adaptions to the trial are made
* Who has the ultimate authority to stop or modify the study e.g. the CI, Trial Steering Committee, or the Sponsor?
* The stopping guidelines:
  + Criteria for stopping for harm are often different from those for benefit and might not employ a formal statistical criterion
  + Stopping for futility occurs in instances where, if the study were to continue, it is unlikely that an important effect would be seen (i.e. there is a low chance of rejecting the null hypothesis).

The protocol should also describe how missing data will be dealt with. The following should be considered:

* The strategies to maximise follow-up and prevent missing data
* How recording of reasons for missing data will be undertaken
* How missing data will be handled in the analysis and whether there are any planned methods to impute missing outcome data, including which variables will be used in the imputation process (if applicable)

The procedure for reporting any deviation(s) from the original statistical plan should be included in the protocol.

# **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. A risk/benefit analysis plus risk management of all interventions involved in the trial should be included.

The following should be described:

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

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 phlebotomist. Follow trust standard operational procedures. |

# **RECORDING AND REPORTING OF ADVERSE EVENTS**

# 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. * Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences |
| \* 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. | |

# Assessments of Adverse Events

Each adverse event (AEs) will be assessed for severity, causality, seriousness and expectedness as described below. The period of time over which AEs must be reported and recorded must be clearly stated in the protocol. The point where recording/reporting usually starts is from the time of consent.

# 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 |

# Causality

The assessment of relationship of adverse events to the intervention is a clinical decision made by the Investigator (or delegated medically qualified person) 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)). 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 / SAE Log and/or SAE form (amend as required).

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

|  |  |
| --- | --- |
| **Category** | **Definition** |
| *Related* | A causal relationship between the intervention and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. |
| *Not related* | There is no reasonable possibility of a causal relationship between the intervention and an adverse event. |
| *Not Assessable* | Unable to assess on information available. |

# Expectedness

All SAEs assigned by the Investigator or delegate as suspected to be related to the intervention will be assessed for expectedness against the current SmPC, Manual of Operation (amend as appropriate) or clearly defined in this protocol.

|  |  |
| --- | --- |
| Category | Definition |
| *Expected* | An adverse event which is consistent with the information about the intervention listed in the current SmPC, 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 current SmPC, 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 SmPC, 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 that won’t require additional reporting.

# Recording of Adverse Events

Choose the most appropriate sentences:

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).

All adverse events will also be recorded on the non-CTIMP Adverse Event (AE) log, and stored in the site files (provided by the JRO). If you are recording AEs in a database, e.g. electronic health records system or electronic CRF, detail process for recording and extracting here.

# Procedures for recording and reporting Serious Adverse Events (SAEs)

All serious adverse events will be recorded in the medical records and the CRF, and the sponsor’s SAE log (the Sponsor’s AE log and SAE 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 AE and SAE logs will be stored in the TMF (if single site)/Investigator Site File (if multi-site) and may be subject to Sponsor monitoring and auditing.

All SAEs (except those specified in the protocol as not requiring reporting to the Sponsor) will be reported to the Sponsor within 24 hours of becoming aware. The CI/PI or designated individual will complete the Sponsor’s online Research Incident Reporting Form (<https://redcap.slms.ucl.ac.uk/surveys/?s=NE5dypTdFo>) within 24 hours 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 SAE is unexpected and thought to be related to the intervention, this must be reported by the Investigator to the main REC that approved the study within 15 days of the Investigator becoming aware of the event, using the non-CTIMP safety report to REC form. This form can be found on the HRA website: <https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/>. The Sponsor should be copied into this, so they are aware. Discuss with the JRO Quality Assurance team in the first instance.

If there is a CTU involved in the management of this trial, include details for how incidents will be managed, and how these will be notified to the Sponsor.

Refer to the *JRO SOP for Reporting Research Incidents, Events and Complaints in UCL/UCLH sponsored non-CTIMPs* for further details and to facilitate completion of this section of the protocol. This SOP can be found on the JRO website SOPs and Templates pages.

# Managing serious adverse events across research sites (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 reports (clearly marked as follow-up) should be completed via <https://redcap.slms.ucl.ac.uk/surveys/?s=NE5dypTdFo> and submitted to the JRO as further information becomes available.

# Serious Adverse Events (SAEs) 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 not 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 SAE 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.

