**Quantitative Protocol Development Tool**

**Guidance for use**

**This template can be used for clinical Studies that do not fall under the definition of a Clinical Study of an Investigational Medicinal Product (CTIMP). If your study is a CTIMP then you can use the HRA template** [Protocol - Health Research Authority (hra.nhs.uk)](https://www.hra.nhs.uk/planning-and-improving-research/research-planning/protocol/)

**The blue text is for information and guidance only. Any sections not relevant please delete.**

***All guidance text in blue should be deleted once completed.***

**FULL/LONG TITLE OF THE STUDY**

**SHORT STUDY TITLE / ACRONYM**

**RESEARCH REFERENCE NUMBERS**

**STUDY REGISTRY NUMBER AND DATE**

**PROTOCOL VERSION NUMBER AND DATE**

**OTHER RESEARCH REFERENCE NUMBERS**

**SPONSOR / CO-SPONSORS / JOINT-SPONSORS**

**FULL/LONG TITLE OF THE STUDY**

*Aim: To identify the study to enable retrieval from literature or internet searches. It should be immediately evident what the study is investigating and on whom to allow rapid judgment of relevance.*

*For intervention or exposure studies a structured title should contain:*

* *Information on participants*
* *Intervention (exposure)*
* *Comparison groups*
* *Outcomes*
* *Phase*
* *Study design*

**SHORT STUDY TITLE / ACRONYM**

*Aim: To provide a summary of the long title. It is usually the title used on information sheets and consent forms for research participants or others giving consent or assent on their behalf.*

*The short title should be:*

* *Sufficiently detailed to make clear to participants what the research is about in simple English*
* *If acronyms are used the full title should explain them. The proposed acronym should not drive the long title*

**PROTOCOL VERSION NUMBER AND DATE**

*Aim: To track changes to the document for study conduct, review, and oversight so it is clear which is the most recent document.*

*Version control:*

* *All draft versions should be numbered 0.1, 0.2 etc.*
* *The final version for submission should be numbered 1.0*
* *The changes made relative to the previous protocol version should be listed after submission*
* *Post approval, any changes to the document should be clearly listed with new version control and a summary of changes. See Appendix 6.*

**RESEARCH REFERENCE NUMBERS**

|  |  |
| --- | --- |
| **IRAS Number:** | The unique identifier generated by IRAS for the project. This will be the primary reference number used by REC, HRA and sites to identify the project and should be quoted in all project related correspondence. |
| **ISRCTN Number / Clinical Studys.gov Number:** | Accepted registers include:   * International Standard Randomised Controlled Trials Number (ISRCTN) Register. This register accepts registration of randomised controlled Trials and any other research study designed to assess the efficacy of health interventions in the human population. * Registration is a formal condition of REC approval for clinical trials only (needs to meet one of the first four categories of IRAS project filter questions). For all other studies check with the Sponsor as to their requirements (a charge may apply). * ClinicalStudys.gov. This is a register of studies in the United States and around the world. |
| **SPONSORS Number:** | Generated by the Sponsor. Enter if applicable |
| **FUNDERS Number:** | Generated by the funder. Enter if applicable |

# SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the national guidelines for the conduct of clinical research.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies and serious breaches of GCP from the study as planned in this protocol will be explained.

|  |  |  |
| --- | --- | --- |
| **For and on behalf of the Study Sponsor:** | | |
| Signature:  ...................................................................................................... |  | Date: ....../....../...... |
| Name (please print):  ...................................................................................................... |  |  |
| Position: ...................................................................................................... |  |  |
| **Chief Investigator:** | | |
| Signature: ...................................................................................................... |  | Date: ....../....../...... |
| Name: (please print):  ...................................................................................................... |  |  |
| **Statistician:** |  |  |
| Signature: ...................................................................................................... |  |  |
| Name: (please print):  ...................................................................................................... |  |  |
| Position: ...................................................................................................... |  |  |

# 

# KEY STUDY CONTACTS

Insert full details of the key study contacts including the following

|  |  |
| --- | --- |
| Chief Investigator | Full contact details including phone, email and fax numbers |
| Study Co-ordinator, if appropriate | Full contact details including phone, email and fax numbers |
| Sponsor | Full contact details including phone, email and fax numbers  The sponsor can be defined as the individual, company, institution, or organisation assuming overall responsibility for the initiation and management of the Study, and is not necessarily the main funder. Sponsorship responsibilities may be shared by joint- or co-sponsors |
| Joint-sponsor(s)/co-sponsor(s), if relevant | Full contact details including phone, email and fax numbers of ALL organisations assuming sponsorship responsibilities as a joint- or co-sponsor/s (If applicable) |
| Funder(s) | Names and contact details of ALL organisations providing funding and/or support in kind for this Study |
| Clinical Trial Unit, if using | Full contact details including phone, email and fax numbers (If applicable) |
| Key Protocol Contributors | Full contact details including phone, email and fax numbers (If applicable) For example: imaging lead, pathology lead. |
| Statistician | Full contact details including phone, email and fax numbers |
| Committees (if applicable) | Full contact details including phone, email and fax numbers |

# i. LIST of CONTENTS

|  |  |
| --- | --- |
| **GENERAL INFORMATION** | **Page No.** |
| TITLE PAGE |  |
| RESEARCH REFERENCE NUMBERS |  |
| SIGNATURE PAGE |  |
| KEY STUDY CONTACTS |  |
| i. LIST of CONTENTS |  |
| ii. LIST OF ABBREVIATIONS |  |
| iii. STUDY SUMMARY |  |
| iv. FUNDING |  |
| v. ROLE OF SPONSOR AND FUNDER |  |
| vi. ROLES & RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES, GROUPS AND INDIVIDUALS |  |
| vii, PROTOCOL CONTRIBUTERS |  |
| viii. KEYWORDS |  |
| ix. STUDY FLOW CHART |  |
| **SECTION** | |
| 1. BACKGROUND |  |
| 2. RATIONALE |  |
| 3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS |  |
| 4. STUDY DESIGN |  |
| 5. STUDY SETTING |  |
| 6. PARTICIPANT ELIGIBILITY CRITERIA |  |
| 7. STUDY INTERVENTION & PROCEDURES |  |
| 8. SAFETY REPORTING |  |
| 9. STATISTICS AND DATA ANALYSIS |  |
| 10 DATA MANAGEMENT |  |
| 11 MONITORING, AUDIT & INSPECTION |  |
| 12 ETHICAL AND REGULATORY CONSIDERATIONS |  |
| 13 DISSEMINATION POLICY |  |
| 14 REFERENCES |  |
| 15. APPENDICIES |  |

**ii. LIST OF ABBREVIATIONS**

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

AE Adverse Event

AR Adverse Reaction

CI Chief Investigator

CRF Case Report Form

CTU Clinical Trials Unit

DMC Data Monitoring Committee

GCP Good Clinical Practice

ICF Informed Consent Form

ICH International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.

