**Information on Clinical Trial Protocol Template – please read before starting**

This protocol template has been designed primarily for Clinical Trials which are subject to the Medicines for Human use (Clinical Trials) Regulations 2004, and Amendments. It has been specifically adapted for non-commercially sponsored studies.

An algorithm is available to help you decide whether or not your trial is a Clinical Trial under the regulations. This is usually, but not always, sufficiently helpful, especially regarding studies involving Healthy Volunteers.

See <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/317952/Algothrim.pdf> If you remain unsure about your trial, CTRG or R&D staff will be happy to advise you.

The template is available for use by all investigators who are carrying out clinical trials sponsored by the University of Oxford or Oxford University Hospital (OUH) NHS Foundation Trust if they so wish. However, there is no requirement to do so, provided that an alternative GCP-compliant protocol is used. Other templates are available, for example, the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) protocol guidelines for minimum protocol content at <http://www.spirit-statement.org/spirit-statement/> or guidance available via the HRA protocol development tool at <https://www.hra.nhs.uk/planning-and-improving-research/research-planning/protocol/>

All advisory text and quotations from GCP are highlighted in yellow. These should all be deleted before finalising the document. All sample text is in ‘basic text’ style. This text of course will be altered or deleted as required while you produce the draft. Where advisory text regarding <relevant possible options> is inserted into sample text, delete as needed.

Where a section is not relevant, this should be stated clearly and the section header retained. There may be instances where rearrangement of the subsections within section 9 is appropriate, in order to match with the order of trial processes. Instructional text for deletion/rearrangement is highlighted in blue.

Repetition of information throughout the protocol is not necessary; it may be useful to cross-reference other sections of the protocol to avoid repetition.

Should you require any assistance, contact either CTRG (University) or R&D (NHS) as early as possible in the planning stage:

<https://researchsupport.admin.ox.ac.uk/ctrg>

<https://www.ouh.nhs.uk/researchers/default.aspx>

**Trial Title: Lung CT Scan Analysis of SARS-CoV2 Induced Lung Injury**

**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:** INRT388334

**EudraCT Number**: 2023123456IN

**Date and Version No**: 6th Dec 2023

|  |  |
| --- | --- |
| **Chief Investigator:** | Rajesh Khatwa |
| **Investigators:** | Priyanka, Vivek |
| **Funder:** | SAP CIM |
| **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: Lung CT Scan Analysis of SARS-CoV2 Induced Lung Injury**

**EudraCT Number**: 2023123456IN

**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.

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# KEY TRIAL CONTACTS

|  |  |
| --- | --- |
| **Chief Investigator** | Rajesh Khatwa |
| **Sponsor** | Oxford University Hospitals NHS Foundation Trust/University of Oxford |
| **Funder(s)** | SAP CIM |
| **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

|  |  |  |  |
| --- | --- | --- | --- |
| Trial Title | **Lung CT Scan Analysis of SARS-CoV2 Induced Lung Injury** | | |
| Internal ref. no. (or short title) | **SARS-CoV2** | | |
| Trial registration |  | | |
| Sponsor | Oxford University Hospitals NHS Foundation Trust/University of Oxford | | |
| Funder | SAP CIM | | |
| Clinical Phase |  | | |
| Trial Design |  | | |
| Trial Participants | 50 | | |
| Sample Size | 10 | | |
| Planned Trial Period | 01-01-2023 till 31-12-2023 | | |
| Planned Recruitment period |  | | |
|  | Objectives | Outcome Measures | Timepoint(s) |
| Primary |  |  |  |
| Secondary |  |  |  |
| Intervention(s)   * IMP(s) * nIMP(s) * Other intervention(s) |  | | |
| 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

OBJECTIVES AND OUTCOME MEASURES

|  |  |  |
| --- | --- | --- |
| **Objectives** | **Outcome Measures** | **Timepoint(s) of evaluation of this outcome measure (if applicable)** |
| **Primary Objective** |  |  |
| **Secondary Objectives** |  |  |
| **Exploratory Objectives** |  |  |

# TRIAL DESIGN

# PARTICIPANT IDENTIFICATION

## Trial Participants

Participants with Covid symptoms of high severity and and/or healthy volunteers aged 30-50

## Inclusion Criteria

* 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.
* Blood Sugar level 120mm/dl fasting

## Exclusion Criteria

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.
* BP above 140

# TRIAL PROCEDURES

## Recruitment

## Screening and Eligibility Assessment

## Informed Consent

## Randomisation

## Blinding and code-breaking

## Baseline Assessments

## Subsequent Visits

## Sample Handling

## Early Discontinuation/Withdrawal of Participants

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.

