**Trial Title: insert full title including brief reference to the design, disease or condition being studied, and primary objective**

**Internal Reference Number / Short title:** This should be assigned by the Investigator/department (may be deleted if not required)

**Ethics Ref:** Insert

**IRAS Project ID:** Insert

**EudraCT Number**: Insert

**Date and Version No**: Insert

|  |  |
| --- | --- |
| **Chief Investigator:** | Insert name and contact details, including institutional affiliations |
| **Investigators:** | Insert names of key collaborators, including institutional affiliations |
| **Sponsor:** | Oxford University Hospitals NHS Foundation Trust/University of Oxford Delete as appropriate  (Address of Sponsor) |
| **Funder:** | Insert details of organisation providing funding |
| **Chief Investigator Signature:**  **Statistician Signature:** | The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol |

Please declare any/no potential conflicts of interest

**Confidentiality Statement**

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee and Regulatory Authorities unless authorised to do so.

**Optional page: Protocol signatures continued**

For multi-site trials, the Principal Investigator at each site should sign below to document that the protocol has been read and understood before the protocol is filed in the site ISF. If the same PI covers more than 1 site both sites might appear here, but otherwise there is no requirement for signatures of multiple (or all) PI signatures to appear here together.

Example (amend as appropriate):

**Trial Title:** insert full title

**EudraCT Number**: insert

**Protocol Date and Version No**: insert

**Protocol signature page**

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |
| **Principal Investigator** (Please print name) |  | **Signature** |  | **Site name or ID number** |  | **Date** |

Following any amendments to the protocol, this page must be updated with the new protocol version number and date and re-signed by the site PI.

TABLE OF CONTENTS

To update table of contents, hover cursor over the table and ‘right click’. Choose ‘update field’, then ‘update entire table’.

[1. KEY TRIAL CONTACTS 6](#_Toc531685811)

[2. LAY SUMMARY 7](#_Toc531685812)

[3. SYNOPSIS 7](#_Toc531685813)

[4. ABBREVIATIONS 8](#_Toc531685814)

[5. BACKGROUND AND RATIONALE 9](#_Toc531685815)

[6. OBJECTIVES AND OUTCOME MEASURES 10](#_Toc531685816)

[7. TRIAL DESIGN 11](#_Toc531685817)

[8. PARTICIPANT IDENTIFICATION 11](#_Toc531685818)

[8.1. Trial Participants 11](#_Toc531685819)

[8.2. Inclusion Criteria 12](#_Toc531685820)

[8.3. Exclusion Criteria 12](#_Toc531685821)

[9. TRIAL PROCEDURES 13](#_Toc531685822)

[9.1. Recruitment 13](#_Toc531685823)

[9.2. Screening and Eligibility Assessment 13](#_Toc531685824)

[9.3. Informed Consent 13](#_Toc531685825)

[9.4. Randomisation 14](#_Toc531685826)

[9.5. Blinding and code-breaking 14](#_Toc531685827)

[9.6. Baseline Assessments 15](#_Toc531685828)

[9.7. Subsequent Visits 15](#_Toc531685829)

[9.8. Sample Handling 16](#_Toc531685830)

[9.8.1 Sample handling for trial purposes 16](#_Toc531685831)

[9.8.2 Sample handling for tissue bank 16](#_Toc531685832)

[9.8.3 Sample handling for standard of care 16](#_Toc531685833)

[9.9. Early Discontinuation/Withdrawal of Participants 16](#_Toc531685834)

[9.10. Definition of End of Trial 18](#_Toc531685835)

[10. TRIAL INTERVENTIONS 18](#_Toc531685836)

[10.1. Investigational Medicinal Product(s) (IMP) Description 18](#_Toc531685837)

[10.1.1. Blinding of IMPs 19](#_Toc531685838)

[10.1.2. Storage of IMP 19](#_Toc531685839)

[10.1.3. Compliance with Trial Treatment 19](#_Toc531685840)