ISF Investigator Site File (This forms part of the TMF)

ISRCTN International Standard Randomised Controlled Studys Number

NHS R&D National Health Service Research & Development

PI Principal Investigator

PIC Participant Identification Centre

PIS Participant Information Sheet

QA Quality Assurance

QC Quality Control

RCT Randomised Control Trial

REC Research Ethics Committee

SAE Serious Adverse Event

SAR Serious Adverse Reaction

SDV Source Data Verification

SOP Standard Operating Procedure

SSI Site Specific Information

SUSAR Suspected Unexpected Serious Adverse Reaction

TMF Trial Master File

SMG Study Management Group

SSC Study Steering Committee

# iii. STUDY SUMMARY

It may be useful to include a brief synopsis of the study for quick reference. Complete information and, if required, add additional rows.

|  |  |  |
| --- | --- | --- |
| Study Title |  | |
| Internal ref. no. (or short title) |  | |
| Clinical Phase, if relevant |  | |
| Study Design | Intervention:  Control Group: | |
| Study Participants |  | |
| Planned Sample Size |  | |
| Intervention duration |  | |
| Follow up duration |  | |
| Planned Study Period |  | |
|  | Objectives | Outcome Measures |
| Primary |  |  |
| Secondary |  |  |

# iv. FUNDING AND SUPPORT IN KIND

|  |  |
| --- | --- |
| **FUNDER(S)**  (Names and contact details of ALL organisations providing funding and/or support in kind for this study) | **FINANCIAL AND NON FINANCIALSUPPORT GIVEN** |
|  |  |
|  |  |
|  |  |

**v. ROLE OF STUDY SPONSOR AND FUNDER**

*Aim: To clarify the potential influence of sponsor and funders over the study*

*The sponsor can be defined as the company, institution, or organisation assuming overall responsibility for the initiation and management of the study, and is not necessarily the main funder. Identification of the study sponsor provides transparency and accountability.*

*The protocol should explicitly outline the roles and responsibilities of the sponsor(s) and any funder(s) in study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results. It is also important to state the obligation of the sponsor or funder in terms of the final decision regarding any of these aspects of the study.*

**vi. ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS. If required**

***Study Management Committees (if required – check with Sponsor and undertake a Risk Assessment, if needed)***

*Aim: To outline the various committees or groups involved in Study coordination and conduct.*

*There are three main Study management groups which may be involved in the set up and management of a clinical study, depending on the study size, design, number of sites and documented risk assessment of the study. For each committee/group the protocol should state their roles and responsibilities and degree of independence from Sponsor and Investigators. If not included in the document the protocol should state where the information on the committee/group can be found.*

*Study Steering Committee*

*The SSC must have a majority independent representation, including the*

*Chair, meet regularly and send reports to the sponsor. Lay members or patient representatives are desirable*

*Data Monitoring (and ethics) Committee*

*Independence is a key characteristic of a Data Monitoring Committee where the committee members 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.*

*Study Management Group*

*The Study Management Group should meet regularly to ensure all practical details of the study are progressing well and working well and everyone within the study understands them.*

*For guidance on Study Steering Committees & Data Monitoring Committees follow this link*

[*http://www.hra.nhs.uk/documents/2013/10/data-monitoring-committees-in-clinical-Studys.pdf*](http://www.hra.nhs.uk/documents/2013/10/data-monitoring-committees-in-clinical-trials.pdf)

*For guidance on Data Monitoring Committee Charters follow this link*

[*http://www.ema.europa.eu/docs/en\_GB/document\_library/Scientific\_guideline/2009/09/WC500003635.pdf*](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003635.pdf)

**vii. Protocol contributors**

*Aim: To describe all the contributors to the protocol*

*The protocol should:*

*Describe the input of relevant expertise from individuals for example, statisticians, pathologists and radiation experts.*

*Describe in what aspects of the protocol design have patients, service users, and/or their carers, or members of the public been involved.*

|  |  |
| --- | --- |
| **viii. KEY WORDS:** | Insert relevant key words to describe the study; no more than 6 phrases |

# ix. STUDY FLOW CHART

*Aim: To give readers a schematic overview of the study*

A flow diagram should be included.

Careful consideration must be given by the protocol authors to ensure that the protocol is sensibly structured and ordered to allow users of the document to follow the patient and study pathway accurately and with ease. Flow diagrams are helpful tools to guide users of the protocol through the patient and study pathway, for instance a participant pathway detailing intended fit of the screening and recruitment process with usual practice may be helpful for complex intervention study’s and a schedule of events in table format is also recommended. The schedule of events can be included where most appropriate in the protocol.

*Key information to convey includes the timing of all study activity, starting from initial eligibility screening, each study visit through to study close-out and long term follow-up; time periods during which study interventions will be administered; and the procedures and assessments performed at each visit (with reference to specific data collection forms, if relevant)*

# 1 BACKGROUND

*Aim: To place 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 Intervention for the indication and contain:-*

* *an up-to-date systematic review of relevant studies, new research should build on formal review of prior evidence*
* *a brief description of the proposed study*
* *a description of the population to be studied*
* *if no data is available, include a statement that there is no available clinical research data to date*

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

# 2 RATIONALE

*Aim: To explain why the research questions being asked are important and why closely related questions are not being covered.*

*This should include:*

* *a clear explanation of 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 you think the intervention might be an improvement on those treatments, why the treatment difference is clinically important to patients and if it is realistic. The treatment difference is often referred to as the minimum clinically important difference or the difference we should not want to miss.*
* *this justification is particularly important if the study proposes to use the Intervention:*
  + *in children or in adults unable to consent for themselves*
  + *the indication/ medical condition compromises the participant’s tolerance*
  + *in healthy volunteers*
* *it should also include an explanation and justification as to the choice of control interventions especially if it involves withholding or delaying standard of care*

## **2.1 Assessment and management of risk**

## *Aim: To describe a risk/benefit analysis plus risk management of the intervention involved in the study*

*The following should be described:*

## *the known and potential risks and benefits to human participants*

## *how high the risk is compared to normal standard practice*

* *frequency of risk*
* *how the risk will be minimised/managed*

# 3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

*Aim: To define the primary research question, to address a specific hypothesis and to clearly define the secondary objectives*

*The objectives are generally phrased using neutral wording (e.g., “to compare the effect of intervention A versus intervention B on outcome X”) rather than in terms of a particular direction of effect.*

**3.1** **Primary objective**

*Aim: To define the primary research question, to address a specific hypothesis*

*The protocol should define:*

* *The primary research question e.g. “Does the experimental treatment increase 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 to use in the development of a specific research question are the PICOT criteria:*

*P Population (patients) - What specific patient population are you interested in?*

*I Intervention (for intervention studies only) - What is your investigational intervention?*

*C Comparison group - What is the main alternative to compare with the intervention?*

*O Outcome of interest - What do you intend to accomplish, measure, improve or affect?*

*T Time - What is the appropriate follow-up time to assess outcome*

**3.2 Secondary objectives**

*Aim: To clearly define the secondary objectives*

*The protocol should describe the secondary objectives which:*

* *may or may not be hypothesis-driven*
* *may include secondary outcomes*
* *may include more general non-experimental objectives (e.g., to develop a registry, to collect natural history data)*

**3.3 Outcome measures/endpoints**

*Aim: To define primary and secondary endpoints/outcomes for the study which usually appear in the objectives and sample size calculation or justification.*