* 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

## Definition of End of Trial

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

# TRIAL INTERVENTIONS

## Investigational Medicinal Product(s) (IMP) Description

### 10.1.1. Blinding of IMPs

If there is no blinding of IMPs in the trial, please state that clearly and retain the section header.

### 10.1.2. Storage of IMP

### 10.1.3. Compliance with Trial Treatment

### 10.1.4. Accountability of the Trial Treatment

### 10.1.5. Concomitant Medication

### 10.1.6. Post-trial Treatment

## Other Treatments (non-IMPS)

## Other Interventions

# SAFETY REPORTING

Please refer to the risk-adapted approach document as some of the following sections may be adapted based on your trial classification

<https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf>

Define the safety reporting window for the trial with a clearly stated starting point (e.g., from time of consent, from first administration of intervention etc.) and clearly stated end point (e.g.30 days after last administration of the IMP, point that the participant completes the trial, end of trial). Note the end point will depend on the nature of the IMP. Advanced Therapy Medicinal Products, for example, have specific requirements over and above those for most trials and the MHRA and EMA websites should be consulted for their evolving guidance on ATMPs.

Confirm the limit of investigator follow up of AEs (e.g., follow up until event resolution or stabilisation, to participant completion of the trial, to trial end etc.). Confirm if the follow up requirement is the same for all AEs or differs for some events (e.g., follow up until event resolution required for related events only).

## Adverse Event Definitions

|  |  |
| --- | --- |
| 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 trial 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 trial 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 * results in persistent or significant disability/incapacity * consists of a congenital anomaly or birth defect\*.   Other ‘important medical events’ may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.  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.  \*NOTE: Pregnancy is not, in itself an SAE. In the event that a participant or his/her partner becomes pregnant whilst taking part in a clinical trial or during a stage where the foetus could have been exposed to the medicinal product (in the case of the active substance or one of its metabolites having a long half-life) the pregnancy should be followed up by the investigator until delivery for congenital abnormality or birth defect, at which point it would fall within the definition of “serious”. |
| Serious Adverse Reaction (SAR) | An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial 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 Reference Safety Information for the medicinal product in question set out:   * in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product * in the case of any other investigational medicinal product, in the approved investigator’s brochure (IB) relating to the trial in question. |

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

\* NOTE if use of effective contraception is a protocol requirement a section on Contraception and Pregnancy should be added to the Safety Reporting Section of the protocol. See the MHRA website for Clinical Trial Facilitation Group’s guidance document on what constitutes effective contraception and pregnancy testing recommendations.

<https://www.gov.uk/government/publications/common-issues-identified-during-clinical-trial-applications/useful-resources>

## Assessment results outside of normal parameters as AEs and SAEs

Confirm which trial assessments are relevant (e.g., only laboratory results or also others such as ECGs, chest x-rays or other scans). Specify any predefined criteria for ‘abnormality’ that signify that an out of range result is to be reported as serious (e.g., Grade ≥3 elevation of ALT or AST lasting 8 days or more). Consider providing tables of adverse event grading criteria for the relevant trial assessments (e.g., a Laboratory AE Grading Chart indicating the limits at which ‘out of range’ laboratory results are Grade 1, Grade 2, Grade 3, and the point they are reportable as SAEs etc.). Where relevant, confirm if the clinical significance of an abnormal result will be determined on a case by case basis by the medically qualified investigator.

## Assessment of Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Example:

**Related**: The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause.

**Not Related**: The adverse event is probably produced by the participant’s clinical state or by other modes of therapy administered to the participant.

Note: where the SAE form used for the trial employs additional options for expressing the probability of the causal relationship (e.g., definitely related, probably related, possibly related, probably not related and definitely not related) the binary definitions above may need to be supplemented and/or modified. If the SAE form includes the option ‘possibly related’ there should be a clear statement of whether events reported as ‘possibly related’ will be managed as not related or as related i.e., may be assessed as a SUSAR.

