

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.

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 (entered into the Footer):

- 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

Research reference numbers

| | |
|--------------------------|--|
| IRAS Number | |
| Sponsor reference number | |
| ISRCTN number | |
| REC reference number | |

This protocol has regard for the HRA guidance

Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to adhere to the signed University of Birmingham's Sponsorship CI declaration.

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 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 from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: Date:/...../.....

Name: (please print):.....

Sponsor statement:

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

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Key study contacts

Insert full details (including phone and email numbers, as applicable) of the key study contacts, including the following:

Chief Investigator

Study Co-ordinator

Sponsor

Joint-sponsor(s)/co-sponsor(s)

Funder(s)

Key Protocol Contributors

Committees

Medical Oversight (if applicable)

Study summary

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)

Study Design

Study Participants

Planned Size of recruitment target (if applicable)

Follow up duration (if applicable)
Planned Study Period
Research Question/Aim(s)

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 FINANCIAL SUPPORT GIVEN |
|---|---|
| | |
| | |

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 whether the sponsor(s) or funder(s) controls the final decision regarding any of these aspects of the study.

Roles and responsibilities of study management committees/groups and individuals

Aim: To outline any committees or groups involved in study coordination and conduct.

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.

Patient & Public Involvement Group:

Public involvement plays an important role in study design and planning and can help reduce delays in approvals. Public involvement in study design and study documentation can help with the acceptability of a study to the public which in turn can assist with study set-up and recruitment. Ongoing involvement of the public can help understand blockages to recruitment and the acceptability and relevance of study findings.

For guidance on Patient & Public Involvement follow this link:

<http://www.invo.org.uk/find-out-more/information-for-researchers/>

Protocol contributors

Aim: To describe all the contributors to the protocol.

The protocol should:

- Explicitly outline the roles and responsibilities of the sponsor and any funders in study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.
- It is also important to state whether the sponsor or funder controls the final decision regarding any of these aspects of the study.
- Describe in what aspects of the protocol design have patients, service users, and/or their carers, or members of the public been involved.

KEY WORDS: Insert relevant key words to describe the study; no more than 6 phrases. This may be useful for future use when searching for relevant publications e.g. Medical Subject Headings.

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. A schedule of events can be included as an appendix to the protocol.

For study designs using less complex methods a Gantt chart or timeline of activity outlining the timing of study management is helpful.

Study protocol

Insert title, consistent with the title on the front page

1. Background

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

The background should be supported by appropriate references to published literature on the area of interest:

- A thorough literature review of relevant studies and analysis, 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.

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/aim(s) being addressed are important and why closely related questions are not being covered.

This should include:

- A clear explanation of the research question/aim(s) 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 participants or wider service delivery.
- A contextual framing of the research question/aim(s) in relation to relevant policy and historical and/or literature bases.

3. Theoretical framework

Aim: To describe the theoretical framework for the study.

- A clear explanation of the proposed approach and why it is suitable to address the gaps outlined in the BACKGROUND section.
- Briefly outline a system of concepts, from published literature, that frames your study.
- Can be presented either visually or textually.

4. Research question/aims

Aim: To define the primary research question/aim(s)

The objectives may be phrased using neutral wording (e.g. "to explore renal patients' perceptions of their first dialysis session") rather than in terms of a particular direction of effect.

4.1. Objectives

Aim: To clearly define the study's objectives (there may be more than one).

4.2. Outcome

Aim: To outline potential broad outcomes for the study which will reflect the research question aim(s).

5. Study design and methods of data collection and data analysis

Aim: To describe the study design. To clearly describe the data collection methods and outline the roles involved in data collection. To clearly describe the data analysis methods.

A suitable design should be chosen to reflect the aim(s) of the study and the chosen theoretical framework. A suitable design might include ethnography, interviews, focus groups, documents, and so on.

Study procedures and timelines should be defined, including randomisation and blinding where applicable.

The number of expected participants and justification for participant population should be detailed.

Data collection methods (including identifying source documents) should be described in detail.

- Observation- What will be observed? What resources or equipment will be used if recording observation? Who will be observing?
- In-Depth Interviews- How will the prompt guide or interview schedule be developed? Who is conducting the interviews? By telephone or in person? How are the interviews being recorded?
- Focus Groups-Who is leading the focus group? How are the focus groups being recorded?

