**JRMO Research Protocol for**

**MHRA Regulated Studies**

***General NOTE:*** *Green text is template text or guidance and should be removed and replaced with trial specific text. Black text should not be altered or removed. Please insert “n/a” if a section is not applicable to your protocol. This enables the Joint Research management Office (JRMO) team to see you have considered all sections. As part of the review these will be removed.*

*This protocol is written based on a UK based study- Alterations can be made to specific words ( REC to ethical committee for example) when used for a multi country studies.*

**Full Title** *<full title of study>*

*<Choose a descriptive study title that includes phase (e.g. phase I, phase II, etc.), design (e.g. randomised, double-blind, placebo-controlled, etc.), the investigational drug / device / intervention, and target disease(s). It should be immediately evident what the study is investigating and on whom to allow rapid judgment of relevance>*

**Short Title** *<short title of study>*

*<Provide a summary of the long title, using a short title or acronym. The short title is used on information sheets and consent forms for research participants. The short title should be sufficiently detailed to ensure it is clear to participants what the research is about in lay language>*

*<Before choosing an acronym (instead of a short title), consider:*

* *Whether any studies already exist with the same acronym (search the internet and check with the JRMO).*
* *Whether the same acronym is used by regulators, finance, or governance teams.*
* *Whether the acronym causes offence, particularly if the study is international.>*

*<For follow-up studies it is discouraged to use the same titles (e.g. Banana and then Banana II) to ensure studies easily distinguished from other Research Ethics Committee (REC) approved studies, thereby avoiding administrative errors during the study management.>*

*<If acronyms are used the full title should explain them. The proposed acronym should not drive the long title.>*

**Sponsor** *<Delete as applicable>*

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**IRAS Number** *<IRAS number>*

**EudraCT Number** *<EudraCT number>*

**Sponsors REC Reference** *<REC Reference number>*

**Chief Investigator** *<Chief Investigator title and name >*

*<Chief Investigator job title>*

*<Chief Investigator postal address>*

*<Chief Investigator telephone number>*

*<Chief Investigator email address>*

**Study Contacts**

*<Include phone, email, and fax numbers of all the key study contacts. Use shared/ study specific email addresses where possible>*

|  |  |
| --- | --- |
| **Trial Coordinator / Study Manager** | *<These can be generic contact details to ensure continuity if there are staff changes>**<Postal address>**<Phone number>**<Email address>**<Fax number>* |
| **Funder(s)** | *<Complete for each organisation providing funding and/or support in kind>**<Postal address>**<Phone number>**<Email address>**<Fax number>* |
| **Clinical Trials Unit**  | *<If not applicable, delete this row>**<Postal address>**<Phone number>**<Email address>**<Fax number>* |
| **National Coordinating Centre(s)** |  *Please insert as applicable for multi country trials. This row can be deleted if not applicable* |
| **Statistician** | *<Postal address>**<Phone number>**<Email address>**<Fax number>* |
| **Trial pharmacist** | *<Postal address>**<Phone number>**<Email address>**<Fax number>* |
| **Committees** **(IDMC, TSC, TMG)** | *<List each committee (note that a TSC and TMG is mandatory) and their Chair and outline their role. Include details of how chair can be contacted.>* |
| **Key protocol contributors** | *<Describe all contributors to the protocol. In relation to the study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results:**Explicitly outline the roles and responsibilities of the sponsor and any funders.**State whether the sponsor or funder control any final decisions regarding any of these aspects.>* |
| *<Protocol contributor>* | *<Postal address>**<Phone number>**<Email address>**<Fax number>* |
| *Add rows as necessary*  |  |

**List of laboratories** *<name of laboratory>*

*<Name of head of laboratory>*

*<Postal address of laboratory>*

*<Telephone number of laboratory>*

*<Email address of main contact at laboratory>*

*<REPEAT FOR EACH LABORATORY>*

*<*

**List of central facilities** *<Name of central facility>*

*<Name of head of central facility>*

*<Postal address of central facility>*

*<Telephone number of central facility>*

*<Email address of main contact at central facility>*

*<REPEAT FOR EACH CENTRAL FACILITY>*

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II. Glossary of terms and abbreviations

*<Please define all unusual or ‘technical’ terms related to the trial. Add as appropriate to your trial and maintain alphabetical order for ease of reference.>*

III. Signature page

**Chief Investigator Agreement**

The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

**Chief Investigator name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Statistician’s Agreement**

The study as detailed within this research protocol plan will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments, and ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for ensuring the statistical work in this protocol is accurate, and for the statistical analysis and oversight of this study.

**Statistician’s name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Principal Investigator Agreement Page**

The clinical study as detailed within this research protocol **(Version XXX, dated XX XXX XX)**,or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the UK Policy Framework for Health and Social Care Research , the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

**Principal Investigator Name:**

**Principal Investigator Site:**

**Signature and Date:**

IV. Synopsis

*Please complete full protocol first and then populate this section –delete this text*

|  |  |
| --- | --- |
| Full title | *<Full title of study>* |
| Short title and / or acronym | *<Short title of study>* |
| Sponsor |  |
| MHRA Risk level | *<Type A, B,C with a brief justification (see risk assessment >* |
| Phase of the trial | *<e.g. I, II, III, IV.>* |
| Medical condition or disease under investigation | *<Medical condition or disease under investigation.>* |
| Study design and methodology | *<Type of study e.g. single-blind, double-blind, randomised controlled, cross-over, etc.> <e.g. single, multi-site (<10. <25), international, NHS, NHS and non-NHS, Non-NHS.>* |
| Planned number of participants | *<Number of participants expected to be recruited in the whole study.>* |
| Objectives |  |
| Inclusion and exclusion criteria | *<Summarise inclusion and exclusion criteria Ensure this matches section <<XX>>>* |
| Investigational Medicinal Product(s) | *<List each Investigational Medicinal Product including dose and route of administration>* |
|  |  |
|  |  |
|  |  |
| Treatment duration | *<Where participants may be exposed to different treatment durations, give the range and maximum duration a participant may be exposed to treatment.>* |
| Follow up duration | *<Follow up duration.>* |
| End of Trial definition | *<Ensure this matches section <<XX >>>* |

# 1.0 Introduction

## 1.1 Background

*<Explain the study in the context of available evidence.>*

*<The background should be supported by appropriate references to the published literature on the disease or condition, its treatment, and the use of the study drug for the indication. It should include:*

* *An up-to-date systematic review of relevant studies; new research should build on formal review of prior evidence.*
* *Discussion of research topic including:*
	+ *Historical background.*
	+ *Study population.*
	+ *Disease type.*
	+ *Treatment, including current standard of care.*
* *A brief description of the proposed study.*
* *A description of the population to be studied.*
* *The investigational product(s) and their mechanism of action.*
* *The device(s) being investigated and / or radiation exposure if applicable.*
* *Relevant data from pre-clinical / non-clinical studies that potentially have clinical significance, and from relevant previous clinical studies.*
* *A high-level summary of relevant data from previous clinical studies, particularly regarding:*
	+ *Efficacy.*
	+ *Safety.*
	+ *Tolerability.*
	+ *Pharmacokinetics.*
	+ *Pharmacodynamics.*
* *If no data is available on the investigational product, include a statement to this effect. For early phase studies, clearly state the number of participants who have received the IMP(s).>*

*<The background 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 necessary. >*

## 1.2 Rationale for study design

*<Explain why the research questions being asked are important. The HRA guidance requests explanations when closely related questions are not being covered; however, only provide this where needed and if the question not being addressed is intrinsically linked to the study.>*

*<Explain:*

* *The research question / hypothesis and the justification of the study, i.e. why the question is worth asking and, through consultation with public and patient groups, why this is worthwhile to patients. Replication to check the validity of previous research is justified, but unnecessary duplication is unethical.*
* *The currently available treatment(s) and their limitations.*
* *Why the IMP(s) might be an improvement on currently available treatments, why the treatment difference is clinically important to patients, and if it is realistic. The treatment difference is often referred to as the minimum clinically important difference or the difference we should not want to miss. A drug which reduces everyone’s systolic blood pressure by 2 mm of mercury may be genuinely effective, but the effect would not form the basis of a routine intervention. This justification is particularly important if the study proposes to use the IMP:*
	+ *In children or in adults unable to consent for themselves.*
	+ *In higher doses.*
	+ *For longer duration.*
	+ *In a participant population that might metabolise / respond differently (e.g. hepatically or renally impaired participants, children, elderly, or immunocompromised individuals).*
	+ *In combination with another medicinal product.*
	+ *The indication / medical condition compromises the participant’s tolerance.*
	+ *In healthy volunteers.*
* *The rationale for the use of a placebo (or not) in the study if one is being used.>*

*<Include an explanation and justification as to the choice of control interventions / comparators especially if it involves withholding or delaying standard of care.*

*The rationale should be supported by appropriate references to the published literature>*

## 1.3 Assessment and management of risk

*<Describe the risk / benefit analysis. If the IMP(s) is to be used outside its license, describe risk management measures and / or processes. Build on the summary information presented in the background section.>*

*<Describe:*

* *The known and potential risks and benefits to participants.*
* *How high the risk is compared to normal standard practice.*
* *Justification for the choice of:*
	+ *Route of administration.*
	+ *Dosage.*
	+ *Dosage regimen.*
	+ *Treatment period(s).*
* *Pre-clinical data (with reference to current literature) including:*
	+ *Non-clinical pharmacology.*
	+ *Drug metabolism.*
	+ *Pharmacokinetics.*
	+ *Toxicological data.*
* *Clinical data, including all previous clinical data relating to the IMP within the indication of investigation as documented within the literature.*
* *How the risk(s) will be minimised / managed.>*

*<Consider the starting dose, dose increments, administration of doses, and the resources required by site(s), particularly in terms of facilities and staff, procedures, type of participants, and staff training required.>*

This trial is categorised as: *<Please chose type of study.*

*Type A = No higher than the risk of standard medical care (studies are those testing authorised medicinal products in accordance with the marketing authorisation in an EU member state).*

*Type B = Somewhat higher than the risk of standard medical care, (studies are those testing authorised medicinal products according to treatment regimens outside the marketing authorization).*

*Type C = Markedly higher than the risk of standard medical care, (studies are those testing non-authorised medicinal products).*>

# 2.0 Trial objectives

## 2.1 Primary objective(s)

*<Define the primary research question, addressing a specific hypothesis: e.g. “To compare the effect of treatment A versus treatment B on the levels of protein X in the blood”. There is usually only one primary objective, the rest are secondary objectives.* *The objectives are generally phrased using neutral wording (e.g., “to compare the effect of intervention A versus intervention B on endpoint X”) rather than in terms of a particular direction of effect. The wording of the objectives should be unambiguous and specific: the results of the trial will be judged on the extent to which the objectives were satisfied>*

*<Define:*

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

*<A useful guide in the development of a specific research question is the PICOT criteria:*

* *P: Population (participants) - What is the specific participant population of interest?*
* *I: Intervention - What is the investigational intervention?*
* *C: Comparison group - What is the main alternative to compare with the intervention?*
* *O: Outcome of interest - What is the intended accomplishment, measure, improvement or affect?*
* *T: Time - What is the appropriate follow-up time to assess outcome?>*

## 2.2 Secondary objective(s)

*<Describe the secondary objectives, which:*

* *May or may not be hypothesis-driven (i.e. may not be related to the primary research hypothesis).*
* *May include secondary endpoints.*
* *May include more general non-experimental objectives (e.g. to develop a registry, to collect natural history data).*
* *May ascertain answers that are related to the safety and/or efficacy (e.g. “To assess the safety of treatment A in condition X”).>*

## 2.3 Endpoints

### 2.3.1 Primary endpoint(s)

*<Identify a single response variable (primary endpoint) to answer the primary research question.* *In this section please define primary endpoints for the trial, which usually appear in the objectives and sample size calculation.*

*An ideal endpoint is valid, reproducible, relevant to the target population, and responsive to changes in the health condition being studied. The COMET website (Core Outcome Measures in Effectiveness Trials provides a common set of key trial endpoints and it is beneficial to ascertain whether there is a core endpoint set relevant to the trial. This does not preclude inclusion of additional relevant endpoints.*

*This section should define:*

* *The endpoint of main interest (primary endpoints).*
* *Whether the endpoint reflect efficacy (beneficial effect) or harm (adverse effect).*
* *The rationale for the choice of trial endpoint.*

