STUDY CONDUCT SOP

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Implementation plan

For studies that are being set up, the BTC-SOP-TM-001 Study Start Up applies.

For ongoing studies applicable sections of this Standard Operating Procedure (SOP) (e.g. study monitoring) should be implemented as far as possible immediately after the implementation date, unless impractical for the circumstances e.g. too close to the end of study.

For studies that are closing (as defined by protocol) or approaching the end date, the BTC-SOP-TM-003 Study Closedown should apply, in conjunction with this SOP, 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 Please note that versions may be superseded before their planned review date.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 QA channel.

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1. PURPOSE

This Standard Operating Procedure (SOP) describes the procedures for conducting a research study at the Bristol Trials Centre (BTC).

2. SCOPE

This SOP applies to all research studies undertaken by BTC staff. It covers the period from opening of the first participating site (or being able to start the study where applicable, e.g. for a data only study), until the end of research activities (i.e. when the study is ready for close down, reporting and archiving). It applies to all BTC personnel involved in the development or implementation of processes pertinent to conducting a study.

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

“Research study” (or “study”) refers to health-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 certain outcomes and certain groups of people. It includes clinical trials of investigational medicinal products (CTIMPs) and/or medical devices, or advanced therapy medicinal products (ATMP).

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 (TMF), Trial Management Group (TMG), etc., for research studies other than clinical trials.

3. DEFINITIONS, ACRONYMS AND ABBREVIATIONS

3.1 Definitions

For definitions, acronyms and common abbreviations refer to the BTC-RES-TM-001 Definitions and Acronyms available on the BTC Teams QA 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 practice guidance.
- Ensure that participants' privacy is protected, and any disclosure of a participant's confidential information is managed appropriately.
- Review amendments and determine whether amendments are substantial; sign off all amendments before they are submitted to applicable review bodies for approval/opinion; keep records of all amendments to the study.
- Ensure that a study-specific delegation log is maintained up-to-date for each study to document team members' responsibilities.
- Ensure that adequate arrangements are in place for maintaining and assuring the quality of data collected.
- Ensure that the investigators, research team and research sites remain suitable.
- Maintain appropriate study oversight.
- Ensure that arrangements for monitoring the research, including its conduct and the ongoing suitability of the protocol in light of adverse events or other developments remain adequate.
- Implement and maintain robust systems and processes to prevent and detect deviations, research misconduct or serious breaches of Good Clinical Guidance (GCP) and/or the protocol.
- On discovery of a potential breach, determine whether this is a serious breach and if so, ensure that a Corrective and Preventive Action (CAPA) plan is put in place and for reporting it to applicable review bodies.
- Ensure that procedures and arrangements for reporting (e.g. progress reports, safety reports) remain adequate and are adhered to.
- Ensure that arrangements for implementing appropriate urgent safety measures to protect participants against any immediate hazard remain adequate.
- Oversee safety reporting and reporting of relevant safety events to the Research Ethics Committee (REC).
- Ensure ongoing review of safety in the study.
- Maintain approvals, usually submitting annual progress and safety reports.
- Ensure that valid insurance/indemnity is maintained for the duration of the study.
- Maintain the TMF.

In addition, for a CTIMP, it is the responsibility of the sponsor(s) or delegate to:

- Update the Investigator Brochure (IB) or IMP Dossier (IMPD) (if either are in place) as significant new information becomes available.
- Check for updates to the Summary of Product Characteristics (SmPC)
- Ensure that the use of an IMP in a clinical trial conforms to the Clinical Trials Regulations and GCP guidelines.
- Supply the participating research site(s) with an adequate supply of IMP.
- Oversee drug accountability.
- Send reports to the MHRA, including electronic reporting of Serious Unexpected Serious Adverse Reaction (SUSARs), as and when required.
- Review Protocol deviations and decide if onward reporting of a serious breach to the MHRA should be taken, in conjunction with the CI.
- Prepare and submit Developmental Safety Reports (DSURs) to the MHRA.

Any delegation must be in writing, but the sponsor retains legal responsibility for ensuring that formal processes are in place to maintain oversight of all delegated functions.

4.2 Chief Investigator (CI) or delegate

It is the responsibility of the CI or delegate to:

- Review and amend the protocol as necessary, making sure amendments receive approvals from applicable regulatory bodies prior to implementation (unless an urgent safety measure is required).
- Provide details of the amendment, including copies of revised documents, to all participating investigators and study teams.
- Continue to ensure that staff to whom they delegate responsibility are appropriately qualified, experienced and trained.
- Notify the sponsor immediately after being made aware of any Serious Adverse Events (SAEs) as described in the protocol.
- Supply the sponsor and the REC with supplementary information regarding the SAE/SUSAR as requested.

In addition, for CTIMPs, it is the CI or delegates responsibility to:

- Ensure that systems and processes relating to the handling, management and administration of the IMP remain fit for purpose.
- Review compliance with the study specific instructions.
- Ensure that the PIs at the participating research sites are aware of any updates to instructions relating to the handling and management of the IMP(s) and that staff continue to receive appropriate training.
- Provide supplementary information pertinent to safety reporting to MHRA as requested.

4.3 Principal Investigator (PI) or delegate

It is the responsibility of the PI or delegate to:

- Ensure amendments to the study are processed according to the Research and Development (R&D) department procedures at their research site to allow the impact of the amendment to be assessed and relevant local arrangements put into place.
- Ensure the study team receive appropriate training on any amendments.
- Ensure that onward reporting of safety events to the study coordinating centre/sponsor is carried out according to the protocol/study manual/working instructions.
- Review SAEs and assign causality as per the protocol.

In addition, for CTIMPs, it is the PI or delegates responsibility to:

- Be thoroughly familiar with the appropriate use of the IMP(s), as described in the protocol, the current Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC) and/or other information sources provided by the sponsor.
- Ensure that members of the local research team maintain appropriate qualifications and are trained in study specific procedures relating to the management and handling of the IMP(s).
- Ensure that IMP accountability at the research site is maintained; some of the IMP related responsibilities may be delegated to the 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 applicable approvals are in place before an IMP is dispensed at their site.
- Maintain appropriate arrangements for drug accountability, storage, dispensing and destruction of the IMP, as applicable.
- Ensure that a pharmacy specific site file is maintained.

