**Guidance for using the UHBW Protocol Template for Sponsored Studies (Non-CTIMP)**

The accompanying protocol template can be used for UHBW sponsored studies that do not fall under the relevant Medicines and Medical Devices regulations, including trials that may involve an intervention, a data-only study, or feasibility studies. The term “study” is used to capture all other types of research in the guidance below.

The UHBW template is not intended to be used for Clinical Trials of Investigational Medicinal Products (CTIMPs), New Device trials (including use of devices for new purpose) or High Risk trials sponsored by UHBW. An algorithm can be used to help you decide whether or not your study falls under the Clinical Trials Regulations: <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/317952/Algothrim.pdf>

For studies that fall within the scope of the relevant Medicines and Medical Devices regulations please use the Health Research authority (HRA) template. For qualitative research only studies, please also use the HRA templates. Using the HRA templates will make it easier for HRA to review, but not all studies fall neatly into these categories. HRA templates are available at: <https://www.hra.nhs.uk/planning-and-improving-research/>

For complex interventional trials, studies involving children, please contact the Research and Development (R&D) Department ([Research@uhbw.nhs.uk](mailto:Research@uhbw.nhs.uk)) for further advice. Similarly, if you intend any part of your study to take place outside of the UK (including data collection).

**General Advice**

Please use the accompanying “UHBW protocol template” document, which contains section headings and standard wordings. The guidance below should be referred to when completing this. Please also read all relevant UHBW Standard Operating Procedures and Guidance, available on the UHBW website: <https://www.uhbristol.nhs.uk/research-innovation/>

When writing your protocol, we recommend that you follow the order of the section headings provided in the Table of Contents template. However, they can be adapted or marked as not applicable as required. We suggest you put “N/A” against the main heading if not applicable, and delete subsections (for example on sample collection)

UHBW standard protocol wording will be given in the template and must be included in the protocol – **please do not delete the standard wording.** This is the wording taken from UHBW guidance document “GD\_005 Standard\_wording\_for\_non IMP Protocols”.

To help you write your protocol, advice sections and optional text sections have been included as listed below.

**Use of text colours in the guidance document below:**

|  |  |
| --- | --- |
| **Black** **text** | As in the Protocol Template. Standard wording must be included in the protocol, please do not removed. Other sections may be marked as N/A or deleted if not relevant for your study. |
| Purple text | UHBW guidance |
| Blue text | HRA guidance taken from HRA templates |

**General advice for writing your protocol:**

1. Be concise to help other readers understand your project. Consider using flow charts/tables and bullet points wherever possible.
2. Be consistent with terminology e.g. ‘participants’ not ‘patients.
3. All abbreviations should be written in full when used for the first time and added to the Abbreviations List included in the protocol.
4. For UHBW Sponsorship purposes, please observe version control. All draft versions should be numbered 0.1, 0.2 etc.
5. The first draft should be saved as [Study short name/acronym] v 0.1 [Date] DRAFT. The final version for submission should be numbered v 1.0.

Be aware that changes to the protocol during the Sponsorship process may impact on your other study documents. When finalising your protocol ready for REC/HRA submission, please ensure that the contents of the protocol are consistent with the IRAS Form, Patient Information Sheet, Consent Form etc.

**Please note: This template is based on the HRA standard template guidance. The HRA CTIMP Protocol Development Tool order of content and has been adapted to be used for UHBW non-commercial, non-CTIMP, sponsored studies.**

**Graphical user interface, application

Description automatically generated**

Please include other logos as appropriate e.g. Funders, collaborators, study specific logo etc. Ensure that agreement to use the logos has been obtained from the relevant organisation.

# TITLE PAGE

|  |  |
| --- | --- |
| **Full/long title of study** | Should make clear what the study is about and enable easy identification of relevance from literature searches |
| **Short title/study acronym** | Maximum 70 characters to comply with IRAS form.  Should make clear what the study is about in plain English. Any acronyms should be explained in the full title. |
| **Protocol version number /date** | UHBW require first protocol submission to REC/HRA to be v 1.0. |
| **IRAS Number** | To obtain this number, register your project on IRAS via <https://www.myresearchproject.org.uk/> |
| **ISRCTN/Clinicaltrials.gov number** | It is a good practice requirement that all research is registered on a public research register. The R&D department can advise the appropriate register, if required. |
| **Sponsor** | University Hospitals Bristol and Weston NHS Foundation Trust (UHBW). |
| **Sponsor reference number** | This will be allocated by R&D at Sponsorship and will take the format XX/XXXX/XXXX e.g. CH/2022/1000 |
| **Funder name and reference number (if applicable)** | State name of funder and their reference |
| **Chief Investigator** | Chief Investigator Name,  Job title,  Employer,  Employer’s address,  e-mail address |
| **Sponsor Representative** | [Insert RMF name]  Research and Development  University Hospitals Bristol and Weston NHS Foundation Trust  East wing, Ground Floor,  St James Court,  Cannon Street,  Bristol, BS1 3LH  R&DSponsorship@uhbw.nhs.uk |