*For each endpoint, the trial protocol should define four components:*

* *The specific measurement variable, which corresponds to the data collected directly from trial s (e.g. all-cause mortality).*
* *The -level analysis metric, which corresponds to the format of the endpoint data that will be used from each trial for analysis (e.g., change from baseline, final value, time to event).*
* *The method of aggregation, which refers to the summary measure format for each study group (e.g., mean, proportion with score > 2).*
* *The specific measurement time point of interest for analysis.>*

*<The primary endpoint should be a clear, indisputable, quantitative measure of effect that will be the focus of the primary analysis and will drive the choice of sample size (e.g. “The primary endpoint is 28 day survival”). If the endpoint can be measured more than once during the study, state precisely which time point constitutes the primary endpoint. Describe any rules, references, or programmes for calculating derived values, and describe what form it will take for analysis (e.g. continuous, categorical, or ordinal).>*

*<In the majority of cases there is only one primary endpoint. The exception is studies comparing a new diagnostic or measurement technique to an existing standard. In this case, it is acceptable to have two co-primary endpoints: the old and the new technique.>*

### 2.3.2 Secondary endpoint(s)

*<Identify well-established endpoint(s) of clinical importance that in theory could be the primary endpoint in another study. There can be any number (within reason) of secondary measures, although they should all be relevant to the declared aims of the study.>*

## 2.4 Exploratory or tertiary endpoints

*<If applicable, identify any other endpoints which are not well established. Delete this section if it is not applicable.>*

## 2.5 Objectives and end points summary

|  |  |
| --- | --- |
| Primary Objective | Primary Endpoint  |
|  |  |
| Secondary Objective | Secondary Endpoint  |
|  |  |

## 2.6 Study design

*<Describe the study design that will answer the research question, including:*

* *The overall study design (e.g. double-blind, placebo-controlled, parallel design, open labeled, observational, etc.). The framework of a study refers to its ability to test treatment:*
	+ *Superiority (treatment is superior to placebo or comparator treatment).*
	+ *Non-inferiority (not worse than the comparator treatment).*
	+ *Equivalence (treatment is similar to the comparator treatment).*

*Common designs include:*

* + *Parallel group design (each group of participants receives only one study treatment).*
	+ *Cross-over design (each participant is given all study treatments in successive periods. The order in which the participants receive each treatment is usually determined at random).*
	+ *Factorial design (two or more treatments are evaluated separately and in combination against a control. For instance, in a factorial design to assess the effect of drug A and drug B for the treatment of pain, participant would receive drug A only, drug B only, a combination of drug A and B, or placebo).*
	+ *Cluster randomised controlled studies (the treatment is randomised to groups of participants (e.g. families, all people attending a specific clinic, etc.) rather than individuals).*
	+ *Group sequential (endpoints are assessed in a group and sequential manner, e.g. an interim analysis is conducted after a pre-determined number of participants are recruited, and the study is terminated if the null hypothesis is rejected. This cycle of recruiting a group and performing an interim analysis continues until the maximum number of participant groups are recruited and analysed).*
	+ *Multiple-armed design (study with more than two arms, e.g. a three-armed study comparing a treatment with inactive control / placebo, and an alternative active treatment).*
* *The expected duration of participation.*
* *Number of visits participants will have to make.*
* *Sequence and duration of all study periods (e.g. screening, wash-out period treatment, post-treatment follow-up).*
* *Any special dietary or ‘life-style’ requirements that will be imposed (e.g. no smoking or alcohol for a week before and after each dose; a low fat or high fat diet, fasting for two hours between doses, etc.).>*

*<For exploratory and pilot studies, explain the design will permit gathering of preliminary information on the intervention (e.g. harm, pharmacokinetics, etc.) and the feasibility of a full-scale trial.>*

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

*<Provide a schematic overview of the study. A flow diagram should be included.>*

*<Consider how to ensure the participant and study pathways are clearly and accurately presented. Flow diagrams are helpful tools to illustrate the participant and study pathway, particularly for complex interventional studies. It is recommended that the schedule of events is included in the protocol.>*

*<Ensure the following information is clearly conveyed:*

* *The timing of each visit (from eligibility screening through to study close-out).*
* *Time periods during which study interventions will be administered.*
* *The procedures and assessments performed at each visit (with reference to specific data collection forms, if relevant).*
* *Activities involved during each clinic visit (e.g. blood tests or scans, treatment, diary completion, adverse event monitoring, physical examination etc.).>*

*<See example below.>*



## 2.7 Study setting

*<Describe where the study will be run and any site-specific requirements. Include whether:*

* *It is a single- or multi-center study.*
* *There are any PICs (Participant Identification Centres).*
* *There is any National coordinating centres if this is an international study.*
* *The study is taking place in NHS and / or non-NHS setting (e.g. Universities, Health and Social Care settings, educational settings).*
* *It is international (if so, are all sites located the EU, and are any sites located outside of the EU).*
* *There are any site-specific requirements to run the study.*
* *There are different ‘types’ of site (e.g. imaging, recruiting, treating, continuing care centres, etc.) and the specific requirements for each site.>*

*<Also describe:*

* *Where a list of the participating sites can be found.*
* *Eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists).*
* *The population and where potential participants are identified:*
	+ *What are the usual care pathways?*
	+ *Are participants with the condition of interest found in primary or secondary care?*
	+ *Are all sites NHS sites or non-NHS sites?*
	+ *If using secondary care sites, will primary care PICs be needed to recruit?>*

*<The National Institute of Health Research Clinical Research Network feasibility resources may be helpful in determining the appropriate study setting in terms of site requirements and participant population.>*

# 3.0 Patient Evaluability and Replacement

## 3.1 Target Accrual

*<Insert target recruitment figures>*

## 3.2 Participant identification and recruitment

*<Describe:*

* *Who will identify participants?*
* *Will any databases or search engines be used?*
* *Whether identification will involve reviewing or screening identifiable personal information of patients, service users or any other person? If so, will this be undertaken by members of the direct care team or will Section 251 exemption be applied for? See the HRA website for details relating to ‘Section 251’).*
* *The sources of identifiable personal information that will be used to identify potential participants. Normally only a member of the patient’s existing clinical care team should have access to patient records without explicit consent in order to identify potential participants, check whether they meet the inclusion criteria, and make the initial approach to patients. If the research proposes to use someone outside the direct clinical team to identify suitable participants or as first contact with the participant, the reasons for this should be explained, and justified, both here and in the IRAS from.*
* *Whether any participants will be recruited through Patient Identifications Centres (PICs)?*
* *Whether any participants will be recruited by publicity (e.g. posters, leaflets, adverts, or websites)?*
* *The arrangements for referral if participants will be identified by a separate research team.*
* *If patient or disease registers will be used to identify potential participants. If so, include a brief description of the consent and confidentiality arrangements of the register.*
* *Who will make the eligibility decision (for CTIMPs this is deemed a medical decision, and as such must be confirmed by a medical practitioner).>*

*<Certain studies, such as cluster trials, incorporate a separate screening process relevant to that trial design. In such cases it may be appropriate to collect more detailed information regarding screened participants. If applicable, explain what information will be collected and the justification for collecting this information.>*

# 4.0 Informed consent procedures

Informed consent will be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study and are outside standard, routine care at participating sites. This includes collection of identifiable participant data *<unless the study has prior approval from the Confidentiality Advisory Group (CAG) and the Research Ethics Committee (REC); if these approvals are being obtained, confirm that data collection will not occur until these permissions have been granted.>*

The Principal Investigator (PI) has overall responsibility for the informed consent of participants at their site and will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP), and Declaration of Helsinki. If delegation of consent occurs, then details will be provided in the site delegation log.

*<State who can receive consent within the study. Consent should be received by a medical practitioner unless otherwise requested, justified, and agreed in advance with the Sponsor. If a non-medical practicing team member will be delegated to receive consent, the consent form must be counter-signed by the PI prior to any IMP being taken or procedure performed.>*

The right of a participant to refuse participation without giving reasons will be respected. The participant will remain free to withdraw at any time from the study without giving reasons and without prejudicing their further treatment and will be provided with a contact point where they may obtain further information about the study. Where a participant is required to re-consent (for example if new Research Safety Information becomes available during the study, or following an amendment that affects the participant, or new information needs to be provided to a participant) it is the responsibility of the PI to ensure this is done in a timely manner and prior to the next dose of IMP (where applicable).

*Fully describe the consenting process, including:*

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

*<As stipulated by GCP, the participant should be given ample time to consider giving their consent for the study. 24 hours is traditionally considered the minimum period of time for an individual to consider their participation. If, for any reason, less than 24 hours is to be given, document arrangements along with justification.*

 *The date that the Participant Information Sheet (PIS) is given to the participant must be documented within the participant’s notes to verify that sufficient time has been given.>*

## 4.1 **Vulnerable participant considerations**

*< State clearly if the study will involve the participation of vulnerable participants or not (use HRA definitions) If yes, insert the following statement:>*

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

*< If vulnerable participants will be excluded, please ensure this is reflected in the exclusion criteria (section 6.2).>*

## 4.2 Writing, reading, and translation considerations

*<Where the participant population may include participants, who cannot read or write, require translators, appropriate alternative methods for supporting the informed consent process should be employed. This may include allowing an independent witness to date and sign on a participant’s behalf (in the case of problems with reading or writing), providing Participant Information Sheets in other languages, or in a format easily understood by the participant population (e.g. video clip).>*

*<State what arrangements will be implemented at site(s) to support the consent process for these participants. For example:*

* *If verbal translation is needed, will this be via a hospital interpreter or a personal interpreter? Are telephone translation services acceptable? Be mindful that different sites may have different resources available.*
* *If translated written material is to be provided to participants, are these to be provided by the sponsor, or translated locally? What arrangements are in place to confirm the accuracy of the translation (e.g. back translation)?*

*<To comply with the Welsh Language Act 1993, studies involving sites in Wales must translate the Participant Information Sheets and Consent Forms into Welsh or provide them bilingually where this is requested by a participant at a research site.>*

## 4.3 Participants lacking capacity

*<Describe how consent from participants lacking capacity will be obtained. If this section is not relevant to the study, please delete it.>*

*< The legal frameworks relating to all research requires that persons incapable of giving legal consent be given special protection.>*

*<A person is assumed to have the mental capacity to make a decision unless it is shown to be absent. Mental capacity is considered to be lacking if, in a specific circumstance, a person is unable to make a decision for him or herself because of impairment or a disturbance in the functioning of their mind or brain. Participants with mental incapacity should not be included in clinical studies if the same results can be obtained using persons capable of giving consent. They should only be included where there are grounds for expecting that their taking part will be of direct benefit to that participant population, thereby outweighing the risks. Sections 30-33 of the Mental Capacity Act 2005 do not apply to CTIMPs, but the remainder of the act does insofar as it is relevant to conducting a clinical trial. >*

*<Where the study does not exclude participants who lack the capacity to consent for themselves (for example, in cases where the research is related to the disease / illness causing mental incapacity) the full procedure for consent by a legal representative must be included in the protocol, along with appropriate information sheets and consent forms.>*

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

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

## 4.4 Minors

*<Detail how assent from minors will be obtained. If this section is not relevant to the study, please delete it.>*

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

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

*<*

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

**4.5 Consent for Ancilliary Studies**

*< Describe the consenting procedure for ancillary studies and samples collected for future research. If not applicable, please delete this section.>*

*<State:*

* *When and where biological specimens for ancillary studies will be acquired and stored during the study.*
* *If the biological specimens:*
	+ *Will be used for a specified subset of studies.*
	+ *Will be stored within ethically approved research tissue banks (RTB) for future (specified or unspecified) research (give REC reference number(s) if known).*
	+ *Will be used to form a new ethically approved RTB.*
	+ *Will be stored under license pending any of the above.*
* *What options participants will be given in respect to their participation in ancillary research, detailing:*
	+ *Whether participation in the ancillary research is required for participation in study or if participants may opt out but still participate in the main study.*
	+ *Whether consent will be obtained for the use of their specimens in specified protocols.*
	+ *Whether consent will be obtained for use in future research unrelated to the clinical condition under study.*
	+ *Whether consent will be obtained for submission to an unrelated bio-bank.*
	+ *Whether consent will be obtained to be contacted by study investigators for further information, study invitations, and consent-related purposes.*
* *Whether their withdrawal from the ancillary research is possible and what will happen to material provided up to that point. Describe:*
	+ *If the specimens will be coded and identifiable.*
	+ *What withdrawal means in this context.*
	+ *What information derived from the specimen related research will be provided to them, if any.*
	+ *What will happen to samples already provided by the participant.*
* *If the samples will be shared with any third parties (e.g. funders, collaborators), if these third parties are commercial in nature, and if they are inside or outside of the UK.*
* *Whether consent will be sought for genetic testing, and if genetic testing will occur whether the results of this testing will be provided to the participant.*
* *If incidental findings are possible and how they will be reported post analysis.>*