## Procedures for Reporting Adverse Events

Note it may be possible to adopt a risk adapted approach here; consider whether all non-serious AE’s need to be reported on the trial CRF, taking into account the safety profile of the IMP i.e. if the safety profile of the IMP is very well known then you may not need to report all or any non-serious AEs. If you decide not to report all non-serious AEs then state this and provide justification for not doing so.

If all (or, all related) non-serious AEs are to be reported on the trial CRF, consider adapting text below as appropriate:

<All/all related> AEs occurring during the safety window for the trial as defined above that are observed by the Investigator or reported by the participant, will be reported on the trial CRF, <whether or not attributed to trial medication>.

The following information will be reported on the CRF: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

Non-serious AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed up <either until resolution, or the event is considered stable>.

It will be left to the Investigator’s clinical judgment to decide whether or not an AE is of sufficient severity to require the participant’s removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must <Insert statement of requirements/conditions here (e.g., undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable)>. The statement should be consistent with information specified in section 9.9: Early Discontinuation/Withdrawal of Participants above, and outlined in the Participant Information Sheet.

## Reporting Procedures for Serious Adverse Events

Note it may be possible to adopt a risk adapted approach here taking into account the nature of the disease under study and the safety profile of the IMP; consider whether all adverse events meeting the criteria for seriousness above will be subject to immediate reporting. Note certain foreseeable and predefined SAEs do not need to be reported immediately, these should be clearly specified and the decision(s) justified.

All SAEs <other than those defined in this protocol as not requiring reporting> must be reported on the SAE Reporting Form to the Sponsor or delegate immediately or within 24 hours of Site Study Team becoming aware of the event being defined as serious.

### 11.5.1. Events exempt from immediate reporting as SAEs

If relevant: specify if types of hospitalisation are not classed as SAEs: e.g., Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute a serious adverse event; e.g., Hospitalisation for procedures and treatments specified within the protocol, and standard supportive care for the disease under study are not SAEs, and do not require SAE reporting.

If relevant: specify if deaths due to the disease under study are exempt from reporting as SAEs (with instruction as to where in the trial CRF the information about this is captured).

If relevant: specify if disease progression/ relapse/ recurrence are exempt from reporting as SAEs (with instruction as to where in the trial CRF the information about this is captured).

If this section is not relevant to the trial, please state that clearly and retain the section header.

### 11.5.2. Procedure for immediate reporting of Serious Adverse Events

If the trial is multicentre, or if the single research site and the sponsor delegate office are separate, you need to consider the coordination of SAE reporting for the whole trial and outline the plan for that here.

Example (amend as needed):

* Site study team will complete an SAE report form for all reportable SAEs.
* Where the SAE requires immediate reporting, the SAE report form will be scanned and emailed to <insert the relevant name and contact details for the sponsor delegate i.e., for the coordinating centre/CRO/CTU/CI team> immediately i.e., within 24 hours of site study team becoming aware of the event.
* Site study team will provide additional, missing or follow up information in a timely fashion.

The processes for receipt, acknowledgement, and review of reported SAEs at the sponsor delegate’s office should also be outlined.

Specify who will review the SAE once reported to the sponsor delegate and the timelines for this. (e.g., pharmacovigilance officer, a local safety committee, nominated clinician, the trial DMC/DMSC). Review of SAEs must be timely, taking into account the reporting timeline for a potential SUSAR. The SAE review will include an assessment of expectedness using the Reference Safety Information (RSI) current at the time of the event.

It must be clear if the assessment of expectedness is completed at the reporting site by the local investigator or is made centrally by the sponsor delegate (e.g., PV officer, SAE Panel, Local safety Committee etc.). The design of the trial’s SAE form and any completion guidelines provided to site(s) should reflect this.

If needed please contact your Sponsor (CTRG/R&D reviewer) for further assistance.