# PROTOCOL VERSION HISTORY

|  |  |  |  |
| --- | --- | --- | --- |
| **Amendment No.**  State whether Substantial Amendment (SA) or Non-substantial amendment (NSA) | **Version No.** | **Version Date** | **Brief summary of change(s) and reason for update.** |
| Initial Application | 1.0 | [Insert date] | Not applicable. |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

UHBW as Sponsor will advise on the type of amendment upon review

# SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor’s SOPs, and other regulatory requirements.

I (investigator) 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
* that no activity will commence at participating sites until Sponsor green light is confirmed
* that I will make the findings of the study publicly 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): |  |
| ..................................................................................................... |  |
|  |  |
|  |  |
| **Interventional studies only**  **Research and Development representative as Study Sponsor:** |  |
| Signature: | Date: |
| ...................................................................................................... | ....../....../..... |
|  |  |
| Name (please print): |  |
| ..................................................................................................... |  |
|  |  |
| Position |  |
| ..................................................................................................... |

**Management of amendments to the protocol**

* The Sponsor’s signature is required for interventional study protocols only.
* Only major (substantial) amendments require the re-signing of the protocol

**Major amendments**

The Chief Investigator’s and Sponsor signatures (if applicable) are required for major amendments to the protocol.

**Minor amendments:**

No signatures are required for minor amendments, but an e-mail trail of Sponsor and Investigator oversight will be required as evidence in the Trial Master File (TMF).

# KEY CONTACTS

Insert full details of the key study contacts including the following:

|  |  |
| --- | --- |
| **Chief Investigator** | Enter the Chief Investigator’s contact details (correspondence address, email and phone number), including correspondence address and emergency contact details |
| **Study Co-ordinator/Clinical Trials Unit** | Full contact details including phone numbers and email address |
| **Sponsor** | University Hospitals Bristol and Weston NHS Foundation Trust  Full contact details including phone numbers and email address.  The sponsor can be defined as the individual, company, institution, or organisation assuming overall responsibility for the initiation and management of the study, and is not necessarily the main funder. Sponsorship responsibilities may be shared by joint- or co-sponsors |
| **Joint-sponsor(s)/co-sponsor(s)** | Full contact details including phone numbers and email address of ALL organisations assuming sponsorship responsibilities as a joint- or co-sponsor/s (If applicable) |
| **Funder(s)** | Names and contact details of ALL organisations providing funding and/or support in kind for this study |
| **Key Protocol Contributors** | Full contact details including phone numbers and email address (If applicable) |
| **Study Management and Oversight Committees** | Name of each committee  Chair of each committee  Full contact details including phone numbers and email address for the Chair |
| **Statistician** | Full contact details including phone numbers and email address (If applicable). |

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# LAY SUMMARY

Please include a lay summary below. A suggested length is 300-500 words

This should be a brief summary of your research project that is written with members of the public in mind, rather than researchers or professionals. It should be concise, written in plain English, avoiding the use of jargon or formal language and should explain any technical terms that need to be included. It may be helpful for you to approach a local Patient and Public Involvement (PPI) group to read through your summary to ensure that it can be easily understood.

# SYNOPSIS

Please include a brief synopsis of the study in the table below for quick reference. This summary should provide sufficient information for the reviewer to be able to easily identify the aims, objectives and key study methods. If required, please add additional rows.

|  |  |
| --- | --- |
| **KEY STUDY INFORMATION** |  |
| **Study Title** | Full study title |
| **IRAS Number** |  |
| **Study Design/Type** | e.g. Observational, prospective, cohort study or randomised controlled trial etc. |
| **Study Participants** | e.g. patients with the relevant condition [name disease area], healthy volunteers etc. |
| **Planned Sample size** | Total number of planned participants. Also state the numbers of patients in each study arm, if applicable. |
| **Planned Study Period** | Do not insert planned dates.  This section should indicate the length of the study as a whole in months |
| **End of study definition** | e.g. ‘The end of the trial will be after all participants have completed follow-up, all data queries have been resolved and the database has been locked.’ And/or could include final report to funder |
| **Single site or multi-site** | Single-site or multi-site |
| **Research Aim(s)** | See below for guidance |
| **Research objectives** | See below for guidance |
| **Intervention(s) (if applicable)** | See below for guidance |
| **Archiving period** | The R&D department can advise on the duration, if required. |
| **SAMPLES (If applicable)** | Indicate types of samples collected.  List name(s) and address(es) of tissue banks or institutions if the sample storage and/or analysis is external to UHBW. |
| **DATA** | For GDPR, please state who will be the named Data Custodian, the Data controller and Data Processor(s) for your study.  List name(s) and address(es) of institutions if the data storage and/or analysis is external to UHBW. |