4.5 Bristol Trials Centre (BTC), University of Bristol (UoB)

It is the responsibility of the BTC to:

- Oversee the conduct of the research study ensuring the rights, safety and well-being of participants is maintained and that the integrity of the data is not compromised.
- Facilitate the detection and reporting of deviations and research misconduct and implementation of corrective and preventive actions.
- Report observations of suspected research misconduct, deviations or serious breaches of GCP and/or the protocol and ensure onward reporting in compliance with this SOP and applicable regulations.
- Ensure that members of BTC staff are appropriately trained for their role and maintain individual training records.

4.6 SOP Authors or delegate

It is the responsibility of the SOP authors or an appropriately qualified/trained delegate 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 Intranet.

5. SPECIFIC PROCEDURES

5.1 Identification and screening of potential research participants

Following HRA approval for the study and green light/agreement between the sponsor and the research site that recruitment can begin, potentially eligible research participants can be identified and approached, as detailed in the protocol or study manual.

Individuals identifying and approaching potential participants must be listed on the delegation log.

Prior to participants' consent, access to identifiable information must be limited to clinical care team or members of the research team who are also part of the clinical care team of the potential participants; unless explicit permission has been sought from the appropriate regulatory bodies or a participant has self-referred and provided identifiers themselves. The amount of identifiable information gathered and the number of people who have access to identifiable information should be minimised.

All recruitment materials require HRA approval /REC review prior to implementation.

No study data collection or other study procedures should take place until informed consent has been received unless the study has regulatory approval to collect data without prior consent (e.g. emergency setting, or section 251 support).

A screening log should be in place to document all potential participants considered for enrolment, the date and the outcome.

Chronological enrolment of participants should be documented in a participant enrolment log or equivalent.

It may be required to keep a record of screening failures for prospective study participants who are found to be ineligible.

Participant eligibility must be confirmed by the PI or delegate or an authorised member of staff, as per protocol, and must be conducted and documented prior to receiving informed consent. Exceptionally, where this is not feasible or efficient, consent can be obtained before the eligibility is confirmed by the PI or delegate, however, randomisation cannot happen prior to eligibility being confirmed and documented, and consent being obtained. This approach should be described in the protocol.

Any queries regarding participants' eligibility should be referred to the PI or delegate. Where queries cannot be resolved locally they should be referred to the CI.

5.2 Informed consent process

Informed consent is defined as "a process by which a participant (or person with parental responsibility or a legal representative) voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate".

5.2.1 When can the process start?

The informed consent process can commence when all applicable regulatory and local approvals are in place:

- REC favourable opinion;
- HRA and/or HCRW approval;
- Clinical Trials Authorisation for CTIMPs/ATMPs;
- Research site confirmation of capacity and capability;
- Sponsor confirms that the site initiation process is complete and the site has received the green light to begin the study (see BTC-SOP-TM-001 Study Start Up).

5.2.2 Who can take consent?

All members of the research team involved in the process of consent/assent should be qualified by experience and have appropriate training. They must have completed the study Delegation Log/Site Responsibility Log, which must also be signed and dated by the PI.

For CTIMPs, unless otherwise agreed with the sponsor and approved by REC, a clinical doctor is required to confirm eligibility and consent participants. The delegation of the informed consent process to a research nurse may be considered for low risk CTIMPs, taking into account the nature of the trial, and must be given a favourable opinion by the REC.

All those responsible for obtaining informed consent must have a comprehensive understanding of the study, potential treatments, safety implications and associated side effects.

5.2.3 Providing information to the potential participant

All individuals asked to consider taking part in research shall be given the adequate information about the research, presented in terms and in a form that they can understand, in order to make an informed decision about whether to participate or not.

NB: The same requirements for providing information apply to a person with parental responsibility (in a study involving minors), or a consultee (in a study involving adults lacking capacity), or a legal representative (in a CTIMP).

The potential participant must be given the most recent version of the Patient Information Sheet or Leaflet (PIS/PIL), which has been approved by the HRA and/or REC and any other applicable review body. A record of which version of the PIS/PIL each participant received must be kept.

The potential participants must be given enough time to read the PIS/PIL and consider participation. Reference to timeframes can be found in the study specific protocol and/or the REC application for the study.

A verbal explanation should be provided to the potential participant (including family/friends/carers if appropriate) in addition to providing a PIS/PIL. The participant needs and dignity must be taken into consideration, and a private area should be used for consent process if undertaken face to face, and/or if required.

Time for questions and discussion must be given and questions adequately addressed.

The language used to describe the study should be clear and concise and in terms that the potential participant can understand. Medical terminology should be explained in lay language. The language used when giving information to children must be age appropriate.

Other media or non-text-based approaches can be provided if appropriate and the required approvals have been given (REC/HRA/MHRA) e.g. videos, animations, infographic cards, brochures and audio may all be used as patient-friendly introductions to complement, or replace, the paper information sheet.

Participants must be provided with contact details where they may obtain further information about the study. If appropriate an out-of-hours contact number should be provided.

The participants should be provided with information about their rights and processing of their data, including information about withdrawal from the study.

Neither the investigator nor any member of the clinical research team should coerce or unduly influence a potential participant to participate or to continue to participate in a study. It should be made clear to the potential participant that declining to take part in the study will not affect their future care or treatment and that they are free to withdraw from future involvement with the study at any stage, without providing a reason.

For postal/online surveys or self-administered questionnaire-based research, it is not necessary to provide a separate PIS/PIL or consent form if participants are provided with adequate information to enable them to reach a decision whether to participate or not, usually as part of the survey/questionnaire itself or a covering letter. Return of a completed questionnaire may be taken as 'implied consent'.

