STUDY START UP SOP

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Implementation plan

This Standard Operating Procedure (SOP) should be implemented immediately after its implementation date for studies that are in start-up at the time the SOP is implemented.

For ongoing studies that are beyond the start-up phase the applicable sections of this SOP (e.g. opening new sites) should be implemented as far as possible immediately after the implementation date. Otherwise, the Study Conduct SOP (BTC-SOP-TM-002) and/or Study Closedown SOP (BTC-SOP-TM-003) should be implemented, as applicable.

If unsure, the Trial Portfolio Leads and/or Quality Assurance Manager should advise.

Note to User:

It is your responsibility to ensure that you are using the latest approved version of this SOP. Please note that versions may be superseded before their review date.

THIS IS AN UNCONTROLLED VERSION WHEN PRINTED.

If you are reading this document in printed form, please check that the version number and date match the most recent SOP's details. Current versions of all Bristol Trials Centre (BTC) SOPs and accompanying documents are available on the BTC Teams channel.

Contents

1. PURPOSE

This Standard Operating Procedure (SOP) describes the procedures to be followed for setting up a research study at the BTC.

2. SCOPE

This SOP applies to all research studies undertaken by BTC staff. It covers the period from confirmation of funding being awarded i.e. execution of the funding agreement / issue of the funding letter, as applicable, until opening of the first participating site or being able to start the study where applicable, e.g. for a data only study. It applies to all personnel involved in the development or implementation of study start up processes.

Chief Investigators (CI) must be made aware of this SOP and, as a minimum, be signposted to the SOP.

“Research study” (or “study”) refers to health and social care-related research projects (interventional trials or observational studies) involving people, samples and/or data, that are aimed at evaluating a medical, surgical, or behavioural intervention, or studying health related outcomes and/or groups of people defined by a health condition or intervention. It includes Clinical Trials of Investigational Medicinal Products (CTIMPs) or Advanced Therapy Medicinal Products (ATMPs) and clinical investigations for medical devices.

NB: Throughout this document the terms ‘research’, ‘study, ‘research project’, and ‘trial’ will be used interchangeably to denote those projects which fall under the remit of the UK Policy Framework for Health and Social Care Research 2017. The word “Trial” is accepted to be used when associated with established terms such as Trial Master File, Trial Management Group, etc., for research studies other than clinical trials.

3. DEFINITIONS, ACRONYMS AND ABBREVIATIONS

For definitions, acronyms and common abbreviations refer to BTC-RES-TM-001 Definitions and Acronyms available on the BTC Teams channel.

4. RESPONSIBILITIES

Any delegation of responsibilities should be formally agreed by all parties and clearly documented.

4.1 Sponsor(s) or delegate

It is the responsibility of the Sponsor(s) or delegate to:

- Ensure that studies are managed and conducted according to all relevant local, national, and international laws, and good clinical practice (GCP) guidance. Guidance, regulations and laws governing research in the UK include but are not limited to the following:
    - UK Policy Framework for Health and Social Care Research;
    - Common law duty of confidentiality;
    - Data Protection Act, 2018;

  - Human Tissue Act, 2004; Human Tissue (Scotland) Act 2006;
  - Mental Capacity Act, 2005; Adults with Incapacity (Scotland) Act, 2000;
  - The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019 (subsequently referred to in this document as the Clinical Trials Regulations);
  - UK Medical Devices Regulations 2002.

- Ensure that participants' privacy is protected, and any disclosure of a participant's confidential information is managed appropriately.
- Ensure that a risk assessment is carried out prior to awarding sponsorship to assess the potential risks to the safety and rights of the research participants, risks to the reliability of the study results and risks to the Sponsor's institution.
- Ensure that the CI is appropriately trained and qualified to run the study.
- Ensure that the study is managed and financed in an appropriate way.
- Ensure that arrangements are in place before a study starts to cover the potential legal liabilities of the various parties arising from the research, as applicable.
- Ensure that appropriate contracts are in place and that research projects are conducted in accordance with the terms and conditions of any applicable agreements.
- Ensure that the protocol and associated documents adhere to the principles of GCP before they are submitted to any of the regulatory authorities.
- Ensure that all applicable regulatory approvals are in place prior to the recruitment of participants into a research study.
- Select and approve potential investigator(s) and participating sites by assessing and confirming their suitability. Once a site is approved it is the Sponsor's responsibility to initiate the site prior to recruitment.
- Ensure that a monitoring plan is in place at a level appropriate to the risk assessment performed by, or on behalf of, the Sponsor.
- Ensure that there is the intent that information about the study is publicly available before the research begins.

In addition, for CTIMPs or ATMPs, it is the responsibility of the Sponsor(s) or delegate to:

- Confirm the CTIMP or ATMP status of a study and apply to the Medicines and Healthcare products Regulatory Agency (MHRA) for a Clinical Trial Authorisation (CTA), including submissions of all notifications and amendments thereafter.
- Ensure that sufficient safety and efficacy data are available to support human exposure as proposed in the study protocol.
- Ensure that an up-to-date Investigator's Brochure (IB), Investigational Medicinal Product Dossier (IMPD) or Summary of Product Characteristics (SmPC) (as required) is made available to the investigator and update the IB as significant new information becomes available.
- Ensure that the use of the Investigational Medicinal Product (IMP) in a CTIMP conforms to the Clinical Trials Regulations and subsequent amendments, and GCP guidelines.
- Ensure that the IMP (including active comparators/placebo, if applicable) are characterised as appropriate to the stage of development of the product and that the IMP is manufactured in accordance with any applicable Good Manufacturing Practices (GMP).
- Supply the participating site(s) with an adequate supply of IMP.

- Ensure that written procedures are in place for the handling and storage of IMP(s) for the trial. The procedures should address receipt, handling, storage, dispensing, recall and return and/or destruction of unused IMP(s).
- Ensure that the CI is a health professional as defined in the Clinical Trials Regulations. This means a person registered in the UK as a doctor, dentist, nurse or pharmacist.

In addition, for studies involving a medical device (clinical investigations), it is the responsibility of the Sponsor(s) or delegate to:

- Confirm the status of a study and inform the MHRA for a clinical investigation as part of the process to obtain a UKCA / CE / CE UKNI marking for a medical device, or a UKCA/CE UKNI/CE-marked device that has been modified or is to be used for a new purpose. The MHRA should be informed at least 60 days before starting the investigation.
- Ensure information is available to demonstrate compliance with all relevant essential requirements as listed in Part II of the UK Medical Devices Regulations 2002, Annex I.
- Ensure that any adverse incidents involving a medical device undergoing clinical investigation are reported to the manufacturer, or directly to the MHRA via the online system.
- Report to all concerned members states all (i) SAEs causally related to the device, comparator or procedure, (ii) device deficiencies that may have led to an SAE and (iii) events in non-EU countries involved in the clinical investigation.
- Provide quarterly summary reports to the MHRA of all serious adverse events.
- Notify the MHRA of all deviations relating to UK study sites as soon as they have been made aware of them.

4.2 Chief Investigator (CI) or delegate

It is the responsibility of the CI or delegate to:

- Ensure that sponsorship for the research study (at least in principle) has been obtained before Research Ethics Committee (REC) and/or Health Research Authority (HRA) and/or MHRA approvals (clinical trial authorisation or no objection)are sought.
- Ensure that adequate resources are in place to conduct the research. This includes funding, staff and infrastructure.
- Identify, at the earliest possible stage, the appropriate Sponsor Representative who is able to sign off documentation (e.g. Integrated Research Application System (IRAS) applications, protocol amendments, etc) on behalf of the Sponsor.
- Identify potential investigators and participating sites/institutions prior to Sponsor involvement.
- Ensure that the appropriate agreements with participating sites are in place before the study commences at sites.
- Prepare the study protocol and gain the necessary approvals to conduct the study.
- Ensure that a REC Favourable Opinion and/or HRA Approval, and regulatory approvals, as applicable, are in place before the research study commences.
- Ensure that all necessary local approvals and formal confirmations of capacity and capability are in place at the participating sites (as applicable) before recruitment commences at sites.

- Ensure that Principal Investigators (PIs) at the participating sites are educated in the study-specific working instructions and that staff receive appropriate training.
- Facilitate contract activity (e.g. payments to centres, recruitment rates).
- Set up and maintain the Trial Master File (TMF)/Study File.
- Define the data items to be collected and included on the Case Report Form (CRF).

In addition, for CTIMPs/ATMPs,

It is the responsibility of the CI or delegate to:

- Ensure that the use of the IMP is compliant with GCP and applicable regulations.
- Ensure that study specific working instructions relating to the handling, management and administration of the IMP are in place and remain fit for purpose for the duration of the study.
- Ensure that PIs at the participating sites are educated in the study-specific working instructions relating to the handling and management of the IMP and that local staff receive appropriate training.

4.3 Principal Investigator (PI) or delegate

It the responsibility of the PI to:

- Identify the local study team, facilities and financing needed to deliver the study at the participating site.
- Assess the acceptability and feasibility of the study protocol and ensure that the study team are familiar with the protocol and all related study documentation provided to them by the central research team/coordinating centre.
- Ensure that the responsibilities of each team member are recorded in the study delegation log.
- Ensure that research staff are appropriately qualified and trained in study specific procedures relating to the conduct of the study.

In addition, for CTIMPs/ATMPs,

It is the responsibility of the PI to:

- Be thoroughly familiar with the appropriate use of the IMP as described in the protocol, the current IB, IMPD or SmPC and in other information sources provided by the Sponsor/CI.
- Ensure that research staff are appropriately trained in study specific management and handling of the IMP.
- Be responsible for the IMP accountability at the participating site (some of the IMP related responsibilities may be delegated to research team or an appropriately qualified trial pharmacist).

4.4 Trial Pharmacist (CTIMPs only)

It is the responsibility of the trial pharmacist (where applicable) to:

- Make sure that all approvals are in place before an IMP is dispensed.
- Ensure that a pharmacy specific file is set up.

- Be familiar with trial specific working instructions relating to the handling, management and administration of the IMP.
- Set up appropriate arrangements for accountability, storage, dispensing and destruction of the IMP, as applicable.

4.5 Bristol Trials Centre (BTC), University of Bristol

It is the responsibility of the BTC to:

- Advise/assist with the preparation of the protocol and other study documentation and data collection tools.
- Review study documents for GCP and legal compliance.
- Provide advice on the types of regulatory approvals required and, where delegated by the Sponsor/CI, apply for applicable approvals.
- Attend initial study start-up meetings with the Sponsor.
- Attend appropriate Trial Management Group (TMG) meetings leading up to submission of applications for the applicable review bodies approvals.
- Acquire any knowledge and skills required to conduct the research study, including being familiar with the protocol and relevant documentation, applicable SOPs, and attending GCP training where/as appropriate.
- Ensure staff working with identifiable participant information are aware of their responsibility to maintain participants' confidentiality.

4.6 SOP Author or delegate

It is the responsibility of the SOP author to:

- Generate, finalise, and release the SOP in accordance with the BTC-SOP-QM-001.
- Ensure that the SOP remains fit for purpose.
- Ensure that the SOP is reviewed and amended as required.
- Provide relevant training and education materials to ensure that staff are aware of their responsibilities in relation to SOP content and management.