# LIST OF ABBREVIATIONS

Some common abbreviations are below. Please delete/add as necessary. Keep in alphabetical order. Within the text of the protocol, define at first use.

|  |  |
| --- | --- |
| **Abbreviation** | **Full text** |
| **CI** | Chief Investigator |
| **CRF** | Case Report Form |
| **GCP** | Good Clinical Practice |
| **GP** | General Practitioner |
| **HRA** | Health Research Authority |
| **ICF** | Informed Consent Form |
| **ISF** | Investigator Site File (This forms part of the TMF) |
| **NHS** | National Health Service |
| **PI** | Principal Investigator |
| **PPI** | Patient and Public Involvement |
| **PIS/PIL** | Participant Information Sheet/Leaflet |
| **RCT** | Randomised Control Trial |
| **REC** | Research Ethics Committee |
| **R&D** | Research and Development |
| **SMG** | Study Management Group |
| **SSC** | Study Steering Committee |
| **SOP** | Standard Operating Procedure |
| **TMF** | Trial Master File |
| **TMG** | Trial Management Group |
| **TSC** | Trial Steering Committee |
| **UHBW** | University Hospitals Bristol and Weston NHS Foundation Trust |

# FUNDING

|  |  |
| --- | --- |
| **Funders**  Names and contacts of all organisations providing funding and /or funding in kind for this study.  Please state the funders reference number if applicable. | **Financial and Non-Financial support given** |
|  |  |
|  |  |

# ROLES AND RESPONSIBILITIES

## Role of sponsor and funder

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

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.

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 usually the main funder for non-commercial studies in the UK. 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.

## Study team

Outline the roles of individuals within the study team: e.g. Chief investigator, study manager, statistician, qualitative researcher, database manager

## Trial/study management committees/groups and individuals

The following advice will depend on whether (or not) your study can be defined as a clinical trial. For the purposes of this template, which excludes CTIMPs, investigational medical devices and complex interventional trials, your study may be a clinical trial if it can be defined as:

* any other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice.

**Roles and responsibilities if your study is a Clinical Trial (not all committees may be required for trials that are feasibility studies)**

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

There are three main trial management groups which may be involved in the set up and management of a clinical trial, depending on the trial size, design, number of sites and documented risk assessment of the trial. 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.

**• Trial Steering Committee**

The TSC must have a majority independent representation, including the Chair, meet regularly and send reports to the sponsor. Lay members or patient representatives are desirable.

**• Data Monitoring (and ethics) Committee**

Independence is a key characteristic of a Data Monitoring Committee where the committee members are completely uninvolved in the running of the trial and who cannot be unfairly influenced (either directly or indirectly) by people, or institutions, involved in the trial.

**• Trial Management Group**

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

For guidance on Trial Steering Committees & Data Monitoring Committees follow this link

<http://www.hra.nhs.uk/documents/2013/10/data-monitoring-committees-in-clinical-trials.pdf>

For guidance on Data Monitoring Committee Charters follow this link

<http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003635.pdf>

**Roles and responsibilities if your study is not defined as a Clinical Trial**

**Aim of this section:** **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.

Groups may include: Study management group; Study Steering Group; PPI Group

## Protocol Contributors

**Aim of this section**: **To describe all the contributors to the protocol.**

The protocol should:

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

Describe the input of relevant expertise from individuals for example statisticians.

# KEY WORDS

Please 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

# BACKGROUND

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

The background should be supported by appropriate references to the published literature on the disease, condition or area of interest and contain:

• a thorough literature review of relevant studies, new research should build on

formal review of prior evidence

• a brief description of the proposed trial/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.

# 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/aims, hypothesis (if applicable) and the justification of the study/trial 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. Replication to check the validity of previous research is justified, but unnecessary duplication is unethical.

**Interventional Studies**

* For interventional studies, this section should include the currently available treatment(s) and their limitations, why you think the intervention might be an improvement on those treatments, why the treatment difference is clinically important to patients and if it is realistic.
* 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.

**Qualitative Studies**

* For qualitative studies, a contextual framing of the research question/aim(s) in relation to relevant policy and historical and/or literature bases may be useful.
* The theoretical framework for the study should be included to give:
  + - A clear explanation of the proposed approach and why it is suitable to address the gaps outlined in the BACKGROUND section.
    - A brief outline a system of concepts, from published literature, that frames the study. This can be presented either visually or textually.

# OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

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

**Interventional trials**

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.

**For non-interventional studies**

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.