If electronic consent (eConsent) is used in a study, potential research participants are provided with the information they need to make an informed decision via a tablet, smartphone or digital multimedia. Guidance is provided in a joint statement by HRA and MHRA on seeking and documenting consent using electronic methods, which is available on the HRA website.

The practice of giving information about the study to participants should be an on-going process performed by all members of the research and/or multidisciplinary team (as appropriate). This is particularly significant with the introduction of protocol amendments and the availability of important new information that may be relevant to the participants' willingness to continue participation in the study. In these cases, the changes should be highlighted to the participant. If the participant feels that they then need more time to consider, this must be accommodated.

5.2.4 Obtaining and recording informed consent

Informed consent must be received from participants prior to any study-related procedures being undertaken unless other arrangements apply (e.g. deferred consent) and REC approval has been obtained for the respective approach.

In most cases, investigators must document the informed consent process (if applicable) by use of a written consent document, however electronic methods may be used for seeking, confirming and documenting informed consent for participation in research, to supplement the traditional approach or, where appropriate, replace it. The consent form should be on headed paper, with the study title and IRAS ID clearly displayed.

When the person obtaining consent is satisfied that the potential participant has been fully informed, understands what study participation entails and agrees to take part, their agreement with each statement contained in the consent form can be indicated by initialling or ticking

boxes, or providing the answer 'yes' or 'no' after each statement. The consent form should then be signed and dated by the participant and the authorised person who has conducted the discussion. A signature on a consent form does not in itself make consent valid. If signatures are captured via wet ink, names should be printed clearly next to the signatures. Parent(s)/Guardian(s) must sign the consent form and children the assent form in the same manner.

If the consent is on paper, copies of the signed and dated consent form should be made. The original should be filed in the relevant section of the TMF or with the participants Case Report Form (CRF), a copy should be given to the participant and a copy should be filed in the patient's medical records, along with a copy of the PIS/PIL. For participants who are not patients (e.g. healthy volunteers, children in nursery setting) there is no need to file a copy in the medical records. The co-ordinating centre may also require copies.

For primary and secondary care studies the process of obtaining informed consent should also be documented in the participant's medical records detailing the study title and date of consent. If the potential participant declines to consent this should also be recorded in the medical notes.

If eConsent is the method used, the informed consent can be documented via an electronic device such as a smartphone, tablet or computer, using electronic signatures or similar electronic methods where enabled. A combination of methods may be used e.g. consent may be given verbally or by telephone, followed by signing a paper copy at a later time. In some circumstances (e.g. interviews in qualitative research) verbal consent may be audio recorded whereby the participants agree to standard statements read out by the researcher; there is no need to sign paper copies at a later date.

In any case, it should be recorded in relevant sections of the TMF or CRF or patient medical notes, as appropriate, that consent from the participant has been obtained.

For CTIMPs, the HRA /MHRA joint statement sets out the legal and ethical requirements for eConsent and expectations regarding the use of electronic signatures.

Participants with capacity who are unable to physically sign a paper or electronic document (e.g. are not able to read or write, or who are visually impaired etc.) may provide consent orally in the presence of an independent witness or by any other means of communication (such as using augmentative and alternative communication methods).

Copies of the signed consent forms from potential participants who do not go forward to participate in the study should also be retained.

In the event of there being an unexpected delay between consent and time of the intervention (anticipated timelines should be defined in the PIS), the participant should be re-approached, to ensure that consent and eligibility remain valid.

Consent to remain in the study should be checked with the participant (and parent/guardian, legal representative or consultee) at each study visit. If changes are made to the PIS/PIL or consent form during the study, which are considered relevant to participants who have signed previous versions and are still participating in the study, they should be asked to sign the new version of the consent form and be provided with the new PIL, but not before the updated documents are approved by the REC/HRA. This ensures that they are willing to continue participating in the study under the new conditions.

5.2.5 Consent process for minors

A full explanation of the study (including the objectives, risks, inconveniences) must be given to the person with parental responsibility for the minor in order that they may provide consent for the minor to participate in the study.

The minor should be given information regarding the study according to his/her level of understanding from staff that have experience in dealing with minors and the person receiving consent must respect their wishes.

For CTIMPs, a minor means a person under the age of 16 years and will be treated as such until they turn 16. A person with parental responsibility or a legal representative must provide consent on behalf of the child. The MHRA Good Clinical Practice Guide provides a hierarchy for determining who should be approached to give informed consent on behalf of a minor prior to their inclusion in the trial. In cases where the child has been involved and is judged competent to give assent then he/she should sign the (assent) form. It is also good practice to document the child's view where they are not judged competent to give assent.

Where a minor reaches the age of 16 during the conduct of a CTIMP they should be re-consented (using the appropriate PIS/PIL and informed consent forms) where their participation on the clinical trial is continued.

For other types of research there is no legal age for consenting. Young people aged between 16 and 18 are usually competent to give consent for participation in research. If the child has sufficient understanding and intelligence to understand fully what is proposed in the research, they should be deemed competent and consent for themselves. Dependent on the study, competence may be a common-sense decision, assessed clinically or assessed by a competence tool. In most cases, it is advisable to involve the parents/guardians in the decision-making process and obtain parental/guardian assent. If the child is not deemed competent to consent, a person with parental responsibility should be approached to provide consent. Consent forms for a participant's legal representative should address them directly and should be written appropriately. The consent form must be clear that they are being asked for consent on behalf of the research participant. The child's assent should be obtained, usually on a separate assent form, in addition to the consent of the parent/guardian.

A child can refuse to participate or withdraw from the study independently, and by any form of communication. The person obtaining consent/assent must respect their wishes.

If new information considered relevant to participants decision to continue participation becomes available, and/or changes are made to the PIS/PIL or consent form during the study, the parent(s)/guardian(s) should be asked to sign the new consent forms, and children the new assent forms. Additionally, in long term studies where the child becomes competent to consent for themselves, the research team should obtain his/her formal consent to continue in the study.

5.2.6 Consent for adults lacking capacity

The definition of an incapacitated adult under the Clinical Trials Regulations is "an adult unable by virtue of physical or mental incapacity to give informed consent".