Data analysis methods may include content analysis, the constant comparative method, framework analysis, interpretative phenomenological analysis, and so on. The methodology for analysis linked to outcome measures should be described.

The protocol should clearly describe how and by whom data will be (for example)

- Transcribed.
- Coded.
- De-identified.
- Stored/Transferred.
- Accessed.
- Archived.

Any software to be used in assisting the analysis should be specified.

The process for human tissue collection, storage, processing and analysis (to include destruction/storage after use) should be detailed, where applicable.

6. Study setting

Aim: To state where the data will be collected, explain what activities will take place in that site, and justify the choice of site and any special requirements.

The protocol should address:

- Where and how you are accessing your participants?
- How the research setting is appropriate to address the research question/aim(s)?
- If it is a multicentre or single centre study.

- If there are any site specific requirements to run the study.

Outline if there are different 'types' of activity being undertaken at each site (e.g. identifying or recruiting) and what the specific requirements are for each.

7. Participant recruitment

7.1. 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 verifiable inclusion and exclusion criteria. Inclusion criteria should define the population the study is aiming to include.

The choice of criteria can affect recruitment and attrition to the study.

7.1.1. Inclusion criteria

The following are examples:

- Sex.
- Age range.
- Ethnicity.
- Socio economic grouping.
- Clinical condition.
- Location.
- Ability to provide informed consent

7.1.2. Exclusion criteria

These are usually dependant on the inclusion criteria. The following are examples:

- Outside of stated age range.
- Outside of stated location.
- Gender.

7.2. Recruitment target

Aim: To clearly explain and justify the detail of sampling in terms of volume and technique.

7.2.1. Size of recruitment target

Aim: to explain the rationale behind the size of the target recruitment.

It may not always be possible to estimate the size of a target recruitment e.g. if you continue recruiting until you reach saturation. This section should describe and justify how your recruitment strategy answers your research question/aim(s).

7.2.2. Recruitment technique

Aim: To describe the selection of participants.

This section should detail the methods of selection used for example:

- At random, snowball, convenience sampling, purposive sampling?
- Where has the recruitment technique been derived from?
- What is the rationale for this recruitment strategy? The rationale should reflect the methodological and theoretical framework for the study.

7.3. Recruitment

Aim: To describe how participants are identified and recruited.

This section should give details of the participant eligibility screening process for the project including methods of identifying eligible participants.

7.3.1. Participant identification

The following should be described in the protocol (as applicable):

- Who will identify the participants and what method will be used?
- Who will identify participants?
- What resources will be used?
- Will any participants be recruited through Patient Identification Centres (PICs)?
- Will any participants be recruited by publicity; posters, leaflets, adverts or websites?
- Will CRNs be involved, and will it be registered on the NIHR portfolio?
- Details of the sources of identifiable personal information that will be used to identify potential participant. In the case of healthcare research on patients usually 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.

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

For guidance on payments to participants please follow this link:

<http://www.hra.nhs.uk/documents/2014/05/hra-guidance-payments-incentives-research-v1-0-final-2014-05-21.pdf>

7.3.2. Consent

Informed consent must be obtained prior to the participant undergoing any activities that are specifically for the purposes of the study.

The protocol should fully describe the process of gaining informed consent which could involve:

- 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 documents) which must be approved by the REC, 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, unless defined by law. 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

For a very limited range of activities – such as some ethnographic observations – individuals in a research setting may not be deemed to be research “participants” and it may not be possible to gain

consent from each individual observed. In such instances, a full explanation should be given of how the rights and privacy will be protected for those observed or otherwise involved in some way in a research activity for which it is not proposed to gain individual consent.

For further details on the ethical considerations of informed consent for 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/>

The process for withdrawal, including the subsequent impact on data and sample storage should be detailed.

8. Safety reporting

For definitions refer to *Glossary of Terms*.

Aim: To explain how Adverse Events, Adverse Reactions and Serious Adverse Events will be recorded and reported.

The protocol should define and clarify what safety reporting will be undertaken and how this will be recorded.

9. Ethical and regulatory considerations

Aim: To explain how the research question/aim(s) and design/methods fit into the ethical and regulatory framework. A clear explanation of the risk and benefits to the participants should be included as well as addressing any specific needs/considerations of the participants. State how the data collection methods used uphold the dignity of the participants.