The protocol shouldclearly define the study’s objectives. (There may be more than one).

## Primary objective

**Aim: To define the primary research question, to address a specific hypothesis (if applicable)**

* If you are including a hypothesis then the hypothesis should be stated in quantifiable terms; e.g. “the intervention will result in 12 months of improved overall X compared to standard care

## Secondary objective(s)

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)

### Outcome measures/endpoints

For interventional trials this section should define the primary and secondary endpoints/outcomes for the trial which usually appear in the objectives and sample size calculation.

### Primary outcomes

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 trial. 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 trial 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

### Secondary outcomes

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

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

For non-interventional/qualitative studies:

Outline the potential broad outcomes for the study which will reflect the research question aim(s).

# STUDY DESIGN AND SETTING

## Study design

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

This section should be a top-level summary (full details of the study are described later in the protocol). It should include the following information:

* + Study design – Is your study observational, qualitative, parallel group design, randomised, blinded, pragmatic etc.
  + Study framework (usually for interventional studies) -Does it test superiority, non-inferiority, equivalence or is it exploratory to review the feasibility of conducting a full-scale study?
  + Include an description of the expected duration of your study and, if applicable (i) the duration of participant involvement and number/types of visits, and (ii) any follow-up.
  + An overview of the data collection process, (e.g. face-to face or virtual interviews, questionnaires (paper, electronic or both), routine data collection from hospital records etc.) describing the methods with a brief justification of why this method is used.

## Study setting

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

This should be a succinct summary of the study and it should include:

* If it is a single centre or multi-centre study (give initial estimation of number of sites (make clear it is an estimate).
* Where the research activity will take place, e.g. hospitals, GP surgeries, at home, community groups etc.
* 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
* Consideration of the participant population. Where and how you are accessing your participants? 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?

# PARTICIPANT ELIGIBILITY CRITERIA

**AIM: This section should describe and define the study population.**

The choice of criteria can affect recruitment and attrition to the study as well as its generalisability.

This section should set out precise definitions of which participants are eligible for the trial, defining both inclusion and exclusion criteria. Inclusion criteria should define the population the trial is aiming to include and indicate the generalisability of the trial 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 trial 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.

## Inclusion criteria

Examples:

* Participants capable of giving informed consent, or if appropriate, participants having an acceptable individual capable of giving consent on the participant’s behalf (e.g. parent or guardian of a child under 16 years of age).
* Gender (justification must be made if excluding)
* Age range (include upper and lower limits)
* Clinical parameters, compliance with EACH parameter for each participant will need to be clearly documented.

## Exclusion criteria

Examples:

The participant may not be enrolled on the study if any of the following apply:

* Females of childbearing potential who are pregnant, planning pregnancy or breastfeeding.
* Participants unable to give informed consent.
* Other clinical conditions/diseases etc. that would prohibit inclusion in the study.
* Any contraindications to study intervention or procedures
* Co-enrolment (or recent participation) in other trials that may affect the safety of the participant or the integrity of the study data etc.

## Equality, diversity and inclusion considerations

Aim: to ensure that you have considered how to make your study equitable and inclusive, especially participant recruitment, and that this reflects your sample population (if this is covered elsewhere in the protocol please state where). The NIHR have an EDI toolkit which you may find useful:  
<https://www.rdsresources.org.uk/edi-toolkit>

# STUDY PROCEDURES

Aim: To provide a clear and concise timeline of the trial visits, enrolment process, procedures, interventions (if applicable), 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. If not at the trial site, the timelines for notification of these results to the trial team, especially if they are outside of the range etc. A defined, appropriate, visit window should be established e.g. +/-3 days.

Add a schedule of procedures as an appendix, if appropriate.

## Recruitment

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

**For clinical trials**

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

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

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

**For clinical trials and other studies**

* Who will identify the participants and what method will be used?
* Who will identify participants/sample?
* 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?
* 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.

### Participant identification

The following should be described: -

* 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 trials, incorporate a separate screening process relevant to that trial design – in such cases it may be appropriate to collect more detailed information regarding screened participants.
* It should be clear who will confirm eligibility.
* The protocol should also state how the recruitment centres/Patient Identification Centres (PIC) -if applicable, will be identified and selected.

### Screening

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

* ECG
* laboratory tests
* biopsies and samples
* scans

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

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

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

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

* diagnostic procedures undertaken prospectively to confirm the eligibility of potential participants for the trial 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 trial; or
* diagnostic procedures scheduled at formal time-points within the trial 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 trial.

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.

## Payment

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

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

## Informed consent

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes the taking of informed consent of participants at their site. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent is acceptable, then details should be provided.