4.7 SOP user

It is the responsibility of the SOP user to:

- Ensure compliance with this document.
- Review procedures during use of the SOP and inform the author of any changes required
- Undertake training on all aspects of this SOP and record training on the BTC Teams channel.

5. SPECIFIC PROCEDURES

5.2 Trial Master File (TMF), Investigator Site File (ISF) and Pharmacy Site File (PSF)

5.1.1 Introduction

The Clinical Trials Regulations state that all clinical trial information shall be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. It is a legal requirement to maintain a TMF for all CTIMPs within the scope of the Regulations.

Although a legal requirement only for CTIMPs, the general principles will apply for the filing of study related documentation for all other research studies undertaken by BTC staff.

5.1.2 Study infrastructure

At the beginning of a research study a University of Bristol Shared mailbox, Microsoft Teams Group and a BRMS file-store study folder should be set up as soon as possible. Guidelines for the set-up and standard Teams configuration are included in working instructions on the BTC Teams channel. Study set-up requirements are described in the BTC Study Start Up Checklist located on the BTC Teams channel.

5.1.3 Establishing the TMF

The TMF is a filing system necessary for the effective storage and location of essential documents that allow for the conduct of a research study, the integrity of study data and compliance of a study with GCP to be evaluated, facilitating the reconstruction of the study.

The CI is responsible for establishing and maintaining the TMF and archiving the TMF at the end of the study with agreement from the Sponsor; however, this is usually delegated to BTC and it should be documented accordingly in a Delegation Log or a Matrix of Responsibilities or similar document.

The TMF should be started as soon as possible at the beginning of a research study. The documents that should be contained, including the structure/organisation of the sections and folders are listed in the BTC TMF template (BTC-TEMP-TM-001 Trial Master File Contents) located on the BTC Teams channel.

The BTC TMF template (BTC-TEMP-TM-001 Trial Master File Contents) should be used unless the Sponsor mandates use of their own template.

The TMF should be stored in a safe and secure location with restricted access. Only members of the research team should have access to the TMF.

The TMF (or documents within) should specify where original source data are held and, if appropriate, who to consult for access to the documentation. The location of all documentation related to the study but stored separately from the rest of the TMF (e.g. confidential source data such as consent forms etc.) must be signposted within the TMF index or by using a file note.

Study specific sections may be added. Where a particular document or section is not required for a study, a file note should be present to justify why that document/section is not present.

As documents may need to be amended during a project, it is important that amendment chronologies are kept, indicating changes and the dates they are implemented. The original

document must always be retained. In paper TMFs, old versions of documents should be struck through and marked as superseded to ensure they are not mistaken for current documents. In electronic TMFs, the superseded documents should be filed separately from current versions.

Documents should be maintained in a legible condition, with prompt retrieval possible. All of the TMF (including any electronic documents) must be made available to the Sponsor or regulatory authorities upon request for the purpose of monitoring, audit or inspection.

The TMF must be maintained throughout the lifetime of the study and archived at the end of the study for a set period of time which will be defined in the protocol and/or applicable agreements. All essential documents must be archived.

Archiving requirements should be considered at an early stage to ensure budget provision, reservation of archiving space, etc.

Archiving arrangements are described in the Study Closedown SOP (BTC-SOP-TM-003).

5.1.4 Establishing the ISF

An ISF should be produced for each participating site, as soon as approached by the Sponsor/CI to consider participation, and the UK Local Information Pack is received. The ISF is part of the TMF.

The ISF will contain documentation relating to the local participating site i.e. participant consent forms, local screening and recruitment logs. There may be duplication as some documents are also retained in the TMF, but this is required to maintain a clear documentation trail for monitoring and audit purposes.

The ISF should be filed in a secure location, accessible to all members of the local research team.

After the study closes at a site the ISF must be archived for a set period of time which will be defined in the site agreement.

Archiving arrangements are described in the Study Closedown SOP (BTC-SOP-TM-003).

5.1.5 Establishing the Pharmacy Site File (PSF)

Where the study is a CTIMP, a Pharmacy Site File (PSF) may be set up and kept at the pharmacy department. The following documents must be in place in the Pharmacy Study File (PSF):

- The current approved version of the protocol
- Instructions for pharmacy (pharmacy manual)
- Instructions for randomisation (if applicable)
- Instructions for unblinding (if applicable)
- IB(s)/SmPC(s)
- The delegation and signature log completed by all pharmacy staff involved with the study
- CVs and GCP training certificates of pharmacy staff on the delegation log.

If a Pharmacy Site is not set up, the above documents can be filed in the ISF. After the study closes the PSF must be archived for a set period which will be defined in the site agreement.

Archiving arrangements are described in the Study Closedown SOP (BTC-SOP-TM-003).

5.1.6 Establishing the Laboratory Site File

Where a study conducted by the BTC involves the collection, receipt, processing, storage or destruction of research samples, a study specific laboratory file should be set up (see BTC-SOP-LAB-001). If a laboratory file is not set up, a file note should be added to the TMF to justify why such document is not required**.**

After the study closes at a site the Laboratory Site File must be archived for a set period of time which will be defined in the site agreement.

Archiving arrangements are described in the Study Closedown SOP (BTC-SOP-TM-003).

5.2 Protocol Development

5.2.1 Introduction

The research protocol forms an essential part of a research study. It should describe the objectives, design, methodology, statistical considerations and methods used to ensure the safety of the study participants and/or integrity of the data collected. It should contain sufficient detail for members of the research team to ensure adherence to the methods outlined and enable the review bodies to fully understand the proposed study.

GCP principles should be observed when preparing protocols for all research studies.

5.2.2 Development of protocol

The CI along with the study manager and/or other senior BTC staff will identify individuals with relevant experience to contribute to the development of the protocol. It is often the case that the co-applicants would be protocol authors, and other expertise will need to be brought in as needed e.g. to provide statistical input, pharmacy information, specialist clinical/scientific advice, etc.

The protocol should be circulated to all contributors for review. BTC should review all protocols and subsequent amendments to ensure that they adhere to the principles of GCP before they are submitted to any of the review bodies. Any peer review documentation should be filed in the TMF.

The HRA have developed protocol templates which can be found on the HRA website. The use of this guidance and template is not mandatory. The protocol may be developed in line with other BTCs protocols for studies of a similar nature.

The study Sponsor protocol must be used where this is mandated

Where appropriate, the protocol may refer to information listed in other documents, e.g. the IB, IMPD or SmPC, Trial Steering Committee (TSC) or Data Safety and Monitoring Committee (DSMC) remit and membership.

5.2.3 Version Control

All iterations of the protocol and supporting documentation should be version controlled. The procedures for version control, dating and naming documents described in the Quality Management Systems SOP (BTC-SOP-QM-002) must be followed.

5.2.4 Protocol Sign off

The protocol authors (those defined on the protocol contact page) must sign the author signature pages of the first final full version of the protocol prior to initial submissions to the review bodies. Wet ink signatures or electronic confirmation of approval of the protocol will be acceptable.

A copy of the protocol author signature page/confirmation of acceptance must be kept in the TMF.

The signature pages can be held as a separate document to the protocol and a single signature page for each of the key collaborators, or evidence of sign off (e.g. email confirmation) will be accepted.

Some Funders require review and approval of the protocol before submissions for regulatory reviews. If applicable, evidence of Funder approval of the protocol should be filed in the TMF.

5.2.5 Protocol Revisions

If revisions are necessary to the protocol, the CI and/or the study manager and/or BTC senior management usually identifies the group of collaborators/members of staff with responsibilities relating to the revisions. The Sponsor, Funder, and TSC/DMSC if applicable, should be informed of any changes to a protocol and their agreement to these obtained before submission for regulatory reviews.

All changes should be tracked using the track changes function and comments should be made using the respective function in Word. A summary of changes should be included (or provided separately) for reference. All electronic copies of final versions of the protocol must be kept.

The CI and those key collaborators whose role in the study will be affected by the respective amendments need to sign the author signature pages of final full versions. Wet ink signatures or electronic confirmation of approval of the protocol will be acceptable.

Submissions of amendments for the review bodies approvals is covered in the Study Conduct SOP (BTC-SOP-TM-002).

5.3 Arranging and maintaining sponsorship

5.3.1 Introduction

Under the UK Policy Framework for Health and Social Care Research, all health and social care research must have a Sponsor. For CTIMPs it is also a legal requirement to have a Sponsor.

The Sponsor of a study is usually the CI's employer, or the NHS organisation where the study is undertaken, or the lead site for multi-centre studies, but may be another organisation.

A Sponsor can delegate specific responsibilities to any individual or organisation that is willing and able to accept them but this must be documented in writing.

5.3.2 Obtaining sponsorship

The CI or delegate can initiate the process of arranging sponsorship either at the time of preparation and submission of the research grant application if required to do so by the funding body or Sponsor, or on receipt of the grant award letter / approval of funding. To ensure that there are no implications with respect to the Sponsor's insurance policy, this process should be initiated as soon as possible.

The CI and BTC should consider who would be the most appropriate Sponsor for the research and make an informal inquiry to the relevant organisation.,

An institution may approach another organisation to act as Co-Sponsor or Joint Sponsor for a study and to assume some of the sponsorship responsibilities; if so, the delegation of responsibilities between the two Sponsors must be agreed, documented and authorised by appropriate representatives of both Sponsor institutions/organisations.

Sponsorship in principle is sometimes issued to assist with the funding applications.

Once sponsorship has been agreed/confirmed (by authorising the IRAS or CWoW form) a copy of the IRAS or CWoW application and/or a copy of the sponsorship letter to the CI (if issued) must be stored in the TMF/Study File.

Where an institution is approached for sponsorship, the CI must follow the potential Sponsor's specific processes. Sponsorship must be confirmed prior to the start of a research study and this should include adequate and appropriate insurance/indemnity cover for the study.

5.3.3 Maintaining sponsorship

The CI or delegate should fulfil all requirements stipulated by the Sponsor in their sponsorship letter and/or agreement, and any subsequent revisions.

5.4 Contracts/Agreements

5.4.1 Introduction

The purpose of a research contract is to set out the roles and responsibilities of the parties involved in a research project, e.g. academic institution, Sponsor, academics, researchers, students, funding body, etc.

5.4.2 Contracts between the Funder and the Institution holding the grant

The Funder will issue a contract to the grant holder, usually the Sponsor or the organisation employing the CI. The funding contract outlines terms and conditions governing the conduct of the research project as well as obligations of the Funder and recipient. As a minimum, it should contain a description of the work to be undertaken, financial contribution and a timeline of study payments, publication rights of results, agreed liabilities and indemnity.

Where amendments are required, these are usually initiated by the institution holding the grant and should be processed according to provisions of the contract.

Although the CI will not normally be a signatory to the funding contract, the CI or a delegated team member should be given the opportunity to review draft contracts and any subsequent amendments.

Once all parties and the CI or designated team member have reviewed and agreed the contract, it must be signed by the parties as per local processes (e.g. by the appropriate contract department of the institution holding the grant).

A copy of the funding contract must be retained in the TMF.