Legally, adults must be assumed to be capable of taking decisions unless the opposite has been demonstrated for a particular decision. Where doubt exists, the CI/PI or another experienced clinician/practitioner should formally assess the capacity of the individual to make

an informed decision about participation in a research project. This assessment and the conclusions should be recorded in the medical records.

The participant must be given information regarding the study and its risks and benefits according to their level of understanding. For those individuals able to form an opinion based on the information provided, their wish to participate must be respected by the person taking consent.

For a CTIMP, to involve an adult who lacks capacity, the informed consent of a legal representative is required, on behalf of the participant. The MHRA Good Clinical Practice Guide provides a hierarchy for determining what type of legal representative should be approached to give informed consent on behalf of an incapacitated adult prior to inclusion of the participant in a CTIMP.

An individual should not be enrolled into the trial if it is contrary to a formal advance decision or any other form of statement made in advance by the individual whilst competent. The legal representative may withdraw the participant from the trial at any time by revoking his/her informed consent.

The opinion of the legal representative about enrolment should be formally documented and a written and signed consent form obtained. The role of the legal representative, their relationship to the participant and the response of the participant should also be documented.

For all other research studies, advice from a consultee should be sought on whether an adult lacking capacity to consent would wish to be included in the research study or not. Consultees are not asked to give consent on behalf of the adult, but rather to provide an opinion on the views and feelings of the potential participant. The advice given by consultees should be recorded on a Consultee Declaration Form (rather than a Consent Form).

If a participant has lost capacity after they have already consented to take part in a study, the benefits and harm that could occur from their continued participation in the research should carefully be considered, and the provisions of the applicable regulations/law must be followed. For CTIMPs, consent from an adult to participate in a trial remains valid after loss of capacity providing the trial is not significantly altered.

For all other research, consent does not endure the loss of capacity, and the researchers must monitor capacity where they have any reason to think that it might change. If a participant loses capacity during a research project, advice from a consultee must be sought on whether the participant should remain in the study.

Guidance on the principles of consent when involving adults not able to consent for themselves is provided on the HRA website.

If your study involves recruitment from UK nations outside England, further requirements may be applicable. For Non-CTIMP studies, provisions in the Mental Capacity Act 2005 (for England and Wales), the Adults With Incapacity (Scotland) Act 2000 or the Mental Capacity Act (Northern Ireland) 2016 must be followed for decision making on behalf of adults aged 16 and over who are unable to make decisions for themselves. For CTIMPs, the Clinical Trials Regulations apply (UK-wide). Relevant HRA guidance should be followed.

5.2.7 Consent in emergency situations

In emergency situations, potential participants may be recruited without prior consent if:

- treatment needs to be given urgently

- it is necessary to take urgent action for the purposes of the study
- it is not reasonably practicable to obtain consent from a parent/guardian or legal representative, or to seek advice from a consultee
- the procedure is approved by an NHS REC
- consent is sought from a parent/guardian or legal representative as soon as possible, or a consultee is consulted as soon as possible to seek advice on the participant's likely views and feelings.

Participants (adults) recruited in such a manner must be involved in the on-going consent process and asked to give their own consent when and if they are able/regain their capacity to give consent.

For CTIMPs, the law is the same across the UK although the details of who can give consent may vary between nations. For non-CTIMPs, the law regulating how children or adults can be included in your research will vary, depending on where in the UK the research takes place. The guidance provided on the HRA website should be followed.

5.2.8 Changes in participant study participation status

Consent to take part in a research study may be revoked by the participant, or a parent/guardian of a child, at any point in time, from the whole study, or partially (e.g. stop the study intervention but continue in sample collection and questionnaires).

Under the GDPR, data already collected up to the point of participant indicating that they wish to stop participation in the study, can be kept and used in analysis; however the participant should be made aware of this and any specific requests they may have should be noted.

Change of participation status should be documented in the TMF or with the participants' CRF, as applicable.

At participating sites using electronic patient records, the change of participation status should be documented in the electronic record, for example adding a scanned form or note to the record. At sites using paper records, a signed and dated note should be added in the participant medical records to say that the participant has changed the level of participation in the study. This should be clearly and appropriately documented, so that it is possible for study personnel to proceed adequately, e.g. still send the questionnaire to the participant when due/as applicable.

If applicable, a copy of the form documenting the change in patient study participation status (if a separate form is used) should be stapled to the consent form in the participant's notes and/or the consent form should be marked to record the change.

5.3 Randomisation and blinding

A randomised controlled trial (RCT) is the standard by which interventional studies are judged since other study types are open to numerous potential biases. Randomisation is a process by which participants are randomly assigned to treatment groups in an unbiased and balanced manner such that neither the participant or the investigator can influence which treatment group the participant is assigned to.

The protocol should describe the method of randomisation and any stratification/minimisation factors.

Blinding is the process that keeps one or more parties involved in a study (e.g. the investigator team and/or the participant, pharmacy, etc) unaware of what treatment group participants have been randomised to. Blinding ensures that no bias is introduced when making safety and efficacy assessments.

Randomisation and blinding procedures should be determined for individual research studies by discussion between the methodologist (if applicable), study statistician (or designee), the database manager (if applicable), the trial manager and the CI. The degree of blinding (e.g., who is blinded, when and how) should be documented in the study protocol.

Following completion of the informed consent/consultee advice/waiver of consent process, and any post-consent eligibility checks, the study's randomisation procedures can start.

When a participant is randomised in a study, the following information should be collected and documented:

- Participant randomisation number/ number (if applicable);
- Date of randomisation
- Randomisation group/arm;
- Intervention reference in blinded studies (e.g. IMP pack number);

If the study is blinded, unblinding should only carried out if authorised, or in accordance with the study protocol, unless necessary (i.e. urgently for a safety reason). In all cases of premature unbinding (e.g. accidental unbinding, unblinding due to a serious adverse event) of the investigational product(s)/treatment, the investigator should promptly document and notify the sponsor or delegate of the incident and people involved.