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

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

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

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

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

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

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

The protocol should fully describe the process which typically involves:

* discussion between the potential participant or his/her legally acceptable representative and an individual knowledgeable about the research about the nature and objectives of the trial 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

General good practice in research (and the basis of legal frameworks relating to both CTIMPs and non-CTIMPs) require that persons incapable of giving legal consent should be given special protection.

A person is assumed to have the mental capacity to make a decision unless it is shown to be absent. Mental capacity is considered to be lacking if, in a specific circumstance, a person is unable to make a decision for him or herself because of impairment or a disturbance in the functioning of their mind or brain. In practice for participants with mental incapacity this means that they should not be included in clinical trials if the same results can be obtained using persons capable of giving consent and should only be included where there are grounds for expecting that their taking part will be of direct benefit to that participant, thereby outweighing the risks. The Mental Capacity Act 2005 does not apply to CTIMPs.

The Clinical Trial Regulations define a child as a person under the age of 16 years of age. The legal framework and ethical considerations for involving young people (between the ages of 16 and 17) in research are set out in the Department of Health Reference Guide to Consent for Examination or Treatment (2009) and should be referred to for any trial including young people (between the ages of 16 and 17). In practice for young people and children this means that only medicinal products which are likely to be of significant value for young people and children are fully studied and the protection of participating children is fully considered.

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/>

Where the trial allows the inclusion of participants 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.

**Additional consent provisions for collection of participant data and human tissue in ancillary studies** *(if applicable)*

Aim: to describe the consenting procedure for ancillary studies (if applicable)

The protocol should state:

* if data and/or biological specimens for ancillary studies will be acquired, transferred and stored during the trial (in line with section 17.7).
* if the data and/or biological specimens will be used for a specified subset of studies or for submission to ethically approved research tissue banks for future specified or unspecified research
* what options participants will be given in respect to their participation in ancillary research including:
  + whether participation in the ancillary research is required for participation in trial or if participants may opt out but still participate in the main trial
  + consent for the use of their data and specimens in specified protocols
  + consent for use in future research unrelated to the clinical condition under trial
  + consent for submission to an unrelated bio-bank
  + consent to be contacted by trial investigators for further informational and consent-related purposes
* whether their withdrawal from the ancillary research is possible and what will happen to material provided up to that point:
  + for example if the data and/or specimens will be coded and identifiable
  + what withdrawal means in this context
  + what information derived from the specimen related research will be provided to them, if any

## Randomisation scheme (if applicable)

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

The protocol should describe:

* The method of randomisation e.g.:
* simple randomisation based solely on a single, constant allocation ratio is known as simple randomisation. Simple randomisation with a 1:1 allocation ratio is analogous to a coin toss. No other method of allocation surpasses the bias prevention and unpredictability of simple randomisation
* restricted randomisation which includes any randomised approach that is not simple randomisation including:-
  + Blocked randomisation
  + Biased coin and urn randomisation
  + Stratified randomisation
* if an un-equal treatment allocation will be used and a justification for its use
* if the allocation ratio will adaptively evolve over the course of the trial 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 trial 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 trial protocol as knowledge of these details might undermine randomisation by facilitating deciphering of the allocation sequence. Instead, this specific information should be provided in a separate document with restricted access to protect the trial from selection/allocation bias

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

### Method of implementing the randomisation/allocation sequence

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

Successful randomisation in practice depends on two interrelated aspects:

1) generation of an unpredictable allocation sequence and

2) concealment of that sequence until assignment irreversibly occurs.

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

### Blinding and Emergency unblinding

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

The protocol should explicitly describe:

* who will be blinded to intervention groups including:
  + trial participants
  + care providers
  + outcome assessors

A full description is essential and ambiguous terminology such as “single blind”, “masked” or “double blind” should not be used.

Emergency unblinding

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

The trial code should only be broken for valid medical or safety reasons e.g. in the case of a serious 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. Participant always to clinical need, where possible, members of the research team should remain blinded.

The protocol should provide a description of the code break method (e.g. code break envelopes, via randomisation list, via interactive voice/web response system). Where the sponsor requires code break to be managed by a particular department/ individuals, this should be explicitly described in the protocol including the rationale for the decision.

## Trial assessments

Aim: To clearly describe the trial assessments.