# 5.0 Participant allocation

*<Overview of randomisation/registration/screen failure process>*

*<Give details of the eligibility screening process, including information to be collected regarding participants who are screened and are not randomised / registered, where data is being collated for Consolidated Standards of Reporting Trials (CONSORT) or similar for reporting the generalisability of the results. If a decision is made to not collect this information, the justification should be documented.>*

# 6.0 Participant eligibility criteria

*Eligibility criteria should be clear and unambiguous. Please ensure that criteria could not be “open to interpretation”. Take care to ensure inclusion and exclusion criteria do not contradict each other. Bear in mind each criteria will need to be Source data verified (e.g. Life expectancy <6 months- how would this be documented?)*

## 6.1 Inclusion criteria

*<Set out precise criteria and definitions stating which participants are eligible to participate in the study, e.g.:*

* *Able and willing to give informed consent (additional measures must be in place if children, vulnerable adults, or adults unable to give consent are included).*
* *Gender.*
* *Age range.*
* *Description of study population or cohort (clinical diagnosis).*
* *Ethnicity.*
* *Socio-economic grouping.*
* *Clinical parameters such as disease type, life expectancy, screening test, results or parameters, and anything else that is relevant or specific to the study or procedure.>*

## 6.2 Exclusion criteria

*<Set out precise criteria and definitions that determine when an individual is ineligible to participate. The study should exclude sub-groups of the population due to e.g. safety and other clinical risks or burdens to the participant. For example:*

* *Inability to understand written and / or verbal English.*
* *Concurrent or recent exposure to relevant drugs within a given period (that consequently have not been eliminated from the participant’s system).*
* *Incompatible current treatments.*
* *Previous treatments (especially significant medical history of illness or disease; be specific about their relevance).*
* *Uncontrolled concomitant disease requiring clinical evaluation.*
* *Allergens to excipients of IMP and placebo.*
* *Other malignancies and past medical history.*
* *Concurrent or recent participation on another CTIMP.*
* *Contraindications to study treatment.*
* *Considerations relating to pregnancy, breast-feeding, and contraception (consult a pharmacist, SmPC, and MHRA guidance). Include possibility of partner pregnancy.*
* *Vulnerable individuals (this should correspond with statements relating to vulnerable individuals in section 4.1).>*

*<Consider the statement below for participants of childbearing potential and remove if not applicable.>*

Participants are not considered to be of childbearing potential if they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are postmenopausal (include a clinical definition if appropriate, e.g. FSH).

*<Refer to the IMPs SmPC(s) or IB(s) to clarify specific requirements.>*

# 7.0 Study Schedule

## 7.1 Schedule of treatment for each visit

*<Provide a clear and concise timeline of the study visits, enrolment process, interventions, and assessments performed on participants. Outline all treatments and interventions that the participant will undergo at each visit during their participation within the study.>*

## 7.2 Schedule of assessment (in diagrammatic format)

*<Use a table format to detail the schedule of assessments that the participant will undergo at each visit (see example below). Use timing windows (e.g. day 28+/- 2 days) wherever possible.* *Be sure to specify any treatment breaks – for example for dose escalation decisions.>*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Assessment** | **Screening** | **On-study treatment phase** | **Follow up visits** | **End of Study** |
| History and physical | x | x | x | x |
| Weight  | x | x | x | x |
| Chest X-ray | x |  |  |  |
| ECG | x | x |  |  |

## 7.3 Randomisation method

*<Describe the randomisation procedures for the study. If this section is not applicable, please delete it.>*

*<The randomisation system should be discussed with the study statistician and Sponsor and must be validated for use. The system, method, vendor, and backup systems to be used must be fully described.>*

*<Describe the process of how treatments will be allocated between participants in enough detail to enable a full reproduction of the process.>*

*<Describe:*

* *The method of randomisation, e.g.:*
	+ *Simple randomisation, based solely on a single constant allocation ratio is known as simple randomisation (e.g. 1:1).*
	+ *Restricted randomisation, which includes any randomised approach that is not simple randomisation including:*
		- *Blocked randomisation.*
		- *Biased coin and urn randomisation.*
		- *Stratified randomisation.*
* *Whether an un-equal treatment allocation will be used and if so, a justification for its use.*
* *If the allocation ratio will adaptively evolve over the course of the study, and if so, provide a short overview statement to that effect with a reference to the full description in the “Interim Analysis” section.*
* *Whether minimisation is going to be used. Minimisation assures similar distribution of selected participant factors between study groups. The first participant is truly randomly allocated; for each subsequent participant, the treatment allocation that minimises the imbalance on the selected factors between groups at that time is selected. That allocation may then be used, or a choice may be made at random with a heavy weighting in favour of the intervention that would minimise imbalance (for example, with a probability of 0.8).>*

*<Full details of a restricted randomisation scheme (including minimisation) should not be included in the study protocol as knowledge of these details might undermine randomisation by facilitating deciphering of the allocation sequence. Instead, this specific information should be provided in a separate document with restricted access.>*

## 7.4 Randomisation procedure

*<Describe the randomisation procedure. If this section is not applicable, please delete it.>*

*<Describe:*

* *How sites randomise their participants (provide links to websites, contact telephone and fax numbers, or email contact addresses).*
* *The system to use be used (e.g. a web based randomisation and treatment allocation system).*
* *Who will access the randomisation system at each site.*
* *Who is responsible for randomisation at site.*
* *How the allocation will be documented (e.g. will the system provide an immediate allocation with a confirmatory email?).*
* *Who will be provided with a copy of the treatment allocation or randomisation number.*
* *How randomisation codes will be accessed out-of-hours or in an emergency.>*

## 7.5 Cohort allocation / sequential allocation

*<Describe the treatment allocation if it is different to randomisation (e.g. cohort allocation or sequential allocation). If this section is not applicable, please delete it.>*

## 7.6 Blinding

*<Describe the blinding process. If this section is not applicable, please delete it.>*

*<A full description is essential and ambiguous terminology such as “single blind” or “double blind” should not be used. Describe in detail the blinding process to avoid bias. Explicitly describe:*

* *Who will be blinded to intervention groups, including:*
	+ *Study participants.*
	+ *Care providers (including pharmacy).*
	+ *Endpoint assessors.*
	+ *Committees.*
	+ *Parties blinded in respect to SUSAR reporting.*
* *The comparability of blinded interventions (e.g. similarities in appearance, use of specific flavours to mask a distinctive taste).*
* *The timing of final unblinding of all study participants (e.g. after the data set is locked).*
* *Strategies to reduce the potential for unblinding (e.g. pre-study testing of blinding procedures but also consider management of test results that could lead to Investigator unblinding, describe in detail how this will be managed). Ensure that unblinding one participant would not inadvertently cause their entire cohort to be unblinded>*

*<When blinding of study participants and care providers is not possible because of obvious differences between the interventions, blinding of the endpoint assessors can often still be implemented. It may also be possible to blind participants or study personnel to the study hypothesis in terms of which intervention is considered active.>*

## 7.7 Unblinding

*<Describe the unblinding process, including out of hours processes. If this section is not applicable, please delete it.>*

*<Clearly describe the conditions and procedures for unblinding. The investigator is responsible for the medical care of the individual study participant (Declaration of Helsinki section 3, and GCP section 4.3) and the coding system in blinded studies should include a mechanism that permits rapid un-blinding (ICH GCP 5.13.4). The sponsor expects a 24-hour unblinding service to be available unless there are exceptional circumstances. This should be discussed and agreed with the sponsor on a case by case basis and should be fully documented here.>*

*<The blind 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 health care professional to know what the participant is receiving before the they can be treated). Barts Health Pharmacy does not have the facility to act as a central or local unblinding service. Discuss the appropriate responsible person with the GCP Manager.>*

*<There must be arrangements in place so that healthcare professionals can quickly unblind a participant if knowledge of the treatment assignment is necessary to determine optimal medical treatment. This can include giving participants emergency medical cards with the contact details of the research team.>*

The code breaks for the study will be held *<please add location and department>* and are the responsibility of *<add role>*. In the event a code break is required, the Investigator or responsible delegate will use the code break to confirm the participant’s treatment allocation and relay this information to required individuals. If the person requiring the unblinding is not associated with the study team, that health care professional will notify the Investigator team that an unblinding is required for a study participant.

*<Explain:*

* *If any approvals by the coordinating team (e.g. the CI) will be necessary before unblinding participants. If this step is included, it must not unduly delay the unblinding process; describe how it will be ensured that this does not delay the unblinding of the participant and their subsequent care.*
* *How unblinding requests will be verified as legitimate (and not, for example, a request by a participant to satisfy their curiosity).*
* *How unblinding will occur.*
* *How unblinding and the reasons for it will be documented, both locally and centrally (in medical records, in the Trial Master File, in the Investigator Site File, in the Case Report Forms or other data collection worksheets, and the final study report and statistical reports).*
* *How the unblinded information will be conveyed to the individual who made the unblinding request.*
* *The arrangements for reporting and unblinding SUSARs (refer to the pharmacovigilance section of the protocol).*
* *How written information will be disseminated to the Data Safety Monitoring Committee (DSMC) for review in accordance with the DSMC Charter, where relevant.>*

The PI or delegate will notify the CI in writing as soon as possible following the code break detailing the necessity of the code break.

## 7.8 Study assessments

*<Provide a narrative to add information not contained in the table such as routine care, details of specific tests (procedural details), etc. Double check narratives and tables to ensure consistency. Including a full description of every assessment is unnecessary if it only repeats the table schedule.>*

*<Describe the study assessments at each time point, including:*

* *The baseline data that need to be collected (N.B. only data that form part of the predefined data set which are essential for analysis should be collected).*
* *All study procedures and assessments (including those that are part of routine care where data will be collected).*
* *The timing of the assessments, broken down into visit numbers as appropriate.*
* *The detail of any run-in or washout periods.*
* *The time points for assessment data (e.g. “The following are to be recorded each month for the first 12 months and every three months afterwards:*
	+ *History and clinical examination.*
	+ *Assessment of the toxicity of the previous course.*
	+ *Weight.*
	+ *Full blood count.*
	+ *Biochemical series.*
	+ *Chest X-ray”).*
* *How compliance will be checked (will participants be required to return used blister packs? How will participant compliance be determined when they are dosed at home?).*
* *When diary cards will be checked and collected.*
* *Assessment data required at the end of study visit.*

## 7.9 Follow up procedures

*<If any follow up procedures are applicable, ensure that they are documented. If this section is not relevant to the study, please delete it.>*

*<All tests and procedures must be included in the study budget and should be listed here (although routine tests should be documented as standard care). Include the exact timeline over which the participant will be followed up and the frequency of follow up. Any long term / passive follow (e.g. HES (Hospital Episodes Statistics) follow up, or flagging) is a follow up activity and should be clearly described here.>*

*<As sponsor, Queen Mary University of London (Queen Mary) and Barts Health NHS Trust (Barts Health) require a minimum follow up period (usually based on the half-life of the IMP) following the last dose of IMP. Follow up periods must be agreed with the sponsor in advance and require a strong justification to be provided here.>*

# 8.0 Participant, Study, and Site discontinuation

*<It is always within the remit of the responsible physician to withdraw the participant from the study for appropriate medical reasons. This can be (but is not limited to) individual adverse events or toxicities, new information gained about a treatment, or if it is felt to be in the participant’s best interest.>*

*<Describe:*

* *Under what circumstances (and how) participants will be withdrawn from the study and / or investigational product treatment by the PI (including whether the participant would continue to be part of the study if IMP was withdrawn for specific reasons).*
* *What actions will be followed should a participant wish to withdraw.*
* *The procedure for data collection and follow up for withdrawn participants, and whether data will still be required / used.*
* *The procedure for tissue collection and follow up for withdrawn participants, and whether tissue will be required / used.*
* *What documentation will be completed on participant withdrawal (including recording reasons for withdrawal and any follow-up information collected with timing).*
* *Whether (and how) participants will be replaced.*
* *Whether withdrawn participants can be re-entered on this study.*
* *The follow up of participants that have withdrawn from the treatment / study.*
* *What will be done with any samples and data already collected.>*