Randomisation processes are further detailed in the BTC-SOP-ST-001 Statistics.

If the randomisation system used by study sites is electronic (e.g., a secure web-based application), there must be a written procedure in place for ‘manual’ randomisation should the web-based application be unavailable (e.g., due to a power or IT failure). The procedure must be readily available at all times during the study, and not allow instances of ‘manual’ randomisation to go undetected. Reasons for ‘manual’ randomisation should be fully documented and reviewed by the TMG to ensure the integrity of the study is maintained.

The delegation Log must include names of staff who will randomise participants.

5.4 Recording, Managing and Reporting Adverse Events

5.4.1 Introduction

In order to ensure the safety of participants it is necessary to monitor safety. To do this, adverse events (AEs) and serious adverse events (SAEs) need to be adequately recorded and reported to the sponsor, regulatory authorities and other interested parties, such as a Data Monitoring and Safety Committee (DMSC). The PI is responsible for identifying and reporting AEs and SAEs.

This section describes the process for recording, managing and reporting AEs for both CTIMPs and non-CTIMPs.

The Sponsor should maintain overall responsibility for the conduct and reporting of the study and so there should be mechanisms in place to demonstrate oversight of activities contracted/ delegated to ensure participant safety and data integrity.

5.4.2 Definitions specific to safety reporting

Reference Safety Information (RSI)	A list of medical events that defines which reactions are expected for the IMP thus determining which Serious Adverse Reactions (SARs) require expedited reporting.
Adverse Event (AE)/ Adverse Reaction (AR)	An AE is any untoward medical occurrence in a participant, including occurrences that are not necessarily caused by or related to that product or intervention. An AR is an untoward and unintended response in a participant where an association has been or can be made between the IMP, medical device or intervention and the adverse event experienced. Not all adverse events are adverse reactions, but all adverse reactions are adverse events.
Expected Adverse Event	An AE with a nature and/or a severity that is expected of the study intervention as defined in the protocol and/or the RSI (as defined above).
Anticipated Event	An AE that is 'likely to occur' in relation to other interventions/ procedures that the study population are undergoing as part of their routine care (not the study intervention) or are symptoms of their disease or a sign of disease progression. For example, in a trial of an IMP delivered during surgery, the complications of surgery itself may be considered 'anticipated'.
Unexpected Adverse event	An AE where nature and/or severity is not expected or is not consistent with the information set out in the study protocol or the RSI.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	An adverse event or adverse reaction that is defined as serious - *see below in 5.4.3.*
Suspected Serious Adverse Reaction (SSAR)	Any serious adverse reaction that is suspected (possibly or probably or definitely) to be related to the IMP, medical device or intervention.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any adverse reaction that is both serious and unexpected, meaning that its nature and severity are not consistent with the applicable information about the medicinal product, device or intervention set out in the protocol and/or agreed RSI.

5.4.3 Assessment of Adverse Events

5.4.3.1 Seriousness

The seriousness of an adverse event will be assessed by the investigator. An adverse event is defined as serious if it:

(a) results in death;
(b) is life threatening*;
(c) requires hospitalisation or prolongation of an existing hospitalisation;
(d) results in persistent or significant disability or incapacity; or
(e) results in a congenital anomaly or birth defect.

Any other event which may jeopardise the participant or require intervention to prevent one of the other outcomes listed in the definition above, should also be treated as serious.

*Life threatening in the definition of an SAE refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

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5.4.3.2 Expectedness

The expectedness of an adverse event shall be determined according to the RSI or as defined in the study protocol:

Expected	Event previously identified and described in the RSI and/or protocol
Unexpected	Event not previously described in the RSI and/or protocol.

5.4.3.3 Anticipated events

The protocol may also list anticipated events which are likely to have a different reporting procedure to other SAEs. If applicable, all SAEs should be reviewed against the protocol to establish if they are considered an anticipated event. Please note that the distinction between anticipated and expected adverse events is a recent development in BTC processes and in some studies ‘anticipated events’ may be listed as ‘expected adverse events’ in the study protocol. It should be agreed at the beginning of the study which AEs can be defined as disease-related, or surgery-related and therefore not subject to expedited reporting.

5.4.3.4 Causality

All SAEs need to be classified according to their relatedness to the intervention, unless otherwise agreed (e.g. in the protocol). For example, causality may not be required for expected SAEs.

Causality should be assessed using the definitions below:

Not related	Causal relationship of the onset of the event, relative to administration of the intervention, is not reasonable or another cause can by itself explain the occurrence of the event.
Unlikely to be related	Causal relationship of the onset of the event, relative to administration of the intervention, is unlikely and it is likely there is another cause, which can by itself explain the occurrence of the event.

Possibly related	Causal relationship of the onset of the event, relative to administration of the intervention, is reasonable but the event could have been due to another, equally likely cause.
Probably related	Causal relationship of the onset of the event, relative to administration of the intervention, is reasonable and the event is more likely explained by the intervention than any other cause.
Definitely related	Causal relationship of the onset of the event, relative to administration of the intervention, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

Where an event is assessed as possibly related, probably related, or definitely related the event is an adverse reaction.

For a CTIMP, the causality assessment must be performed by clinically trained staff, who is on the delegation log.

5.4.3.5 Intensity assessment

If needed, the assessment of intensity will be based on the investigator's clinical judgement using the following definitions:

Mild	An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
Moderate	An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe	An event that prevents normal everyday activities.

NB: The term 'severity' is often used to describe the intensity (severity) of a specific event. This is not the same as 'seriousness', which is based on participant/event outcome or action criteria.

If the intensity of an expected event becomes greater than expected, the event should be considered as unexpected.

5.4.4 Identification and Classification of Adverse Events

Adverse events may be identified through the following methods (NB: this list is not exhaustive):

- During routine data collection of adverse events whilst the participant is in hospital.
- At each study visit, and sometimes through study questionnaires, participants will be asked whether they have experienced any AEs or had any hospital admissions since their last visit. Any AEs will be investigated to ascertain their nature and severity.
- Self-reported by the participants.