The protocol should also include a justification of how the protocol is in line with relevant legislation or requirements to gain approval to conduct the study at the proposed sites.

9.1. Assessment and management of risk

Aim: To describe a risk analysis plus risk management if the researcher were to come into information which had safeguarding implications.

- A clear explanation of any risk/potential risks of the study.
- A risk management plan for dealing with any potential risk/harm to the participant. For example whilst undertaking an interview the researchers obtain information that the participant is suicidal. What mechanisms for safeguarding the participant would be put in place? Who should the information be shared with to mitigate harm to the participant?
- A management plan for dealing with safeguarding issues for potential harm to others. For example if the participant discloses information about intention to harm others. What mechanisms for safeguarding others outside of the research would be put in place? Who should the information be shared with to mitigate harm to others?

9.2. Research Ethics Committee (REC) and other Regulatory review & reports

Aim: to demonstrate that the study will receive ethical review and approval from the necessary regulatory bodies

The protocol should state that:

- Before the start of the study, a favourable opinion will be sought from a REC (researchers should check if they are required to gain a favourable opinion from the UK Health Departments Research Ethics Service NHS REC) or other REC approval) for the study protocol, informed consent forms and other relevant documents e.g. advertisements.

For NHS REC reviewed research

- Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.

- All correspondence with the REC will be retained.
- 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.
- 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.
- 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.

Regulatory Review & Compliance

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.
- 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.

Amendments

Aim: to describe the process for dealing with amendments

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, R&D, regulatory agencies).
- How the amendment history will be tracked to identify the most recent protocol version.

Guidance on the categorisation of amendments for studies involving the NHS can be found on the HRA website. <http://www.hra.nhs.uk/resources/after-you-apply/amendments/>

9.3. Peer review

Aim: to describe the peer review process for the study which should be instigated and/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 National Institute Health Research (NIHR) Clinical Research Network (CRN) provide the following standard for peer review for studies:

High quality peer review

Peer review must be independent, expert, and proportionate:

- a) 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.

- b) 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 qualitative aspects of the study.
- c) 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.

9.4. Patient & Public Involvement

Aim: to describe the involvement of the 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;

- The acceptability of the research
- Design of the research
- Management of the research
- Undertaking the research
- Analysis of results
- Dissemination of findings

Guidance on involving the public in research can be found on the INVOLVE website.

<http://www.invo.org.uk/>

9.5. Protocol compliance

Aim: to demonstrate how protocol compliance will be managed

Protocol deviations, non-compliances, or breaches are departures from the approved protocol.

The protocol should state that:

- 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.

The protocol should detail how the quality of the study will be assured, and what monitoring will take place (as applicable).

The process for reporting suspected Serious Breaches must be detailed.

9.6. 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

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?

9.7. Indemnity

Aim: to fully describe indemnity arrangements for the study

The following areas should be addressed in the protocol:

1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research?
2. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research?
3. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct 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.
4. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?
5. 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)

NB Usually the responsibility for sections 1&2 lie with the sponsor, section 3 with the participating site and section 4 with the sponsor. Section 4 is not mandatory and should be assessed in relation to the inherent risks of the study; however, it may be a condition of REC favourable opinion to have these arrangements in place.

For further current information about insurance at University of Birmingham, please see <https://intranet.birmingham.ac.uk/finance/insurance/Clinical-Trials.aspx>

9.8. End of study and archiving

Clarify the definition of the end of the study and archiving arrangements, including timelines for archiving

9.9. 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.
- If it is envisaged that that dataset will be used for secondary analysis this can only be undertaken with the consent of the participants. All patient documentation should reflect the future use of these data in research.

10. Dissemination policy

10.1. Dissemination policy

Aim: to describe the dissemination policy for the study

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 reviewed 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, presentation etc.
- If it is 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.

10.2. 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, known as the Vancouver Protocol).

11. 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.

12. Appendices

12.1. Appendix 1- Required documentation

List here all the local documentation you require prior to initiating a participating site (e.g. CVs of the research team, Patient Information Sheet (PIS) on headed paper etc.).

12.2. Appendix 2 – Schedule of Procedures

12.3. Appendix 3 – 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.