*An ideal endpoint/outcome is valid, reproducible, relevant to the target population, and responsive to changes in the health condition being studied. The COMET (Core Outcome Measures in Effectiveness Trials* [*www.comet-initiative.org*](http://www.comet-initiative.org) *) provides a common set of key study outcomes and it is beneficial to ascertain whether there is a core outcome set relevant to the study. This does not preclude inclusion of additional relevant outcomes.*

*The protocol should define:*

* *the endpoint/outcome of main interest (primary outcome 3.4)*
* *the remaining endpoints/outcomes (secondary outcomes 3.5)*
* *whether the endpoint/outcome reflect efficacy (beneficial effect) or harm (adverse effect)*
* *the rationale for the choice of study endpoint/outcome*
* *For each endpoint/outcome, the study protocol should define four components:*
* *the specific measurement variable, which corresponds to the data collected directly from study participants (e.g. all cause mortality);*
* *the participant-level analysis metric, which corresponds to the format of the outcome data that will be used from each Study participant 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*

**3.4 Primary endpoint/outcome**

*Aim: To identify a response variable (primary endpoint/outcome) to answer the primary research question.*

*The primary endpoint/outcome should be a clear, quantitative measure that will be the focus of the primary analysis and will drive the choice of sample size, e.g. “The primary endpoint/outcome is 28 day survival.” It is important to state the time point at which the endpoint/outcome will be measured if it is possible to be measured more than once during the study. The protocol should describe any rules, references or programmes for calculation of derived values and describe what form the outcome will take for analysis (e.g. continuous, categorical, ordinal)*

*Since the sample size must be specified and justified, either based on precision of estimates or power of a test, this almost always relates to the primary endpoint/outcome. It is typical to specify a single primary outcome/endpoint. However, sometimes co-primary outcomes are specified and the sample size must be large enough to detect the smallest expected effect on the various outcomes and the type 1 error must be shared across the outcomes. One exception to this is feasibility studies for which, usually, multiple primary (feasibility) outcomes are specified and the sample size is selected on the basis of acceptable precision of estimates (e.g. recruitment rate, retention, variability of outcome) from which the size of the follow-on study will be planned.*

**3.5 Secondary endpoints/outcomes**

*Aim: To identify a series of well established endpoints of clinical importance that in theory could be the primary endpoint in another study*

*This should be a sequence of concise statements referring to observations that say nothing about the study objectives or analysis. There can be any number of secondary measures, although they should all be relevant to the declared aims of the study.*

**3.6 Exploratory endpoints/outcomes**

*Aim: To identify any other endpoints/outcomes which are not well established.*

**3.7 Table of endpoints/outcomes**

*Aim: To give a clear and concise representation of all end/points/outcomes of the study.*

|  |  |  |
| --- | --- | --- |
| **Objectives** | **Outcome Measures** | **Timepoint(s) of evaluation of this outcome measure (if applicable)** |
| **Primary Objective** | Describe the outcome measures and how/when they will be measured during the study.  Outcome measures should reflect the objectives. It is important that only one outcome measure is selected as it will be used to decide the overall results or ‘success’ of the study. 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 7  Example: Concentration of protein X in blood samples from participants on each treatment | Example: Blood sampling at day 0 and day 28 post-treatment |
| **Secondary Objectives** | As above |  |
| **Tertiary Objectives** Please add if applicable, otherwise delete this row | As Above |  |

# 4 STUDY DESIGN

*Aim: To describe the ideal design for the research question and what the study is designed to show.*

# 5 STUDY SETTING

*Aim: To describe where the study will be run and any site specific requirements*

*The protocol should include:*

* *if it is a multicentre or single centre study*
* *if there are any site specific requirements to run the study*
* *Whether there are different ‘types’ of site (e.g. recruiting, treating, continuing care, etc.) and what the specific requirements are for each*
* *where a list of the participating sites can be found*
* *if applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)*
* *consideration of the participant population and where they are found. What are the usual care pathways? Are patients with the condition of interest found in primary or secondary care? If using secondary care sites, will primary care Participant Identification Centres (PICs) be needed to recruit participants, or are patients found in secondary care?*

*The National Institute for Health Research Clinical Research Network feasibility resources may be helpful in determining the appropriate study setting in terms of site requirements and patient population:*

**6 PARTICIPANT ELIGIBILITY CRITERIA**

*Aim: To define the study population*

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

*The eligibility criteria should be clear so they can be applied consistently through the study and definitions for the timelines and flexibility of each eligibility criterion must be carefully considered to ensure that arbitrary or un-workable definitions are not used. The choice of criteria can affect recruitment and attrition to the Study as well as it generalisability.*

**6.1 Inclusion criteria**

* *participants capable of giving informed consent, or if appropriate, participants having an acceptable individual capable of giving consent on the participant’s behalf (e.g. parent or guardian of a child under 16 years of age)*
* *gender*
* *Age*
* *clinical parameters, compliance with EACH parameter for each participant will need to be clearly documented*

**6.2 Exclusion criteria**

**7 STUDY PROCEDURES**

Add schedule of procedures as an appendix, if appropriate

Aim: To provide a clear and concise timeline of the study visits, enrolment process, interventions, and assessments performed on participants

The protocol should describe what the procedures/assessments are at each visit and where they will be undertaken i.e. hospital/ GP surgeries/ at home and if not at the study site the timelines for notification of these results to the Study team, especially if they are outside of the range etc. A defined, appropriate, visit window should be established e.g. +-3 days.

**7.1 Recruitment**

*Aim: to describe how patients are identified and recruited*

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

*Anonymised information on participants who are not randomised / registered for CONSORT reporting should include:*

* *age,*
* *gender,*
* *ethnicity (if applicable),*
* *whether the patient is registered or not registered,*
* *the reason not eligible for Study participation, or if they are eligible but declined*

**7.1.1 Participant identification**

*The following should be described in the protocol: -*

* *who will identify participants*
* *what resources will be used*
* *will identification involve reviewing or screening the identifiable personal information of patients, service users or any other person(if so will this be undertaken by members of the normal clinical team or will Section 251 –* [*http://www.hra.nhs.uk/about-the-hra/our-committees/section-251/what-is-section-251/*](http://www.hra.nhs.uk/about-the-hra/our-committees/section-251/what-is-section-251/) *- be applied for?)*
* *will any participants be recruited through Participant Identification Centre’s*
* *will any participants be recruited by publicity; posters, leaflets, adverts or websites*
* *details of the sources of identifiable personal information that will be used to identify potential participant. 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 or make the initial approach to patients. If the research proposes to use someone outside the clinical team to identify suitable participants or as first contact with the participant, the reason for this should be explained*
* *The arrangements for referral if the participants are to be identified by a separate research team*
* *If patient or disease registers are used to identify potential participants a brief description of the consent and confidentiality arrangements of the register should be included*

**7.1.2 Screening**

*Aim: To list any screening requirements such as laboratory or diagnostic testing necessary to meet any noted inclusion or exclusion criteria such as: -*

* *ECG*
* *laboratory tests*
* *biopsies and samples*
* *scans*

*Any assessments and or procedures performed as part of routine care which will be used to screen patients for eligibility will require defined timelines (e.g. x-rays within the last 6 months). Specify the maximum duration allowed between screening and recruitment (if applicable).*

*Screen failures i.e. patients who do not meet eligibility criteria at time of screening may be eligible for rescreening participant to acceptable parameters. If this is the case then the process needs to be clearly laid out.*