If the participant has suffered an AE it will be necessary to refer to the study protocol to identify the correct procedure for recording/reporting as this will be dependent on **seriousness**, **causality** and **expectedness** of the event.

PIs or delegates at each local participating site will evaluate each event, before reporting it to the CI/delegate (e.g. BTC) unless otherwise agreed. The study protocol must detail who will take responsibility for the assessment and reporting of such events to the Sponsor and CI or delegate (e.g. BTC).

For non-CTIMP studies, if a serious adverse event occurs that falls outside of the list of expected adverse events as listed in the protocol (and is therefore 'unexpected') causality (relatedness) to the intervention will need to be classified.

For both CTIMP and non-CTIMP studies, unexpected events are also classified according to intensity/severity (i.e. mild, moderate or severe).Study specific requirements for classifying AE and SAEs should be described in the study protocol.

5.4.5 Reference Safety Information (RSI) (CTIMPs only)

RSI defines which events are expected for the IMP being administered to participants in a clinical trial. It does not include events anticipated for a particular disease area. The RSI should be clearly defined. It is often a clearly-identified section within the Investigators Brochure (IB), if the IMP does not have a marketing authorisation, or Summary of Product Characteristics (SmPC).

Prior to a clinical trial commencing, the CI will determine what RSI will be used to determine expectedness of any adverse events.

A change to RSI is submitted via a substantial amendment to the MHRA and cannot be implemented until approval is issued. A proposed change to the RSI is not urgent safety information.

Every member of the research team must use the same version of the RSI at the same time; this is essential when investigators are conducting the expectedness assessment.

NB: All adverse events (and by extension all SAEs and SUSARs) should be assessed against the RSI that was in place at the time of the event, irrespective of the version that may be in place at the time of any potential follow-up information being received. Updating RSI does not allow the downgrade of previously reported SUSARs. Further information pertinent to RSI for clinical trials is available on the MHRA Inspectorate blog.

5.4.6 Recording Adverse Events

The CI or delegate should decide in advance how to record and report AEs, whether expected or not. It should be documented in the study protocol and agreed in consultation with the Sponsor.

It may be decided that all, or only some, non-serious AEs are to be recorded. Whatever option is chosen, it must be consistent with the purpose of the study and risk assessment.

The extent of recording of data for non-reportable events should be decided on a study by study basis.

5.4.7 Reporting

A detailed explanation of the safety reporting procedures should be included in the protocol and should clearly specify the time frame in which to record AEs/SAEs and send reports to the sponsor and regulatory authorities. Details of SAEs that require expedited reporting to the Sponsor should be recorded on an approved form.

5.4.7.1. Reporting to Sponsor

SAEs will be reported to the Sponsor through expedited reporting channels as specified in the protocol.

Relevant SAEs should be notified to the sponsor as soon as the research team become aware of the event, usually within 24 hours (as per Sponsor's requirements). This will consist of an initial detailed report of the event and will be monitored at regular intervals with follow-up reports (where applicable) submitted in accordance with the relevant Sponsor's requirements within agreed timeframes until the event has been resolved (including death). Sending the initial report should not be delayed, even if information is missing. In these cases, the incomplete form should be sent immediately, and the completed report sent as soon as the additional information becomes available. Initial reports can also be made via telephone if agreed with the sponsor.

Follow-up of events with long term ongoing symptoms should be reviewed on a case-by-case basis by the research team and sponsor to assess if further follow-up reports are required or a less frequent reporting schedule can be agreed. If an event is already resolved when the initial report is sent, no follow-up forms are required.

5.4.7.2 Reporting to the REC

Expedited reporting

For **Non-CTIMPs**, the sponsor or delegate must report:

- All SUSARs within 15 days of becoming aware of the event.

The 'Non-CTIMP safety report to REC form' should be used to notify the REC, which is available on the HRA website.

For **CTIMPs**, the sponsor or delegate must report:

- Fatal or life-threatening SUSARs within 7 days of becoming aware of the event, with any follow-up information to be reported within a further 8 days.
- All other SUSARs within 15 days of becoming aware of the event.

For **CTIMPs not submitted via combined review**: email the REC with the REC Safety Report Form (CTIMPs) . Form and guidance are available on the HRA website.

For **CTIMPs submitted via combined review**: submit SUSARs as per MHRA guidance. The MHRA will liaise with the REC if deemed appropriate. There is no requirement to email the REC.

Annual safety reporting

In addition, for CTIMPs, the Sponsor (or delegate) should submit annual safety reports on the safety of participants (called Development safety update reports (DSUR)).(Reporting to MHRA is further detailed below.)

For CTIMPs not submitted via combined review: email to the REC along with the REC Safety Report Form (CTIMPs). All annual safety reports should be in the format for DSUR set out in the ICH E2F guidelines.

For CTIMPs submitted via combined review: The DSUR should be submitted via IRAS. There is no requirement to separately notify the REC, the MHRA will liaise with the REC if deemed appropriate.

5.4.7.3 Reporting to MHRA

Expedited reporting

The sponsor or delegate must report to MHRA:

- Fatal or life-threatening SUSARs within 7 days of becoming aware of the event, with any follow-up information to be reported within a further 8 days.
- All other SUSARs within 15 days of becoming aware of the event.

For CTIMPs not submitted via combined review: Submit to the MHRA as per the guidance on the MHRA website and to the REC which issued the favourable ethical opinion as described above.

For CTIMPs submitted via combined review: submit to the MHRA as per the guidance.

You should submit SUSARs in one of the following ways:

- using the eSUSAR website
- using the ICSR Submissions
- using the MHRA Gateway

Annual reporting

A DSUR must be compiled and submitted for all CTIMPs. This must be done on the first anniversary of the date of the CTA approval.

The DSUR should include:

- a cover letter listing all IRAS IDs and/or EudraCT numbers of trials covered by the DSUR (if more than one concurrent trial on a single IMP);
- an analysis of the participants' safety in the concerned clinical trial(s) with an appraisal of its ongoing risk/benefit;
- a line listing of all suspected serious adverse reactions (including all SUSARs) that occurred in the trial(s), including all SUSARs from third countries;
- an aggregate summary tabulation of SUSARs that occurred in the concerned trial(s)
- region-specific information as per Guideline on how to increase transparency.