5.4.3 Collaboration agreements

A collaboration agreement may be required for work involving two or more research partners on a research project. This agreement should set out the responsibilities, roles and rights of collaborating parties working in conjunction on the specific project. It should describe how the overall project will be managed between the parties.

The agreement is often drawn up following a joint award/research funding contract and the terms of this main award should be reflected in the collaboration agreement. It may also contain funding terms, for example transfer of funding from the lead partner to the other collaborators.

A copy of the collaboration agreement should be retained in the TMF.

5.4.4 Site agreements

For all research studies which are clinical trials and clinical investigations (including CTIMPs, medical device studies, other interventional trials, etc.), it is expected that a signed agreement between the Sponsor and the participating organisation will be in place before the research commences at the site.

The model Non-Commercial Agreement (mNCA) template has been developed to meet the requirements of non-commercial Sponsors and the NHS/Health and Social Care (HSC) (or other) bodies undertaking the research, and it is designed to be used without modification or negotiation. It has been developed for a range of interventional research scenarios, including clinical trials, medical device studies, research using patient data and research using human tissue.

Use of bespoke site agreements, or modifications to the mNCA should be discouraged for non-commercial research.

For non-interventional research it is expected that a non-commercial Organisation Information Document (OID) is used as the agreement between Sponsor and participating research site, in place of the mNCA.

Guidance and model agreement templates are provided on the IRAS website.

For Participant Identification Centres (PICs) sub-contracting arrangements should be put in place between the participating organisation research site and the PIC, using the Model Non-Commercial Participant Identification Centre Agreement (mNC-PICA), available on the IRAS website.

The study should not commence at the participating site(s) concerned until the appropriate agreements are in place, as applicable.

Copies of the signed site agreement and/or OID must be kept in the TMF and ISF.

Other Model agreements available via IRAS templates for supporting documents include (but are not limited to) the UK template Hub and Spoke Agreements, the Model Material Transfer Agreement, a Standalone Data Processing Agreements, a Model Confidentiality Disclosure Agreement (mCDA).

5.4.5 Other third-party contracts/agreements

Certain research activities may need to be delegated to other third-party organisations (e.g. manufacturers, external laboratories, randomisation providers, central pharmacies, as well as other service providers). The CI is responsible for identifying what trial functions may need to be

delegated to an external vendor and for determining the level of risk associated with the tasks being delegated. Due diligence should be carried out when selecting any vendor to ensure the vendor can perform the services to applicable standards and regulations. This does not apply to academic/NHS collaborations.

A risk-based approach should be taken when assessing vendor suitability based on the level of risk associated with the study and prior experience of the vendor. A variety of assessment methods will be used when assessing the suitability of a vendor, including but not limited to:

- Assessment of expertise
- Prior experience of working with the vendor
- Obtaining appropriate references where applicable
- Assessment of the vendor's quality system and/or written procedures
- Cost/budget.

The type of assessment undertaken will be determined on a case-by-case basis and will follow University of Bristol procurement processes where applicable. If you have a budget of £25,000 or more to spend on a single service or goods, you must discuss your requirement with the Procurement Department and you must not make any agreement with new or existing suppliers without their involvement.

Some services may already be provided for University by external organisations under a University framework or call off contract (e.g. Sealed Envelope, Language Line) Where this is the case, a separate assessment of suitability may not be required for the same organisation to provide the same services for research purposes.

Once a third-party vendor has been selected, the Sponsor (or delegate) or other party as appropriate should liaise with third parties to put in place any other contracts/agreements if/as required. There should be clear instructions within the vendor contract detailing the process to be followed in the event of instances of non-compliance or poor performance.

Documentation to support the vendor selection, process of assessment and selection decisions should be clearly documented and filed in the TMF.

Copies of any third-party agreements should be kept in the TMF.

5.4.6 Financial disclosure

The CI or delegate should ensure that the financial arrangements are transparent and that they follow the terms and conditions of the contract.

If required by the Funder or Sponsor, each member of the research team who is directly involved in the treatment or evaluation of study participants should provide a financial disclosure statement. If completed, this should be filed in the TMF and /or ISF.

5.5 Indemnity/Insurance

It is a Sponsor's responsibility to ensure there is provision for indemnity or compensation in the event of injury or death attributable to a study, and any insurance or indemnity to cover the liability of the investigator(s) and Sponsor(s).

Where an NHS organisation is the Sponsor, indemnity is provided through NHS schemes. Independent contractors (e.g. GP practices, NHS dental practices) or the staff members they employ are not normally covered by NHS indemnity. Where the research study involves NHS

patients under the care of independent contractors, indemnity for harm to participants resulting from clinical negligence is provided through professional indemnity.

The CI or delegate should check that appropriate indemnity arrangements are in place to cover the design, management and conduct of the study, prior to the start of recruitment, and that these are clearly detailed in the contract and/or protocol, and the participant information leaflet/sheet (PIL/PIS).

It is the Sponsor's responsibility to maintain valid insurance for the duration of the study. The CI or delegate must inform the Sponsor of any substantial amendments made to the study in order to ensure that the insurance and indemnity cover remains valid.

University of Bristol members of staff are covered under a separate policy. To obtain confirmation of insurance cover, contact the University of Bristol Division of Research, Enterprise and Innovation (DREI) office.

5.6 Risk Assessment

5.6.1 Introduction

The risk assessment process is a careful examination of what could cause harm, who/what could be harmed and how, and risks to the study integrity. Reasonably foreseeable risks associated with a research study, and actions to control the risks so far as is reasonably practicable, should be identified and documented as soon as possible, usually during the sponsorship process.

5.6.2 Carrying out a risk assessment

It is the responsibility of the Sponsor to ensure that there are adequate risk management measures in place as well as resources and infrastructure to manage and mitigate all risks that are identified within a research study. The BTC should input into the Sponsor's risk assessment process when/if approached.

The BTC should carry out a risk proportionate assessment for each research study managed in the Centre in order to determine the level of quality management required during the study. The risk assessment process is further described in the Quality Management Systems SOP (BTC-SOP-QM-002).

Study monitoring activities should be identified based on the risk assessment. Specific requirements for monitoring identified in the risk assessment should be captured in a study monitoring plan or other study procedure. The BTC Quality Management Plan (BTC-CHK-TM-005 Quality Management Plan) should be used be used to record how aspects of the study are being/will be monitored.

The development of appropriate safety management procedures should also be considered – see below Section 5.7.4 Safety Management Procedures.

The Sponsor and, where appropriate, site staff, should be made aware of the content of the risk assessment. The risk assessment, all mitigating actions identified for completion by the study team and the deadline for each action's completion, as well as any subsequent updates, should adequately and promptly be communicated to the relevant personnel.

The risk assessment documentation and any subsequent revisions should be kept in the TMF.

For CTIMPs, examples of risk assessments are provided on the MHRA forum concerned with GCP.

5.6.3 Review of Risk Assessment

The risk assessment should be an ongoing process. Each time there are changes to the perceived risks and mitigating circumstances these must be agreed by the TMG and CI and documented.

Review of Risk assessment is further detailed in the Study Conduct SOP (BTC-SOP-TM-002).

5.7 Management of Safety Events

5.7.1 Introduction

The Sponsor is responsible for the on-going safety evaluation of the IMP or study intervention. The roles and delegated responsibilities pertinent to recording, management and reporting of safety data must be agreed and clearly documented.

Appropriate monitoring of safety data during the conduct of a study can ensure timely alteration or termination of the study to protect participants from potentially harmful study treatment or procedure.

Full details of safety reporting processes including definitions are provided in the Study Conduct SOP (BTC-SOP-TM-002).

5.7.2 Collection of safety data

The first aspect of safety management is collection of data related to adverse events (AEs) and serious adverse events (SAEs). The CI or delegate should decide in advance how to record and report AEs and SAEs.. It should be agreed at the beginning of the study which AEs can be defined as expected in relation to the reference safety information or anticipated in the study population. These should be defined in the protocol and would therefore not be subject to expedited reporting.

5.7.3 Reference Safety Information (RSI)

For CTIMPs, prior to a study commencing, the CI or delegate will determine what RSI will be used to determine causality of any adverse events. This information is usually contained in a section within the IB (for IMPs without marketing authorisation for the use being researched) or SmPC (for IMPs that have a marketing authorisation). The RSI must be included as part of the initial CTA application and should be clearly identifiable.

5.7.4 Safety Management Procedures

If applicable, study specific safety management procedures should be developed for interventional studies during the set-up stage of a study. The procedures should be aligned with the risks involved and in accordance with the agreement in place for reporting methods with the Sponsor. The following components should be considered:

- Roles, responsibilities, processes and timelines
- Processing and data entry of AEs and SAEs

- Follow-up process for AEs and SAEs
- Causality assessment (investigator and/or Sponsor) and individuals responsible for reviewing expectedness of AEs
- Safety reporting procedures
- Identifying and mitigating any change in the risks for patients
- Blinding / unblinding
- Safety Reports
- Arrangements at participating sites.

5.7.5 Safety reporting

Safety reports are submitted to the Sponsor, MHRA, the REC, and oversight groups throughout the lifecycle of a study (as applicable).

The Sponsor or delegate should ensure that these reports are developed and submitted to the relevant committees and regulatory authority, on time (as applicable).

An independent DMSC, if deemed applicable, should be established to assess at intervals the progress of a research study, the safety data, and the critical efficacy endpoints (if applicable), and to recommend to the TSC whether to continue, modify, or stop a study.

5.7.6 Arrangements at participating sites

The CI or delegate must ensure that all research team members are in possession of current safety information about the product, procedure or intervention under study. For CTIMPs all members of the research teams must use the same version of the RSI at the same time.

The PIs (or delegate) are responsible for identifying and reporting AEs and SAEs at their sites. The safety management procedures, or the protocol or relevant working instructions, must document the reporting procedures and any applicable local arrangements and timelines. Relevant training should be provided to the local research teams.

The process for recording, managing and reporting AEs and SAEs is further described in the Study Conduct SOP (BTC-SOP-TM-002).

5.8 Monitoring and Independent Oversight

All studies conducted by BTC staff must be conducted in accordance with the BTC SOPs. Arrangements for the management of studies will vary according to the nature of the study and requirements. The process by which a study is managed should be described in the study protocol.

The management of the project is the responsibility of the CI; a separate Trial Management Group (TMG) is usually set up to assist with this function. The TMG will be responsible for all aspects of the day to day running of the trial/study from set up to close down.

An independent TSC and/or DMSC may be set up to oversee the running and outputs of the study and data quality, respectively.

Some Funders require to be informed of the TSC/DMSC membership by completing an oversight group nomination form. The Funder then formally invites the members.

Guidance provided on the NIHR website regarding independent oversight committees should be followed.

5.8.1 Central coordinating team

The study manager/coordinator or delegate will be responsible for the day-to-day running of the study, e.g. obtaining approvals, reporting to TSC, DMSC and HRA/REC, managing the budget, drafting reports and research papers, as required/applicable. The study manager will report to the CI regularly. They will liaise closely with the other members of the study team and will ensure that all individual research components are undertaken in a timely manner and within budget.