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

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

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

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

**7.1.3 Payment**

*The protocol should also detail all intended payments to participants e.g. reasonable travel expenses for any visits additional to normal care.*

[*http://www.hra.nhs.uk/documents/2014/05/hra-guidance-payments-incentives-research-v1-0-final-2014-05-21.pdf*](http://www.hra.nhs.uk/documents/2014/05/hra-guidance-payments-incentives-research-v1-0-final-2014-05-21.pdf)

**7.2 Consent – see** [Informing participants and seeking consent - Health Research Authority (hra.nhs.uk)](https://www.hra.nhs.uk/planning-and-improving-research/best-practice/informing-participants-and-seeking-consent/)

**And HRA transparency wording** [Transparency wording for all sponsors - Health Research Authority (hra.nhs.uk)](https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/templates/transparency-wording-for-all-sponsors/)

*The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes the receiving of informed consent of participants at their site. They must 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 is acceptable then details should be provided.*

*Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the Study and are out-with standard routine care at the participating site (including the collection of identifiable participant data unless the Study has prior approval from the Confidentiality Advisory Group (CAG) and the Research Ethics Committee (REC))*

*The right of a participant to refuse participation without giving reasons must be respected.*

*The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment and must be provided with a contact point where he/she may obtain further information about the study. Data and samples collected up to the point of withdrawal can only be used after withdrawal if the participant has consented for this. Any intention to utilise such data should be outlined in the consent literature. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner.*

*The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence*

*Where the participant population is likely to include a significant proportion of participants who cannot read or write, require translators or have cognitive impairment, appropriate alternative methods for supporting the informed consent process should be employed. This may include allowing a witness to sign on a participant’s behalf (in the case of problems with reading or writing), or allowing someone to date the form on behalf of the participant, or providing Participant Information Sheets in other languages or in a format easily understood by the participant population (in the case of minors or cognitive impairment).*

*The protocol should specify what arrangements the sponsor considers to be appropriate at site(s) to support the consent process for these participants. For example, if verbal translation is needed, should this be via a hospital interpreter or a independent interpreter; are telephone translation services acceptable; if translated written material is to be provided to participants, are these to be provided by the sponsor, or translated locally, and what arrangements are in place to confirm the accuracy of the translation, e.g. back translation; if age appropriate information for minors is to be provided, what age ranges is this divided into; if parent/guardian consent for a minor to participate is being sought, what are the acceptable relationships of the guardian to the minor?*

*Note that for studies involving sites in Wales, to comply with the Welsh Language Act 1993, the Participant Information Sheets and Consent forms must be translated into Welsh or provided bilingually where this is requested by a participant at a research site.*

*The protocol should fully describe the process which typically involves:*

* *discussion between the potential participant or his/her legally acceptable representative and an individual knowledgeable about the research about the nature and objectives of the study and possible risks associated with their participation*
* *the 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 regulatory requirements and legal requirements*
* *the 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 particular 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 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.*

**7.3 The randomisation scheme** (if randomised study)

Aim: to provide an overview of the process of how treatments will be allocated between participants in enough detail to theoretically enable a full reproduction of the process.

The protocol should describe:

* The method of randomisation e.g.:
* simple randomisation based solely on a single, constant allocation ratio is known as simple randomisation. Simple randomisation with a 1:1 allocation ratio is analogous to a coin toss. No other method of allocation surpasses the bias prevention and unpredictability of simple randomisation
* restricted randomisation which includes any randomised approach that is not simple randomisation including:-
  + Blocked randomisation
  + Biased coin and urn randomisation
  + Stratified randomisation
* if an un-equal treatment allocation will be used and a justification for its use
* if the allocation ratio will adaptively evolve over the course of the study and a short overview statement to that effect with a reference to the full description in the “Interim Analysis” section
* if 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 to protect the study from selection/allocation bias

Sponsors should provide detailed guidance on the randomisation scheme to individual sites ahead of recruitment.

**7.3.1 Method of implementing the randomisation/allocation sequence**

Aim: to describe how the allocation sequence will be run in the study.

Successful randomisation in practice depends on two interrelated aspects:

1) generation of an unpredictable allocation sequence and

2) concealment of that sequence until assignment irreversibly occurs.

*Protocols should describe details of the randomisation/registration procedure/method. Describe how patients will be allocated to Study treatments/groups.*

*For example,*

* the system to be used (e.g. a web based randomisation/treatment allocation system) and whether delegated to a third party provide,
  + Telephone randomisation/ registration with fax/email confirmation . If this is the case, include the telephone number and the ‘opening hours’ for randomisation/registration.
  + Faxed randomisation with fax/email confirmation. If this is the case, include the fax. number and the ‘opening hours’ for randomisation/ registration.
  + Remote randomisation/ registration process (IXRS). If this is the case, include reference to training manual, location and site staff access to remote system. Give details of the randomisation/ registration procedure.

*State who will receive new patient/randomisation alerts. Describe how these alerts will be received*

***7.4 Blinding (If relevant)***

Aim: to describe the blinding process to avoid bias in detail. If blinding is not to be used then justification should be provided. If a non-randomised study then this section can be deleted.

**7.5 Emergency Unblinding (If relevant)**

Aim: to provide a clear description of the conditions and procedures for unblinding. If the study is not blinded then this section can be deleted.

**7.6 Baseline data**

Aim: To clearly describe the baseline data that needs to be collected. NB only data that forms part of the predefined data set essential for analysis should be collected.

*The following should be considered:*

* *the relevance of each baseline variable. Do not include a variable solely on the grounds that it is always recorded, if there is genuinely no interest in the variable*
* *do any of the procedures need to be undertaken in a certain order or in a certain way – i.e. sitting vs standing, left arm vs right arm, fasted state*
* *are explanations needed? E.g. if 3 measurements are to be taken and averaged that should be explained*
* *for particularly complex procedures or those that differ from routine standard practice, these should be detailed in full. E.g. if a 6 lead ECG is normal routine practice but the study requires a 12 lead EGC this will need to be made clear to avoid potential errors*
* *if there are any translational aspects of the Study for example the collection of blood or tissue samples, this should be detailed in the relevant sections of the protocol (e.g., assessments section, analysis section, storage of samples section etc)*
* *if specialist, non standardised assessments are required, care should be taken to detail exactly what needs to happen during the assessment*
* *It is an offence under the data protection act to process data that is irrelevant or excessive for the purpose for which it was collected. CRFs must therefore collect only the information directly relevant to the objectives and outcome measures detailed in the protocol. Collecting additional data not so specified is not permissible.*

**7.7 Study Intervention and Assessments**

*Aim: To clearly describe the study intervention and all study assessments.*

*The protocol should describe:*

* *The intervention*
* *all study procedures and assessments, including those that are part of routine care*
* *the timing of the assessments should be detailed and broken down into visit numbers as appropriate, for example clearly defined visit window i.e. +-3 days*
* *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*
* *Etc.*
* *when diary cards should be checked*
* *any use of electronic patient reported outcome devices. In general, if third parties are involved in the provision of services related to the assessment or data collection then this should be detailed.*
* *assessment data required at the end of study visit*
* *the methods and timing for assessing, recording and analysing efficacy parameters e.g.:*
* *the values/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 if required*