The protocol should describe:

* all trial procedures and assessments, including those that are part of routine care
* the timing of the assessments should be detailed and broken down into visit numbers as appropriate, for example clearly defined visit window i.e. +-3 days
* the detail of any run-in or washout periods
* the time points for assessment data e.g. The following are to be recorded each month for the first 12 months and every three months afterwards:
* History and clinical examination
* Assessment of the toxicity of the previous course
* Weight
* Full blood count
* Biochemical series
* Chest X-ray
* Etc.
* how compliance will be checked if home dosing
* when diary cards should be checked
* any use of electronic patient reported outcome devices. In general, if third parties are involved in the provision of services related to the assessment or data collection then this should be detailed.
* assessment data required at the end of trial visit
* the methods and timing for assessing, recording and analysing efficacy parameters e.g.:
* the values/scores that will determine success or failure and how they will be assessed if appropriate
* Survival e.g.: These will be measured from the date of randomisation and will be reported for all deaths due to all causes. The cause of death is to be recorded in all instances
* Quality of life assessments if required

### Baseline data

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

The following should be considered:

* the relevance of each baseline variable. Do not include a variable solely on the grounds that it is always recorded, if there is genuinely no interest in the variable
* do any of the procedures need to be undertaken in a certain order or in a certain way – i.e. sitting vs standing, left arm vs right arm, fasted state
* are explanations needed? E.g. if 3 measurements are to be taken and averaged that should be explained
* for particularly complex procedures or those that differ from routine standard practice, these should be detailed in full. E.g. if a 6 lead ECG is normal routine practice but the trial requires a 12 lead EGC this will need to be made clear to avoid potential errors
* if there are any translational aspects of the trial 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.

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

Trial 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 trial analysis and interpretation.

### Qualitative assessments

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

This section should detail any qualitative component to the trial and provide a rationale for the timing and tools for assessment, for example measuring the acceptability of the intervention or measuring reasons for non-adherence to trial medication . 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 trial 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](file:///\\ims.gov.uk\data\Users\GBEXPVD\EXPHOME14\WBowen\Data\Desktop\Protocol%20Template\Final%20CTIMPs\www.sphsu.mrc.ac.uk\Complex_interventions_guidance.pdf)

## 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 trial (or certain aspects of the trial) for appropriate medical reasons, be they individual adverse events or new information gained about a treatment.

The protocol should therefore:

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

## Clinical samples: collection, storage and analysis

If details are provided in a laboratory/pathology manual there is no requirement to duplicate information in the protocol

Aim: To describe the procedure for dealing with biological samples

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

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

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

“It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the 2018 Data Protection Act. Biological samples collected from participants as part of this trial 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.”

# 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 sample. 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.

## Research Governance Statement

The protocol should state that: this study will be conducted in accordance with:

* The principles of Good Clinical Practice, as set out in the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines
* The UK Policy Framework for Health and Social Care Research.

## 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?

## 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](https://www.gov.uk/government/publications/health-research-ethics-committees-governance-arrangements)) 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](http://www.hra.nhs.uk/resources/hra-approval-guidance-for-sponsorschief-investigators-working-collaboratively-with-nhs-organisations-in-england/#3).
* For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as [amended](http://www.hra.nhs.uk/resources/after-you-apply/amendments/).

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

In all instances 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/>

## End of study

The end of study date needs to be defined. For example, it could be last patient last visit, but this will not reflect time needed for data cleaning, analysis and report-writing.

1. **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.

# 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 patients and the public in research can be found on the NIHR website:  
<https://www.nihr.ac.uk/documents/briefing-notes-for-researchers-public-involvement-in-nhs-health-and-social-care-research/27371>

# PROTOCOL COMPLIANCE

Aim: to demonstrate how protocol compliance will be managed

## Protocol Deviations

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.

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

Aim: to demonstrate how serious breaches will be managed

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

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

The protocol should state that:

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

# DATA PROTECTION AND PATIENT CONFIDENTIALITY

Aim: To describe how patient confidentiality will be maintained and how the study is compliant with the requirements of the Data Protection Act 2018

The protocol should state that all investigators and study site staff must comply with the requirements of the Data Protection Act 2018 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?

# DATA MANAGEMENT

## Data collection tools and source document identification

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

### Source Data

ICH E6 section 1.51, defines source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

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

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

### Source Documents

ICH E6 1.52, defines source documents as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

### Case report forms

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

* adequate collection of data has been performed
* proper audit trails can be kept to demonstrate the validity of the trial (both during and after the trial)
* only the data required by the protocol are captured in the CRF (using the CRF to capture secondary data not required for the trial may be a criminal beach of the Data Protection Act, makes the CRF unnecessarily complicated, and can make it more difficult to extract the primary data for analysis)

### CRFs as Source Documents

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

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

The protocol should:

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

## Data handling and record keeping

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

GCP requires that sponsors operating such systems validate the system, maintain SOPs for the use of the system, maintain an audit trail of data changes ensuring that there is no deletion of entered data, maintain a security system to protect against unauthorized access, maintain a list of the individuals authorized to make data changes, maintain adequate backup of the data, safeguard the blinding of the trial and archiving of any source data (i.e. hard copy and electronic). If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data. The sponsor should use an unambiguous participant identification code that allows identification of all the data reported for each participant. Sponsors are responsible for ensuring compliance with the requirements outlined above when tasks are subcontracted. There should be no loss of quality when an electronic system is used in place of a paper system.