The study manager may undertake monitoring procedures at a level appropriate to a risk assessment performed by the Sponsor and/or according to a monitoring plan (or other practical guidance that shows the methods, responsibilities and requirements for monitoring) to ensure delivery of the study in accordance with the protocol and the statutory instruments. Also refer to Section 5.6.2 Carrying out a risk assessment in this SOP and Section 5.3.2.1 Monitoring Plan in the Quality Management SOP (BTC-SOP-QM-002).

The monitoring activities should be based on the risk assessment. The specific requirements for the monitoring of the study and the expectations for the provision of information (e.g. to and from sites) and follow-up of monitoring activities should be clearly communicated and documented.

5.8.2 Trial Management Group (TMG)

The study will/may be managed by a Trial Management Group (TMG) (or similar e.g. Study Management Group), which will meet by teleconference/videoconference or face to face at regular intervals. The scope of the group and frequency of meetings etc, is usually captured in the group's terms of reference or detailed in the protocol. The exact composition of the TMG will vary depending on the nature of the study but it is typically the CI (usually chairing) or delegate, the trial manager and other members of the study team (e.g. BTC lead, statistician, data manager, pharmacist (for CTIMPs)) responsible for the day-to-day management of the study. Minutes should be taken during TMG meetings and filed in the TMF.

5.8.3 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision for the study and make recommendations during the study to the TMG, CI, Sponsor (and Funder if applicable) about continuation of the study or alterations to the study. The TSC is typically made up of independent members (with no direct involvement in the conduct of the study) e.g. clinicians, scientists, statisticians, patient representative(s) and should have an independent chairman.

The procedures for TSC formation, remit and membership should be detailed in the protocol and/or a TSC Charter. The Charter should be filed in the TMF.

Not all trials/studies will require a TSC. For some small, simple studies there may only be one group/committee with the function of both the TMG and TSC.

Copies of TSC meeting minutes should be shared with the Sponsor and Funder (as applicable) and filed in the TMF.

5.8.4 Data Monitoring and Safety Committee (DMSC)

For interventional studies it is recommended to establish an independent DMSC to advise the TSC, CI and Sponsor (and Funder if applicable) on safety issues. The DMSC should be completely independent of the CI and the Funder/Sponsor.

A DMSC Charter should formalise the membership, responsibilities, and reporting mechanisms of the committee. A copy of the Charter should be kept in the TMF.

Not all studies will require a DMSC. For some studies there may only be one group/committee with the function of both the TSC and DMSC.

Minutes (or recommendations/reports) should be provided to the TSC, CI and Sponsor/Funder, as applicable, and copies should be kept in the TMF. The DMSC will make recommendations to the TSC about any safety issues.

5.9 Public Involvement

5.9.1 Introduction

The public involvement responsibilities of the research team are defined in the UK Policy Framework for Health and Social Care Research. Principle Four of the Framework: Patient, Service User and Public involvement states that 'Patients, service users and the public are involved in the design, management, conduct and dissemination of research, unless otherwise justified.'

5.9.2 Best practice in public involvement

Most Funders require researchers to show how they plan to involve patients and the public in their research. The IRAS application form also asks for this information. Where users have not been involved, researchers must show clear justification for not including them. Public and Patient Involvement (PPI) is about researchers working as partners with the people their research will affect. Members of PPI groups who are involved in a research study are referred to as research partners.

Connections with public involvement groups, networks, or individuals should be established at the earliest possible stage (ideally from the design stage), but PPI can be incorporated at different stages of the study lifecycle.

NIHR INVOLVE have developed guidance for researchers on how patients and the public can be involved in research and the HRA also provides guidance on their website.

The National Standards for Public Involvement are a national framework to improve the quality and consistency of public involvement in research. They include indicators to signal whether PPI in research meets the standards

5.9.3 Involving people in research studies

The study team should establish who the most suitable people are to involve in the research, e.g. people with a particular condition; families and carers of people with the condition; men/women, young/old; general public; is there anyone which should be excluded? There may be a suitable PPI group already in existence but where this is not the case the trial manage will need to set up a study-specific PPI group.

The trial manager may need to provide a role description and person specification and collect expressions of interest from any potential research partners, and to advertise for and invite members of the public to specific PPI activities. Involvement may need to be formalised and the trial manager should produce a Terms of Reference to cover this. Various PPI templates are located on the BTC Teams channel.

The remit of involvement should be clearly communicated to any PPI group. It should also be clear on which aspects feedback is not required and the things that cannot change e.g. where a particular procedure must be undertaken in a certain way.

Other specifics of the commitment should be communicated to the research partners such as need to attend certain meetings, travel, review of documents, frequency of meetings and duration, accessibility to venue, mode of communication, etc.

Training should be provided to members of the PPI groups as appropriate. The trial manager or PPI lead should develop training materials to give new members the appropriate background to understand the research environment and the specifics of the study they are to contribute to.

PPI members should be paid for their time as well as reimbursed for expenses. The NIHR provides guidance on reward and recognition offered for such contribution.

Anyone who is involved should be kept up to date for the duration of their participation.

5.10 Case Report Form (CRF) Development

5.10.1 Producing the CRF

A CRF is a printed, optical, or electronic document designed to record protocol-required information to be reported to the Sponsor on each trial subject. It is the responsibility of the CI or delegate to define the data items to be collected and included on the CRF and to approve the CRF and any amendments made to it.

The main purposes of a Case Report Form (CRF) are:

- To provide data required to answer the research question
- To provide de-identified data to the Sponsor
- To provide the Sponsor evidence of participant compliance

Individuals with relevant experience, on the basis of their job role and qualifications, will contribute to the development of the CRF, e.g. to provide statistical/IT/design input, pharmacy information, specialist clinical/scientific advice.

CRFs should be designed to collect the information required to meet the aims of the study and to ensure the eligibility and safety of the participant, and that the study has been conducted as per the protocol and GCP.

Study specific CRF completion guidelines may be generated, if required. These are recommended where the study is multicentre to facilitate consistency of data entry across sites or where data collection is complex.

CRFs shall be stored in a secure location when the trial is active and archived as required (see Study Closedown SOP (BTC-SOP-TM-003).

CRFs should be available for monitoring and inspection by a Sponsor representative and regulators.

CRFs should always match with source data (unless the CRF is the source data). Any discrepancies shall be clearly noted, and the reason explained (see CRF Completion section in the Study Conduct SOP (BTC-SOP-TM-002)). CRFs may also be source data. Source data should be defined in the protocol.

All final versions of the CRF must be kept in the TMF and all changes to final versions used for data collection should be documented. The control of CRF versions should follow the general guidance provided in the Quality Management Systems SOP (BTC-SOP-QM-002).

5.10.2 Approval of CRFs

The CI or delegate, the study statistician and the study database manager or delegate, must sign the approval page of all finalised versions of the CRF or an approval record should be kept. This must be completed before the CRF is used to collect study data.

A copy of the CRF approval signature page or approval record must be kept in the TMF. The CI or delegate should ensure that the CRF is reviewed and approved by the Sponsor before implementation, if not delegated to the CI/BTC.

CRFs do not require approval from the REC/HRA, however, where forms are self-completed by the participant (for example questionnaires or diary cards) and form part of the CRF, the relevant approvals for these documents should be sought.

5.10.3 Amending the CRF

Any amendments required to the CRF after approval should be sent to the CI (and TMG if applicable), for review.

Any amendment which affects the data collected should be communicated to the study statistician, and any issues identified during review should be addressed.

The agreed version should be approved as described above.

The implementation date should be documented.

5.11 Data Integrity

5.11.1 Introduction

Adequate and robust data management procedures are critical to ensure the generation of high-quality and reliable study data. Efficient data collection and management is an essential component of a clinical trial and only data that are relevant for the purpose of a clinical trial should be recorded.

The data management processes typically encompass the design and production of the data capture tool for the collection of subject data from the site, the design and construction of the database, the processing of the data, database lock, production of a final data set and statistical analyses.

5.11.2 Data protection

Throughout the data management process, all trial data must be kept in a secure location and in accordance with the General Data Protection Regulations (GDPR) and in accordance with

information supplied in the REC application, protocol, PIL/PIS and consent forms. Data needs to be managed in a way that preserves their accuracy, integrity and legibility with user access restrictions and data retrievable by designated personnel only. This applies to electronic and paper records.

5.11.3 Data Protection Impact Assessment (DPIA)

Conducting a DPIA is a legal requirement for any type of processing, including certain specified types of processing that are likely to result in a high risk to the rights and freedoms of individuals

GDPR requires a DPIA to be undertaken where any initiative will involve:

- the systematic and extensive evaluation of personal data by automated means, including profiling, resulting in decisions that would have significant effects for those individuals
- the processing of special categories of personal data or personal data relating to criminal convictions and offences on a large scale; or
- the systematic monitoring of a publicly accessible area on a large scale.

REC approval procedures and a risk assessment should incorporate the requirements of a DPIA as far as possible, but for higher risk research activities it may be necessary to conduct a separate DPIA. Guidance on what to consider when deciding if a DPIA is required for a study is outlined by the Information Commissioner's Office.

Please refer to Sponsor requirements to determine what assessment criteria should be used in determining if a DPIA is required. Where it has been concluded that a DPIA is unnecessary and will not be undertaken, the reasons for this should be documented.

If a DPIA is required this should be completed at the outset of any project, or change to an existing system or process, that involves the collection or handling of personal information.

5.11.4 Data Management

How the data are to be managed both during and after the conduct of a research study must be documented. This may be within the trial protocol or as a Data Management Plan (DMP).

The extent of the data management activities described in the DMP or protocol are dependent on the complexity of the study and the associated risks.

The content of the DMP may include:

- Types and sources of data
- Data flow from all sources
- Description of procedures for data collection (e.g. electronic or paper CRFs)
- Consideration given to as to whether any files will be posted, faxed, submitted on the internet or transferred electronically)
- A list of source documents
- Description of which data (including safety) are collected and recorded in the CRF
- Database systems to be used for handling study data, including requirements for access control, security and audit trail.
- Data validation (details of data validation and cleaning, discrepancy, and query management)
- Non-CRF data considerations (ECG, blood test results, other laboratory results and subsequent reconciliation of data)
- Data coding conventions

- Details of serious adverse events (SAE) collection and reconciliation
- Study specific data transfer requirements
- Type and schedule of data management status reports / tracking metrics
- Time point and procedure for database lock(s)
- Data entry guidelines
- Data correction rules
- Details of the procedure for unresolved queries, protocol deviations, non-compliance with procedure, file notes which will be presented to the study statistician
- Outline the duration and location of record/database retention.

If a DMP is used this should be agreed at the TMG prior to enrolment of the first participant into the study but may need to be updated as and when additional information becomes available.

5.11.5 Source data

Source data is defined as the first place where data which will be used for the study are written. Complete and accurate source documentation is critical for all clinical research.

It is important to establish and document which documents will provide source data for the study; source data could include hospital records; laboratory notes; participants' diaries or questionnaires; evaluation checklists; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; subject files; and records kept at the pharmacy (e.g. pharmacy dispensing records) or at the laboratories.

A CRF may also be a form of source data when the data is entered directly onto the CRF.

Source documents are considered essential documents and must be archived. Archive requirements apply to essential documents kept at research sites.