# 9.0 Laboratories and samples

*< Please read the guidance of each subsection and insert the required details for your study when applicable. Insert “n/a” in any section that does not apply to your study.*

*If Laboratory results are being collected, state this clearly and move on to section 15.*

*The study laboratory manual may contain the information required by these sections of the protocol. Where this is the case, provide a high-level summary of the laboratory procedures in this section and refer readers to the laboratory manual for further information.>*

## 9.1 Central laboratories

*<Name the central laboratories that will be used and the tests / analysis that will be conducted. Define the type of laboratory (academic, vendor, commercial partner, location) and which endpoints or objectives the tests relate to.>*

*<List each central laboratory (including those within Queen Mary and Barts Health) with a named contact and full contact details. All labs should be appropriate vendor assessed and contacted to ensure GCP compliance. Detail the analysis methodology for the samples, and state if this includes any test that is not considered ‘standard’ for diagnostic purposes. Document whether the tests are under CPA accreditation, and the documents that are needed from each laboratory.>*

## 9.2 Local laboratories

*< All labs should be appropriately GCP compliant. Detail the analysis methodology for the samples, and state if this includes any test that is not considered ‘standard’ for diagnostic purposes. List the documents that are needed from each laboratory and describe what a site should do if the planned processes fall outside of their UKAS accreditation.>*

*<If the lab is an NHS lab, but the test they are performing is for all sites, then they are a central laboratory.>*

## 9.3 Sample collection, labelling, and logging

*<Detail the process of sample collection/ labelling and logging.>*

*<Detail:*

* *Sample type(s) (e.g. whole blood, plasma, serum, saliva, urine, stool, fresh tissue biopsy, paraffin tissue block etc.).*
* *Volume of sample(s) to be collected.*
* *Types of tubes, containers, swabs to be used for sample collection, and whether these will be provided by the sponsor or sourced locally by site(s).*
* *Sample processing arrangements (e.g. centrifugation (how soon after collection should samples be spun, how long for, at what speed, at what temperature)).*
* *Sample labelling procedures (samples should be labelled with a unique study identification code only).*
* *Sample logging procedures (how information will be logged and collected e.g. date / time of sample collection, date sample is sent to laboratory, temperature of sample etc.).*
* *Anonymisation procedures (any sample sent to a central laboratory should be pseudo-anonymised)*
* *Whether existing stored human tissue (or other human biological materials) are being used in the study (i.e. from an ethically approved research tissue bank or diagnostic archive). If so, provide:*
	+ *Tissue bank name(s).*
	+ *HTA license number(s).*
	+ *Full contact details of the custodian of the tissue bank(s).*
	+ *An explanation regarding how the samples will be released to the researcher (anonymous, linked anonymous, identifiable to the researcher?).*
	+ *Details regarding whether consent has been given to use the samples in this or other research.>*
	+ *Please ensure  you discuss with the Tissue bank what if any data they would require/wish to accompany the sample.   The PIS and consent form would need to  clear state this. Consents to transfer a sample to a tissue bank or retain it for future research  does not mean  the participants has agreed for any of their data (for example age, sex, treatments, outcome) to be given or transferred to the tissue bank.*

## 9.4 Sample transfer, chain of custody, and accountability

*<Detail:*

* *Where the samples will be transferred from and to (name the lab site(s) including their legal entity e.g. Queen Mary, Barts Health).*
* *The method of transfer to the site lab and any transfer requirements (e.g. on dry ice).*
* *The deadline for transferring samples after collection.*
* *The chain of custody.*
* *Documentation of sample handling at lab.>*

## 9.5 Sample analysis procedures

***<*** *Detail the analysis methodology for the samples, and state if this includes any test that is not considered ‘standard’ for diagnostic purposes. If appropriate insert a summary only and statement “See lab manual”.*

*Describe:*

* *The deadline for analysing samples after they have been collected.*
* *An overview of the process and methods of sample analysis.*
* *What will happen to the samples after they have been analysed (will they be stored or destroyed?).*
* *Whether the research could produce findings of clinical significance for sample / tissue donors or their relatives (if so, describe the arrangements be made to notify the individuals concerned).*
* *Whether the research will involve the analysis or use of human DNA in the samples (if so there needs to be a separate consent box in the Informed Consent Form and in Participant Information Sheet. International studies are likely to require a separate Genetic Analysis PIS).>*

## 9.6 Sample Storage Procedures

*<Describe:*

* *The deadline for placing the samples in controlled storage conditions after collection / processing / analysis.*
* *How long samples will be stored for.*
* *What will be done with the samples after the storage period has elapsed (e.g. destruction).*
* *Whether any samples will be held in long-term storage for future ethically approved research or transferred to an ethically approved tissue bank (in which case appropriate consent and Human Tissue Act implications need to be considered and addressed).*
* *Whether samples will be destroyed if the participant withdraws consent, and the procedure for doing so (e.g. the Tissue Custodian (normally the CI) will inform the lab who will ensure the samples are destroyed per HTA requirements and that this is documented. N.B this process needs to be described in the Participant Information Sheet).*
* *The required storage and temperature conditions (where possible, state a permitted temperature range rather than a single required temperature, as this will avoid unnecessary temperature deviations).*
* *The Anonymisation arrangements of stored samples.*
* *Contingency plans (e.g. in case of power cuts or freezer failures).>*

## 9.7 Sample and result recording and reporting

*<Explain:*

* *How results and data generated by laboratories will be recorded and reported (including the location and format the report will take).*
* *Whether samples or data will be shared with collaborators (commercial or non-commercial) and how such data will be anonymised.>*

## 9.8 Sample Management at End of study

*<At the end of the study, samples could be destroyed, used in another ethically approved research study, stored in a research tissue bank, or returned to sites (e.g. histological blocks).>*

*<If samples will be destroyed at the end of the study, state:*

* *When the samples will be destroyed (e.g. after analysis, after a set storage period, etc.).*
* *Whether samples will be destroyed in accordance with the Human Tissue Authority’s Code of Practice.>*

*<If the samples will be used in another ethically approved research study, the new study must be open before this study ends. State:*

* *That participants will give informed consent for their samples to be used in future ethically approved research (update participant information sheet and consent form accordingly).*
* *The arrangements for transferring the samples from the old study to the new study. Include information about physical transfer and Anonymisation.>*

*<If the samples will be transferred to a licensed research tissue bank, state:*

* *That participants will give informed consent for their samples to be stored in a tissue bank for use in future research (update the participant information sheet and consent form accordingly).*
* *The arrangements for transferring the samples to the tissue bank. Include information about physical transfer and Anonymisation.>*

*<If any samples will be returned to sites then state the arrangements for doing so.>*

# 10.0 Study medication

*The IMP management plan and Site Pharmacy manual may provide detailed guidance about the management of IMP at site. It is acceptable to add a high-level summary of the information in these sections and reference the pharmacy manual for further detail.*

## 10.1 Name and description of Investigational Medicinal Product(s) (IMP)

*In this section provide a full description of the investigational drug(s) to be used plus any medical device, food supplement, radiation, surgery, behavioral interventions, etc. that form part of the trial.*

*According to the definition of the EU clinical trial directive 2001/20/EC, an investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation, but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form. Information about the comparator product/placebo should also be given in this section.*

*For this section of the protocol you might find the following document useful to read: “Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials”.*

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

*The MHRA have an algorithm on their website to assist in the assessment of whether a product is an IMP and whether authorisation from the MHRA is required. If further assistance is required, please contact the MHRA helpline.*

*<. This section should be drafted by the CI team and then reviewed by the sponsor pharmacist.>*

*<For labelling requirements, refer to Volume 4. Good Manufacturing Practices, Annex 13. Manufacture of investigational medicinal products, July 2010. Where a medication is to be used in its normal indication and standard therapeutic dose, labelling exemptions may apply. Contact Sponsor Pharmacist for advice. For CTIMPs using chemotherapy treatment the National Cancer Research Network (NCRN) Chemotherapy and Pharmacy Advisory Service (CPAS) Guidance should be referred to in drafting this section of the protocol.>*

*<For each IMP (including placebo(s)), specify:*

* *The chemical name.*
* *The chemical form,*
* *The dose.*
* *The route of administration.*
* *A concise description.*
* *Whether a specific brand must be used/ or generic use is permissible.*
* *Packaging and labelling requirements.*
* *Supply arrangements.*
* *Storage requirements.*
* *Dispensing procedures.*
* *Accountability processes.>*

**11.0 Legal status of IMP**

*<For each IMP, state:*

* *Whether they are licensed for use (in the UK or other countries).*
* *The licensed indication.>*

*<If the IMP is either unlicensed in the UK or is ring-fenced commercially supplied IMP, then the following statement should be inserted:>*

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

*<NIMPs are medicinal products which are not classed as an IMP in a study, and are any product supplied to study participants according the protocol which are NOT under investigation. Examples include concomitant or rescue / escape medication used for preventive, diagnostic, or therapeutic reasons, and / or medication given to ensure that adequate medical care is provided for the participant during a study. Note that placebos are considered IMPs.>*

*<For each NIMP, specify:*

* *The chemical name.*
* *The chemical form,*
* *The dose.*
* *The route of administration.*
* *A concise description.*
* *Whether a specific brand must be used.*
* *Packaging and labelling requirements.*
* *Supply arrangements.*
* *Storage requirements.*
* *Dispensing procedures.*
* *Accountability processes.>*

*<Clearly define any treatment breaks that are required by the protocol, for example to make a decision on dose escalation. Clearly describe how participants should be managed during this treatment break.>*

## 11.2 Legal Status of NIMP

*<For each NIMP, state:*

* *Whether they are licensed for use (in the UK or other countries).*
* *The licensed indication.>*

*<If the IMP is either unlicensed in the UK or is ring-fenced commercially supplied IMP, then the following statement should be inserted:>*

The trial will be carried out under a Clinical Trial Authorisation (CTA). The drug is therefore only to be used by the named investigators, for the participants specified in this protocol, and within the trial.

## 11.3 IMP Manufacturer(s) and supply arrangements

*<Describe the procedures for the shipment, receipt, distribution, return, and destruction of the medicinal products, including placebos.>*

*<For multicentre studies where supply details may vary between sites, this section should cover only the aspects that are applicable to all sites.>*

*<For each IMP and NIMP, describe:*

* *The name of the supplier.*
* *Supply arrangements.*

*Whether it will be drawn from hospital stock or provided by the manufacturer. If it will be drawn from hospital stock, confirm whether it will be ring-fenced for the study. If the provider is a pharmaceutical company, state whether study stock or commercial supplies will be utilised.*

*Details of any special supply processes, e.g. a triggered release process or central* supply to all sites from a 3rd party.>

*<Provide the details of the manufacturer for each of the products to be used. A supply mechanism is required between the sponsor and the provider of each medicinal product to ensure that supply is available in accordance with the participant regimen. This must be discussed with pharmacy and the IMP supplier during study set-up.>*

*<If the drug is to be sent to other countries, extra regulatory requirements must be fulfilled. For example, the services of a qualified person (QP) will be needed for medicinal products being sourced from outside the EU. This should be identified very early in the study design as the regulatory requirements can be significant and will need to be documented on the Clinical Trial application documents to be submitted to competent authorities.>*

*<<Summary of Product Characteristics (SmPC) / Investigator Brochure (IB) delete as appropriate>>* *delete as appropriate>>*

*<The study documentation must include either an IB or SmPC for each IMP used in the study. Licensed drugs will have an SmPC which should be agreed with the sponsor Pharmacist . For unlicensed drugs, the IMP manufacturer should provide an IB.>*

*<For each IMP and NIMP, state the SmPC or IB to be used, including the document date and, where available, the version number.>*

*<Describe the arrangements for checking for, and implementing updates to, the SmPC / IB.*

*Note that the RSI is detailed in section 19.3.specific version of RSI should not be included here>*

## 11.4 Packaging and labelling of IMP(s), placebo(s), and NIMP(s)

*<For each medicinal product, describe:*

* *How they will be prepared.*
* *How they will be stored after preparation.*
* *Shelf life after preparation.*
* *How they will be packaged (including the appearance and containers in which they will be supplied).*
* *How they will be labelled (IMPs must be packaged and labelled in accordance with Annex 13 (Manufacture of Investigational Medicinal Products).>*

