Research Protocol Template

<Study Acronym/Short Title>

<Full study title>

<Version number and date>

MAIN SPONSOR: MEaP Academy Community Training and Research Institute (MaCTRI)
FUNDERS: xxx
STUDY COORDINATION CENTRE: MaCTRI
NRES reference: xxx

Protocol authorised by:		
Name & Role	Date	Signature

Study Management Group
Chief Investigator:
Co-investigators:
Statistician:
Study Management:

For general queries, supply of study documentation, and collection of data, please contact:
Study Coordinator:
Address:
Tel:
E-mail:
Fax:
Web address:

Clinical Queries
Clinical queries should be directed to xxx who will direct the query to the appropriate person

Sponsor
MaCTRI is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact:

Brow House
1 Mabfield Road
Manchester
Tel: 0161 666 0572

Funder
[Who is funding the study]

This protocol describes the xxx study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be

conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Contents

1 INTRODUCTION - Text in blue is for guidance only.

1.1 Background

Aim: To place the study in the context of available evidence.

The background should be supported by appropriate references to the published literature 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
- relevant data from preclinical/non-clinical studies

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.

1.2 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.

For interventional studies also include:

1 the currently available treatment(s) and their limitations, why the treatment difference is clinically important to patients and if it is realistic.

2 it should also include an explanation and justification as to the choice of control interventions comparators especially if it involves withholding or delaying standard of care

2 STUDY OBJECTIVES

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.

2.1 Primary Objective

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

The protocol should define:

- the hypothesis which should be stated in quantifiable terms
- the null and the alternative hypotheses

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

2.2 Secondary Objective

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)

2.3 Primary endpoint/outcome

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

The primary endpoint/outcome should be a clear, unarguable, quantitative measure of effect that will be the focus of the primary analysis and will drive the choice of sample size. Less is more e.g. "The primary endpoint/outcome is 28 day survival." It may be pertinent to list the time point at which 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 it will take for analysis (e.g. continuous, categorical, ordinal)

Since there is only one choice of sample size, which may be based on the statistical power for the single primary analysis, there can only be one primary endpoint/outcome. The exception to this is in a study that is comparing a new diagnostic or measurement technique to an existing standard. In which case, it is acceptable to have two co-primary endpoints: the old and the new technique.

2.4 Secondary endpoint/outcome

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 STUDY DESIGN

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

4 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 recruitment centres and individuals who will perform the interventions (e.g., nurses, physiotherapists)
- 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 of Health Research Clinical Research Network feasibility resources may be helpful in determining the appropriate study setting in terms of site requirements and patient population:

- Commercial:
  - http://www.crn.nihr.ac.uk/can-help/life-sciences-industry/feasibility/
  - http://www.crn.nihr.ac.uk/can-help/life-sciences-industry/
  - https://www.submitmystudy.nihr.ac.uk/
- Non-commercial:
  - http://www.crn.nihr.ac.uk/can-help/funders-academics/

5 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. Such definitions can affect eligibility due to the fact that eligibility waivers are usually not permitted by Regulatory Authorities. The choice of criteria can affect recruitment and attrition to the study as well as it generalisability.

5.1 Inclusion Criteria

[Include justifications, if necessary]

- subjects capable of giving informed consent, or if appropriate, subjects having an acceptable individual Icapable of giving consent on the subject's behalf (e.g. parent or guardian of a child under 16 years of age)
- gender
- Age
- clinical parameters

5.2 Exclusion Criteria

[Include justifications, if necessary]

5.3 Withdrawal Criteria

[Describe procedures for stopping early]

6 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.

6.1 Recruitment

Aim: to describe how patients are identified and recruited

6.1.1 Patient 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/ - be applied for?)

- will any participants be recruited through PICs
- 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
- Certain studies, such as cluster studies, incorporate a separate screening process relevant to that study design – in such cases it may be appropriate to collect more detailed information regarding screened participants.
- It should be clear who will confirm eligibility. NB in a CTIMP this must be confirmed by a medical practitioner.

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 subject 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.

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

6.2 Consent

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

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 personal 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.

Where the study allows the inclusion of subjects who lack the capacity to consent for themselves (for example, in cases where the research is related to the disease / illness causing mental incapacity) the full procedure for consent by a legal representative must be included in the protocol, along with appropriate information sheets and consent forms.