For CTIMPs not submitted via combined review: DSURs should be submitted to the MHRA as per the guidance on the MHRA website. DSURs must be submitted electronically via the MHRA Submissions portal using the Human Medicines Tile.

For CTIMPs submitted via combined review: DSURs should be submitted via IRAS where at least one of the trials was submitted through combined review. There is no requirement to separately notify the REC, the MHRA will liaise with the REC if deemed appropriate. A shortened DSUR is available for 'Type A' trials (i.e. trials in which the risk to the patient from the IMP is considered to be no greater than that of standard medical care) and for trials where all participants have completed treatment and are only in follow-up.

5.4.7.4 Oversight Groups/Committees

DMSC or other oversight groups/committees (e.g., Trial Management Group (TMG), Trial Steering Committee (TSC)) may review SAEs to identify trends and may provide recommendations including implementation of urgent safety measures. The roles and

responsibilities of the trial oversight groups should be specified in the protocol and committee charter.

If non-serious AEs are to be recorded as part of the study, they should be recorded in the CRF and, if required, periodically reported to the DMSC.

The CI or delegate should keep the Sponsor, the REC and the MHRA informed of any significant findings and recommendations by an independent DMSC (or equivalent).

All adverse event/reactions recorded during a study must be subject to statistical analysis as determined by the protocol.

5.4.7.5 Clinical Incidents

Any SAE that falls within the criteria defined in the sponsor's or participating site's Clinical Incident / Serious Incident Policy should be additionally reported to the clinical governance team as per local policies.

5.5 Urgent Safety Measures

5.5.1 Definition of circumstances

An urgent safety measure is a procedure which is not defined by the protocol and is required to protect clinical trial participants from any immediate hazard to their health and safety and does not require a substantial amendment to be submitted before it is implemented. Examples of safety issues that may require an urgent safety measure include:

- A Serious Adverse Reaction (SAR) that was unexpected or had an unexpected outcome;
- A clinically important SAR occurring with greater frequency than anticipated;
- A significant hazard, such as lack of efficacy with an IMP used to treat a life-threatening disease;
- Any new information relating the IMP that could affect patient safety.

An urgent safety issue may also occur as a result of trial procedures, rather than as a result of an intervention being investigated, for example it may be identified that a trial related assessment exposes participants to unforeseen risk requiring an urgent amendment of trial conduct.

5.5.2 Immediate measures to be taken

If a reported incident indicates that an immediate change in a trial procedure, or a temporary halt to a trial, may be necessary in order to protect clinical trial participants from any immediate hazard to their health and safety the following procedure should be followed:

- On becoming aware of an incident that may require an urgent safety measure, the details of the incident should be recorded; details should include the location of the incident/s, who was involved and the nature of the incident/s, the outcome of the incident/s, any information given to participants, and any actions planned and/or completed.

- The CI, Sponsor, and/or other designated individual (such as a senior member of the BTC), and/or the TMG, and/or the TSC, and/or the DMSC should be provided with full details of the incident.
- The CI, Sponsor and/or TMG should then consider whether urgent safety measures are necessary to protect participants against any immediate hazard. Any discussion and/or decision should be documented.

5.5.3 Implementation of an urgent safety measure

Once it has been decided that an urgent safety measure is required the following procedure should be followed:

- For studies not approved via combined review (CTIMPs and non-CTIMPs), the REC must be notified of the urgent safety measure by email within three days. The notice should set out that such measures have been taken and the reasons why.
  For CTIMPs (detailed instructions are provided on the MHRA website), the Sponsor or another delegated individual should phone the Clinical Trials Unit at the MHRA to discuss the issue with a medical assessor, ideally within 24 hours and no later than 3 days of measures being taken. In practice this may be done in parallel to identifying the necessary corrective and preventive actions required, and discussions with the MHRA medical assessor may inform these actions (unless it is absolutely clear from the initial assessment that no further action is required). The person calling will be asked for several bits of information, including details of the affected IMP(s) and other trials, being run by the same and different Sponsors, that are affected by the urgent safety measure. Where any of this information is not available during the initial call it should be provided as soon as possible.
- Written notification of the measures taken and discussed with the medical assessor, must be provided to the MHRA, within 3 days from the date the measures were taken. For trials not approved via Combined Review you will be instructed to send an email to the medical assessor who assessed the urgent safety measure over the phone. If at least one of the trials covered by the urgent safety measure has gone through the Combined Review process, then the urgent safety measure written notification should be submitted via IRAS. In this case, no additional notification is required to the REC.
- The research team, if not involved in the decision-making process, should be informed that urgent safety measures are to be implemented so that the proposed actions can be agreed and implemented.
- The requirement to initiate an urgent safety measure and the proposed corrective and preventative action (CAPA) should be communicated to all participating sites. immediately (i.e. within 24 hours of the decision). Each PI (or a delegate) must acknowledge receipt and confirm that the measure(s) have been implemented.
- The implemented urgent safety measure(s) (e.g. amendment to protocol, temporary halt to the trial or premature closure of the trial) must also be submitted to the MHRA (CTIMPs) and HRA/REC as a substantial amendment (Amendment tool plus any updated document including the changes agreed with the medical assessor) within approximately two weeks of notification to the MHRA and/or REC.
- The amendment should be marked as being in response to urgent safety measures, and in the case of a CTIMP, should detail the medical assessor initially contacted. For studies not submitted via combined review, a copy of the urgent safety measure notification should be submitted with the amendment.