5.11.6 Database development and validation

Once the CRF has been designed in accordance with the protocol, a database to store the information collected should be designed. The database should be validated and deemed fit for purpose through user acceptance testing. This process should be documented and saved within the TMF.

Depending on the size and type of study this database could be a spreadsheet, or a Data Management System may be required.

The database should allow changes to be made to the data in a documented manner and should not delete the original data entry to ensure an audit trail for the data is maintained.

The database should be secure, with appropriate security measures to prevent unauthorised access to the data, with a list identifying those individuals permitted to make changes to the data.

There should be adequate backup for the data. If there is blinding involved in the study, the data entry and processing systems should allow this to be maintained.

Data management processes should include validation to ensure the most accurate 'clean' set of data is provided for the statistical analysis.

The database development processes, configuration management, testing and validation are described in the BTC IT SOPs (BTC-SOP-IT-001, BTC-SOP-IT-003, BTC-SOP-IT-004, BTC-SOP-IT-005).

5.11.7 Data Linkage to Routine Data

In addition to data collected within a study, data may also be used from existing data sets, often referred to as routine data, for example NHS Digital. Each organisation who holds and provides data has guidance which should be followed. See the organisation for each relevant nation for specific, and up to date, guidance. Applications and provision of the data can be a lengthy process (e.g. several months) so ample time should be given.

If you intend to incorporate routine data in your study, where relevant, you should review what supporting information you need to include in patient-facing documents such as the PIL/PIS, Consent Form/s and Privacy Statement; see the HRA for further information.

Important elements of an application to use routine data may, for example, include:

- the legal basis under which you access the data
- the security of your data handling and storage systems
- technical feasibility - whether it is possible to provide what is being requested
- the purpose for wanting the data, including what benefits will be yielded for health and social care in the UK.

As part of the application process, you will likely need to liaise with the Information Governance (or equivalent) team(s) from your Data Controller and Data Processor organisation(s) regarding data security (e.g. Data Security and Protection Toolkit).

5.12 Participant facing study documentation

5.12.1 Introduction

The HRA provides online guidance for researchers on consent, and how to prepare materials to support this process: However, requirements by the Funder/Sponsor for participant-facing documentation should be observed. These may include branding logos or Funder disclaimers or acknowledgments.

All study documentation should be named, version controlled and dated as described in the Quality management SOP (BTC-SOP-QM-002).

BTC study team should review all participant-facing documentation and subsequent amendments before they are submitted to any of the review bodies to ensure that they meet a standard that adheres to the principles of GCP.

Other forms of media may be developed for a study, such as video recordings or slides and must be reviewed by BTC study team and included in the application for regulatory authorities' review.

Further information on the informed consent process is included in the Study Conduct SOP (BTC-SOP-TM-002).

5.12.2 Preparation of Participant Information Leaflet / Sheet (PIL/PIS)

The participant information leaflet (PIL) and consent form (section below) are key documents and a major consideration during ethical review. The PIL should be developed in conjunction with the CI, research nurses and other members of staff as appropriate. When developing the PIL the HRA guidance and templates should be considered, unless the Sponsor requires that Sponsor-specific templates be used. PIL templates can be modified to accommodate different types of

studies and under-served groups, e.g. for use in paediatric trials or other groups with specific needs (e.g. visually impaired participants). The templates provided on the HRA website include all information that should be found in the PIL according to GCP guidelines and guidance on design and style of PILs.

The PIL should be designed for each appropriate age/competence range and use pictures if appropriate. The age ranges may differ depending on the type of study, the condition or the population being approached. In general, unless the study only involves neonates and very young children, separate PILs should be produced for children. Suggested age groups are 10 years and under and for children aged 11-15 years. Information leaflets must be produced for parent(s)/guardian(s) if the participants are under 16 years of age.

Consultee information leaflets and consultee declarations or legal representative PIL and consent forms must be prepared and submitted for studies where participants lack capacity (under the Mental Capacity Act 2005 (or the Adults with Incapacity (Scotland) Act 2000) or Clinical Trials Regulations respectively).

Further information about these provisions is available on the HRA website.

For studies submitted through Radiation Assurance (see below in 5.14.3) a generic risk statement will need to be chosen for the assessment in IRAS and should be included in the PIL.

5.12.3 Preparation of Consent Form

GCP requires evidence of 'informed consent' in writing or in an alternative form i.e. verbal consent if the research is deemed low risk e.g. consent to interview or consent to complete questionnaires.

If written consent is used, the consent form must be designed so that it captures the participant's signature, and the date consent was given or otherwise marked, by the person being approached for consent. If conducted face to face, the consent form must also capture the signature of the person taking consent and the date consent was taken.

Comprehensive guidance and consent form templates are provided on the HRA website.

eConsent (electronic methods for seeking, confirming, and documenting informed consent) can be considered either to supplement the paper-based approach or, where appropriate, as a replacement for it. The guidance on legal and ethical requirements for seeking and documenting consent using electronic methods published as a joint MHRA and HRA statement should be observed. The relevant guidance and the statement are provided on MHRA and HRA websites.

5.12.4 Preparation of other participant-facing study documentation

Other participant-facing documents may include, but are not limited to the following:

- Advertising material
- Participant invitation letters
- Participant questionnaires (NB: for validated questionnaires you may need copyrights or licences, or to seek author's permission to use them in the study).

All participant facing documents must receive a REC favourable opinion and/or HRA and Health and Care Research Wales (HCRW) approval before use.

5.13 Submissions to review bodies

5.13.1 Integrated Research Application System (IRAS)

The Integrated Research Application Systems (IRAS) are online systems for applying for permissions and approvals for health and social care/community research in the UK.

CTIMPs or combined trials of an investigational medicinal product and an investigational medical device (IMP/Device trials) applications must be submitted using the relevant part of the IRAS.

Detailed instructions on what to submit and how to submit applications, including the combined review for CTIMPs and combined IMP/device trials, are published on the IRAS Help, and must be observed. A step-by-step guide to using IRAS and an e-learning module are available on the IRAS website.

5.13.2 NIHR Portfolio adoption

The National Institute for Health Research (NIHR) Portfolio of studies consists of clinical research studies that are eligible for support from the Clinical Research Network (CRN) in England. The NIHR CRN can help with study feasibility, set up and delivery of research to time and target.

These services are available to all studies, regardless of location, study type, study size, therapy or research area, provided they meet certain eligibility criteria, as outlined on the NIHR website.

Applications to be considered for NIHR CRN support should be made through IRAS, or where HRA Approval is not required, through the relevant Local Clinical Research Network. CTIMPs led from England which are applying for HRA approval through the combined review service must apply for NHIR CRN support through the Non-commerical Portfolio Application service in CPMS.

5.13.3 Deciding which regulatory approvals are required

IRAS captures the information needed for the relevant approvals from the following review bodies:

- Administration of Radioactive Substances Advisory Committee (ARSAC)
- Confidentiality Advisory Group (CAG)
- Gene Therapy Advisory Committee (GTAC)
- Health Research Authority (HRA) and Health and Care Research Wales (HCRW) for projects seeking HRA & HCRW Approval
- Medicines and Healthcare products Regulatory Agency (MHRA)
- NHS / HSC R&D offices
- NHS / HSC Research Ethics Committees
- Her Majesty's Prison and Probation Service (HMPPS)
- Social Care Research Ethics Committee

IRAS uses filters to ensure that the data collected and collated is appropriate to the type of study and the permissions and approvals required. For further details see the HRA,IRAS and review body websites. The HRA website includes a decision tool to help inform the relevant approvals required for a study.

It is important that the IRAS filter questions are answered correctly. If you are unsure, please obtain further advice from the Sponsor or BTC Trial Portfolio Leads.

5.14 Submissions to the Health Research Authority (HRA)

5.14.1 Studies which can be approved through the HRA and HCRW approval process

Projects meeting all the following criteria are suited for HRA and HCRW Approval:

- The lead NHS R&D Office is in England or Wales

- It is a project-based study type. That is a study described by any of the types of study listed on IRAS except “research tissue banks” and “research databases”:
    - a Clinical Trial of an Investigational Medicinal Product (CTIMP) (with the exception of Phase 1 trials in healthy volunteers taking place outside the NHS)
    - a Clinical Investigation or other study of a Medical Device
    - a combined trial of an Investigational Medicinal Product and an Investigational Medical Device
    - a Clinical Trial to study a novel intervention or randomised Clinical Trial to compare interventions in clinical practice
    - a basic science study involving procedures with human participants
    - a study administering questionnaires/interviews for quantitative analysis, or using mixed qualitative/quantitative methodology
    - a study involving qualitative methods only
    - a study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
    - a study limited to working with data (specific project only).
- NHS premises and/or NHS patients and/or NHS staff in England and/or Wales are participating in the project.

Further information to determine whether a research study requires HRA and HCRW approval is provided on the HRA website.

Studies led from England or Wales with sites in Northern Ireland or Scotland will be supported through existing UK-wide compatibility systems, by which each country accepts the centralised assurances, as far as they apply, from the lead nation without unnecessary duplication.

If a project is led from Scotland or Northern Ireland and involves NHS/HSC sites in England and/or Wales you should apply through the appropriate NHS/HSC permission process for that lead nation. Compatibility arrangements are in place so that HRA and HCRW Approval will then be issued for the English/Welsh sites.

NB: The process for submitting the IRAS Form is the same regardless of whether a project needs NHS REC review or which of the UK nations the lead NHS/HSC R&D office is in.

Where a project will not be managed as research there is no need to apply for HRA Approval or to an NHS REC. However, you should contact the clinical governance or research and development (R&D) office of the organisation at which the project will be conducted to discuss what other local review arrangements or sources of advice may apply. For example, there may be standard guidelines on the conduct of clinical audit. The Caldicott Guardian will be a source of advice on the use of patient data.

5.14.2 Technical Assurance

Technical Assurance is the coordinated review process for studies that involve pharmacy (CTIMPs) and/or ionising radiation. There are two types of Technical Assurances – Pharmacy Assurance and Radiation Assurance.

Both Pharmacy Assurance and Radiation Assurance need to be completed **before** applying for relevant regulatory approvals e.g. REC, HRA & HCRW Approval, or ARSAC.

You can apply for Pharmacy Assurance at any time point up to and including the data on which you e-submit your IRAS form for HRA and HCRW Approval. The HRA recommend that studies should be submitted Pharmacy Assurance no later than three weeks prior to submission for REC review.

Submissions for Radiation Assurance should be made before Part B Section 3 of the IRAS Form has been completed and authorised.

There is a standardised review fee for both Pharmacy and Radiation Assurance. Information can be found on the HRA website.

Guidance provided on the HRA and IRAS websites should be followed.

5.14.3 Research Ethics Committee (REC)

Research Ethics Committees review research applications and give an opinion about whether the research is ethical, ensuring the protection of the rights, safety and well-being of participants involved in a research study and providing public assurance of that protection.

For most applications to the HRA, the REC review forms part of the overall HRA and HCRW Approval process. For some projects that do not require HRA and HCRW Approval, such as research tissue banks and research databases, or Phase 1 trials in healthy volunteers taking place outside the NHS, REC review is still required.

Studies that do not require NHS REC review (e.g. studies where the participants are not NHS patients) should still seek REC review e.g. from a Higher Educational Institution REC.