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

http://www.hra.nhs.uk/resources/before-you-apply/consent-and-participation/consent-and-participant-information/

6.3 Randomisation

Aim: to provide a full description of the process of how treatments will be allocated between subjects 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.

6.3.1 Method of implementing the 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:

- the system to use be used e.g. a web based randomisation/treatment allocation system
- who will access this at each site
- how the allocation will be documented e.g. will the system provide an immediate allocation with a confirmatory email
- who else will be provided with a copy of the treatment allocation or randomisation number etc.
- how will randomisation codes be accessed out-of-hours or in an emergency

6.4 Blinding

Aim: to describe the blinding process to avoid bias in detail. If blinding is not to be used then justification should be provided.

The protocol should explicitly describe:

- who will be blinded to intervention groups including:
    - study participants
    - care providers
    - outcome assessors

  A full description is essential and ambiguous terminology such as "single blind" or "double blind" should not be used.
- the comparability of blinded interventions e.g. similarities in appearance, use of specific flavours to mask a distinctive taste
- the timing of final unblinding of all study participants (e.g., after the creation of a locked analysis data set)
- any strategies to reduce the potential for unblinding such as prestudy testing of blinding procedures.
- when blinding of study participants and care providers is not possible because of obvious differences between the interventions, blinding of the outcome assessors can often still be implemented. It may also be possible to blind participants or study personnel to the study hypothesis in terms of which intervention is considered active.

6.5 Unblinding

Aim: to provide a clear description of the conditions and procedures for unblinding.

The study code should only be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the patient is receiving before the participant can be treated. Subject always to clinical need, where possible, members of the research team should remain blinded.

The following information should be inserted into the protocol:

- the code breaks for the study are held [please add relevant department] and are the responsibility of [please add personnel]
- in the event a code is required to be unblinded a formal request for unblinding will be made by the Investigator/treating health care professional
- if the person requiring the unblinding is a member of the Investigating team then a request to the holder of the code break envelope/list, or their delegate will be made and the unblinded information obtained
- if the person requiring the unblinding is not the CI/PI then that health care professional will notify the Investigating team that an unblinding is required for a study subject and an assessment to unblind should be made in consultation with the clinical and research teams
- on receipt of the treatment allocation details the CI/PI or treating health care professional will continue to deal with the participant's medical emergency as appropriate
- the CI/PI documents the breaking of the code and the reasons for doing so on the CRF/data collection tool, in the site file and medical notes. It will also be documented at the end of the study in any final study report and/or statistical report

- the CI/Investigating team will notify the Sponsor in writing as soon as possible following the code break detailing the necessity of the code break
- the CI/PI will also notify the relevant authorities.

6.6 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
- 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.

6.7 Study Assessments

Aim: To clearly describe the study assessments.

The protocol should describe:

- 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
- 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:
  - Weight
  - Full blood count
  - Biochemical series
  - Chest X-ray

- Etc.
- assessment data required at the end of study visit

6.8 Long term follow-up assessments

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

If patients will be monitored after the active treatment phase has closed the protocol should describe:

- The frequency of follow-up (including questionnaires)
- 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.

6.9 Qualitative assessments – nested studies

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

6.10 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 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 subjects will be withdrawn from the study
- Give details of documentation to be completed on subject withdrawal (including recording reasons for withdrawal and any follow-up information collected with timing)
- Whether and how subjects are to be replaced
- The follow up of subjects that have withdrawn from the treatment / study
- State under what circumstances the study might be prematurely stopped.

6.11 Storage and analysis of samples

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 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 ADVERSE EVENTS

7.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

1 Results in death
2 Is life-threatening – refers to an event in which the subject 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
3 Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
4 Results in persistent or significant disability or incapacity
5 Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

7.2 Reporting procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

7.2.1 Non serious AEs

All such events, whether expected or not, should be recorded using a file note and stored in the study master file.

7.2.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to <condition>, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:

1 'related', ie resulted from the administration of any of the research procedures; and
2 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Contact details for reporting SAEs
Fax: xxx, attention xxx
Please send SAE forms to: xxx
Tel: xxx (Mon to Fri 09.00 – 17.00)

8 STATISTICS AND DATA ANALYSIS

If applicable, the study statistician should write this section. Remove sections that are not applicable to your study type.

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.

8.1 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 studies 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 studies 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., exploratory nature of pilot studies; pragmatic considerations for studies 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 studies 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.