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

## Access to Data

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

## 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.

# STATISTICS AND DATA ANALYSIS

Where possible the statistician should write this section.

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

## 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 trials 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 trial power or report the power that will be available (given the proposed sample size) for other important outcomes or analyses because trials 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 trials 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 trials 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 trial validity.

## 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.

## Statistical analysis plan

Aim: to fully describe the statistical analysis plan

### 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/>)

### Primary outcome analysis

Plans for statistical analyses of the primary outcome including:

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

### Secondary outcome analysis

Plans for statistical analysis of each secondary outcome. In general the use of hypothesis tests may not be appropriate if the trial 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.

### Subgroup analyses

Aim: to describe sub-group analyses

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

### Adjusted analysis

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

### Interim analysis and criteria for the premature termination of the trial

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

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 trial is ongoing
* whether these individuals will remain blinded (masked) to trial groups
* how the integrity of the trial implementation will be protected (e.g., maintaining blinding) when any adaptations to the trial are made
* who has the ultimate authority to stop or modify the trial e.g. the Chief Investigator, trial steering committee, or sponsor
* the stopping guidelines
  + Criteria for stopping for harm are often different from those for benefit and might not employ a formal statistical criterion
  + Stopping for futility occurs in instances where, if the trial were to continue, it is unlikely that an important effect would be seen (i.e., low chance of rejecting null hypothesis)
    - if pre-specified interim analyses are to be used for other trial adaptations such as sample size re-estimation, alteration to the proportion of participants allocated to each trial group, and changes to eligibility criteria.

NB in CTIMPs recommendations made by the DMC must be expedited to the MHRA where they are deemed relevant for the safety of participants participating within the trial (refer to the EU Guidance Document ‘Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use’).

### Participant population

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

Protocols should describe:

* the participant populations whose data will be subjected to the trial analysis – both for the primary analysis and any applicable secondary analyses e.g.
* All-randomised population: Any participant randomised into the trial, regardless of whether they received trial drug
* All-treated population: Any participant randomised into the trial that received at least one dose of trial drug
* Protocol-compliant population: Any participant who was randomised and received the protocol required trial drug exposure and required protocol processing
* if the participant is to be included in the analysis will vary by outcome e.g. analysis of harms (adverse events) is sometimes restricted to participants who received the intervention, so that absence or occurrence of harm is not attributed to a treatment that was never received. To avoid:
* selection bias, an “as randomised” analysis retains participants in the group to which they were originally allocated
* attrition bias, out-come data obtained from all participants are included in the data analysis, regardless of protocol adherence

These two conditions (i.e., all participants, as randomised) define an “intention to treat” analysis, which is widely recommended as the preferred analysis strategy.

### 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 trial results under different methods of handling missing data.

## Other statistical considerations

Aim: to describe any other statistical consideration pertinent to the trial.

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

## 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

# SAFETY REPORTING

Requirements for safety reporting will differ depending on the type of study, and risk. Please refer to UHBW SOP on “Research safety reporting”: Adverse events will be recorded and reported in accordance with UHBW’s Research Safety Reporting SOP. *NB identify events that may be excluded from expedited reporting because they are commonly associated with the clinical procedures taking place (e.g. wound infection); these should be agreed with the sponsor prior to submission to REC. Identify reference documents used to justify this decision.*

# QUALITY ASSURANCE, RISK ASSESSMENT AND MONITORING

Give details of data monitoring and how quality assurance will be checked. UHBW sponsored studies need to comply with UHBW SOPs unless a different arrangement is agreed in advance. A monitoring plan may be needed. Note that monitoring and risk assessments should be proportionate to the type of study being done, e.g. more detail required for an interventional full trial than for a non-interventional study.

## Risk Assessment

A formal risk assessment may or may not be required depending on study type – UHBW R&D will advise. Where a risk assessment is required this will be carried out in conjunction with R&D before your study starts and will be ongoing throughout the study.

## Monitoring, audit and inspection

Aim: to describe the procedures for monitoring audit and inspection (if this information is supplied as part of a monitoring plan then this section should reference it and not duplicate its detail).

Note: A detailed monitoring plan may not be necessary but if included should be proportionate to the study being done.

Where applicable the protocol should state:

* Whether a Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG), TSC and CI based on the trial risk assessment which may include on site monitoring. This will be dependent on a documented risk assessment of the trial.
* 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 trial investigators and sponsor of the monitoring personnel
* The processes reviewed can relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial 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 trial dataset or performing site visits
* Any obligations that will be expected of sites to assist the sponsor in monitoring the trial. These may include hosting site visits, providing information for remote monitoring, or putting procedures in place to monitor the trial 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.