**7.8 Long term follow-up assessments**

*Aim: To clearly describe the long term follow-up assessments*

*If patients will be monitored after the intervention has finished the protocol should describe:*

* *The frequency of follow-up visits*
* *duration of follow-up period*
* *assessments to be carried out*
* *how the follow up due to the research differs from standard of care*
* *retention strategies*
* *how patients will be identified as ‘lost to follow-up’*
* *measures taken to obtain the information if visits or data collection time-points are missed.*
* *which outcome data will be recorded from protocol non-adherers*

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

**7.9 Qualitative assessments *(If relevant)***

*Aim: To describe any qualitative research that forms part of the study*

*This section should detail any qualitative component to the study and provide a rationale for the timing and tools for assessment, for example measuring the acceptability of the intervention. This section should also detail instructions for the timing and administration of measures and whether the nested qualitative component is optional or not. Timing should include the window around the time point for which each questionnaire/ focus group/interview should be completed, details regarding chasing of questionnaires and how participants with missing baseline measures will be followed-up. NB Any data that contribute to the outcome/ endpoints of the study should ideally be included in the case report form with a signature of the reviewer.*

*Further information on nested studies can be found in the Medical Research Council’s guidance on developing and evaluating complex interventions.*

[*www.sphsu.mrc.ac.uk/Complex\_interventions\_guidance.pdf*](http://www.sphsu.mrc.ac.uk/Complex_interventions_guidance.pdf)

**7.10 Withdrawal criteria**

*Aim: To give a full description of the withdrawal criteria*

*It is always within the remit of the physician responsible for a patient to withdraw a patient from a Study (or certain aspects of the Study) for appropriate medical reasons, be they individual adverse events or new information gained about a treatment.*

*The protocol should therefore:*

* *Describe under what circumstances and how participants will be withdrawn from the Study Intervention.*
* *Attention should be paid to what aspects of the Study the participant is withdrawing/ been withdrawn from. Are there certain aspects of the Study that you wish to continue? For example withdrawal from further treatment, withdrawal from translational aspect or complete withdrawal.*
* *Give details of documentation to be completed on participant withdrawal (including recording reasons for withdrawal and any follow-up information collected with timing)*
* *Whether and how participants are to be replaced*
* *The follow up of participants that have withdrawn from the treatment / Study*
* *State under what circumstances the Study might be prematurely stopped.*

**7.11 Storage and analysis of clinical samples**

***(if details are provided in a laboratory/pathology manual there is no requirement to duplicate information in the protocol) (If relevant)***

Aim: To describe the procedure for dealing with biological samples

The protocol should describe the procedure for dealing with biological samples:

* the criteria for the collection, analysis, storage and destruction of biological samples
* the record keeping requirements for processing, transfer and storage should be clearly outlined
* the arrangements for sample collection
  + sample type(s) e.g. whole blood, plasma, serum, saliva, urine, stool, fresh tissue biopsy, paraffin tissue block
  + 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 must be 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)
* the arrangements for sample analysis
  + whether samples will be tested/analysed locally or sent to a central facility
  + how soon after collection should the samples be analysed or shipped
  + if the samples are to be shipped, include details of the arrangements for this (e.g. on dry ice), indicate whether the sponsor or the site(s) will be responsible for arranging the courier to transport the samples
  + what will happen to the samples after they have been analysed; will they be stored or destroyed (see below)
* the storage arrangements for samples
  + how soon after collection should the samples be put under storage conditions
  + how long will the samples be stored for, and what will be done with the samples after this time (e.g. destruction)
  + where samples will be stored; locally at site(s) or sent to a central storage facility (and shipping arrangements if the latter)
  + whether any samples will be held in long-term storage for future unspecified use, or held in an ethically approved tissue bank (in which case consent and Human Tissue Act need to be considered and addressed)
  + what conditions should the samples be stored under (if samples are to be stored in specialist fridges or freezers e.g. a -80°C freezer, then it is beneficial to specify that samples will be stored at -80°C +/- 10°C (or the tolerance to which you specify), rather than to state -80°C. This will avoid numerous notifications of temperature deviations, when not really required)
* the destruction arrangements for samples
  + when the samples will be destroyed; after analysis, after a set storage period?
  + how the samples should be destroyed
  + how destruction should be recorded
  + that for any specialist sample handling, processing and or shipment, a lab manual will be available and to refer to the manual

The following statement sets out the responsibilities of the Study site in regard to samples and can be included in the protocol if appropriate.

*“It is the responsibility of the Study site to ensure that samples are appropriately labelled in accordance with the Study procedures to comply with the 1998 Data Protection Act. Biological samples collected from participants as part of this Study will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.”*

**7.12 Definition of the end of Study.**

*The definition of the end of the study should be documented in the protocol. In most cases, this will be the date of the last visit of the last participant or the completion of any follow-up monitoring and data collection described in the protocol. For studies involving human tissue, the analysis of the samples should be undertaken as part of the data collection****before****the end of study is declared.*

*Any retained tissue for possible future evaluation after the end of study has been declared should be with the appropriate licence, and should be undertaken as described in the protocol and within the terms of consent from the donors– otherwise a new proposal for REC review would need to be submitted.*

*Any change to this definition after approval has been given for the research should be notified as an amendment to the appropriate review body(ies).*

[Ending your project - Health Research Authority (hra.nhs.uk)](https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/)

# 8 SAFETY REPORTING – for full details on what to report see

# [Safety reporting - Health Research Authority (hra.nhs.uk)](https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/)

**8.1 Definitions**

|  |  |
| --- | --- |
| **Term** | **Definition** |
| **Adverse Event (AE)** | Any untoward medical occurrence in a participant to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention. |
| **Adverse Reaction (AR)** | An untoward and unintended response in a participant to the intervention |
| **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 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, believed with reasonable probability to be due to one of the Study treatments, based on the information provided. |

*Chief Investigators should consider what would be expected AEs/SAEs in the participant cohort and that are likely to be encountered in line with the clinical history or standard of care. The CI should be clear whether or not all AEs need to be recorded and escalated for assessment if they look like they meet the criteria of an SAE or if only certain AEs/SAEs should be recorded, assessed and escalated.*

*For further guidance on what Safety Reporting is needed for the study refer to the Health Research Authority website*

[*Safety reporting - Health Research Authority (hra.nhs.uk)*](https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/)

# 9 STATISTICS AND DATA ANALYSIS

*Where possible the statistician should write this section.*

*The sub-headings given below are suggestions. However, if a Statistical Analysis Plan is to be produced separately, state this here and condense the most relevant information from the sub sections here.*

**9.1 Sample size calculation**

Aim: To define how the planned number of participants was derived

*This section should detail the methods used for the determination of the sample size and a reference to tables or statistical software used to carry out the calculation. Sufficient information should be provided so that the sample size calculation can be reproduced.*

*For Studys that involve a formal sample size calculation, the guiding principle is that the planned sample size should be large enough to have a high probability (power) of detecting a true effect of a given magnitude, should it exist. Sample size calculations are generally based on one primary outcome; 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 outcomes or analyses because study’s are often underpowered to detect harms or subgroup effects.*

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

*Formal sample size calculations typically require the power to be specified and the following values with justification:*

* *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. For example: an absolute difference in response rates between arms of zero.*
* *significance level: what risk is acceptable of concluding the treatment is effective, when in reality the treatment is ineffective.*
* *In Studys with continuous outcomes 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, it should be considered whether the sample size should be increased to account for multiple testing.*
* *Software used for the calculation should be stated.*
* *All information required to recreate the sample size calculation should be provided.*
* *Attrition rates should be estimated and the sample size should be inflated to account for this (e.g. loss during follow up, death, reliability of measurements etc.).*

*NB an appropriate level of statistical advice should be sought to ensure Study validity.*

**9.2 Planned recruitment rate**

*Aim: to estimate the planned recruitment rate*

Realistic estimates of expected accrual rate and duration of participant entry based on estimated sample size should be provided. This section may also include information such as the number of recruiting centres, the size / percentage of the population that is captured by the eligibility criteria, the expected consent rate, and the expected screen failure rate. This information will help sites to determine whether they are likely to be able to recruit their target number of participants.