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

8.2 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.

8.3 Statistical analysis plan

Aim: to fully describe the statistical analysis plan.

8.3.1 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)
- plans to produce a consort flow diagram (http://www.consort-statement.org/)

8.3.2 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 of the method and structure of the data (e.g. unpaired, paired, clustered) etc.)
- plans for handling multiple comparisons, missing data, non-compliers, spurious data and withdrawals in analysis
- plans for predefined subgroup analyses
- statement regarding use of intention to treat (ITT) analysis
- description of any non-statistical methods that might be used (e.g. qualitative methods)

8.3.3 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.

8.4 Subgroup analyses

Aim: to describe sub-group analyses

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

8.5 Adjusted analysis

Aim: to describe any adjusted analysis to account for imbalances between study groups (e.g., chance imbalance across study groups in small studies), 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

8.6 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
- 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.

8.7 Subject population

Aim: to describe the subject populations whose data will be subjected to the study analysis.

Protocols should describe:

- the subject populations whose data will be subjected to the study analysis – both for the primary analysis and any applicable secondary analyses e.g.
- All-randomized population: Any subject randomized into the study, regardless of whether they received study drug
- All-treated population: Any subject randomized into the study that received at least one dose of study drug
- Protocol-compliant population: Any subject who was randomized and received the protocol required study drug exposure and required protocol processing

- if the participants 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.

8.8 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.

8.9 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

8.10 Economic evaluation

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

9 DATA HANDLING

9.1 Data collection tools and source document identification

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

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
- describe the methods used to maximise completeness of data e.g. telephoning subjects 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

9.2 Data handling and record keeping

The protocol should also describe procedures for data handling and:

- describe what software (e.g. Access, MACRO) is to be used for data entry.
    - NB An Excel spreadsheet is far from ideal for the majority of studies
- provide details of the methods to be used to ensure validity and quality of data (e.g. double entry, cross validation etc.) which should be proportionate to the study.
- describe how data will be stored and backed up securely, including any data storage requirements for sites
- if data will be transferred, describe the method of transfer to be used and the security arrangements in place to ensure the security of the data during transfer where data are transferred electronically this must be in accordance with the UK Data Protection Act 1998)
- whether data will be transferred outside of the EEA (note that explicit consent from participants is required if their personal data is to be transferred outside of the EEA where data protection arrangements may not be as robust)
- arrangements to anonymise or pseudonymise the data (if, when, and how this will be done; who will do it)document and detail if there is a disaster recovery plan.
- state who is responsible for data entry and quality
- state who is responsible for data analysis

9.3 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.

9.4 Archiving

Archiving of study documentation will be authorised by the sponsor following submission of the end of study report.

The protocol should include the following details which can be obtained from the current version of SOP 15 Archiving:

    - 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

10 MONITORING, AUDIT & INSPECTION

Aim: to describe the procedures for monitoring audit and inspection

The protocol should state:

- 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.

11 REGULATORY ISSUES

11.1 Ethics Approval

The Chief Investigator has obtained approval from the xxx Research Ethics Committee. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. All correspondence with the REC will be retained in the study master file.

Substantial amendments that require review by REC will not be implemented until the REC and NHS R&D department grants a favourable opinion.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. The Chief Investigator will notify the REC of the end of the study, and 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.

11.2 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:

- **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.
- **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.
- **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.

11.3 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/

11.4 Regulatory Compliance

Aim: to demonstrate that the study will comply with regulations

The protocol should state that:

- before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will apply for NHS permission from the site's Research & Development (R&D) department
- for any amendment that will potentially affect a site's NHS permission, the Chief Investigator/ Principal Investigator or designee will confirm with that site's R&D department that NHS permission is ongoing (note that both substantial amendments, and amendments considered to be non-substantial for the purposes of REC and/or MHRA may still need to be notified to NHS R&D)

For studies *using ionising radiation the protocol should state that:*

- the procedures are compliant with the Ionising Radiation (Medical Exposure) Regulations, and appropriate review by a Medical Physics Expert and Clinical Radiation Expert has been undertaken, and
- Where a study involves the administration of radioactive substances the protocol should clearly identify that a current Administration of Radioactive Substances Advisory Committee (ARSAC) certificate will be required for each site and, where exposures are additional to normal standard of care, a research ARSAC certificate will be required for each site

NB Ionising radiation includes:

  - X-rays, CT scans, DXA scans
  - Radiotherapy (including brachytherapy and radionuclide therapy, using unsealed sources)
  - Radionuclide studies (including nuclear medicine imaging, PET-CT and in vitro measurements)
  - Administration of a radioactive substance

Neither MRI nor ultrasound involve ionising radiation.