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

## 11.5 Accountability

*<For each medication, describe how they will be accounted for. Include the process for receipt of shipments once arrived at site.>*

## 11.6 Assessment of compliance

*<For each medicinal product describe how compliance will be assessed. Define:*

* *Monitoring procedures (e.g. getting participants to complete a diary card, package returns).*
* *Recording of participant compliance information (what will be recorded, when and where, e.g. will participants:*
	+ *Be asked to keep a diary?*
	+ *Bring unused or part-used medication(s) and packaging to each visit?*
	+ *Have pill counts completed?*
	+ *Have ointment tubes weighed at stipulated visits?*
	+ *Have specific blood tests being performed at specified clinic visits etc.)?*
* *How non-compliance will be documented by the investigator and reported to the sponsor.*
* *The minimum IMP compliance acceptable for participant to continue on the study, (e.g. 80% doses taken).*
* *Follow-up of non-compliant participants.*
* *Strategies for improving compliance (these should be strategies that can be easily implemented in clinical practice so compliance in the real-world setting is comparable to that observed in the study).>*

## 11.7 Drug storage

*<For each IMP and NIMP, detail:*

* *Storage arrangements (drugs must be stored in pharmacy unless there is a strong justification for storing it elsewhere. If not stored in pharmacy, describe the conditions for storage and any procedures for checking that appropriate temperatures are maintained etc.).*
* *Storage conditions (as detailed in the IB or SmPC) and how these will be monitored.*
* *Whether they will be supplied to the study team for re-constitution outside of the pharmacy department.*
* *Any storage instructions once dispensed from pharmacy (e.g. stored in a fridge at X°C and used within 24 hours depending on the requirements of the product).*
* *Chain of custody arrangements, and how they will be achieved, including:*
	+ *Chain of receipt.*
	+ *Storage arrangements (including any special arrangements if necessary, e.g. freezer availability, storage of large containers of medicinal products).*
* *The process for managing storage excursions and who is responsible for managing excursions.>*

*<Site pharmacies are responsible for dispensing in line with their local dispensing procedures and excursion management normal practices.>*

## 11.8 Prescription and Dispensing of IMP(s), placebo(s), and NIMP(s)

*<Describe the prescriptions that will be used (e.g. template forms that will be agreed with the sponsor Pharmacy representative).>*

*<State whether Pharmacy will be provided with a current site delegation log to ensure they are aware who the assigned prescribing healthcare professionals working on the study are, and that will only dispense medication if prescribed by these individuals. If not, provide a justification.>*

*<There should be a dispensing guideline in place within pharmacy. Each member of staff who dispenses the medicinal product(s) signs the local / pharmacy dispensing log to document appropriate tracking. Any members of the study team should ensure that they have had study specific training and their involvement should be demonstrated by the study specific delegation log. If there are any special circumstances which require storage of the drug outside pharmacy there must be measures in place that dictate how this will be achieved, e.g. fridge will have limited access and be secure / calibrated, if any temperature excursions occur, log them accordingly. Site pharmacies are responsible for dispensing in line with their local dispensing procedures and excursion management normal practices.>*

## 11.9 Administration of IMP(s), placebo(s), and NIMP(s)

*<For each medicinal product, describe:*

* *How it will be administered (including any specific equipment required).*
* *Justification of route of administration.*
* *Dosing schedules (including any special instructions, e.g. in relation to requirements surrounding food).*
* *Any further dosing or administration information.>*

## 11.10 Destruction, return, and recall of IMP(s) and placebo(s)

*<Describe how destruction/ return and recall of IMPs will occur. For hospital stock IMP the recall will be as per local site procedures. Ensure details from any IMP manufacture or Distributer agreement is accurately reflected here. Full details can be located in the IMP Management plan and /or manual, but an outline must be detailed here. As a minimum, detail if sites will be expected to return medication, destroy it on site and how recall will be managed.>*

## 11.11 Dosage schedules

*<Give a precise and complete description of the dosage schedules.*

*For each drug, describe:*

* *Frequency of administration.*
* *Timing of each dose (including length of dosing where appropriate, e.g. 5mg/kg (to a maximum of 250mg) infused over 8 hours).*
* *Maximum dosage allowed each time the drug is given.*
* *Methods for individualised doses (if applicable).*
* *Drug calculation (if applicable).*
* *Maximum duration of treatment of a participant, i.e. the total amount of time the participant will be receiving the IMP (not necessarily the length of participant participation in the study).*
* *Whether treatment breaks are permitted.*
* *Whether missed doses are permitted and how they should be managed.*
* *Changes to doses as infants and children grow.>*

## 11.12 Dosage modifications and delays

*<For each medicinal product, detail:*

* *Events which would require the dose to be modified, e.g. in the case of certain adverse events (specify the exact dose modifications and events).*
* *Any stopping rules.*
* *Any requirements or processes that may involve dose reductions or delays, and their associated methods and schedules.*
* *Whether the dosage will be modified in accordance with the participants’ results (e.g. lab results, including what the results should be) and whether this will be completed under controlled hospital conditions or whether the participant will be required to adjust their own dosages following medical guidance at home.*
* *Whether the dose can be modified due to participant request.*
* *If dose delay permitted, maximum permitted pause / criteria for restart*

## 11.13 Management of <IMP>-specific adverse events

* *Procedures in the event of toxicity reactions (if applicable) e.g. is it possible to reduce the dosage or if any rescue medication may be administered.>*

## 11.14 Known drug reactions and interventions with other therapies

## 11.15 Recommended concurrent treatment

*<Optional – e.g. anti-emetics prior to chemo>*

## 11.16 Prohibited medication

*<Identify any known drug reactions or interaction with other therapies. For each medicinal product, outline:*

* *Any prohibited concomitant medications or therapies.*
* *The risks, including special precautions and contra-indications (these can be linked to the medicinal products safety assessments detailed in section xx).>*

*<Check that this list of contraindicated medications corresponds with the exclusion and withdrawal criteria, and that all concomitant medications received during the treatment phase will be recorded in the relevant Case Report Form (CRF).>*

*<For each medicinal product, describe:*

* *Prohibited prior and concomitant medication (including timelines, e.g. how long to wait after taking study drugs before being able to take prohibited medications).*
* *Any treatments participants should not take whilst on treatment (this may also include non-medicinal products).*
* *Whether the CRFs capture data on prior or concomitant therapies.*
* *Possible interactions or effects that could confound the results and conclusions.*
* *Rescue medication(s) that may be prescribed (e.g. for placebo-controlled studies in which the population receiving placebo medication would reasonably be expected to require “relief of symptoms” that will not be achieved with placebo medication).>*

## 11.17 Study restrictions

*<Describe any non-treatment study restrictions whilst on the active phase of the study, including dietary restrictions.>*

## 11.18 Management of overdose

## 11.19 Precautions regarding contraception

Consider both participant and partner.

## 11.20 Arrangements for post-study access to IMP and care

*<The Declaration of Helsinki 2013 states that “*In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process*” and that “*in clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.*”>*

*<Describe what care (interventions, benefits, etc.) the sponsor will continue to provide to participants after the study is completed, including whether funding arrangements are in place to continue to supply study drug. Provide justification if continued access to the study treatment(s) will not be funded.>*

# 12.0 Equipment and Devices

*<Outline any equipment and / or devices used outside of standard practice. This includes clinical and non-clinical equipment,*

 *If a device will be used which does not have a GB or UK CA mark, or will be used outside of its licensed indication, confirm with the GCP team whether this constitutes a device study and will require use of the devices protocol template.>*

*<For each device and item of equipment, provide:*

* *The device / equipment name.*
* *A description.*
* *The reason for its use in the study.*
* *Whether it is:*
	+ *Pre-GB or UK CA marking (speak to GCP Managers as the Devices protocol template may be required) or Post Marketing Surveillance.*
	+ *Not used as part of standard care but as part of the protocol, although not under investigation.*
	+ *Used as part of standard care.*
	+ *Routinely used in different clinical area.*
	+ *Being used within its licensed purpose (if not, speak to GCP Managers as the Devices protocol template may be required).*
	+ *Routinely available or whether it will be provided to sites.*
* *The manufacturer’s name.*
* *The GB or UK CA mark number (from the GB or UK CA mark certificate).*
* *Information regarding how long it has been in use.*
* *Details regarding whether it is on loan, or is a gift to the site / sponsor:*
	+ *If loaned or gifted, confirm whether it is registered on the Department of Health MIA (Master Indemnity Scheme). If not, there may be a requirement for this to be undertaken by the Device Company before the study can be approved.*
	+ *Does the company providing or loaning it want the study data in order to make a regulatory submission to apply for a license to use it in a new application? If yes, please discuss this with the JRMO GCP and contracts team).*
* *Information regarding set up, frequency of calibration, and of maintenance (within the NHS, this should correspond with Clinical Physics requirements (typically annually for maintenance checks). Within the NHS all research device and related equipment must receive Clinical Physics approval whether they are under investigation or used as part of the protocol. See Clinical Physics for guidance).*
* *Details regarding what training will be required and provided prior to use.*
* *Storage location and requirements (refer to its manual as required).*
* *Custodian contact details (for multi-site studies state that this must be delegated by the PI).*
* *Insurance arrangements information.*

# 13.0 Pharmacovigilance

## 13.1 General definitions

|  |  |
| --- | --- |
| **Term** | **Definition** |
| Adverse Event (AE) | Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. |
| Adverse Reaction (AR) | An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.The phrase "*response to an investigational medicinal product*" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions. |
| Serious Adverse Event (SAE) | A serious adverse event is any untoward medical occurrence that:* Results in death.
* Is life-threatening.
* Requires inpatient hospitalisation or prolongation of existing hospitalisation *<may define what constitutes hospitalisation – e.g. A&E admission, day cases may not be considered hospitalisation>*
* Results in persistent or significant disability/incapacity.
* 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.NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. |
| Serious Adverse Reaction (SAR) | An adverse event that is both serious and, in the opinion of the reporting Investigator or medical assessor, believed with reasonable probability to be due to one of the study treatments, based on the information provided. |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) | A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Reference Safety Information (RSI):* In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product.
* In the case of any other investigational medicinal product, in the investigator’s brochure (IB) relating to the study in question.
 |

## 13.2 Site investigator assessment

The Principal Investigator is responsible for the care of the participant, or in their absence an authorised medic within the research team is responsible for assessment of any event for:

* **Seriousness**

Assessing whether the event is serious according to the definitions given in section 13.1.

* **Causality**

Assessing the causality of all serious adverse events/reactions in relation to the study treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.

* **Expectedness**

Assessing the expectedness of all SARs according to the definition given. If the SAR is unexpected (as per the RSI), then it is a SUSAR.

* **Severity**

Assessing the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term “serious” which is a regulatory definition based on participant/event endpoint criteria.

* + **Mild**: Some discomfort noted but without disruption of daily life
	+ **Moderate**: Discomfort enough to affect/reduce normal activity
	+ **Severe**: Complete inability to perform daily activities and lead a normal life

## 13.3 Reference Safety Information (RSI)

Reference Safety Information (RSI) is the information used for assessing whether an adverse reaction is expected.

*<For each IMP and placebo, detail which document and section is to be used as the RSI for this study (e.g. SmPC or IB section X.X).>*

*<Describe the arrangements for checking for, and implementing updates to, the SmPC / IB.>*

## 13.4 Notification and recording of Adverse Events (AEs) or Reactions (ARs)

All AE and AR’s are to be documented in the participants’ medical notes or other source data documents and the CRF.

Once assessed, if the AE is not defined as SERIOUS, the AE is recorded in the study file and the participant is followed up by the research team.

## 13.5 Notification of AEs of Special Interest (AESIs)

*<Detail any AEs the IMP manufacturer or sponsor deem to be of special interest. AESIs are not SAEs but should be reported in the same timeframe as SAEs. If your study will include AESIs, you should create a separate report form/method of reporting for them.>*

## 13.6 Adverse events that do not require reporting

*<Define any AEs or SAEs that are expected and do not require reporting for this study. For studies where the medicinal products are licensed, it is permissible to state that events or reactions listed in the SmPC do not need to be reported. Define the period for AE reporting (e.g. from randomisation or first dose, until 30 days post final IMP administration).>*

*< In some studies, and disease stages death may be expected or the endpoint of the study. In such cases a common addition is “Death as a result of disease progression and other events that are primary or secondary endpoint measures are often not considered to be SAEs and can be reported in the normal way, on the appropriate CRF if specified here.” Insert if applicable>*

## 13.7 Notification and reporting of Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

All Serious Adverse Event (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be recorded in the participants’ notes, the CRF, the sponsor SAE form and reported to the sponsor (administered by the Joint Research Management Office or agreed representative) *and the IMP provider (as per IMP supply agreement)* within 24 hours of the site becoming aware of the event *(except those specified in this protocol as not requiring reporting)*.