**9.3 Statistical analysis plan**

Aim: to fully describe the statistical analysis plan

**9.3.1 Summary of baseline data and flow of patients**

* *list variables to be used to assess baseline comparability of the randomised groups including for each factor: a definition, any rules, references or programmes for calculation of derived values, what form it will take for analysis (e.g. continuous, categorical, ordinal) and how it will be reported (e.g. means, standard deviations, medians, proportions). Statistical tests of baseline variables should not be performed in randomised Studys.*

*plans to produce a CONSORT flow diagram (*[*http://www.consort-statement.org/*](http://www.consort-statement.org/)*) . For an observational study a flowchart following the STROBE statement would be more appropriate.*

**9.3.2 Primary outcome analysis**

*Plans for statistical analyses of the primary outcome including:*

* *summary measures to be reported*
* *method of analysis (justified with consideration of form of the data ,* [*assumptions*](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/methods.cfm#assump) *of the method and structure of the data (e.g.* [*unpaired, paired*](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/methods.cfm#paired)*,* [*clustered*](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/methods.cfm#hier)*) etc.)*
* *plans for handling multiple comparisons, missing data, non-compliers, spurious data and withdrawals in analysis*
* *plans for predefined subgroup analyses*
* *statement regarding use of* [*intention to treat*](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/methods.cfm#intent) *(ITT) analysis*
* *description of any non-statistical methods that might be used (e.g. qualitative methods)*

**9.3.3 Secondary outcome analysis**

*Plans for statistical analysis of each secondary outcome. 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.*

**9.4 Subgroup analyses**

*Aim: to describe sub-group analyses*

*Subgroup analyses explore whether estimated treatment effects vary 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.*

**9.5 Adjusted analysis**

*Aim: to describe any adjusted analysis to improve power, or account for a known prognostic variable.*

*The protocol should 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 then 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*

**9.6 Interim analysis and criteria for the premature termination of the Study**

*Aim: to describe any interim analysis and criteria for stopping the Study.*

*The protocol should describe:*

* *any interim analysis plan, even if it is only to be performed at the request of an oversight body (e.g., DMC)*
* *include 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 will see the outcome 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, Study steering committee, or sponsor*
* *the stopping guidelines*
  + *Criteria for stopping for harm are often different from those for benefit and might not employ a formal statistical criterion*
  + *Stopping for futility occurs in instances where, if the Study were to continue, it is unlikely that an important effect would be seen (i.e., 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.*

**9.7 Participant population**

*Aim: to describe the participant populations whose data will be subjected to the Study analysis.*

*Protocols should describe:*

* *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 the Study intervention*
* *All-treated population: Any participant randomised into the Study that received at least one Studyoccurrence of the Study intervention*
* *Protocol-compliant population: Any participant who was randomised and received the protocol required Study intervention and required protocol processing*
* *if the participant is to be included in the analysis will vary by outcome 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.*

*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.*

**9.8 Procedure(s) to account for missing or spurious data**

*Aim: to describe how missing data will be dealt with*

*The protocol should describe:*

* *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 outcome 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.*

**9.9 Other statistical considerations.**

*Aim: to describe any other statistical consideration pertinent to the Study.*

*The protocol should describe:*

* *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 in which case it should be included in this section*

**9.10 Economic evaluation *(If relevant)***

*If economic evaluation is to be undertaken this section should include the rationale for inclusion of the economic investigation and means of assessment.*

*NB it should be written by the health economic investigator*

**10 DATA MANAGEMENT**

## **10.1 Data collection tools and source document identification**

## *Aim: to describe procedures for data collection, recording and handling.*

## ***Source Data***

*ICH 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 Study necessary for the reconstruction and evaluation of the Study. Source data are contained in source documents (original records or certified copies)."*

*The basic concept of source data is that it permits not only reporting and analysis but also verification at various steps in the process for the purposes of confirmation, quality control, audit or inspection. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are:*

* *Accurate*
* *Legible*
* *Contemporaneous*
* *Original*
* *Attributable*
* *Complete*
* *Consistent*
* *Enduring*
* *Available when needed*

***Source Documents***

*ICH 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 Study)."*

***Case report forms***

*A case report form (CRF) is a form on which individual patient data required by the Study protocol are recorded. It may be a printed or electronic document (eCRF). The CRF data is used to perform statistical analysis for the Study. Design of individual CRFs will vary from Study to Study, but it is essential that the design ensures that:*

* *adequate collection of data has been performed*
* *proper audit trails can be kept to demonstrate the validity of the Study (both during and after the Study)*

*only the data required by the protocol are captured in the CRF (using the CRF to capture secondary data not required for the Study may be a criminal beach of the Data Protection Act, makes the CRF unnecessarily complicated, and can make it more difficult to extract the primary data for analysis)*

***CRFs as Source Documents***

*If the protocol allows data to be entered directly onto the case report forms (CRF), the CRF would then be considered a source document. If the CRF is then transmitted to the sponsor, it is necessary for the Study site to retain a copy to ensure that the PI has an independent account from the sponsor as to what has occurred during the Study at his/her site. Additional information can be found in ICH E6, section 6.4.9.*

*Guidance can be found here: <http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/08/WC500095754.pdf>*

*The protocol should:*

* *specify whether the data are from a standardised tool (e.g. McGill pain score) or involves a procedure (in which case full details should be supplied)*
* *specify if a non standard tool is to be used, giving detail on its* [*reliability and validity*](http://www.sgul.ac.uk/depts/chs/chs_research/stat_guide/describe.cfm#valrel)
* *describe the methods used to maximise completeness of data e.g. telephoning participants who have not returned postal questionnaires*
* *specify that the investigator /institutions should keep records of all participating patients (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages*

## **10.2 Data handling and record keeping**

## ***(If this information is included in a data management plan then there is no requirement to duplicate this information in the protocol)***

*GCP requires that sponsors operating such systems validate the system, maintain SOPs for the use of the system, maintain an audit trail of data changes ensuring that there is no deletion of entered data, maintain a security system to protect against unauthorized access, maintain a list of the individuals authorized to make data changes, maintain adequate backup of the data, safeguard the blinding of the Study and archiving of any source data (i.e. hard copy and electronic).*