Guidance on which research studies fall under the remit of NHS RECs is published on the HRA website.

All applications for NHS REC review are prepared using IRAS.

5.14.4 Confidentiality Advisory Group (CAG)

If your research project involves accessing confidential patient information without consent in England and Wales, you will need to apply to the Confidentiality Advisory Group (CAG).

Detailed guidance on the process for submitting an application to CAG, which should be checked before completing an application, is provided on the HRA website.

All research applications should be prepared on IRAS and the supporting document requirements are set out in the checklist for the form.

5.14.5 ARSAC

ARSAC research approval must be obtained for all your research projects where the protocol:

- Requires the administration of radioactive substances
- Specifies the frequency, activity or processing for an administration that would otherwise be considered standard care

ARSAC research approval is not required for research projects where:

- The protocol does not specify any administrations of radioactive substances
- The only administration of a radioactive substance mentioned in the protocol is an inclusion criterion that would be received by all participants as part of standard care, for example a trial where all participants must have received a radioiodine therapy to be considered eligible

The application form must be completed via the IRAS. Detailed information on what to submit and how to submit the application is available on IRAS Help. Please also visit the ARSAC website for further information on applying for ARSAC research approval.

5.14.6 Her Majesty's Prison and Probation Service (HMPPS); formerly NOMS

Research projects which require access across Her Majesty's Prison and Probation Service (HMPPS) (including headquarters) and all community-based/custodial providers in England and Wales, including research involving Community Rehabilitation Companies (CRCs) and their subcontractors, Contracted Prisons and Young Offenders' Institutions (YOIs) and Secure Training Centres (STCs) require an application to the HMPPS.

The application form must be completed in IRAS and the instructions provided within must be followed. Further guidance for successful applications is also provided on the HMPPS website.

5.14.7 Submission of Supporting Documents

IRAS applications require the submission of supporting documentation with the completed application form. The documents are the responsibility of the Sponsor, but their completion and/or submission may be delegated to the BTC.

Supporting documents will depend on the type of study. IRAS generates a checklist of supporting documents Please refer to this checklist for the complete list of documentation to be submitted with an application.

The supporting documentation usually comprise (as applicable):

- study protocol
- participant information sheets/leaflets and consent forms
- where applicable, information leaflets and consent/assent forms or declarations for parent/carer/legal guardian, consultee, legal representative, pregnant partner, etc.
- GP letters
- recruiting material
- website content
- questionnaires
- Curriculum Vitae (CV) for the CI, and for student(s) and academic supervisor(s) for PhD and doctoral level student projects
- laboratory manual, pharmacy manual, etc., if used/available.

In addition, for the HRA assessment only (for studies where HRA and HCRW approval is required), for non-commercial research, the following need to be included with the application:

- Organisation Information Document (OID) and
- Schedule of Events or Schedule of Events Cost Attribution Template (SoECAT)
- model agreement (if required)

Version controlled supporting documents should be uploaded to the checklist and all electronic authorisations received before submission. Authorising parties must have created and have access to an IRAS account before they are able to authorise application forms.

Further guidance on what to submit and how to submit the application, as well as templates, are provided on the IRAS website.

5.14.8 The HRA and HCRW Approval review process

Once the IRAS form along with the relevant supporting documents have been submitted, HRA will provide initial validation of the application.

After validation, applications proceed to REC review and/or HRA and HCRW Approval.

Applications that require REC review will be reviewed at a REC meeting. The REC will issue their opinion which may be a final opinion, or they may request additional information and clarification before issuing a final opinion.

In parallel to the REC review, applications that require HRA and HCRW will undergo an initial assessment. The HRA will usually issue an outcome of an initial assessment (sent via email), confirming the documents to be used in the study and the information that sites will need in order to begin to set up the study. The initial assessment also identifies key issues that need to be resolved prior to HRA and HCRW approval. At this stage, the local information pack can be sent to applicable R&D departments at the participating sites (see section 5.19).

HRA and HCRW assessment continues as other regulatory approvals are received. The HRA and HCRW approval cannot be granted until all other applicable regulatory approvals are in place, e.g. REC favourable opinion, CTA or CAG advice on whether an application should or should not be approved.

For studies under the remit of the HRA and HCRW, a study cannot commence before the HRA and HCRW approval letter is issued. Please ensure you read the letter carefully as it will instruct what actions need to be undertaken by R&D departments.

5.14.9 Combined review service (formerly called Combined Ways of Working (CWOW))

The combined review offers a single application for Clinical Trial Authorisation and REC opinion through a co-ordinated review leading to a single UK decision for CTIMPs or combined IMP/Medical Device trials.

Combined review must be used for all new CTIMP and combined IMP/device trials.

For combined review applications for trials requiring Radiation Assurance follow the guidance available on the HRA website prior to starting an application.

The instructions provided on IRAS Help on how to make a submission must be followed.

See further information on clinical trials authorisation applications below in 5.15 Applications for clinical trials authorisation.

5.14.10 Non-NHS REC Review

Where a study is not suitable / does not need NHS REC review (i.e. health or social care research that doesn't involve patients, service users, NHS staff as participants or identifiable

samples/tissue, or identifiable data), it may still have ethical implications and require REC review. Most academic institutions require that applicants undertaking research as part of an academic qualification seek REC review from their University REC. Information on the requirements should be obtained from the respective institution.

5.15 MHRA (Medicines and Medical Devices)

5.15.1 Introduction

The MHRA is the national executive agency responsible for ensuring that medicines and medical devices meet applicable standards of safety, quality and efficacy.

If a study is a CTIMP, the Clinical Trial Authorisation (CTA) will be required before the research can start.

For an investigation of a medical device the MHRA issues a 'no objection' for the proposed investigation to be carried out.

5.15.2 Deciding if a CTA is required

In a CTIMP participants will be administered a product known as an Investigational Medicinal Product (IMP). Medicinal products are substances or combinations of substances which either prevent or treat disease in human beings or are administered to human beings with a view to making a medical diagnosis or to restore, correct or modify physiological functions in humans.

To determine if a study is a CTIMP the MHRA have developed an algorithm to follow, which can be accessed from the MHRA website. Clinical trial mock examples are also described for reference.

5.15.3 Combined review

All new applications will be prepared, submitted and reviewed via the combined review service, as described above in 5.14.

5.15.4 European Union Drug Regulating Authorities Clinical Trial (EudraCT) number

EudraCT is a database of all clinical trials of IMPs commencing in the European Union. The EudraCT number is a unique identifier which is required for all trials conducted with an IMP in EU member states. Please note this is no longer required for trials conducted in the UK.

To obtain a EudraCT number, go to the EudraCT website. EudraCT numbers can only be created for studies conducted exclusively outside of the EU/EEA that are part of a Paediatric Investigation Plan (PIP) and/or in scope of Article 46 of the Paediatric Regulation (EC) 1901/2006 (so called "third country file").

5.15.5 Documents to send with an application

The IRAS portal includes a list of documentation to submit for combined review of your application. The MHRA also provides some additional guidance on some of the documents required for submission.

The MHRA has produced some mock examples of completed IMPDs which set out minimum requirements; these are published on the MHRA website.

5.15.6 Expert Advice

The MHRA may seek advice from the Clinical Trials, Biologicals and Vaccines Expert Advisory Group (CTBVEAG) of the Commission on Human Medicines (CHM) based on an assessment of the risks and how the Sponsor plans to mitigate them or if other issues are identified during the assessment process. Details are available on the MHRA website.

For those type of studies (some first-in-human trials as detailed in the guidance), the Sponsor(s) should contact the MHRA before applying for a CTA.

5.15.7 Risk Proportionate Approach and Notification scheme

A risk proportionate approach to the initiation, management and monitoring of certain clinical trials is possible. The MHRA will perform a risk adapted assessment of certain Type A' trials in which the risk to the patient from the IMP is considered to be no greater than that of standard medical care

These are trials involving medicinal products licensed in any EU Member State if:

the trial relates to the licensed range of indications, dosage and form of the product, or;

the trial involves off-label use (such as in paediatrics and oncology) that is established practice and supported by enough published evidence and/or guidelines.

There is also a notification scheme for CTA applications for Phase 4 and certain Phase 3 clinical studies deemed to be of lower risk. The inclusion criteria for the Notification Scheme can be found on the MHRA website. CTA applications submitted under this scheme will be processed by the MHRA within 14 days, instead of the statutory 30 days.

Applicants whose study meet these criteria should participate in the scheme by registering their interest. The form to register your interest can be found on the MHRA website.

5.15.8 Application fee

The fee is dependent on the type of trial and a full list is on the MHRA website.

Invoices for CTA applications and Substantial Amendment applications are sent directly to the applicant shortly after a valid submission has been established. For details on how to make a payment see the MHRA website. Penalty fees can be incurred for non-payment, as well as suspension of any licence or authorisation, followed by legal proceedings.

5.15.9 Assessment of CTA submissions

The initial combined review assessment will be completed within 30 days of being submitted. . Applications for healthy volunteer trials and Sponsor-determined phase I trials in non-oncology patients may qualify for a shortened assessment time (average 14 days). You should state on your covering letter if you think your trial is eligible.

The outcome of a CTA submission, along with the outcome of the research ethics committee review, will be communicated via the combined review process, and it could be:

- acceptance of the request for a CTA;
- acceptance of the request for a CTA subject to conditions; or
- grounds for non-acceptance of the request for a CTA.

If grounds for non-acceptance are raised, justification/reasons are specified, and applicants will usually have to submit a Response to Further Information (RFI) or amend the application and resubmit.

5.15.10 Notification about a clinical investigation for a medical device

The MHRA must be informed if a Sponsor intends to carry out a clinical investigation as part of the process to obtain a UKCA / CE / CE UKNI marking for a medical device at least 60 days before starting the investigation. A notification will not be required for medical devices that have a mark for the purpose that is under investigation. Details are provided on the MHRA website.

5.15.11 Submitting a clinical investigation for MHRA assessment

The MHRA should be provided with advanced notice of an intention to submit a clinical investigation by emailing the MHRA with basic details about the investigational device, the intended population, the type of study, and estimated application date. Submission documents should be prepared before the notification of a proposed clinical investigation.

Applications are prepared and submitted electronically via IRAS.

The MHRA guidance on compiling a submission and guidance for Manufacturers should be followed when preparing the notification application.

5.15.12 Application fee

The fee rate is based on a single investigational device being used in a study and it depends on the class of the device. Details are provided on the MHRA website.

Applicants will receive an invoice to allow them to make payment for the correct amount once an application has been validated.

5.15.13 MHRA Assessment of clinical investigations

For clinical investigations being conducted in Great Britain the MHRA validates the submission and sends an acknowledgement within 5 working days to confirm that the 60-day assessment has started or to raise any issues. If there are any issues raised, the 60-day assessment will start when a valid response is received.

During the assessment, experts assess the safety and performance of the device as well as the design of the clinical investigation to be carried out. The MHRA will write to applicants if they require further information.

A letter is sent to the applicant by the 60th day with a decision (‘objection’ or ‘no objection’) as to whether or not the proposed clinical investigation can be carried out.

NB: Different processes are applicable for studies involving Northern Ireland.