Nominated co-investigators (as listed) will be authorised to sign the SAE forms in the absence of the PI at the participating sites.

## 13.8 Sponsor medical assessment

Sponsor has delegated the responsibility for oversight of IMP safety profile and medical assessment of AEs, ARs, SAEs and SUSARs to the CI as medical assessor The CI must review all SAEs within 72 hours of receipt. This review should encompass seriousness, relatedness, and expectedness. Day 0 for all SUSARs is when the SAE / SUSAR is received by the CI and / or coordinating team and / or sponsor (whichever is first).

It is noted that the CI cannot downgrade the PI assessment of an event’s causality. If there is disagreement between CI and PI assessment, no pressure should be placed on the PI to alter their assessment, but the CI can liaise with the site PI before the CI’s final decision. The CI and PI assessment can differ.

## 13.9 Procedures for reporting blinded SUSARs

*<If the study is not blinded delete this section.>*

*<Detail the arrangements to allow the sponsor to report un-blinded events to the MHRA and REC. This should be done without breaking the site / CI / research team blinded status.>*

*<If the study is blinded, include the following statement:>*

The CI, as sponsor medical assessor, will assess the event blinded for all possible IMPs, placebos, and combinations.

## 13.10 Urgent safety measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical study participants from any immediate hazard to their health and safety, in accordance with Regulation 30 of the Medicines for Human Use (Clinical Trials) regulations. The measures should be taken immediately. In this instance, the approval of the Competent Authority prior to implementing these safety measures is not required. However, it is the responsibility of the CI to attempt, where possible, to discuss the proposed change with the sponsor and Medical Advisor at the MHRA (via telephone) prior to implementing the change if possible.

The CI has an obligation to inform both the MHRA and Research Ethics Committee in writing **within 3 days** of implementing the Urgent Safety Measure. They must also submit a substantial amendment documenting the changes with 14 days of implementing the urgent safety measure. The JRMO must be sent a copy of the correspondence with regards to this matter as soon as it is sent.

## 13.11 Pregnancy

*<If this section is not applicable delete it. Ensure this section compliments and references the AESI section.>*

*<If the participant population is likely to include females of a child-bearing potential or are the spouse / partner of females of child-bearing potential, include the following text:>*

If a participant becomes pregnant whilst involved in a CTIMP, it is not considered to be an SAE or an AE. However, it is an event that requires reporting, monitoring and follow up. If a participant or participant’s partner becomes pregnant whilst or after taking an IMP, the sponsor should be notified immediately (within 24 hours of site becoming aware of the pregnancy) using the sponsor pregnancy form. The pregnancy reporting procedure will be the same as the SAE reporting route.

The CI (in conjunction with the site PI) should determine if the foetus has been exposed to an IMP. The PI has the responsibility to ensure that the pregnancy form is completed and sent to the sponsor within the agreed timelines. The initial report should be sent within 24 hours of the PI or co-investigator becoming aware of the event and follow up information submitted as and when it becomes available up to agreed follow up time after birth.

The sponsor will arrange for a review of the pregnancy report by an appropriate expert medic (usually a consultant obstetrician). The study team must follow all instructions provided by the sponsor’s expert.

*<State:*

* *Whether the participant can continue on the study or whether the participant has to be prematurely withdrawn from the study if they or their partner become pregnant.*
* *Whether the manufacturer will be informed.*
* *The period of follow up for this study’s IMPs (The PI must follow up the pregnancy until delivery as well as monitoring the development of the fetus for the appropriate time and where clinically appropriate after birth. Any events to the mother or child that occur during this time that could be considered to be a SAE must be reported to the sponsor in line with section 13.7, using the sponsor SAE reporting form.)>*

# 14.0 Annual reporting

## 14.1 Development Safety Update Report (DSUR)

The DSUR will be written by the CI (following Sponsor procedures) and submitted to the sponsor for review prior to submission to the MHRA. The DSUR is due for submission within 60 days of the end of the reporting period. The reporting period is annually from the date on the “*Notice of acceptance letter*” from the MHRA. The sponsor’s delegated Medical Assessor, usually the CI, will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the study. REC will be sent a copy of the DSUR.

*<Add additional requirements for submission for international trials>*

## 14.2 Annual Progress Report (APR)

The APR will be written by the CI (using the HRA’s template) and submitted to the sponsor for review prior to submission to the REC. The APR is due within 30 days of the anniversary date of the “favourable opinion” letter from the REC.

*<Add additional requirements for submission for international trials>*

# 15.0 Statistical and data analysis

## 15.1 Sample size calculation

*<Explain how the planned number of participants was derived. An appropriate level of statistical advice should be sought to ensure study validity.>*

*<Detail the methods used for the determination of the sample size and a reference to tables or statistical software used (including version) to carry out the calculation. Sufficient information should be provided so that the sample size calculation can be reproduced. For studies that involve a formal sample size calculation, 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. Sample size calculations are generally based on one primary endpoint. However, it may also be worthwhile to plan for adequate study power or report the power that will be available (given the proposed sample size) for other important endpoints or analyses because studies are often underpowered to detect harms or subgroup effects.>*

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

*<Formal sample size calculations typically require justification for the following values:*

* *Treatment Effect or Alternative Hypothesis:*
	+ *Is this the smallest size of effect that would be of clinical interest?*
	+ *How is this justified in the form of appropriate references, pilot data or clinical arguments?*
* *Null Hypothesis (a clear statement of the hypothesis, in terms of numerical values, of the treatment being ineffective. E.g. an absolute difference in response rates between arms of zero).*
* *Estimated loss to follow up/drop out rates*
* *Significance level (what risk is acceptable of concluding the treatment is effective, when in reality the treatment is ineffective, whether this is one or two sided?).*
* *In studies with continuous endpoints the standard deviation of the primary endpoint should be included. If previous studies or literature are used to estimate or justify the assumptions made to determine this parameter, or any other parameters relevant to the design (e.g. dropout rate, noncompliance rates median survival rate, response rate), provide references.*
* *If one or more interim analysis(es) are planned, consider whether the sample size should be increased to account for multiple testing.>*
* *The methods and timing for assessing, recording, and analysing efficacy parameters, e.g.:*
	+ *The values and scores that will determine success or failure and how they will be assessed, if appropriate.*
	+ *Survival (e.g.: “These will be measured from the date of randomisation and will be reported for all deaths due to all causes. The cause of death is to be recorded in all instances.”).*
	+ *Quality of life assessments.>*

## 15.2 Planned recruitment rate

*<State the estimated planned recruitment rate. Realistic estimates of expected recruitment rate and duration of participant entry based on estimated sample size should be provided.>*

*<When assessing the feasibility of meeting the recruitment consider:*

* *What are the Power Calculations to meet the end points – can this number of participants be recruited? (section 15/16 ).*
* *Rarity of the disease.*
* *The number of sites. Will more sites or participant identifying centres (PICs) be needed to meet the recruitment target?*
* *Whether the PIs at the proposed sites have a track record of meeting recruitment targets?*
* *Who is responsible for driving recruitment across all sites (e.g. a study coordinator / study manager to track recruitment rates)?*
* *Whether other departments affect recruitment (think of the participant pathway, e.g. genetics study recruiting from both adult and pediatric departments; neonate study recruiting in women’s health)? Will these departments need to assess feasibility of the study design?*
* *Whether anything in the protocol design or inclusion / exclusion criteria may impact recruitment or withdrawals (e.g. additional / painful interventions, additional burdens to the participant such as travel, claustrophobia of MRI scans)?*
* *How many potential participants are currently seen a) per month b) per year?*
* *The anticipated screen failure rates?*
* *The anticipated withdrawal rates (consider previous studies and known side-effects)?*
* *If any competing / similar studies recruiting the same cohort of potential participants?*
* *If the proposed start and end date and duration of funding is realistic to make the recruitment targets feasible?*

## 15.3. End of trial (EOT) definition

*<Provide a clear end of trial definition. It is usually the date of the last participant’s visit, or the date the last data item of the last participant undergoing the trial is collected. Bear in mind that all study activities, including lab work, must be completed prior to EOT being submitted, and the initial data collection into the trial database must be complete.>*

*<Long term passive follow up must be included within the trial duration. It may be suitable to run a non-CTIMP in parallel with the trial in order to conduct long term follow up (thus shortening the study itself). This should be considered if, in the long term, a passive follow up will be used.>*

The CI is delegated the responsibility of submitting the EOT notification to REC and MHRA once reviewed by the sponsor. The EOT notification must be received by the REC and MHRA within 90 days of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the Sponsor, REC, and MHRA within 15 days, including the reasons for the premature termination.

## 15.4 Statistical Analysis

*<Describe a summary of the statistical analysis plan (SAP). The SAP should act as a standalone document. This section should confirm the SAP will be finalised prior to any review or analysis of data.>*

*<Pay careful attention to section 21 of the protocol when developing the SAP to ensure that they match.>*

## 15.5 Summary of baseline data and flow of participants

*<Full detail should be listed in the Statistical analysis plan but a high-level summary should be included here: List variables to be used to assess baseline comparability of the randomised or cohort groups including (for each factor):*

* *A definition.*
* *Any rules.*
* *References or programmes for calculation of derived values.*
* *The form data will take for analysis (e.g. continuous, categorical, ordinal).*
* *How data will be reported (e.g. means, standard deviations, medians, proportions).>*

*<Detail the plans to produce a consort flow diagram. For guidance see the Consort Website (CONSORT: Consolidated Standards of Reporting Trials).>*

## 15.6 Analysis of participant populations

*<Describe the participant populations whose data will be subjected to the study analysis. Include:*

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

*<Detail how to avoid:*

* *Selection bias (an “as randomised” analysis retains participants in the group to which they were originally allocated).*
* *Attrition bias (out-come data obtained from all participants are included in the data analysis, regardless of protocol adherence).*

*<These two conditions (i.e. all participants, as randomised) define an “intention to treat” analysis, which is widely recommended as the preferred analysis strategy. This should be included if applicable.>*

## 15.7 Primary endpoint analysis

*<Explain the plans for statistical analyses of the primary endpoint including:*

* *Summary measures to be reported.*
* *Method of analysis (justified with consideration of form of the data, assumptions of the method and structure of the data (e.g. unpaired, paired, clustered) etc.).*
* *Plans for handling multiple comparisons, missing data, non-compliers, spurious data, and withdrawals in analysis.*
* *Plans for predefined subgroup analyses.*
* *Statement regarding* population for analysis *for example use of intention to treat (ITT) , Full Analysis Set (FAS) or Per Protocol (PP) population analysis as applicable*
* *Description of any non-statistical methods that might be used (e.g. qualitative methods).>*

## 15.8 Secondary endpoint analysis

*<Explain the plans for statistical analysis of each secondary endpoint. In general, the use of hypothesis tests may not be appropriate if the study 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.>*

## 15.9 Safety analysis

*< Safety Analysis should be considered even if safety is also a secondary endpoint.*

*Consider:*

*Demographic and baseline variables*

*Exposure*

*Compliance*

*Serious and non-serious AEs*

*Clinical Laboratory evaluations*

*Any other Clinical safety measures or variables relevant to the study.>*

## 15.10 Subgroup analyses

*<This section is* Optional, if planned from outset

 *Describe sub-group analyses. Subgroup analyses explore whether estimated treatment effects vary significantly between subcategories of study participants. As these data can help tailor healthcare decisions to individual patients, a modest number of pre-specified subgroup analyses can be sensible.>*

## 15.11 Adjusted analysis

*<* Optional, if planned from outset

*Describe any adjusted analysis to account for imbalances between study groups (e.g. chance imbalance across study groups in small studies), to improve power, or account for a known prognostic variable.>*

*<State:*

* *If there is an intention to perform or consider adjusted analyses.*
* *Any known variables for adjustment (if it is not clear in advance which these should be the objective criteria to be used to select variables should be pre-specified).*
* *How continuous variables will be handled.*
* *If unadjusted and adjusted analyses are intended, what the main analysis is.>*