*If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data. The sponsor should use an unambiguous participant identification code that allows identification of all the data reported for each participant. Sponsors are responsible for ensuring compliance with the requirements outlined above when tasks are subcontracted. There should be no loss of quality when an electronic system is used in place of a paper system.*

*Specific principles can be found here:*

[*http://www.ema.europa.eu/docs/en\_GB/document\_library/Regulatory\_and\_procedural\_guideline/2010/08/WC500095754.pdf*](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/08/WC500095754.pdf)

## *If known, include which database will be used to collect the data. If using paper CRFs, state this and include how the data will be collated for analysis. Data should not be stored on USB sticks or personal computers. Avoid using EXCEL as this is not suitable for research data.*

## **10.3 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- in line with participant consent. Will any external organisations or individuals have access to personal data e.g transcription services/other collaborators?*

10.4 Archiving

*Aim: to describe the process for archiving the Study documentation at the end of the Study*

*The protocol should state:*

* *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*
* *all essential documents will be archived for a minimum of 5 years after completion of Study*
* *destruction of essential documents will require authorisation from the Sponsor* *or essential documents can be destroyed after the specified duration of record retention unless notified otherwise by the Sponsor.’. Check your Sponsor requirements.*

### 11 MONITORING, AUDIT & INSPECTION *(If relevant)*

*Aim: to describe the procedures for monitoring audit and inspection (if this information is supplied as part of a monitoring plan then this section should reference it and not duplicate its detail). Discuss requirements with the Sponsor. You can include the following, however this is based on a risk assessment and should be discussed with the Sponsor*

*The protocol should state:*

* *A Study Monitoring Plan may be developed and agreed, if using, by the Study Management Group (SMG), SSC and CI based on the Study risk assessment which may include on site monitoring. This will be dependent on a documented risk assessment of the Study.*
* *The procedures and anticipated frequency for monitoring*
* *If monitoring procedures are detailed elsewhere (e.g., monitoring manual), where the full details can be obtained*
* *The degree of independence from the Study investigators and sponsor of the monitoring personnel*
* *The processes reviewed can relate to participant enrolment, consent, eligibility, and allocation to Study groups; adherence to Study interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection*
* *Monitoring can be done by exploring the Study dataset or performing site visits*
* *Any obligations that will be expected of sites to assist the sponsor in monitoring the Study. These may include hosting site visits, providing information for remote monitoring, or putting procedures in place to monitor the Study internally*
* *Monitoring might be initially conducted across all sites, and subsequently conducted using a risk based approach that focuses, for example, on sites that have the highest enrolment rates, large numbers of withdrawals, or atypical (low or high) numbers of reported adverse events.*

# 12 ETHICAL AND REGULATORY CONSIDERATIONS

**12.1 Research Ethics Committee (REC) review& reports**

Aim: to demonstrate that the Study will receive ethical review and approval

The protocol should state that:

* *before the start of the Study, approval will be sought from a REC for the Study protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters*
* *substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the Study (note that amendments may also need to be reviewed and accepted by NHS R&D departments before they can be implemented in practice at sites)*
* *all correspondence with the REC will be retained in the Study Master File/Investigator Site File*
* *Check HRA guidance on* [*Progress reports - Health Research Authority (hra.nhs.uk)*](https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/progress-reports/#:~:text=Research%20in%20receipt%20of%20HRA%20and%20HCRW%20Approval,by%20a%20REC%2C%20progress%20reports%20are%20not%20required.)
* *it is the Chief Investigator’s responsibility to produce the annual reports as required.*
* *the Chief Investigator will notify the REC of the end of the Study*
* *if the Study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination*
* *within one year after the end of the Study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC* [*Ending your project - Health Research Authority (hra.nhs.uk)*](https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/)

**12.2 Peer review**

*Aim: to descibe the peer review process for the Study which should be instigated or approved by the Sponsor*

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

The NIHR CRN provide the following standard for peer review for studies to be included on their portfolio:

***High quality peer review***

*Peer review must be independent, expert, and proportionate:*

1. ***Independent****: At least two individual experts should have reviewed the Study. The definition of independent used here is that the reviewers must be external to the investigators’ host institution and not involved in the Study in any way. Reviewers do not need to be anonymous.*
2. ***Expert****: Reviewers should have knowledge of the relevant discipline to consider the clinical and/or service based aspects of the protocol, and/or have the expertise to assess the methodological and statistical aspects of the Study.*
3. ***Proportionate****: Peer review should be commensurate with the size and complexity of the Study. Large multicentre studies should have higher level (more reviewers with broader expertise and often independent review committee or board), and potentially international peer review.*

**12.3 Public and Patient Involvement**

Aim: to describe the involvement of Patients and Public in the research

*This section of the protocol should detail which aspects of the research process have actively involved, or will involve, patients, service users, and/or their carers, or members of the public in particular;*

* *Design of the research*
* *Management of the research*
* *Undertaking the research*
* *Analysis of results*
* *Dissemination of findings*

Guidance on involving patients and the public in research can be found on the INVOLVE website. <http://www.invo.org.uk/> also [Improving inclusion of under-served groups in clinical research: Guidance from INCLUDE project (nihr.ac.uk)](https://www.nihr.ac.uk/documents/improving-inclusion-of-under-served-groups-in-clinical-research-guidance-from-include-project/25435)

**12.4 Regulatory Compliance**

Aim: to demonstrate that the Study will comply with appropriate regulations for example

The protocol should state that:

* *Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance. Different arrangements for NHS and non NHS sites are described as* [*relevant*](http://www.hra.nhs.uk/resources/hra-approval-guidance-for-sponsorschief-investigators-working-collaboratively-with-nhs-organisations-in-england/#3)*.*
* *For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as* [*amended*](http://www.hra.nhs.uk/resources/after-you-apply/amendments/)*.*

**12.5 Protocol compliance**

Aim: to demonstrate how protocol compliance will be managed and documented

*Protocol non-compliances are departures from the approved protocol.*

*The protocol should state that:*

* *prospective, planned deviations or waivers to the protocol are not and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the Study protocol*
* *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.*
* *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.*

### 

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

Aim: to demonstrate how serious breaches will be managed

*A “serious breach” is a breach which is likely to effect to a significant degree –*

* 1. *the safety or physical or mental integrity of the participants of the Study; or*
  2. *the scientific value of the Study*

*The protocol should state that:*

* *the sponsor will be notified immediately of any case where the above definition applies or is suspected to apply during the Study conduct phase*
* *the sponsor of a clinical Study will notify the licensing authority in writing of any serious breach of*
  1. *the conditions and principles of GCP in connection with that Study; or*
  2. *the protocol relating to that Study, as amended from time to time, within 7 days of becoming aware of that breach*

**12.7 Data protection and patient confidentiality**

*AIM; To describe how patient confidentiality will be maintained and how the Study is compliant with the requirements of the Data Protection Act 2018*

*The protocol should state that all investigators and Study site staff must comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles.*