5.16 Additional arrangements for CTIMPs and Clinical Investigations of Medical Devices

It is the responsibility of the trial Sponsor to have procedures in place to ensure that the manufacturing, packaging, labelling, releasing and distributing of the IMP/Medical Device is

conducted according to the principles of Good Manufacturing Practice (GMP) and GCP, delegating specific responsibilities accordingly.

There should be a clear delegation of responsibilities for the receipt, storage, administration, accountability, management, return and destruction of IMPs/Medical Devices. A trial-specific SOP or pharmacy/user manual may be written and it should be approved by appropriate personnel.

All protocols for CTIMPs and investigations of medical devices should detail the IMP requirement/intended purpose of the device, including a description of the trial treatment/procedure, provision of the IMP/device, labelling, packaging, storage, dispensing, accountability, route of IMP administration/mode of action of the device, the dosing regimen and any risks and related safety assessments.

5.16.1 IMP Supply / Distribution

Where needed, a process of supplying the IMP to the participating site(s), including qualified person (QP) release and support, distribution, should be put in place between the manufacturing unit/supplier and site at the start of the study. This will be trial specific, and should be approved by the Sponsor.

A research site must not be supplied with an IMP until all regulatory approvals for the trial to start and all local permissions at that particular site are in place.

The supplier of the IMP is responsible for ensuring the quality of the IMP supplied to the research site.

The process of managing the IMP must be clearly documented in the study manual (or equivalent) and may be detailed in the applicable agreement. Items for consideration include:

- the management of stock levels, restocking/ordering of IMP
- transport and storage conditions for the IMP (e.g. acceptable tolerance limits for temperature, humidity, exposure to light)
- processes for the handling and use of the IMP
- prescribing arrangements & forms to be used
- form and strength of the IMP (e.g. capsule, ampoule etc.)
- stability data for IMP
- product defect support / procedures for IMP recall
- returns and destruction
- any other information relevant to the trial.

The process of ordering IMPs should be discussed with the local investigators and pharmacy staff prior to the study commencing at the site(s).

5.16.2 IMP receipt at sites

When all the required regulatory and local approvals and documentation are in place for the local site, and usually after the green light has been issued, the IMP will normally be released to the relevant pharmacy.

The Trials Pharmacist from the relevant pharmacy will be responsible for managing and documenting the receipt of the IMP, including QP release statement for each batch of IMP delivered, code envelopes and randomisation lists, as well as for the storage, dispensing, return and destruction of the IMP for the duration of the study, as agreed with the Sponsor or delegate.

The Sponsor or delegate should ensure that written procedures are provided to the relevant Trials pharmacy and local site team, which document the procedures for the handling and storage of the IMP and include adequate documentation. The procedures should address receipt, handling, storage, dispensing, recall, unblinding, expiry date extensions, temperature excursions, retrieval of unused product from trial participants, and return of any unused IMP to the relevant pharmacy (or alternative location if authorised by the Sponsor and in compliance with the applicable regulatory requirements).

5.16.3 Labelling of IMPs

The labelling requirements of IMPs used in clinical trials must conform to the regulations stipulated in the Clinical Trials Regulations. See above section 5.15.5 (documents to send with an application) for further information.

Additional labelling for trial purposes may not be necessary if the IMP is being used under the conditions stipulated under its licence. If this is the case, (i.e. the medication will only display its original labelling with no trial specific information), the reasons for this should be explained in the CTA application.

In placebo or active controlled trials that are blinded, all study medication should be presented in identical packaging and labelling, in order to maintain the blinding. The exception to this is if blinding of investigator and/or participant is achieved through other means (e.g. administration of study medication by unblinded team members).

5.16.4 IMP accountability

The relevant pharmacy (or appropriate alternative) will be responsible for maintaining accountability records relating to the delivery of the IMP to the local site (shipment and receipt dates), inventory at the site, use by each participant, receipt of unused IMP from participants and return of unused IMP to the Sponsor or delegated department/organisation.

Pharmacy accountability records should include the IMP name, strength, form, quantities, batch/serial numbers, expiration dates and the unique code numbers assigned to the IMP(s) and trial participants (if applicable), as well as temperature monitoring records (if/as required) which document that the IMP was stored as specified by the Sponsor.

5.16.5 Management of medical device(s) for clinical investigations

Arrangements for the management of the medical device(s) under investigation should be clearly specified in the protocol or instructions for use (or equivalent). The PI or delegate is responsible to ensure safe storage, handling and accountability of the medical device(s) used in the clinical investigation.

The PI and site team should be trained in and have good understanding of the medical device and its clinical application.

Labels for the investigational device should state that the device is for clinical investigation only. Investigational devices should be kept separately from devices in routine use.

Arrangements should be in place, where relevant, for decontamination, reprocessing, servicing, maintenance and disposal of the investigational device in conjunction with the Sponsor/Manufacturer.

Tests should be carried out by an adequately trained and appropriately qualified person. Arrangements may need to be put in place to train local staff or source expertise.

Where local testing and issue of local safety certificates are required (e.g. Medical Physics, Clinical Engineering, etc), this should be arranged and any certificates should be obtained before the device can be used.

There should be a clear mechanism for the site personnel to alert the Sponsor/Manufacturer when additional supplies of the device and/or consumables or accessories (e.g. cleaning agents, tools for installing, calibrating and maintaining the devices) are required.

If applicable, unblinding procedures should be clearly communicated in writing.

Criteria for stopping or curtailing the investigation or use of the device should be clearly documented, as well as arrangements for processing and reporting adverse incidents and protocol deviations.

Documentation regarding receipt, storage, use, and return or destruction of the device should be maintained and filed in the TMF and the ISF.

5.17 Additional arrangements for studies involving human tissue samples

Consent to take and process biological samples must be obtained. The exception is the use of waste tissue that is anonymised. Any laboratory work carried out for the purposes of a research study must be done in accordance with the relevant study documentation (BTC Laboratory SOP (BTC-SOP-LAB-001), protocol, laboratory manual (where available), PIL, consent form) and all applicable regulations.

At the start of a study which involves the collection, receipt, processing, storage and/or destruction of research tissue samples, a study specific laboratory site file should be set up. A Laboratory Manual may also be produced if appropriate.

Sample analysis should be performed in accordance with a predefined plan. The research team should agree and document what analyses are to be completed before implementing any analyses. A study specific research sample receipt and storage log should also be set up.

BTC staff running a study that involves collection of research samples should ensure they receive training on all relevant SOPs and ensure that any individual working within the laboratory on their study receives training on the Laboratory SOPs and any specific laboratory procedures, signs the delegation log, completes GCP training if/as appropriate and provides an up to date CV. Laboratory staff are not required to attend training sessions on SOP updates unless the changes impact on the procedures they are carrying out.

At the end of the research, the research samples that are relevant under the Human Tissue Act must be destroyed or transferred to a licenced Tissue Bank in accordance with the approved REC application and HTA regulations. This should be carried out in consultation with the study Sponsor.

If future use is planned, appropriate participant consent must be in place, and you will need to do one of the following:

- apply for ethical approval of a new project
- set up a research tissue bank and obtain a HTA licence
- transfer to a licenced Tissue Bank (under HTA licence).

Laboratory set up and close down procedures and specific guidance are detailed in the Laboratory SOP BTC-SOP-LAB-001.

If samples will be transferred between organisations a Material Transfer Agreement may be needed, please discuss this with the Sponsor.

5.18 Study Registration

All research needs to be registered on a publicly accessible database/register. This is a condition of favourable ethical opinion and for CTIMPs (other than adult phase I trials), this is also a legal requirement.

All studies should be registered on the International Standard Randomised Controlled Trial Number (ISRCTN) registry or equivalent. A study may also be registered with clinicaltrials.gov, however the ISRCTN is the recommended registry.

Both registries accept both randomised trials and observational studies. The ISRCTN registry is open to all study designs in all areas of health care and clinicaltrials.gov accepts clinical studies with human subjects that assess biomedical and/or health outcomes and that conform to any applicable human subject or ethics review regulations.

The HRA will automatically register clinical trials with ISRCTN Registry as one of the steps to ensure research transparency. All clinical trials of investigational medicinal products (CTIMPs) and combined trials of an investigational medicinal product and an investigational medical device (IMP/device trials) submitted on or after 1 January 2022 for combined review in the new part of IRAS will have study information sent directly to ISRCTN for registration.

All studies eligible for NIHR CRN support which have a study identifier can be registered on ISRCTN using the Central Portfolio Management System (CPMS). For further details on how to register a CRN supported study go to the NIHR website.

Registration should occur before the first participant is recruited and no later than six weeks after recruitment of the first participant.

Deferral/exemptions are allowed in some circumstances (e.g. adult phase 1 studies); these must be agreed by or on behalf of the REC. To apply for deferral contact the HRA.

5.19 Participating Site Set-Up

5.19.1 Participating research sites

A research site is defined as the single organisation with day-to-day responsibility for the location where a research project is carried out.

Please note that the research site is not necessarily the location where research activities will actually take place. For example, in a research project where practice nurses from General Practices interview participants in the participant's home, the research site would be the Practice.

5.19.2 Participant Identification Centres (PICs)

PICs are NHS or HSC organisations that identify potential research participants. They are not research sites and should not be treated in the same way as research sites.

An NHS/HSC organisation is operating as a PIC when it meets the following three criteria:

- identifies potential research participants by processing personal data (e.g. through carrying out a search of a patient records database to identify individuals that meet a study's eligibility criteria)
- is following the Sponsor(s) instructions in identifying potential research participants
- directs these potential participants elsewhere without undertaking any further research activity for that study (i.e. the research occurs at another legal entity).

It is recommended that the study team discuss with the sponsor when considering whether to use PICs.

PIC organisations should be detailed within the IRAS form. If PIC sites are added after initial approval a substantial amendment is required. Further information about contractual arrangements for PICs can be found in section 5.4.4 Site agreements.

5.19.3 Site selection

Careful selection of investigator(s) and institution(s) ensures that study resources are directed towards sites with the potential to generate high quality data.

Investigator(s) and participating research site(s) should be selected and assessed by the Sponsor (or CI or delegate).

Participating sites should be included in the initial IRAS application. Following HRA/REC/MHRA approval any further Participating Sites not included in the original IRAS application must be notified to the HRA/REC. For further guidance check the HRA/IRAS websites.

A study specific Expression of Interest (EoI) form may be used in order to collect the same information from all potential sites, including interest and willingness to participate, qualifications and training of site staff, potential for attaining recruitment targets and adequate facilities/ equipment/ resources to undertake the study.

The BTC should remind PIs at participating sites that they must liaise with any local service departments needed for study specific procedures (e.g. radiology, pharmacy, laboratories) as soon as the participating site start-up process commences.

5.19.4 Local Information Pack

Once the Sponsor receives the initial assessment letter (or Approval letter in cases where no initial assessment letter is issued) from the HRA, they (or the BTC if this task is delegated) can contact participating NHS sites to provide them with the UK Local Information Pack and finalise discussions around confirming capacity and capability.