## 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:

1. **Independent**: At least two individual experts should have reviewed the study. The definition of independent used here is that the reviewers must be external to the investigators’ host institution and not involved in the study in any way. Reviewers do not need to be anonymous.
2. **Expert**: Reviewers should have knowledge of the relevant discipline to consider the clinical and/or service based aspects of the protocol, and/or have the expertise to assess the methodological qualitative aspects of the study.

# INSURANCE AND INDEMNITY

Aim: to fully describe indemnity arrangements for the trial

The following areas should be addressed in the protocol:

* 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?
* 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?
* 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 trial 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 trial is covered under their own professional indemnity
* has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?
* if equipment is to be provided to site(s) for the purposes of the trial, 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 trial; however, it may be a condition of REC favourable opinion to have these arrangements in place.

# Financial and other competing interests

Aim: to identify and disclose any competing interests that might influence study design, conduct, or reporting for the chief investigator, PIs at each site and committee members for the overall trial management

At a minimum, disclosure should reflect:

* ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial
* 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.

# FINANCE AND CONTRACTUAL ARRANGEMENTS INCLUDING EQUIPMENT SUPPLY AND INTELLECTUAL PROPERTY

Aim: To list the various contracts and other agreements that will be required for your study, how finances will be managed, any IP considerations and how these will be managed.

For example:

* Sponsor will ensure that appropriate collaboration, subcontract and site agreements are arranged
* IP management to be an item on steering committee meetings; ownership of IP will be set out in main contract with the funder or collaboration agreement.
* Finances will be held at UHBW and flow to other organisations via a collaboration agreement
* Equipment will be supplied free of charge for the study by xxxx and will need relevant approvals for use at sites

# PUBLICATION AND DISSEMINATION

## Dissemination policy

Aim: to describe the dissemination policy for the study/trial

The protocol should state:

• Who owns the data arising from the study/trial.

• That on completion of the study, the data will be analysed and tabulated and a Final Study/Trial Report prepared.

• Where the full study/trial report can be accessed.

• If any of the participating investigators will have rights to publish any of the study/trial 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/trial.

• Whether there are any plans to notify the participants of the outcome of the study/trial, 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/Trial 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.

If your study is an interventional trial, then it is highly recommended that the Consort Guidelines and checklist are reviewed prior to generating any publications for the trial to ensure they meet the standards required for submission to high quality peer reviewed journals etc. <http://www.consort-statement.org/>

## Authorship eligibility guidelines and any intended use of professional writers

Aim: to describe who will be granted authorship on the final study/trial report

The protocol should detail:

* guidelines on authorship on the final study/trial 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).

# DOCUMENT STORAGE AND ARCHIVING

Aim: to describe the process for archiving the trial documentation at the end of the trial.

Please refer to the relevant UHBW SOP before completing this section.

The protocol should state:

* archiving will be authorised by the Sponsor following submission of the end of trial report
* which trial documents the sponsor will be responsible for archiving and which trial documents the site(s) will be responsible for archiving
* the location and duration of record retention for:
* essential documents
* the trial database
* all essential documents will be archived for a minimum of 5 years after completion of trial. 25 years for UHBW paediatric studies
* destruction of essential documents will require authorisation from the Sponsor
* Further information on archiving requirements can be found in UHBW SOPs <https://www.uhbristol.nhs.uk/research-innovation/for-researchers/templates-and-sops/sops>

# REFERENCES

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

# APPENDICES

## APPENDIX 1 Study Flow Chart

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

A flow diagram should be included. Ideally this should fit on one page.

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 procedures can be included as an appendix to the protocol. (See Appendix 1).

For interventional trials a flow chart should include key information to convey the timing of all trial activity, starting from initial eligibility screening, each trial visit through to trial close-out and long term follow-up; time periods during which trial interventions will be administered; and the procedures and assessments performed at each visit (with reference to specific data collection forms, if relevant)

For study designs using less complex methods, a timeline of activity outlining the timing of study activity and management is helpful.

## APPENDIX 1 Schedule of Procedures(Example)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Procedures** | **Visits (insert visit numbers as appropriate)** | | | | |
| **Screening** | **Baseline** | **Week 4** | **Week 8** | **6 Months** |
| Informed consent | X |  |  |  |  |
| Demographics |  | x |  |  |  |
| Medical history |  | x |  |  |  |
| Observation of treatment |  | x | x | x | x |
| Focus Group |  |  |  |  | x |
| Interview |  |  |  | x |  |

## APPENDIX 2 -Data Flow diagram

This should outline in a simple diagram the following:

* Type of data (i.e. personal data)
* Where the data is generated from
* Who the data is shared with
* What systems will be used to process the data (e.g. received in a XX database which is stored on a XX server)
* Security measures in place
* Duration of data flow