# Incidental Findings in Research

Defined as a finding that has potential health or reproductive importance, which is discovered in the course of conducting research, but is unrelated to the aims of the study**.**

Insert details here regarding:

* Whether incidental findings are applicable to your study
* Ensure this is detailed in the Patient Information Sheet and Consent Form, and the process of notifying patients and timeline
* What types might occur during the study (e.g. abnormal results during research scans, blood tests, etc.)
* How they will be identified, reported and acknowledged by the site PI and patient’s clinical care team/GP within 48 hours, and updated to the CI
* How this will be reported to the Sponsor and documented in patient medical records and ISFs.

All research staff must follow participating sites’ incidental findings policies, and training will be provided as part of initiation to the research study (where applicable).

# 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. It is essential that any unblinding mechanism does not unblind the whole study, but only the individual concerned. The actual allocation must not be disclosed to the participant and/or other study personnel including other site personnel, monitors, corporate sponsors or project office staff. There should be no written or verbal disclosure of the code in any of the corresponding participant documents.

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 in the form of a substantial amendment to the relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures.

# Protocol Deviations and 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 protocol violations during the trial conduct phase by completion of the online JRO Research Incident Reporting Form: <https://redcap.slms.ucl.ac.uk/surveys/?s=NE5dypTdFo>. All protocol violations must be recorded on the Protocol Violation Log and filed in the site file (a template of this log will be provided by the JRO).

Protocol deviations are **minor** unintended departures from the expected conduct of the study protocol/SOPs, which **does not impact** the participants’ safety or compromises the integrity of the study data. E.g. a study visit date being outside the window defined in the protocol. Provide examples of what typical protocol deviations may occur in your study, and what your process for recording these will be. Protocol deviations do not need to be reported to the Sponsor, but should be recorded in the Protocol Deviation Log and filed in the site file (a template of this log will be provided by the JRO).

# Reporting incidents involving a medical device (delete if not applicable)

Any adverse incident involving a medical device will 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. Other minor safety or quality problems should be reported along with incidents that appear to be caused by human error.

For multisite studies detail the process for reporting to the manufacturer (e.g. sites to report to central study 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, details and responsibilities for reporting events to the MHRA should be included here.

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

# NHS Serious Incidents and Near Misses (if applicable)

A serious 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.

Serious Incidents and near misses will be reported to the Sponsor and Trust Quality & Safety department as soon as the study team becomes aware of them.

# Complaints from research participants

In the first instance, research participant complaints (patients or health volunteers) will be reported to the CI/PI to investigate, as documented in the patient information sheet(s), and to the Sponsor via [research-incidents@ucl.ac.uk](mailto:research-incidents@ucl.ac.uk), following the *UCL Complaints from Research Subjects about UCL Sponsored Studies and Trials* policy. For participants who are NHS patients, complaints will be reported to the NHS Complaints Manager at the Trust where the recruitment and study procedures were undertaken. Complaints from NHS patients are handled under NHS complaints policies and procedures, with involvement from PALS and the Sponsor where necessary.

# 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.

# 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).

# 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.

# **REGULATORY REVIEW AND PATIENT AND PUBLIC INVOLVEMENT**

# Regulatory Review

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.

The study was deemed to require regulatory approval from the following bodies (list here, e.g. NHS REC Favourable Opinion/UCL Ethics approval and HRA Approval). **Before any site can enrol patients into the study,** the Chief Investigator/Principal Investigator or designee will ensure that the appropriate regulatory approvals have been issued, and NHS Confirmations of Capacity and Capability and Sponsor green lights are in place (delete if there are no NHS sites involved).

For any amendments to the study, the Chief Investigator or designee, in agreement with the Sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments as well as the study delivery team) to confirm ongoing Capacity and Capability for the study.

All correspondence with the Sponsor, REC and HRA will be retained. The Chief Investigator will notify the Sponsor and REC of the end of the study.

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

Within 90 days after the end of the trial, the CI 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.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the Sponsor and to the REC and HRA.

# Peer Review

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

The study has been peer reviewed in accordance with the requirements outlined by UCL.

Choose either (having discussed with the UCLH/UCL Joint Research Office):

* The Sponsor considers the procedure for obtaining funding from (insert funder name) to be of sufficient rigour and independence to be considered an adequate peer review.
* This study has been peer reviewed within UCL by an independent and relevant peer reviewer/committee (amend as required) on (insert date). The Sponsor has accepted these reviews as adequate evidence of peer review.
* This study has been reviewed as part of an educational programme. The Sponsor has verified that the supervisor of the project has undertaken sufficient review of the protocol in line with the requirements of his/her department.

# 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.

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

This may include how these groups will be involved in:

* The acceptability of the research
* design of the research
* management of the research
* undertaking of the research
* analysis of results and dissemination of findings.