[10.1.4. Accountability of the Trial Treatment 19](#_Toc531685841)

[10.1.5. Concomitant Medication 19](#_Toc531685842)

[10.1.6. Post-trial Treatment 19](#_Toc531685843)

[10.2. Other Treatments (non-IMPS) 19](#_Toc531685844)

[10.3. Other Interventions 20](#_Toc531685845)

[11. SAFETY REPORTING 20](#_Toc531685846)

[11.1. Adverse Event Definitions 20](#_Toc531685847)

[11.2. Assessment results outside of normal parameters as AEs and SAEs 22](#_Toc531685848)

[11.3. Assessment of Causality 22](#_Toc531685849)

[11.4. Procedures for Reporting Adverse Events 22](#_Toc531685850)

[11.5. Reporting Procedures for Serious Adverse Events 23](#_Toc531685851)

[11.5.1. Events exempt from immediate reporting as SAEs 23](#_Toc531685852)

[11.5.2. Procedure for immediate reporting of Serious Adverse Events 23](#_Toc531685853)

[11.6. Expectedness 24](#_Toc531685854)

[11.7. SUSAR Reporting 25](#_Toc531685855)

[11.8. Development Safety Update Reports 25](#_Toc531685856)

[12. STATISTICS 25](#_Toc531685857)

[12.1. Statistical Analysis Plan (SAP) 25](#_Toc531685858)

[12.2. Description of Statistical Methods 26](#_Toc531685859)

[12.3. Sample Size Determination 26](#_Toc531685860)

[12.4. Analysis Populations 26](#_Toc531685861)

[12.5. Decision Points 26](#_Toc531685862)

[12.6. Stopping Rules 26](#_Toc531685863)

[12.7. The Level of Statistical Significance 26](#_Toc531685864)

[12.8. Procedure for Accounting for Missing, Unused, and Spurious Data. 26](#_Toc531685865)

[12.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan 27](#_Toc531685866)

[12.10. Health Economics Analysis 27](#_Toc531685867)

[13. DATA MANAGEMENT 27](#_Toc531685868)

[13.1. Source Data 27](#_Toc531685869)

[13.2. Access to Data 28](#_Toc531685870)

[13.3. Data Recording and Record Keeping 28](#_Toc531685871)

[14. QUALITY ASSURANCE PROCEDURES 28](#_Toc531685872)

[14.1. Risk assessment 28](#_Toc531685873)

[14.2. Monitoring 29](#_Toc531685874)

[14.3. Trial committees 29](#_Toc531685875)

[14.3.1 Safety Monitoring Committee 29](#_Toc531685876)

[15. PROTOCOL DEVIATIONS 30](#_Toc531685877)

[16. SERIOUS BREACHES 30](#_Toc531685878)

[17. ETHICAL AND REGULATORY CONSIDERATIONS 30](#_Toc531685879)

[17.1. Declaration of Helsinki 30](#_Toc531685880)

[17.2. Guidelines for Good Clinical Practice 30](#_Toc531685881)

[17.3. Approvals 30](#_Toc531685882)

[17.4. Other Ethical Considerations 31](#_Toc531685883)

[17.5. Reporting 31](#_Toc531685884)

[17.6. Participant Confidentiality 31](#_Toc531685885)

[17.7. Expenses and Benefits 31](#_Toc531685886)

[18. FINANCE AND INSURANCE 31](#_Toc531685887)

[18.1. Funding 31](#_Toc531685888)

[18.2. Insurance 32](#_Toc531685889)

[18.3. Contractual arrangements 32](#_Toc531685890)

[19. PUBLICATION POLICY 32](#_Toc531685891)

[20. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY 32](#_Toc531685892)

[21. ARCHIVING 33](#_Toc531685893)

[22. REFERENCES 33](#_Toc531685894)

[23. APPENDIX A: TRIAL FLOW CHART 34](#_Toc531685895)