***If the trial will be using the University of Oxford /OUH Trial Safety Group, for independent review of SAEs (if this use is required by or agreed with the trial Sponsor) use the following wording (otherwise delete):***

All SAEs <other than those defined in the protocol as not requiring reporting> must be reported on the SAE reporting form to <CTRG/R&D> within 24 hours of the Central Study Team becoming aware of the event. SAEs that are reported late must be accompanied by an explanation for this. <CTRG/R&D> will perform an initial check of the report and request any additional information from the Central Study Team. <CTRG/R&D> will ensure the SAE is reviewed by the TSG Medical Monitor on a weekly basis, (note events reported as related are subject to expedited review procedures). The SAE will also be reviewed at the next quarterly Trial Safety Group meeting. All SAE information must be recorded on an SAE form and scanned and emailed, to the Central study team at <insert appropriate email address>. The central study team are responsible for ensuring that the SAE is reported to <R&D/CTRG> within 24 hours of awareness of an SAE report. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and emailed to <CTRG/R&D>.

Delete CTRG or R&D from instances of <CTRG/R&D> in the paragraph above to retain the Sponsor of the trial. Where Oxford University Hospital NHS Foundation Trust is the Sponsor retain ‘R&D’; for University of Oxford sponsored trials retain ‘CTRG’.

*Note: the template SAE form for use by trials using the University of Oxford /OUH Trial Safety Group, allows for local completion of the assessment of causality AND of expectedness prior to review by the TSG Medical Monitor.*

## Expectedness

Expectedness will be determined according to the approved RSI e.g. in the Investigators’ Brochure/Summary of Product Characteristics. (delete as appropriate, please note some trials may have both)

## SUSAR Reporting

All SUSARs will be reported by the sponsor delegate to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Treatment codes will be un-blinded for specific participants.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

## Development Safety Update Reports

Where appropriate, the IMP manufacturer may be encouraged to submit Development Safety Update Reports (DSURs). In such cases, this must be clearly covered by the relevant agreement.

**Either**

<Name of Company> will submit DSURs once a year throughout the clinical trial, or on request to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

**Or**

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

# STATISTICS

This section should be written by the study statistician.

State whether a Statistical Analysis Plan (SAP) is to be produced separately, and if it is then condense the most relevant information from the SAP sub sections at 12.1 below; otherwise provide full details below of the planned analyses. The sub-headings given below are suggestions. Sub-headings that are not applicable may be deleted entirely.

## Statistical Analysis Plan (SAP)

Example: Either

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan that will be available from the time <that the first participant is recruited>. The SAP will be finalised before <any analysis> takes place.

Or

The plan for the statistical analysis of the trial are outlined below. There is not a separate SAP document in use for the trial.

(delete as appropriate)

## Description of Statistical Methods

Describe the statistical methods to be employed for analysing primary and secondary outcomes. If not provided elsewhere detailed descriptions and definitions of outcomes for all primary and secondary outcomes should be provided here including specific measurement variables, analysis metrics and, where relevant, the time point for each outcome measure. If already described elsewhere, provide cross reference to the relevant protocol section.

## Sample Size Determination

State the estimated number of participants required to demonstrate the study objectives. (Note it is the primary outcome that determines the sample size needed).

Justify choice of sample size, i.e., how was it determined including reflections on (or calculations of) the power of the trial, any statistical assumptions or clinical justifications (where for e.g., the sample size was not arrived at statistically, due to rarity of the disease etc.).

Take into account any potential withdrawals.

## Analysis Populations

Describe the selection of participants to be included in the analyses e.g. all participants as randomised / registered / enrolled (intention to treat); all dosed participants (adverse event analysis); all eligible participants (per protocol analysis); all ‘evaluable’ participants (define ‘evaluability’) etc. Will you include data from participants who have been unblinded?

## Decision Points

Provide details of any interim analysis, including schedule and description of why the interim analyses are to be performed at those time points (as the basis for specified dose escalating decisions or stopping decisions for example). Confirm who will have access to the results and who will make any decisions based on the results.

## Stopping Rules

Describe any formal stopping rules for futility, efficacy or lack of power. Confirm who would make the final decision to terminate the trial.

## The Level of Statistical Significance

State the level of significance to be used.

## Procedure for Accounting for Missing, Unused, and Spurious Data.

Briefly describe the procedure(s) to be used for handling of spurious or missing or unused data (e.g. use of multiple imputation, random effects models or complete case analyses). Describe any possible biases these techniques may introduce. Cross refer to the Data Management Plan (if applicable).