There is a legal and ethical need to justify the use of ionising radiation in research protocols. Be aware that the Ionising Radiation (Medical Exposure) Regulations relate to any research exposure, not only to those additional to routine clinical care.

Procedures involving administration of radioactive material to participants, which differ from standard of care, must be covered by an appropriate ARSAC certificate. Procedures might include:

  - Radionucleotide imaging
  - MUGA scans
  - Brachytherapy

ARSAC certificates are specific to the site, procedure and purpose (diagnosis, treatment, or research) of the administration. Under the current ARSAC arrangements, a research ARSAC certificate is only needed at a site where the administration required by a research protocol is additional to that which participants would receive under routine clinical care at that site (routine procedures will be covered by existing diagnostic or treatment ARSAC certificates held by a certificate holder at the site). Currently research ARSAC certificates are study specific, so each site will need to apply for a research ARSAC certificate for each study that involves administration additional to routine clinical care.

Special consideration should be given to potential variation in procedure at sites; what might be routine at one site could be additional to routine care at another site. Also, care should be taken where the protocol gives sites an option on the testing method, for example heart function may be determined either by echocardiogram or MUGA scan. Sites may intend to use echocardiograms, so not apply for a research ARSAC certificate to cover the MUGA scans, but this would leave them in a difficult position if, due to practical reasons, they were unable to use echocardiograms (e.g. equipment failure, scheduling issues) to perform the tests required by the protocol.

All imaging technologies have the potential to uncover previously unknown pathology. You should always consider how likely such a discovery may be, and how best to handle this discovery when developing research protocols that involve any imaging techniques.

11.5 Protocol compliance

Aim: to demonstrate how protocol compliance will be managed

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. Please refer to SOP 11 Protocol Deviations and violations for more information

The protocol should state that:

- 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.

11.5.1 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 –

  - the safety or physical or mental integrity of the subjects of the study; or
  - 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 during the study conduct phase

11.6 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 1998

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

11.7 Conflicts of Interest

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.

11.8 Indemnity

MaCTRI holds insurance that provides cover for harm arising from the design, conduct and management of the research.

Note that if the study involves sites that are not covered by the NHS indemnity scheme (e.g. GP surgeries in primary care) these investigators/collaborators will need to ensure that their activity on the study is covered under their own professional indemnity

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

11.9 Amendments

Aim: to describe the process for dealing with amendments

If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

If applicable, other specialist review bodies (e.g. CAG) need to be notified about substantial amendments in case the amendment affects their opinion of the study.

Amendments also need to be notified to NHS R&D 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 may still need to be notified to NHS R&D (e.g. a change to the funding arrangements). For studies with English sites processed in NIHR CSP the amendment should be submitted in IRAS to the lead CRN, which will determine whether the amendment requires notification to English sites or may be implemented immediately (subject to REC approval were necessary)

The protocol should describe:

- *the* process for making amendments
- who 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. http://www.hra.nhs.uk/resources/after-you-apply/amendments/

11.10 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 studies, only the steering group has access to the full study dataset in order to ensure that the overall results are not disclosed by an individual study site prior to the main publication
- state if the study will allow site investigators to access the full dataset if a formal request describing their plans is approved by the steering group

12 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
- 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
- whether there are any plans to notify the participants of the outcome of the study, either by provision of the publication, or via a specifically designed newsletter etc.
- if it possible for the participant to specifically request results from their PI and when would this information be provided e.g. after the Final Study Report had been compiled or after the results had been published
- 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.

12.1 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:

a) guidelines on authorship on the final study report

b) criteria for individually named authors or group authorship(The International Committee of Medical Journal Editors has defined authorship criteria for manuscripts submitted for publication)

13 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

14 APPENDICES

Appendix 1 - Summary of investigations, treatment and assessments

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				
Dispensing of study drugs				
Compliance				
Assessment 1 (describe)				
Assessment 2 (describe)				
Assessment 3 (describe)				
Assessment 4 (describe)				
Adverse event assessments				
Physician's Withdrawal Checklist				

Appendix 2 - 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.