[24. APPENDIX B: SCHEDULE OF PROCEDURES 35](#_Toc531685896)

[25. APPENDIX C: SAE REPORTING FLOW CHART 36](#_Toc531685897)

[26. APPENDIX D: AMENDMENT HISTORY 37](#_Toc531685898)

# KEY TRIAL CONTACTS

Insert full details of the key trial contacts including the following; please add/remove headings as necessary.

|  |  |
| --- | --- |
| **Chief Investigator** | Full contact details including phone, email and fax numbers |
| **Sponsor** | Oxford University Hospitals NHS Foundation Trust/University of Oxford Delete as appropriate  Full contact details including phone and email. |
| **Funder(s)** | Names and contact details of all the organisations providing funding and /or support in kind for this trial. |
| **Clinical Trials Unit** | Full contact details including phone, email and fax numbers (If applicable) |
| **Statistician** | Full contact details including phone, email and fax numbers |
| **Committees** | Head of committee  Full contact details including phone, email and fax numbers |

# LAY SUMMARY

It may be useful to include a copy of the lay summary from the IRAS form here. Suggested length, as per IRAS form A6-1 is 300 words.

# SYNOPSIS

It may be useful to include a brief synopsis of the trial for quick reference and/or to use as a standalone document. Complete information and, if required, add additional rows.

|  |  |  |  |
| --- | --- | --- | --- |
| Trial Title | Please ensure this is in accordance with the title page and the IRAS form | | |
| Internal ref. no. (or short title) | Please ensure this is in accordance with the title page and the IRAS form | | |
| Trial registration | Trial identifier, registry name, registration number and date of registration. If not yet registered, name of intended registry. | | |
| Sponsor | Oxford University Hospitals NHS Foundation Trust/University of Oxford Delete as appropriate  (Address of Sponsor) | | |
| Funder | Names and contact details of all the organisations providing funding and /or support in kind for this trial. | | |
| Clinical Phase |  | | |
| Trial Design |  | | |
| Trial Participants |  | | |
| Sample Size |  | | |
| Planned Trial Period | Include both the total length of the project and the duration of an individual participant’s involvement (intervention phase and all follow up – including any long term follow up via medical records and registries etc.). | | |
| Planned Recruitment period | Indicate start and end dates for recruitment | | |
|  | Objectives | Outcome Measures | Timepoint(s) |
| Primary |  |  |  |
| Secondary |  |  |  |
| Intervention(s)   * IMP(s) * nIMP(s) * Other intervention(s) | Provide Formulation, Dose, Route of Administration for each named Investigational Medicinal Product(s)  Where applicable, provide details of non- Investigational Medicinal Product(s) used in the trial.  If there is an additional investigational intervention such as radiotherapy, surgery or device use provide the relevant details here in addition to the IMP details above. | | |
| Comparator | Provide Formulation, Dose, Route of Administration for each named comparator | | |

# ABBREVIATIONS

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

|  |  |
| --- | --- |
| AE | Adverse event |
| AR | Adverse reaction |
| CI | Chief Investigator |
| CRA | Clinical Research Associate (Monitor) |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| CT | Clinical Trials |
| CTA | Clinical Trials Authorisation |
| CTRG | Clinical Trials and Research Governance |
| DMC/DMSC | Data Monitoring Committee / Data Monitoring and Safety Committee |
| DSUR | Development Safety Update Report |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| GTAC | Gene Therapy Advisory Committee |
| HRA | Health Research Authority |
| IB | Investigators Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IMP | Investigational Medicinal Product |
| IRB | Independent Review Board |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| NHS | National Health Service |
| RES | Research Ethics Service |
| OXTREC | Oxford Tropical Research Ethics Committee |
| PI | Principal Investigator |
| PIL | Participant/ Patient Information Leaflet |
| R&D | NHS Trust R&D Department |
| REC | Research Ethics Committee |
| RSI | Reference Safety Information |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SDV | Source Data Verification |
| SMPC | Summary of Medicinal Product Characteristics |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| TMF | Trial Master File |
| TSG | Oxford University Hospitals NHS Foundation Trust / University of Oxford Trials Safety Group |

# BACKGROUND AND RATIONALE

Include the following adding sub headings if needed:

Summarise briefly the main characteristics of the disease being studied and any possible opportunity for better treatment. Include information on the current standard therapy with indication as to why a trial of a new intervention is needed.