## Procedures for Reporting any Deviation(s) from the Original Statistical Plan

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

## Health Economics Analysis

If a health economics analysis is to be undertaken, include the rationale for inclusion of the economic investigation and means of assessment here. (To be written by the health economist).

# DATA MANAGEMENT

A detailed Data Management Plan should be developed in tandem with the protocol. A template DMP is available from the MRC @ *https://mrc.ukri.org/documents/doc/data-management-plan-template/*

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

Or,

The plan for the data management of the study are outlined below. There is not a separate Data Management document in use for the trial. A justification for not developing a separate detailed DMP must be provided here. This will be considered by your sponsor during the sponsor review process.

(delete as appropriate)

## Source Data

Define what will comprise source documents

Example:

Source documents are where data are first recorded, and from which participants’ CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

## Access to Data

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

## Data Recording and Record Keeping

Describe method(s) of data collection, entry and management, including details of data management tools, for example CRF software, etc.

Example:

All trial data will be entered on <to paper CRFs and/or a <<*quote software and validation procedure*>>. Note that ICH GCP (Section 5.5) requires that electronic data entry systems are validated and that Standard Operating Procedures are maintained.

The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

Describe where, and for how long, data will be retained

If no identifiable, personal data will be retained centrally (i.e. by the sponsoring organisation), but rather this will be held at individual sites **only**, please state this explicitly.

If your study will collect samples and intends to make further use of these beyond the study, please be aware that the consent form will need to be retained for the life of the sample to meet HTA traceability requirements.

If participants are given the option to be approached for future research, please be aware that under GDPR, it is necessary to retain the consent form as the basis for retention of details and future approach. Those contact details should be held securely, separately from the research data, and kept updated.

Ensure compliance with the relevant Sponsor organisation’s data policy. For University of Oxford sponsored trials please refer in particular to the University of Oxford’s

Data Protection Checklist <https://researchsupport.admin.ox.ac.uk/policy/data/checklist>

Practical Considerations <https://researchsupport.admin.ox.ac.uk/policy/data/practical>

Cross refer to the Data Management Plan (if applicable).

# QUALITY ASSURANCE PROCEDURES

## Risk assessment

Provide details of how data monitoring and other quality control measures will be performed in the light of risk adaptive approach based on the formal risk assessment.

Example:

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

## Monitoring

Describe arrangements for GCP monitoring

Example:

Regular monitoring will be performed according to the trial specific Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the trial specific Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. Cross refer to the trial Risk Assessment and Monitoring Plan documents

## Trial committees

Provide a separate subsection below for each committee in place for the trial (e.g., Trial Management Group, Trial Steering Committee (or equivalent), Independent Data (Safety) Monitoring Committee, (or the *University of Oxford /OUH Trial Safety Group* if being used), and describe the role(s), frequency of meetings and composition of the committee here. Where applicable, cross refer to the charter document governing the relevant committee for further details.

### 14.3.1 Safety Monitoring Committee

If a trial specific safety monitoring committee / DSMC is to be used, describe arrangements here.

Or

If you are using the Oxford University Hospitals NHS Foundation Trust / University of Oxford Trials Safety Group to centrally review SAEs then the following text should be adapted as appropriate.

The Oxford University Hospitals NHS Foundation Trust / University of Oxford Trials Safety Group (TSG) will conduct a review of all SAEs for the trial reported during the quarter and cumulatively. The aims of this committee include:

* To pick up any trends, such as increases in un/expected events, and take appropriate action
* To seek additional advice or information from investigators where required
* To evaluate the risk of the trial continuing and take appropriate action where necessary

# PROTOCOL DEVIATIONS

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process or IMP administration) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the trial master file.

A standard operating procedure should be in place describing the procedure for identifying non-compliances, escalation to the central team and assessment of whether a non-compliance /deviation may be a potential Serious Breach

# SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

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

(b) the scientific value of the trial”.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the relevant NHS host organisation within seven calendar days.

# ETHICAL AND REGULATORY CONSIDERATIONS

## Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki. NB. The 2008 Declaration of Helsinki provides detail on what must be included in a protocol: funding, sponsorship, affiliations and potential conflicts of interest, incentives to participate, compensation for harm and post-trial access to drugs and care.

## Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

## Approvals

Consider the following example text:

Following Sponsor approval the protocol, informed consent form, participant information sheet <and any proposed advertising material> will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

## Other Ethical Considerations

Include any other general or trial-specific ethical considerations, e.g. use of placebo, involvement of vulnerable participants

## Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

## Participant Confidentiality

Example:

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), <with the exception of the CRF, where participant initials may be added>.  All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants’ personal data.

For University of Oxford sponsored trials please refer in particular to the University of Oxford’s:  
Data Protection Checklist <https://researchsupport.admin.ox.ac.uk/policy/data/checklist>

Practical Considerations: <https://researchsupport.admin.ox.ac.uk/policy/data/practical>

OUH researchers see <https://www.ouh.nhs.uk/privacy/default.aspx>

## Expenses and Benefits

Detail all intended payments to participants and any other benefits (Declaration of Helsinki requirement).

Example:

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

# FINANCE AND INSURANCE

## Funding

Describe financing arrangements, including all the organisations providing finance and /or support in kind for this trial.

## Insurance

Describe insurance arrangements.

**Either** *for OUH sponsored studies:*NHS bodies are legally liable for the negligent acts and omissions of their employees. If participants are harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the trial team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University NHS Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

**Or** *for University of Oxford sponsored studies:*

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd’s of London). NHS indemnity operates in respect of the clinical treatment that is provided.

The section in red is only to be included if there is a clinical procedure taking place during the trial.

## Contractual arrangements

Add to the template text below to describe what the appropriate arrangements for the study are, e.g. it may require multiple separate site agreement(s), collaboration agreements and/or service level agreement(s).

Appropriate contractual arrangements will be put in place with all third parties.

# PUBLICATION POLICY

The publication policy should cover authorship, acknowledgements, and review procedures for scientific publications. If there is a department or institution policy, or agreement, the protocol can refer to it. Consider describing how trial results may be disseminated to trial participants.

Ensure that the publication policy stated here is consistent with any contract applicable to the trial.

# DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Describe what arrangements the sponsor has in place to protect intellectual property rights.

**Either** *for University of Oxford sponsored studies:*

Ownership of IP generated by employees of the University vests in the University.  The protection and exploitation of any new IP is managed by the University’s technology transfer office, Oxford University Innovations.

***Or*** *for OUH sponsored studies:*

Ownership of IP generated by employees of the OUH vests in OUH.  The protection and exploitation of any new IP is managed by the IP and Research Contracts Team at OUH unless it is generated in collaboration with the University of Oxford in which case this is led by the University’s technology transfer office, Oxford University Innovations.

If the section is not applicable state ‘not applicable’ and retain the section header.

# 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.

# REFERENCES

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

# APPENDIX A: TRIAL FLOW CHART

Optional

# APPENDIX B: SCHEDULE OF PROCEDURES

Alter as required, delete from here if the schedule appears in the procedures section above instead.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Procedures** | **Visits (insert visit numbers as appropriate)** | | | | |
| **Visit timing**  **<e.g. Day 0>** | **<e.g. Day 7>** |  |  |  |
| **Screening** | **Baseline** |  |  |  |
| Informed consent |  |  |  |  |  |
| Demographics |  |  |  |  |  |
| Medical history |  |  |  |  |  |
| Concomitant medications |  |  |  |  |  |
| Physical examination |  |  |  |  |  |
| ECG |  |  |  |  |  |
| Laboratory tests |  |  |  |  |  |
| Eligibility assessment |  |  |  |  |  |
| Randomisation |  |  |  |  |  |
| Dispensing of trial drugs |  |  |  |  |  |
| Compliance |  |  |  |  |  |
| <Assessment 1 (*describe*)> |  |  |  |  |  |
| <Assessment 2 (*describe*)> |  |  |  |  |  |
| <Assessment 3 (*describe*)> |  |  |  |  |  |
| <Assessment 4 (*describe*)> |  |  |  |  |  |
| Adverse event assessments |  |  |  |  |  |

# APPENDIX C: SAE REPORTING FLOW CHART

# APPENDIX D: AMENDMENT HISTORY

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Amendment No.** | **Protocol Version No.** | **Date issued** | **Author(s) of changes** | **Details of Changes made** |
|  |  |  |  |  |

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC / MHRA / HRA submission.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee, HRA (where required) or MHRA.