*The protocol should describe:*

* *the means whereby personal information is collected, kept secure, and maintained. In general, this involves:*
  + *the creation of coded, depersonalised data where the participant’s identifying information is replaced by an unrelated sequence of characters*
  + *secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media*
  + *limiting access to the minimum number of individuals necessary for quality control, audit, and analysis*
* *how the confidentiality of data will be preserved when the data are transmitted to sponsors and co-investigators*
* *how long the data will be stored for*
* *who is the data custodian. This is usually the Chief Investigator of the study .* [*https://ico.org.uk/for-organisations/guide-to-data-protection/guide-to-the-general-data-protection-regulation-gdpr/key-definitions/controllers-and-processors/*](https://ico.org.uk/for-organisations/guide-to-data-protection/guide-to-the-general-data-protection-regulation-gdpr/key-definitions/controllers-and-processors/)

12.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall Study management

*Aim: to identify and disclose any competing interests that might influence Study design, conduct, or reporting*

*At a minimum, disclosure should reflect:*

* *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 requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company*
* *any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.*

*However the oversight groups should determine what it is appropriate to report.*

*At the time of writing the protocol not all sites/personnel may have been identified. When this is the case then the protocol should state that this information will be collected and where it will be documented.*

12.10 Amendments

Aim: to describe the process for dealing with amendments

Amendments need to be notified to the [national coordinating function of the UK](http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/preparing-amendments/) country where the lead NHS R&D office is based and communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site. Note that some amendments that may be considered to be non-substantial for the purposes of REC still need to be notified to NHS R&D (e.g. a change to the funding arrangements).

The protocol should describe:

* *the process for making amendments*
* *the Sponsor will be responsible for the decision to amend the protocol and for deciding whether an amendment is substantial or non-substantial*
* *how substantive changes will be communicated to relevant stakeholders (e.g., REC, Study registries, R&D, regulatory agencies)*
* *how the amendment history will be tracked to identify the most recent protocol version.*

*Guidance on the categorisation of amendments can be found on the HRA website and in IRAS.* [*http://www.hra.nhs.uk/resources/after-you-apply/amendments/*](http://www.hra.nhs.uk/resources/after-you-apply/amendments/)

*https://www.myresearchproject.org.uk/help/hlpamendments.aspx*

**12.11 Post Study care**

*Aim: to describe what care the sponsor will continue to provide to participants after the Study is completed, including whether funding arrangements are in place.*

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

The protocol should describe any interventions, benefits, or other care that the sponsor will continue to provide to participants after the Study is completed, and provide justification if continued access to the Study treatment(s) will not be funded. See the link for guidance

<https://www.gov.uk/government/publications/guidance-on-attributing-the-costs-of-health-and-social-care-research>

**12.12 Access to the final Study dataset**

*Aim: to describe who will have access to the final dataset*

The protocol should:

* *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 Studys, 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*

### 13 DISSEMINIATION POLICY

### 13.1 Dissemination policy

Aim: to describe the dissemination policy for the Study

It is highly recommended that the Consort Guidelines and checklist are reviewed prior to generating any publications for the Study to ensure they meet the standards required for submission to high quality peer reviewed journals etc. <http://www.consort-statement.org/>

*The protocol should state*

* *who owns the data arising from the Study*
* *that on completion of the Study, the data will be analysed and tabulated and a Final Study Report prepared* [*Ending your project - Health Research Authority (hra.nhs.uk)*](https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/)
* *where the full Study report can be accessed*
* *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 any funding or supporting body needs to be acknowledged within the publications and whether they have review and publication rights of the data from the Study*

*Describe the plans to notify the participants of the outcome of the Study, either by provision of the publication, or via a specifically designed newsletter etc.* [*https://www.hra.nhs.uk/about-us/news-updates/research-ethics-committee-members-help-develop-new-tool-benefit-people-who-participate-research/*](https://www.hra.nhs.uk/about-us/news-updates/research-ethics-committee-members-help-develop-new-tool-benefit-people-who-participate-research/)*.*

* *if it possible for the participant to specifically request results from their PI and when would this information be provided e.g. after the Final Study Report had been compiled or after the results had been published . This should be added to the consent form*
* *whether the Study protocol, full Study report, anonymised participant level dataset, and statistical code for generating the results will be made publicly available; and if so, describe where, the timeframe and any other conditions for access. The CI is responsible for updating all registries.*

**13.2 Authorship eligibility guidelines and any intended use of professional writers**

Aim: to describe who will be granted authorship on the final Study report

The protocol should detail:

* 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 are going to be hired and how their employment and funding will be acknowledged in Study reports

### *14 REFERENCES*

*List the literature and data that are relevant to the Study, and that provide background for the Study. Please ensure the text contains appropriate cross references to this list*

**15. APPENDICES**

**Study management / responsibilities**

(For multi-centre Studies only)

**Data management**

Include who is responsible for DM if any part of the Study coordination is outsourced or centralised. Also include what data management will entail (CRF checking, data queries/clarifications etc and including timelines for each of these tasks).

**Data protection/confidentiality**

*For example, describe**the potential sharing of personal confidential data and sensitive information between participating sites and the Sponsor organisation or with the CRO/CTU acting on their behalf. It should address the difference between data entered into a secure and validated database with access restricted to key study personnel in line with whatever the participants have consented to in the ICF OR, alternatively, the lawful basis for sharing without consent. Data that may be sent directly e.g. via NHSmail should also be handled in accordance with local organisation policies and processes and guidance is available here* [*https://digital.nhs.uk/services/nhsmail/guidance-for-sending-secure-email*](https://digital.nhs.uk/services/nhsmail/guidance-for-sending-secure-email)

**Study documentation and archiving**

Include details here of who will be responsible for archiving the Study data if any part of the Study coordination is outsourced or centralised. Suggested optional text: “Please note, we are not able to archive source data or the ISF for participating sites, however we can arrange for the payment and set-up of a central archiving facility to be used for the Study”. Delete if not applicable.

Source data may be in the participants’ health records and these need to also be retained for the period indicated in section in line with statutory requirements, National Guidance and site policies.

**Appendix – Example Schedule of Procedures -adapt as required**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Procedures** | **Visits (insert visit numbers as appropriate)** | | | | |
| **Screening** | **Baseline** | **Treatment Phase** | | **Follow Up** |
| Informed consent |  |  |  |  |  |
| Demographics |  |  |  |  |  |
| Medical history |  |  |  |  |  |
| Physical examination |  |  |  |  |  |
| Vital signs |  |  |  |  |  |
| Add ALL Protocol Assessments including bloods/urine etc as applicable both Study specific and routine |  |  |  |  |  |
| Concomitant medications |  |  |  |  |  |
| ECG |  |  |  |  |  |
| Laboratory tests |  |  |  |  |  |
| Eligibility assessment |  |  |  |  |  |
| Randomisation |  |  |  |  |  |
| Assessment 1 (describe) |  |  |  |  |  |
| Assessment 2 (describe) |  |  |  |  |  |
| Assessment 3 (describe) |  |  |  |  |  |
| Assessment 4 (describe) |  |  |  |  |  |
| Adverse event assessments |  |  |  |  |  |

**Example - Safety Reporting Flow Chart**

*A 1 page safety reporting flow chart should be generated for all multi-centre and international Studys to confirm the flow and timelines for reporting of relevant safety information between sites, regulatory agencies, the Sponsor and coordinating site.*

*It is entirely possible that this page will be detached from the protocol and used by Study teams as a guide to the safety reporting requirements for the Study, so please try to make this as clear, yet detailed as possible.*

**Appendix – 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.*

*Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.*