Description of the population to be studied.

Name, description and characteristics of the investigational medicinal product(s) (may include mechanism of action). For CTIMPS, indicate if the IMP has or has not a marketing authorisation in the UK /or in other EU member.

Provide a brief summary of findings from non-clinical studies (if relevant) that potentially have clinical significance and from other clinical trials relevant to this trial.

Summary of the known and potential risks and benefits, if any, to human participants with a cross reference to the fuller detail provided in the safety reporting section if required.

Brief description of the rationale for undertaking the trial with justification for the choice of the trial intervention/IMP(s), and the route of administration, dosage, dosage regimen, and treatment period. If applicable, include explanation for the choice of comparators also.

References to literature and data that are relevant to the trial and that provide background for the trial.

For early phase studies, clearly state the number of patients who have already received the IMP(s).

# OBJECTIVES AND OUTCOME MEASURES

There is usually only one primary objective, the rest are secondary objectives.

The wording of the objectives and outcomes provided below should be clear, unambiguous and as specific as possible – the trial will be judged on how, and how well, the objectives were satisfied. The definitions should include specific measurement variables (e.g., systolic blood pressure or Incidence and severity of adverse events or Disability Rating Index etc.,) analysis metrics (e.g., change from baseline measurement or time to event etc.,) and, where relevant, the time point for each outcome measure. Additional more detailed descriptions and definitions of outcomes for all primary and secondary outcomes may also be provided elsewhere in the protocol (e.g., in the statistics section) with a cross reference to the summary information here.

Complete table below with all relevant information.

Please ensure these are in accordance with those stated in the synopsis above and on the IRAS form.

|  |  |  |
| --- | --- | --- |
| **Objectives** | **Outcome Measures** | **Timepoint(s) of evaluation of this outcome measure (if applicable)** |
| **Primary Objective** Example: To compare the effect of treatment A versus treatment B on the levels of protein X in the blood | Describe the outcome measures and how/when they will be measured during the trial.  Outcome measures should reflect the objectives. It is important that only one primary outcome measure is selected as it will be used to decide the overall results or ‘success’ of the trial. The primary outcome measure should be measurable, clinically relevant to participants and widely accepted by the scientific and medical community.  Assessments of outcome measures should be described in detail in section 9.  Example: Concentration of protein X in blood samples from participants on each treatment arm. | Example: Blood sampling at day 0 and day 28 post-treatment |
| **Secondary Objectives** Example: To assess the safety of treatment A in <insert condition/population> | As above |  |
| **Exploratory Objectives** Please add if applicable, otherwise delete this row | As Above |  |

# TRIAL DESIGN

Briefly summarise the overall trial design by type of trial (e.g., double-blind, placebo-controlled, parallel design, open labelled, observational) and framework (e.g., superiority, equivalence, non-inferiority, exploratory). Avoid repetition as full details will be given in later sections.

Briefly summarise the trial setting (e.g., hospitals, GP surgeries, care homes, academic centres etc.) indicating number of trial sites, types of site (e.g., recruiting, providing intervention, continuing care etc.,) and, where there are non-UK sites naming the countries where trial data will be collected.

Give the expected duration of participant involvement providing concise details of the number of visits, including description of the sequence and duration of all trial periods e.g. screening, treatment, and post-treatment follow-up. Include a chart of the flow of the participant through the study (here, or as an appendix), if appropriate.

Briefly describe processes for collecting data, and why this method will be used (e.g. type of equipment, questionnaire, interview schedule, observation schedule). Avoid repetition as full details will be given in later sections.