## 15.12 Interim analysis and criteria for the premature termination of the study

*<Describe any interim analysis and criteria for stopping the study. If an interim analysis is not included in the protocol it is not permitted to conduct one. This includes any review of data prior to the end of trial definition being met. Consider whether it may be desirable to analyse, publish, or present the data before the end of trial definition.>*

*<Describe:*

* *Any interim analysis plan, even if it is only to be performed at the request of an oversight body (e.g. IDMC).*
* *The statistical methods.*
* *Who will perform the analyses.*
* *When they will be conducted (timing and indications).*
* *The decision criteria (statistical or other) that will be adopted to judge the interim results as part of a guideline for early stopping or other adaptations.*
* *Who (if anyone) will see the endpoint data while the study is ongoing.*
* *Whether these individuals will remain blinded (masked) to study groups.*
* *How the integrity of the study implementation will be protected (e.g. maintaining blinding) when any adaptations to the study are made.*
* *Who has the ultimate authority to stop or modify the study e.g. the Chief Investigator, Trial Steering Committee or sponsor retains the right to stop the study, should the need arise.*
* *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., low chance of rejecting null hypothesis).*
	+ *If pre-specified interim analyses are to be used for other study adaptations such as sample size re-estimation, alteration to the proportion of participants allocated to each study group, and changes to eligibility criteria.>*

*<In CTIMPs recommendations made by the IDMC must be expedited to the MHRA where they are deemed relevant for the safety of participants participating within the study (refer to the EU Guidance Document ‘Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use’).>*

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

*<Describe how missing data will be dealt with, including:*

* *The strategies to maximise follow-up and prevent missing data.*
* *How recording of reasons for missing data will be undertaken.*
* *How missing data will be handled in the analysis and detail any planned methods to impute (estimate) missing endpoint data, including which variables will be used in the imputation process (if applicable). Methods of multiple imputation are more complex but are widely preferred to single imputation methods (e.g. last observation carried forward; baseline observation carried forward), as the latter introduce greater bias and produce confidence intervals that are too narrow. Sensitivity analyses are highly recommended to assess the robustness of study results under different methods of handling missing data.>*

## 15.14 Economic evaluation

*<If economic evaluation is to be undertaken include the rationale for inclusion of the economic investigation and means of assessment. This should be written jointly with the study health economic investigator collaborator if included.>*

*If this section is not relevant to the study, delete it.>*

## 15.15 Other statistical considerations

*<Describe any other statistical consideration pertinent to the study, including:*

* *Procedures for reporting any deviation(s) from the original statistical plan.*
* *Any other statistical considerations (e.g. if there is a requirement for an economic analysis plan).*
* *Withdrawals and any need for replacements.*
* *Definition of evaluable participants.>*

*If this section is not relevant to the study, mark as not applicable*

# 16.0 Data handling and record keeping

## 16.1 Source data and source documents

*<ICH GCP E6 1.52, defines source documents as:*

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

*<ICH GCP E6 section 1.51, defines source data as:*

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

*<A source data location document will be in place for each site that will detail: For each data point to be collected, define:*

* *What will comprise the source data.*
* *What will comprise the source documents.>*

*<Only people who have a 'legitimate relationship' with the patient (i.e. are members of the team providing the patient’s health care) are entitled to have access to their medical records. If anyone else will have access to participants’ data, detail:*

* *Who will have access to the data*
* *What data they will have access to*
* *All written agreements that refer to access to data.>*

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

## 16.2 Case Report Forms (CRFs)

*<A case report form (CRF) is a form on which individual participant data that are required by the study protocol are recorded. It may be a printed or electronic document, and all CRFs should be de-identified. The CRF is used to collect the data that will be used to perform statistical analysis. CRFs must ensure that:*

* *All required data is captured.*
* *No superfluous data is captured (which can make data capture unnecessarily complicated, make data extraction and analysis difficult, and potentially breach the Data Protection Act).*
* *Paper trails are maintained to demonstrate the validity of the study (both during and after the study).>*

*<CRF entries may be source data if the CRF is the site of the original recording (i.e. there is no other written or electronic record of data, e.g. questionnaires completed by participants). If the CRF contains source data and is sent to the sponsor, the study site must retain a copy to ensure that the Principal Investigator can provide access to the source documents to a monitor, auditor, or regulatory agency. Additional information can be found in ICH E6, section 6.4.9.>*

*<State:*

* *All parameters that will be recorded in the CRFs.*
* *When CRFs will be completed.*
* *Who will be responsible for completing the CRFs (note, participants may be responsible for completing questionnaires).*
* *Whether any data will be captured using a standardised tool (e.g. McGill pain score / validated questionnaire).*
* *Whether any data will be captured using a non-standard tool (e.g. questionnaire or pain scale). If so, provide details regarding its reliability and validity.>*

## 16.3 Data capture

*<Describe:*

* *Methods for maximizing completeness of data (e.g. telephoning participants who have not returned postal questionnaires).*
* *Methods for ensuring all interactions with the participant are documented (e.g. unscheduled telephone conversations).*
* *How de-identified data can be linked back to the original participant.*
* *How identifiable documentation will be stored (e.g. informed consent forms).*
* *How de-identified documentation will be stored (e.g. completed CRFs).*
* *What software (e.g. RedCap, Oracle, RAVE, MACRO) will be used for data entry (see SOP 38b for details of minimum requirements and processes).*
* *Methods to ensure validity and quality of data (e.g. double entry, cross validation, etc.), which should be proportionate to the study.*
* *How data will be stored.*
* *How data will be backed up securely (including data storage requirements for sites).*
* *Audit trails (to verify who entered data, who changed data, when each step was done and what was changed).*
* *Interactions between the database and any other electronic systems.*
* *Training of staff to use the database and CRF/e-CRFs and how this will be documented.>*

## 16.4 Transferring and transporting data

*<All data must be handled in accordance with the Data Protection Act (2018). If data is to be transferred outside of the EEA, explicit consent from participants is required as data protection arrangements may not be as robust.>*

*<Identifiable information must not be stored or transported on any portable device (e.g. laptops, memory sticks, CD / DVDs) unless it is encrypted. Similarly, data must not be sent electronically if it is not subject to end-to-end encryption. Queen Mary and Barts Health are two separate Institutions and Barts Health Participant Identifiable Data (PID) cannot be taken out of Barts Health without permission. PID cannot be stored on Queen Mary network without justification and appropriate security measures.>*

*<Site research teams may transfer data to third parties with participant consent, provided it is de-identified. Data should be anonymous or have a unique study identifier which only the site can link to the original participant.>*

*<If data must be transferred, describe:*

* *The method(s) of transfer to be used.*
* *How confidentiality of data will be ensured.*
* *Security arrangements in place to ensure the security of the data during transfer.>*

## 16.5 Data Management

*<Some trials will have a dedicated Data Management Plan to describe their methods of data management. Where this is the case, provide a high-level summary in this section and reference the Data Management Plan.*

*< Summarise the methods used to ensure that collected data is ‘clean.’ This can include:*

* *Source Data Verification at on-site monitoring visits.*
* *Remote monitoring activities.*
* *Automatic query generation in the eCRF.*
* *Self-evident corrections, where explicitly agreed with the site*
* *Final sign-off by site PI>*

*<Explain how the final data will be locked to prevent changes, including whether there will be multiple data locks throughout the study and whether there will be ‘soft’ locks prior to the final data lock. Data lock procedures must be sufficiently robust to protect the final data set.>*

*<Explain how the final dataset will be exported from the study database for analysis, including measures to ensure that the data lock is protected at this stage.*

# 17.0 Confidentiality

The Chief Investigator will be the data custodian for all data generated during the study.

The Chief Investigator and the study team will ensure that all participants’ identities are protected at every stage of the study. To ensure this, at time of consent each participant will be allocated a unique screening number) by *<the coordinating team/amend as appropriate>* before undergoing any screening procedures.

The Principal Investigator is responsible for protecting the identity of participants at their site. Participants will be referred to only by their unique study identifier whenever data is transferred outside of the site, and in all correspondence between the site and the coordinating centre, co-investigators, sponsor, or anyone associated with the study.

*<If identifiable data must leave the site, discuss this with the JRMO to ensure relevant permissions are acquired (such as approval from a Caldicott Guardian) before the study starts. Sending consent forms outside of the site is not acceptable except in exceptional circumstances.>*

No participants will be individually identifiable from any publications resulting from the study.

Information regarding study participants will be kept confidential and managed in accordance with the Data Protection Act (2018), the UK Policy Framework for Health and Social Care and Research Ethics Committee approval. All study data will be stored in line with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments and the Data Protection Act. Study data will be archived in line with the Medicines for Human Use (Clinical Trials) Regulations 2004 and all subsequent amendments, and as defined in the JRMO SOP 20 Archiving.

*<Adapt section accordingly for country specific protocols for international trials.>*

## 17.1 De-identification of participants

*<A screening log should be maintained throughout the study. Usually this includes the potential participant’s initials to allow their identification by relevant site staff. Once the participant has completed screening procedures and is enrolled onto the study, they must be allocated a unique study identifier by <the coordinating team/amend as appropriate>. All data must be de-identified before it is used or sent / transferred from the site.>*

*<If the CI wishes to collect full participant identifiable data, they must explain why (e.g. to perform long term flagging with Hospital Episode Statistics (HES)). The protocol, participant information sheets, and consent forms must clearly explain how and where identifiable data will be sent and kept.>*

*<Participants with rare diseases may be easily identifiable. If the study involves participants with rare diseases it is necessary to ensure the combination of all data collected cannot allow external identification of an individual.>*

*<Describe:*

* *What identifiable information will be collected from the participants and why.*
* *Who will have access to identifiable information and why.*
* *How identifiable data will be de-identified, kept secure, and maintained, including:*
	+ *The creation and use of a unique identifier for each participant (initials with full dates of birth must not be used, but it may be acceptable to use year of birth if age is important).*
	+ *Secure maintenance of the data and the linking code in separate locations.*
	+ *Use of encryption.*
	+ *Password protection of folders and storage media.*
	+ *Limiting access to the minimum number of individuals necessary for quality control, audit, and analysis.*
* *How data will be de-identified, link anonymised, or anonymised (if, when, who by, and how this will be done).*
* *The disaster recovery plan.>*

# 18.0 Monitoring, Audit, and Inspection

## 18.1 Monitoring

A Trial Monitoring Plan will be developed and agreed by the sponsor and Chief Investigator based on the sponsor’s risk assessment, which will include on site monitoring. Monitoring procedures are detailed in the Trial Monitoring Plan.

## 18.2 Auditing

The sponsor retains the right to audit any aspect of the study, study sites, or central facilities. In addition, any part of the study may be inspected by the regulatory bodies, and funders where applicable.

All sites and vendors are asked to inform the sponsor if notified of any Audit or inspection affecting this study

.

# 19.0 Compliance

The CI will ensure that the protocol and study is conducted in compliance with the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, current UK Policy Framework for Social and health care research (2017), GCP guidelines, the World Medical Association Declaration of Helsinki, the Sponsor’s and study specific SOPs, and other regulatory requirements.

The study will not commence until sponsor permission to activate sites is received.

Sites will be individually activated by the CI and team; this will not occur until site approval is granted.

*<For studies using ionising radiation please state in this section that:*

*•The procedures are compliant with the Ionising Radiation (Medical Exposure) Regulations, and appropriate review by a Medical Physics Expert and Clinical Radiation Expert has been undertaken.*

*•Where a study involves the administration of radioactive substances the protocol should clearly identify that a current Administration of Radioactive Substances Advisory Committee (ARSAC) certificate will be required for each site and, where exposures are additional to normal standard of care, a research ARSAC certificate will be required for each site.>*

*<Ionising radiation includes:*

*•X-rays, CT scans, DXA scans.*

*•Radiotherapy (including brachytherapy and radionuclide therapy, using unsealed sources).*

*•Radionuclide studies (including nuclear medicine imaging, PET-CT, and in vitro measurements).*

*•Administration of a radioactive substance.*

*Neither MRI nor ultrasound involve ionising radiation.>*

## 19.1 Non-Compliance

*<Explain how protocol non-compliances will be managed. Protocol deviations, non-compliances, or breaches are departures from the approved protocol.>*

*<\Consider:*

* *Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and sponsor immediately.*
* *The CI and the coordinating team should assess non-compliances and action a timeframe in which they need to be dealt with (this assessment should include the need to escalate to the sponsor.*
* *Corrective and preventative actions (CAPAs) will be assigned (where applicable), and that each action will be given a different timeframe dependent on the severity.>*

*<Outline requirements for recording deviations on a site level.>*

* *Any event with the potential to affect participant safety or data integrity should be reported to the sponsor within 24 hours of the coordinating team becoming aware).*
* *Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used (i.e. it is not acceptable to enroll a participant if they do not meet the eligibility criteria or restrictions specified in the study protocol).*
* *Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.*
* *Systematic failure of both the CI and the study staff adhering to SOPs, protocol, ICH GCP or UK regulations, which leads to prolonged collection of deviations, may constitute breaches or suspected fraud.*

Non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The sponsor will maintain a log of non-compliances to ascertain if there are any trends developing which need to be escalated.