Also check the UCLH/UCL JRO website for PPI workshops and advice.

# **MONITORING AND AUDITING**

[Insert details on appropriate monitoring activities for 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. The degree of monitoring will be proportionate to the risks associated with the trial. Risk will be assessed on an ongoing basis by the Chief Investigator, and adjustments made accordingly (in conjunction with the Sponsor).

Insert details of any additional monitoring support (if applicable), e.g., data/safety monitoring committees.

The Chief Investigator will be responsible for the day to day monitoring and management of the study. The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

The Chief Investigator will inform the Sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

The UCLH/UCL Joint Research Office, on behalf of UCL as Sponsor, will conduct random audits on a selection of studies in its clinical research portfolio. Monitoring and auditing will be conducted in accordance with the UK Policy Framework for Health and Social Care Research, and in accordance with the Sponsor’s monitoring and audit policies and procedures.

# **TRAINING**

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files.

The training section may also include:

* Specific training requirements for staff working on the project
* Specific qualifications and experience required of staff on the project
* Identifying if training may require a renewal at any point throughout the study, and how this will be managed in the study.

# **INSURANCE AND INDEMNITY**

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

Additionally, UCL does not accept liability for sites such as GP surgeries in primary care; investigators/collaborators based in these types of sites must ensure that their activity on the study is covered under their own professional indemnity.

To be inserted for UCL sponsored studies where equipment is being provided to sites for the purpose of the study:

If equipment is to be provided to site(s) for the purpose of the study, [please describe what arrangements will be made for insurance and/or indemnity to meet potential legal liability arising in relation to the equipment (e.g. loss, damage, maintenance responsibilities for the equipment itself, harm to participants or site staff arising from the use of equipment)].

# **RECORD KEEPING AND ARCHIVING**

UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that he/she will archive the Trial Master File at [insert site name] for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. The Principal Investigator at each participating site agrees to archive his/her respective site’s study documents in line with all relevant legal and statutory requirements. Study documents will be archived for a minimum of 5 years from the study end, and no longer than 20 years from the study end.

The Trial Master File will be archived at UCL, in accordance with the UCL Retentions Schedule. It will be archived for a minimum of 5 years from the study end, and no longer than 20 years from study end.

**NB**: UCL do not archive student projects and therefore, the length of storage is not subject to the standard Sponsor requirements.

# **INTELLECTUAL PROPERTY**

If formal site agreements will not be used for the study, but after discussion with the study team, the JRO has determined that there is sufficient need for intellectual property provisions to be covered in a sponsor-site document, insert this text:

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, the study data and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used independently of the study by each participating site, shall belong to UCL. All intellectual property rights deriving or arising from the material or any derivations of the material provided to UCL by the participating site shall belong to UCL. Each participating site agrees that by giving approval to conduct the study at its respective site, it agrees hereby 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 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 or its funder.  This does not permit the disclosure of any of the results of the study, all of which remain confidential.

# **PUBLICATION AND DISSEMINATION**

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. The following should be considered:

* how authorship will be determined (in collaborative studies only)
* who owns the data arising from the study
* that on completion of the study, the data will be analysed and tabulated and a Final Study Report prepared
* where the full study report will be accessed
* if any of the participating investigators will have rights to publish any of the study data
* terms or conditions relating to the funding which may impact upon publication and dissemination
* whether any funding or supporting bodies need to be acknowledged within the publication and whether they have reviewed
* whether there are any plans to notify the participant of the outcome of the study, either by provision of the publication, or via a specifically designed newsletter, letter/email, etc.
* whether the study protocol, full study report, anonymised participant level dataset, and statistical code for generating the results will be made publicly available; and if so, describe where, the timeframe and any other conditions for access.

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]. Resulting publications and/or abstracts will be emailed to the JRO.

# REFERENCES

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

# APPENDICES

Include here a list of the supplementary information and documents that will support the protocol and information contained therein, e.g. PIS, ICF, schedule visit, assessment tools, delegation log, case report forms, questionnaires, scales, tables, charts, diagrams, manufacturer’s brochures.

It is not advisable to insert copies of documents such as the PIS and ICF due to version control and document management issues. You may wish to list the document titles here, or delete if unnecessary.

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

# APPENDICE 1: Schedule of Assessments

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **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 |

# APPENDICE 2: Associated Documents

Include here supplementary information and documents that will support the protocol and information contained therein.

E.g. data dictionary

|  |  |  |
| --- | --- | --- |
| Document Name | Document Version | Document Date |
|  |  |  |
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|  |  |  |
|  |  |  |