Include a flowchart for the project as a whole (here, or as an appendix), if appropriate.

# PARTICIPANT IDENTIFICATION

## Trial Participants

Give an overall description of the trial participants.

Example:

Participants with <medical condition> of <*xyz*> severity and <*other symptoms/disease specific criteria*> and/or healthy volunteers aged <insert age>.

## Inclusion Criteria

Example criteria only (amend as appropriate):

* Participant is willing and able to give informed consent for participation in the trial.
* Male or Female, aged 18 years or above.
* Diagnosed with required disease/severity/symptoms, any specific assessment criteria for these, or, if healthy volunteer trial: be in good health.
* (alter as required) Stable dose of current regular medication (specify type if needed) for at least 4 weeks prior to trial entry. If healthy volunteer trial: have had no course of medication, whether prescribed or over-the-counter, in the four weeks before first trial dose and no individual doses in the final two weeks other than mild analgesia, vitamins and mineral supplements or, for females, oral contraceptives.
* Female participants of child bearing potential and male participants whose partner is of child bearing potential must be willing to ensure that they or their partner use effective contraception during the trial and for 3 months thereafter\*.
* Participant has clinically acceptable laboratory and ECG results (specify any other additional assessments) within <insert duration> of enrolment.
* In the Investigator’s opinion, is able and willing to comply with all trial requirements.
* Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the trial.
* Additional trial specific criteria as required.

\* NOTE where the use of effective contraception is a protocol requirement a section on Contraception and Pregnancy should be added to the safety reporting section with corresponding information in the Participant Information Sheet.

## Exclusion Criteria

Example criteria only (amend as appropriate):

The participant may not enter the trial if ANY of the following apply:

* Female participant who is pregnant, lactating or planning pregnancy during the course of the trial.
* Significant renal or hepatic impairment.
* Scheduled elective surgery or other procedures requiring general anaesthesia during the trial.
* Participant with life expectancy of less than 6 months, or is inappropriate for placebo medication.
* Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant’s ability to participate in the trial.
* Participants who have participated in another research trial involving an investigational product in the past 12 weeks.
* Additional trial specific criteria as required.

Note: ensure each criterion is stated as either an inclusion or an exclusion criterion, but not as both. For example, it is not necessary to include ‘Male or female aged under 18’ among the example exclusion criteria above as this is already covered by the inclusion criterion ‘Male or female, aged 18 or above’.

# TRIAL PROCEDURES

Add a schedule of procedures either here or as an appendix.

## Recruitment

Describe how recruitment centres will be selected.

Describe how potential participants will be identified, approached, screened, and recruited (registered and /or randomised).

## Screening and Eligibility Assessment

Specify the maximum duration allowed between screening and registration and/or randomisation (if applicable).

State that protocol waivers are not permitted.

Describe the screening procedures in detail, such as demographics, medical history, concomitant medication, physical examination, ECG, laboratory tests, biopsies and samples, scans.

Specify if rescreening will be permitted and any conditions or restrictions on this.

If any screening procedures (such as blood sampling) require prior informed consent, then this section should be moved to between ‘Informed Consent’ and ‘Randomisation’. If participants are first consented and then registered to the trial for screening purposes before being later randomised to a trial arm, then place the screening and eligibility section between ‘Informed Consent’ and ‘Registration’. If applicable, provide details of how the registration procedure relates to the randomisation procedure.

## Informed Consent

You need to specify who will take Informed Consent, how, and when it will be taken. Informed Consent must be obtained prior to any trial related procedures being undertaken. In the example below participant\* can be substituted by parent/guardian or legally authorised representative, as appropriate, make sure that the term is consistent throughout the document.

For further details on the ethical considerations of including persons who cannot consent for themselves see the guidance on the HRA website.

Example:

The participant\* must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the trial site.

## Randomisation

If the trial is not randomised include a clear statement to that effect and change the section header to Registration or Enrolment as appropriate. Provide details of the trial registration procedure here (e.g., web-based registration system), notification system and instructions for sites if required.