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

A ‘serious breach’ is a breach which is likely to affect to a significant degree:

* The safety or physical or mental integrity of the participants of the study; or
* The scientific value of the study.

The site Principal investigator is responsible for reporting any potential serious breaches to the sponsor (research.safety@qmul.ac.uk) within **24 hours** of becoming aware of the event.

Please note email address can be changed if agreed with GCP team sponsorship submission**.**

The Chief Investigator is responsible for reporting any potential serious breaches to the JRMO **within 24 hours** of becoming aware of the event.

The sponsor is responsible for determining whether a potential serious breach constitutes a serious breach, and will work with the CI to investigate and notify and report to the MHRA and REC (as applicable) within 7 working days of becoming aware of the serious breach.

# 20.0 Declaration of interests

*<*

*The CI, PIs at each site, and committee members for the overall study management, detail will provided:*

* *All competing interests.*
* *Ownership interests that may be related to products, services, or interventions considered for use in the study or that may be significantly affected by the study.*
* *Commercial ties (e.g. pharmaceutical, behaviour modification, and/or technology companies).*
* *Non-commercial potential conflicts (e.g. professional collaborations that may impact on academic promotion).*

*These will be held within the Trial master file. Please address enquiries to < insert contact>.*

*The sponsor requires all study committee members complete competing interest declarations.*

# 21.0 Peer review

*<All CTIMP studies should undergo scientific peer reviewed by two independent experts in the field (independent of Queen Mary and Barts Health). They should also be reviewed by the CI’s Institute or Clinical Board prior to sponsorship in principle being given by the JRMO (see SOP 14 Peer Review).>*

*<Provide details on who reviewed this study protocol (e.g. the funder or an internal Trust department or committee), but do not include individual names unless the person in question gives their express permission.>*

*<<*See Sponsor SOP 14 for further advice>>

# 22.0 Public and Patient Involvement (PPI)

*<Public involvement is fundamental to ensure high quality clinical research that brings real benefits e.g. for patients and the NHS. Describe the public involvement that has already taken place and how they have informed the development of the study. Describe plans for future public involvement activity, during and after the study.>*

*<The Research Engagement and Diffusion team can provide information and guidance on how to involve patients and the public in studies via* patientsinresearch.bartshealth@nhs.net *or at* [*www.jrmo.org.uk/performing-research/involving-patients-in-research/*](http://www.jrmo.org.uk/performing-research/involving-patients-in-research/)*.>*

# 23.0 Indemnity/ Insurance

*<Delete only one of the statements in black below as appropriate, depending on sponsor institution.>*

*<Queen Mary sponsored>*

The insurance that Queen Mary University of London has in place provides cover for the design and management of the study as well as "No Fault Compensation" for participants, which provides an indemnity to participants for negligent and non-negligent harm.

*OR*

*<Barts Health sponsored>*

The NHS indemnity scheme will apply. It provides cover for negligent harm arising from the design, management, and conduct of the study. The NHS indemnity scheme does not provide “No Fault Compensation”.

# 24.0 Study committees

*<Outline the various committees or groups involved in study coordination and conduct. For all Barts Health and Queen Mary CTIMPS, the CI and statistician should consider the need for committees. As a minimum there should be regular documented Trial Management Group meetings and a Trial Steering Committee with independent representation.>*

*<There are three main trial management groups which may be involved in the set up and management of a clinical study, depending on the study size, design, and number of sites. For each committee / group the protocol should state their roles and responsibilities, and degree of independence from sponsor and Investigators. Each committee must have at least a draft charter in place before permission to activate sites is issued, meetings will be monitored, and minutes reviewed by the sponsor. For guidance on Trial Management Committees please see JRMO SOP 47, HRA website, and MRC website. The JRMO can also provide guidance.>*

*<All committees should have a charter or terms of reference and a list of members. A declaration of interest statement must be provided by all members and reviewed by the committee, and their CV and evidence of commensurate GCP training must be collected.>*

## 24.1 Trial Management Group (TMG)

*<The Trial Management Group (TMG) is mandatory for all MHRA regulated trials. The TMG should meet regularly to ensure all aspects of the study are progressing and working well, and everyone within the study is aware of their required actions. Include an outline of what this group is responsible for and:*

* *State here the frequency and format of the meetings or when the group will be called.*
* *State here whether the TMG will have authority to terminate / prematurely discontinue the study.*
* *Describe the composition of the TMG (please do not list members by name as this means amending the protocol for every change, instead list types or roles e.g. CI, all PIs, statistician, health economist, independent chair, independent medic, etc.).>*

## 24.2 Trial Steering Committee (TSC)

*<The Trial Steering Committee (TSC) is mandated for all MHRA regulated studies & must:*

* *Have a majority of members who are independent of the study (See Sponsor SOP 47 for definition of independent).*
* *Have an independent chair.*
* *Meet regularly.*
* *Send reports to the sponsor.*

*Lay members or patient / carer / public representatives on the committee are desirable and actively encouraged by many charity funders e.g. NIHR, Wellcome Trust.>*

*<Outline what this group is responsible for (e.g. “In accordance with the Trial Terms of Reference, the TSC will periodically review safety data and liaise with the IDMC regarding safety issues”).>*

*<State:*

* *The frequency of the meetings or when the group will be called.*
* *Whether the TSC will have authority to terminate / prematurely discontinue the study.*
* *The committee composition (please do not list members by name as this means amending the protocol for every change, instead list types or roles e.g. CI, all PIs, statistician, health economist, independent chair, independent medic, etc.).>*

## 24.3 Independent data monitoring committee (IDMC)

*<Delete this section if not applicable.>*

*<Discuss the need to have a IDMC with the study statistician. Independence is a key characteristic of a IDMC with committee members who are completely uninvolved in the running of the study and who cannot be unfairly influenced (either directly or indirectly) by people, or institutions, involved in the study. Include an outline of what this group is responsible for (e.g. “In accordance with the study Terms of Reference, the IDMC will periodically review unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis”). The Regulations require that all Serious Adverse Events (SAEs) (unless excluded in the protocol) are reviewed by an appropriate Safety Monitoring Committee.>*

*<State:*

* *The frequency of the meetings or when the group will be called.*
* *Whether the IDMC will have authority to terminate / prematurely discontinue the study.*
* *Whether the IDMC will assess study progress / occurrence of adverse events and all other aspects.*
* *The committee composition (please do not list members by name as this means amending the protocol for every change, instead list types or roles e.g. CI, all PIs, statistician, health economist, independent chair, independent medic, etc.).>*

# 25.0 Publication and dissemination policy

## 25.1 Publication

*<Publications should only occur at predefined time points that correlate to the timings of analysis as defined in the statistical section. Will it be desirable to publish prior to the end of study? Or at interim interval(s), or upon completion of the primary endpoint?*

*It is the CIs responsibility to ensure they meet all requirements laid out by The International Committee of Medical Journal Editors (ICMJE) ( http://www.icmje.org/ )>*

All publications will be sent to the JRMO prior to publication.

*<Responsibility for ensuring accuracy of any publication from this study is delegated to the Chief Investigator. All publications should acknowledge the Sponsor. The correct designation for the sponsor is “*Queen Mary University of London*” and / or “*Barts Health NHS Trust*” as appropriate.>*

The full study report will be accessible via EudraCT or other suitable public website within one year of the End of the Trial Notification.

## 25.2 Dissemination policy

*<Detail:*

* *Who owns the data arising from the study (default is the sponsor, unless an official agreement has been made with a funder).*
* *If a third party is to have access to data (if so, state the conditions here, e.g. anonymous data will be made available in a report six weeks prior to publication, after satisfaction of the End of Trial definition). Consider the funder’s requirement for open access in this section.*
* *Whether any funding or supporting bodies need to be acknowledged within the publications and whether they have review and publication rights of the data from the study.*
* *Whether contributing centres (and participating investigators) will be acknowledged in the final manuscript.*
* *That on completion of the study, the data will be analysed and tabulated and a Clinical Study Report will be prepared on EudraCT.*
* *If any of the participating investigators will have rights to publish any of the study data.*
* *If there are any time limits or review requirements on the publications.*
* *Whether there are any plans to notify the participants of the endpoint of the study, either by provision of the publication, or via a specifically designed newsletter etc.*
* *If it possible for the participant to specifically request results from their PI and when this information would be provided (e.g. after the Clinical Study Report had been compiled or after the results had been published).*
* *Whether the study protocol, full study report, anonymised participant level dataset, and / or statistical code for generating the results will be made publicly available; and if so, describe where, the timeframe, and any other conditions for access.>*

*<Detail any authorship eligibility guidelines and any intended use of professional writers, including:*

* *Guidelines on authorship on the final study report.*
* *Criteria for individually named authors or group authorship (The International Committee of Medical Journal Editors has defined authorship criteria for manuscripts submitted for publication).*
* *If professional medical writers will be hired and how their employment and funding will be acknowledged in study reports.>*

## 25.3 Access to the final study dataset

*<Describe who will have access to the final dataset:*

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

# 26.0 Archiving

*<For studies involving Barts Health participants, undertaken by Barts Health staff, or sponsored by Barts Health or Queen Mary, the approved repository for long-term storage of local records is the Barts Health Modern Records Centre. Note timelines below will need to be altered for ATMPs, see sponsor SOPs>*

During the course of the research, all records are the responsibility of the Chief Investigator and will be kept in secure conditions. When the research study is complete, it is a requirement of the Barts Health Policy that the records are kept for a further 25 years.

Site files from other sites must be archived for 25 years at the external site and will not be stored at the Barts Health Modern Records Centre or within Queen Mary.

Destruction of essential documents will require authorisation from the Sponsor.

*<Describe the process for archiving the study documentation at the end of the study, including:*

* *How archiving will be authorised by the sponsor following submission of the end of study report.*
* *Which study documents the sponsor will be responsible for archiving and which study documents the site(s) will be responsible for archiving.*
* *The location and duration of record retention for:*
	+ *Essential documents.*
	+ *The study database.>*

# 27.0 References

*<List all the literature and data that are relevant and that are referenced in the protocol that provide background for the study. Ensure the protocol text contains appropriate cross references to this list.>*

*<Use Harvard Bibliography style – Queen Mary library guidance below:*

*“*When citing a work, the Harvard style requires the name of the author and the year of publication in brackets, whether it is a book (Weaver, 2005), a book chapter (Fairclough and Silk, 2009), a webpage (Department of Health, 2006) or a journal article by Raikkonen et al. (2004). It is common practice to use et al. in the text when there are more than 3 authors.

Give an alphabetical list of all the references used (a bibliography in A/Z order by author).*”, e.g.:*

*<Department of Health (2006). Fluoridation of drinking water [online]. Available at: http://www.dh.gov.uk/assetRoot/04/13/60/15/04136015.pdf [accessed 13/9/2006].>*

*<Fairclough, P. D. and Silk, D. B. A. (2009). Gastrointestinal disease. In: Kumar, P. and Clark, M., (eds.) Clinical medicine. 7th ed. Edinburgh: Elsevier Saunders, pp.241-318.>*

*<Raikkonen, K., Pesonen, A.K., Jarvenpaa, A.L. and Strandberg, T. E. (2004). Sweet babies: chocolate consumption during pregnancy and infant temperament at six months. Early Human Development, 76 (2), 139-145.>*

*<Weaver, R.F. (2005). Molecular biology. 5th ed. Boston: McGraw-Hill.>*

*<NOTE: Before finalising the protocol, please update the table of contents (right-click any heading and select “Update field”, then change to the option of “Update entire table”).>*

**This protocol is based on JRMO Protocol template for MHRA Regulated Studies;**

**SOP 11a Associated Document 2 v8.0 07.04.2022 FINAL**