The Local Information Pack is the UK-wide mechanism for setting up participating NHS/HSC organisations. It provides a consistent package to support study set-up and delivery across the UK and should be used for all studies with participating NHS/HSC organisations. The Sponsor, or authorised delegate, is responsible for sharing the UK Local Information Pack with participating NHS/HSC organisations.

The local information pack should contain:

- Covering email using standard template format
- Copy of IRAS Form as submitted
- Protocol and amendments
- Participant information and consent documents (without local logos/ headers)

- Localised Organisation Information Document (OID); the OID is required only for non-commercial research
- Relevant model agreement (mNCA) if required
- Localised Delegation log (where applicable, including known research team names but not signatures, or indicate when this will be shared)
- Schedule of Events or Schedule of Event Cost Attribution Tool (SoE/SoECAT)
- Copy of Initial assessment letter (if one is issued) and (when issued) HRA and HCRW Approval letter and final documents
- Any other documents that the Sponsor wishes to provide to the site to support the set up and delivery of the study

If the participating NHS organisations are in England and/or Wales the Sponsor (or delegate) localises the OID(s) and emails it together with the other documents that make up the UK Local Information Pack to the R&D office and study delivery team (PI or Local Collaborator, as applicable) at participating NHS organisation(s). For NIHR portfolio studies, the Sponsor should copy the Local Information Pack to the respective LCRN.

The correct HRA email template should be used when sharing the UK Local Information Pack with participating NHS organisations in England and/or Wales.

If the participating HSC organisations are in Northern Ireland the OID(s) and the Local Information Pack should be emailed to the R&D office and study delivery team (PI or Local Collaborator, as applicable) at participating HSC organisation(s).

If the participating NHS organisations are in Scotland, the localised OID(s), along with the relevant delegation log for the site (if applicable), should be emailed to NRS Permissions Coordinating Centre (CC) who will then make the Local Information Pack available to participating NHS organisations in Scotland (R&D, research teams and networks, as applicable). There is no need to supply documents already electronically submitted as part of the IRAS Form application as they will be made available to participating NHS sites in Scotland via NRS Permissions CC.

5.19.5 Site Approval

Once all the arrangements are in place to deliver a study, the participating NHS organisation will provide confirmation of capability and capacity (C&C), indicating that they are ready to start the study.

For non-NHS sites, a site approval will be required, this must be sent from an organisational email account and confirm the organisation are 1) happy for the study to take place, 2) that they are willing to support the study and 3) they have capacity to support the study.

The Sponsor (or BTC if delegated) should confirm the date at which the site can be activated and/or the study can start at that NHS or non-NHS organisation.

5.19.6 Studies undertaken in primary care settings

Setting up a study in primary care can be complex. Many primary care providers are independent contractors who are responsible for making the decision as to whether or not to participate in any given study. Independent contractors are generally supported by R&D offices with specific expertise in primary care research. However, because of the different ways in which primary care R&D offices are hosted and the different approaches to the role, there are a multitude of different working practices and communication routes across the sector.

It is advised that you contact your local primary care R&D office for assistance to navigate the local permissions. Additional guidance on setting up a primary care study is available on the HRA website.

5.19.7 Site initiation

A site initiation must be completed prior to site activation. This may or may not involve a site initiation visit (SIV); written correspondence or tele/video conferences may be adequate.

The PI, key research staff (i.e. site research nurses, study coordinator, pharmacist, radiologist, etc) must be present during the site initiation (separate meetings/visits can be conducted if they all cannot attend on the same date/time). It is best practice to include the CI where possible (if they are different to the PI).

The site initiation is an opportunity for site staff to obtain clarity on the procedures and interventions within the protocol, study specific documents, source data and PI responsibilities to ensure effective study delivery. Site initiation training (or equivalent, e.g. central training days/remote and/or in person, documents or videos) should be provided as close as possible to the start of recruitment.

The person delegated to conduct the SIV should be thoroughly trained in the study and protocol, including having a good understanding of all study procedures, data collection and CRFs, expected adverse events (AEs), unblinding procedures (for the IMP or intervention as appropriate) and SOPs. This should be documented and reflected on the central coordination delegation log.

The site initiation programme will vary for each study but some common items for training and review are given below:

- Study background, purpose and rationale
- Protocol and amendments
- Inclusion/exclusion criteria
- Screening/enrolment/consent procedures
- Randomisation system and procedure
- Procedures for withdrawals and handling losses to follow up
- Safety reporting
- Sponsor reporting requirements
- eCRF or CRF training and correction/submission procedures which should include clear guidelines as to when the CRF should be completed, how this is checked and monitored by the coordinating team and CI, and how problems are escalated.
- Source document storage procedures
- Study supplies
- Laboratory facilities/accreditation and review of any sample processing or storage areas
- Arrangements/training for any specialised equipment required for the study
- Review instruction on any specialised procedures such as diagnostic tests and special computer programs
- ISF documents and maintenance
- Pharmacy procedures if the study is a CTIMP
- Unblinding procedures
- Site Contacts
- Monitoring activities frequency and expectations
- Site personnel/signature Log (delegation log)
- Enrolment targets/study timeline.

Details of any initiation training should be documented including who provided training, the date and who attended. Any follow-up should be undertaken shortly after the initial training to address questions not answered during the initial stage and to check that any actions have been correctly understood and implemented.

NB: The site initiation training may need to be repeated if the start of recruitment is significantly delayed.

A site will be deemed initiated once all essential documents and approvals are in place and according to Sponsor requirements. This includes:

- Acceptance of the OID (if applicable),SOE or SOECAT, site contract (mNCA) (if required) and any other agreements or accreditations
- Agreement of which documents and systems constitute “source data”, and their location
- The local PI and research team have completed study specific training and are familiar with study requirements, relevant regulations, frameworks, roles and responsibilities
- The site has confirmed capacity and capability
- The site has been provided with relevant documentation, equipment and training to enable site staff to begin the study conduct and recruitment
- Any equipment calibration/certification requirements have been met and certificates are available where required
- Archiving arrangements and retention of site documentation for the study have been discussed
- For a CTIMP:
    - Staff have been trained on the IMP documentation and are satisfied with the IMP management plan (and any other IMP related documents)
    - Details of the IMP storage arrangements are clear
      IMP has been delivered to site or the site is ready to order IMP for when itis required

5.19.8 Site activation letter (or email)

The following checks need to be performed prior to the issuing of the Site Activation letter or email for site to open or begin some activities:

- HRA Approval is in place to include the site
- The central coordinating team and Sponsor have received the signed site agreement (mNCA) (if applicable) and signed and completed OID (if applicable)
- The central coordinating team and Sponsor have received confirmation of capacity and capability
- The central coordinating team have received a copy of the completed delegation log
- The central coordinating team have copies of up-to-date CVs and GCP certificates for the PI and other key staff if required, or equivalent evidence as agreed with the Sponsor
- The central coordinating team have received confirmation from PI(s) that CVs are held locally for all staff on the delegation log, as well as evidence of GCP training if/as required i.e. commensurate with their roles and responsibilities.
- Copies of localised essential documents have been collected by the coordinating team e.g. copies of the participant-facing documentation (e.g. invitation letter, PIL/PIS, consent form) and other study documents (e.g. GP letter).
- Site initiation has been conducted and all additional actions completed
- Access to the data capture and randomisation systems can be activated
- IMP is available (if applicable).
- Equipment needed to deliver the study is available (if applicable)

The Sponsor/CI or delegate should send written confirmation to each site confirming their approval and satisfactory initiation, and when recruitment can begin.

Some Sponsors issue a study level Activation letter, and then the BTC is to issue site level activation letter, while other Sponsors issue it for each site. In any circumstances, copies of the activation letters/emails should be stored in the TMF and the ISF.

6. SUPPORTING DOCUMENTS

Number	Title
BTC-RES-TM-001	Definitions, Acronyms and Abbreviations Relevant to Research Projects and Management of Research
BTC-RES-TM-002	Website References (Trial Management SOPs)
BTC-SOP-TM-002	Study Conduct SOP
BTC-SOP-TM-003	Study Closedown SOP
BTC-SOP-IT-001	Software Development for Clinical Research Computer Systems SOP
BTC-SOP-IT-003	System Backup and Restoration for Clinical Research Computer Systems SOP
BTC-SOP-IT-004	Configuration Management SOP
BTC-SOP-IT-005	Testing Clinical Trials Systems SOP
BTC-SOP-QM-002	Quality Management Systems SOP
BTC-SOP-LAB-001	Laboratory SOP
BTC-TEMP-TM-001	Trial Master File Contents
BTC-TEMP-TM-003	CRFs Change of Participant Statuts template
BTC-TEMP-TM-004	N1 CRF Note to File template
BTC-TEMP-TM-005	Template Guidance for TSC PPI Members
BTC-TEMP-TM-006	PPI PAG EoI Initial Contact Email template
BTC-TEMP-TM-007	PPI Patient Advisory Group Agreement
BTC-TEMP-TM-008	SAE Reporting Forms Template
BTC-TEMP-TM-009	Role description for public contributors
BTC-CHK-TM-001	CRFs eConsent Screening Log Options
BTC-CHK-TM-002 PPI	Checklist for Staff Arranging PPI Meetings
BTC-CHK-TM-005	Quality Management Plan
BTC-CHK-TM-007	Study Start Up Checklist

BTC-FM-TM-002	PPI Meeting Feedback Form
BTC-RES-TM-004	Guidance for PPI PAG
BTC-RES-TM-006	PPI Infographic – After Participant
BTC-WI-TM-002	CRFs Valid Consent Instructions

7. CHANGE HISTORY

Previous version and date	New version and date	Brief summary of review
NIL	V1, 31 March 2021	New document
V1, 31 March 2021	V2, 9 February 2022	Some details of external processes susceptible to change have been removed throughout, mainly from sections on HRA/MHRA processes and submissions for approvals to review bodies; added requirements to follow HRA/MHRA guidance and processes Clarification added throughout to bring the requirements in line with changes in HRA/MHRA processes Clarification that a Laboratory Site File need to be set up where applicable Clarifications regarding study monitoring to mention other monitoring activities responsibilities and requirements for studies where there is no need to have a specific study monitoring plan Addition of sections on applications to ARSAC and to HMPPS Clarification that the central coordination team does not need to collect CVs and GCP certificates for local teams; instead, the PI need to confirm that CVs are held locally for all staff on the delegation log, as well as evidence of GCP training if/as required i.e. commensurate with roles and responsibilities

V2, 9 February 2022	V3, 10 January 2024	Updated references from the BTC Intranet to BTC Teams channel Addition of section on responsibilities for studies involving a medical device (clinical investigations) Clarification added throughout to bring the requirements in line with changes in HRA/MHRA processes mainly from sections on MHRA processes. Addition of section on BTC study infrastructure References to SOP associated documents (e.g. templates and checklists) updated Clarification regarding the Model agreement templates available via IRAS. Update to clarify that EudraCT number no longer required for studies conducted in UK. Clarification added throughout to bring the requirements in line with changes in HRA/MHRA and ISRCTN processes. Some details of external processes susceptible to change have been removed throughout, mainly from sections on HRA/MHRA processes and submissions for approvals to review bodies, including process flow charts, and the section on data protection impact assessment Addition of section on risk proportionate approaches and notification scheme Addition of section on site approval process for non-NHS sites