If applicable, describe how randomisation is going to be carried out for the trial. Specify the method for generating the randomisation schedule / allocation sequence (e.g., block allocation, simple computer generated random numbers, stratified randomisation) and include details of how this will be implemented for the trial (sequentially numbered list, sealed envelopes, telephone or web-based randomisation system). Where computerised systems are used, will there be need for a paper-based back up randomisation procedure for use in emergencies?

Specify who will design the randomisation schedule (e.g., statistician, CRO) and who will hold the allocation code (e.g., pharmacy, independent organisation). Provide details on the timing for randomisation in terms of the participant’s study schedule. Will randomisation be done at the same visit as the baseline visit for example, or must participants return for a randomisation visit? Will there be a run in period? State who will receive notification of a new participant/new randomisation, (e.g., trial pharmacist at site, site PI, central trial manager) and provide details as to how this will be communicated to them.

## Blinding and code-breaking

If there is no blinding in the trial, and/or no code breaking procedure, please state that clearly and retain the section header.

In a blinded trial, specify who it is that is blinded to the allocation; e.g., the participant and/or the treating clinician; the central research team; the (independent) outcome assessors. Describe the steps taken to conceal the treatment/intervention allocation from the blinded parties. For example, it may be necessary that the full details of the method of randomisation not appear in the protocol document, that such information be held separately and confidentially.

If the clinical condition of a participant necessitates breaking the allocation code, describe the procedures for this (who will do this, and how). For example, will individual envelopes per participant per period be supplied so that the code may be broken for a single participant without unblinding the whole trial? Or will the pharmacist access the randomisation schedule if required by the Investigator and supply the needed information? Cross reference to the ‘Safety Reporting’ section on SUSAR reporting and address steps to be taken to conceal the wider randomisation schedule after code-breaking for specific participants.

Note “it is the opinion of the EMA GCP Inspectors Working Group (GCP IWG) and the Clinical Trial Facilitation Group (CTFG) that the responsibility to break the treatment code in emergency situations resides solely with the investigator. Consequently the sponsor <or sponsor delegate> can’t require or insist on being involved in the decision to unblind, stall or delay in any way the unblinding of trial subject treatment in emergency situations.”

Please see number 6 on the following link for further information:

<http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000016.jsp&mid=WC0b01ac05800296c5>

If out of hours code-breaking will not be required due to the risk level of the IMP, state this and justify the decision.

## Baseline Assessments

Specify and describe all baseline assessments. They must reflect the objectives and outcome measures.

If there will only be one visit, this section should be renamed ‘Trial Visit’ and full details of this visit be included. The next section ‘Subsequent Visits’ can be marked not applicable and the section header retained.

## Subsequent Visits

Specify when participants will attend for visits/follow-up, and what assessments will be conducted. Specify if they are clinic visits, telephone assessments, or home visits by the trial staff. Add visit numbers and window periods if applicable. **Clearly number these visits**.

For each visit, list appropriate assessment, and consider inclusion of the following, where appropriate. Refer to the trial schedule of procedures (appendix):

* eligibility check
* assessment of outcome measures
* assessments of safety including general (e.g. physical examination), specific safety assessments (e.g. specific laboratory tests according to the applicable product information and/or population) and adverse event collection
* dispensing of trial drug (and of standard of care drugs, if applicable)
* assessment of compliance with trial intervention /trial drugs
* recording of concomitant medications

## Sample Handling

If not detailed previously, describe the samples that will be taken from each participant (e.g. blood, urine, tissue, etc.), the volume of sample, and the frequency of sampling. Clarify in this section whether the samples referred to in the protocol are taken as part of a standard of care pathway with the results accessed by the research team or are research samples for analysis under this protocol and/or ancillary studies or are taken for future research. Consider using separate sections such as:

### 9.8.1 Sample handling for trial purposes (delete subsection header if not required)

### 9.8.2 Sample handling for tissue bank (delete subsection header if not required)

### 9.8.3 Sample handling for standard of care (delete subsection header if not required)

In each applicable subsection provide brief details as to how the sample will be processed and stored once taken; who for example will have access to the samples (i.e. Trial team only for this project, or will it be stored long-term for use in future ethically approved studies), and duration of storage (destroyed following local (NHS) analysis; stored for 12 months following end of the study etc.). If the samples will be transferred to another organisation, state this clearly providing the name of the receiving institution and the country in which that organisation is situated. Provide an overview of the laboratory analyses that will be performed. Ensure that the appropriate information is included in the participant information sheet with corresponding clause(s) on the consent sheet(s). Note, if samples are being biobanked a separate information sheet and consent form for the biobank is required.

If no samples will be taken, please state that clearly and retain the main section header.

## Early Discontinuation/Withdrawal of Participants

Example:

During the course of the trial a participant may choose to withdraw early from the trial treatment at any time. This may happen for a number of reasons, including but not limited to:

* The occurrence of what the participant perceives as an intolerable AE.
* Inability to comply with trial procedures
* Participant decision

Participants may choose to stop treatment and/or study assessments but may remain on study follow-up.

Participants may also withdraw their consent, meaning that they wish towithdraw from the study completely. In the case of withdrawal from both treatment and active follow up consider the following options for a tiered withdrawal from the study. Not all the options may be relevant to your study. The options elected for use in the study must be covered in the participant information sheet.

According to the design of the trial, participants may have the following three options for withdrawal;

1. Participants may withdraw from active follow-up and further communication but allow the trial team to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care; i.e., CT-Scans, blood results and disease progression data etc.
2. Participants can withdraw from the study but permit data and samples obtained up until the point of withdrawal to be retained for use in the study analysis. No further data or samples would be collected after withdrawal.
3. Participants can withdraw completely from the study and withdraw the data and samples collected up until the point of withdrawal. The data and samples already collected would not be used in the final study analysis. (Any limits to this type of withdrawal where, for example analysis of their data or samples has already been integrated into interim results or dose escalation decisions etc. should be explained in the participant information sheet).

In addition, the Investigator may discontinue a participant from the trial treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

Example only (amend as appropriate):

* Pregnancy
* Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
* Significant protocol deviation
* Significant non-compliance with treatment regimen or trial requirements
* An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
* Disease progression which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures

Specify what follow up of participants that have withdrawn from treatment will consist of.

Provide justification for any procedures and observations that will be required following a complete withdrawal (e.g., clinic visits during a safety wash out period) or that will continue to be required of all participants until the end of the trial; for example, would investigators be required to follow up SAEs until resolution or end of trial? Ensure that the appropriate information on these arrangements is included in the participant information sheet.

Wherever possible the data of randomised participants (or registered participants in the case of non-randomised trials) should be analysed. State whether withdrawal from the trial treatment will result in exclusion of the data for that participant from certain trial analyses. (Note that intention-to-treat analyses and analysis of all participants receiving the trial medication (e.g., most safety analyses) may require admission of data to analysis for participants that are withdrawn from treatment)

State whether or not withdrawn participants will be replaced and describe the conditions and limitations for this.

The type of withdrawal and reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

If a participant is withdrawn from treatment due to pregnancy the pregnancy will be followed-up to outcome. See the Safety Reporting section below.

## Definition of End of Trial

The definition of end of trial must be provided. In most cases the end of trial will be the date of the last visit of the last participant. Where long term follow up of participants is planned, the end of trial must include that follow-up period.

Example:

The end of trial is the point at which all the data has been entered and queries resolved.

# ARCHIVING

Describe the arrangements for archiving the study including location and duration of storage. These details should correspond with those provided in the participant information sheet.

Bkm1

# REFERENCES

Insert references used in text (preferably numbered, or in alphabetical order of first author).

Bkm2