- The substantial amendment must not include changes different from those required as an urgent safety measure. This is due to the fact that unrelated changes may result in rejection.
- The R&D offices at each participating research site should be notified, and supplied with a copy of the appropriate documentation.
- Where appropriate, arrangements for implementing this procedure during extended breaks (for example University closure dates) should be made to ensure cover is in place.
- If appropriate, a further substantial amendment should be submitted to the MHRA and/or HRA/REC to gain permission to recommence a temporarily halted trial.
- If the Sponsor decides not to recommence a temporarily halted trial, the MHRA and REC should be notified within 15 days of this decision. (See BTC-SOP-TM-003 Study Closedown for details of how to do this).
- If appropriate, the event may need to be reported as a clinical incident, in this case refer to the sponsor(s) and the local site Serious Incident /Clinical Incident Information/Policy.

All correspondence relating to urgent safety measures should be filed in the TMF.

5.5.4 Temporary halt

Where the sponsor halts a study temporarily for any reason, the REC and the MHRA (if a CTIMP or medical device investigation) should be notified by submitting a notice of substantial amendment (see Section 5.5.7). The form should clearly explain the reasons for the halt and the scope, e.g. stopping recruitment and/or interrupting the treatment of participants already included. If the temporary halt is due to a safety issue, Urgent Safety Measures procedures described above should be followed.

The CI should also contact the study oversight committees (TMG, TSC and/or DMSC), as appropriate) to discuss the temporary halt.

A decision by the oversight committees should then be made as to whether the reason for the temporary halt can be resolved or not:

- If it can be resolved, and the research can restart, the CI should obtain permission from the sponsor and then make the request to REC, and MHRA, as a further substantial amendment, providing evidence that it is safe to restart, or
- If it cannot be resolved, then early termination is required, in which case the procedures for early termination should be followed as described in the BTC-SOP-TM-003 Study Closedown.

5.6 Maintenance of the TMF

GCP states the requirement to maintain a set of essential documents within a TMF. Details on how to establish the trial master file are described in the BTC-SOP-TM-001 Study Start Up.

5.6.1 Maintaining the TMF

All filing must be done in a timely manner to assist in the successful management of the study and to allow access to the documentation at any time.

As documents need to be amended during a study it is important that amendment chronologies are kept, indicating changes and the dates they are implemented. For paper TMFs, old documents must be struck through, marked as superseded and retained in the TMF alongside the new amended version(s). For ease of location and conformity, all documents must be arranged chronologically, usually with most recent documents at the front of each section.

If an electronic TMF (eTMF) is used, superseded documents must be clearly distinguishable from current documents, usually by use of separate folders.

5.7 Amendments

5.7.1 Introduction

Amendments are changes made to a research project (e.g. the protocol, supporting documents or information provided in the IRAS application form) after regulatory approval has been given.

The sponsor must be notified of any intended amendment. Amendments must not be submitted without prior authorisation from, or on behalf of, the sponsor.

Some funders (e.g. National Institute for Health Research (NIHR)) wish to review amendments to the protocol, and may require that such amendments are also approved by the TSC, before they are sent to the regulatory bodies.

There are two different types of amendments, non-substantial and substantial. It is the sponsor's responsibility to decide in principle whether an amendment is substantial or non-substantial.

Non-substantial amendments are purely administrative changes which do not affect the conduct of the study.

A substantial amendment is identified as an amendment to the terms of the application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the participants of the study;
- The scientific value of the study;
- The conduct or management of the study; or
- The quality or safety of any investigational product used in a clinical trial.

Examples of substantial and non-substantial amendments are provided for guidance on the HRA website.

Correction of typographical errors do not need to be submitted as amendments. There may be other circumstances in which amendments are classified as 'non-notifiable'.

5.7.2 Protocol Amendments

The amended protocol must be signed off by the CI and other relevant authors before submission to any of the regulatory bodies using the protocol author signature page (see BTC-SOP-TM-001 Start Up).

The CI or delegate should check whether the funder of the study also requires notification of protocol amendments, or if there are other requirements, e.g. TSC approval.

Once the study sponsor (and funder where appropriate) has approved the intended protocol amendment, approval from the relevant regulatory bodies can be sought. Details on how to submit an amendment are laid out in section 5.7.4.

5.7.3 Amendments to participant-facing and other supporting documents

Documents which have been modified (and are planned to be submitted as part of an amendment), should show both the previous and new wording so that the changes can be readily identified.

5.7.4 Submission of amendments to review bodies

5.7.4.1 Notifying amendments

If you plan to make an amendment to a research study, you will need to determine whether you need to notify the review bodies from whom you have received approvals.

Further ethical review is required for any substantial amendment made once a favourable opinion has been issued. A favourable opinion must be obtained prior to implementing the amendment, unless it is an urgent safety measure.

For CTIMPs and clinical investigations of medical devices only, substantial amendments should also be notified to the MHRA.

For notification of amendments to any other applicable review bodies e.g. Confidentiality Advisory Group (CAG), Administration of Radioactive Substances Advisory Committee (ARSAC), etc., the guidance provided in IRAS or on the organisations' website should be followed.

5.7.4.2 Amendment Tool

Amendments to project-based research with NHS REC review and/or HRA and HCRW Approval / NHS/HSC R&D permissions must be prepared using the HRA Amendment Tool. The amendment tool and full guidance about the process for handling amendments are provided on IRAS.

The completed Amendment Tool will output the recommended amendment category automatically based on responses to the questions. The Sponsor or authorised delegate is responsible for ensuring that the amendment tool is completed correctly and for comparing the outcomes against their own expectations of how the amendment should be processed. In the event of any discrepancies, the relevant review bodies should be contacted for advice.

For queries on how to complete the Amendment Tool or questions on the results from it, once complete, support can be accessed from the HRA or devolved nation equivalents. Please flag in

the email subject that your query relates to the Amendment Tool so that it can be identified and handled efficiently.

Note: For amendments to Research Tissue Banks (RTBs) and Research Databases (RDBs) the amendment tool should not be completed; instead use the Notice of Substantial Amendment Form (NoSA) generated in IRAS.

5.7.4.3 Online submission

The Amendment Tool (or NoSA Form in the case of RTB and RDB projects) and supporting documentation is submitted online through the amendment portal. On-screen step-by-step instructions are provided to guide applicants through the submission process. An automated email to confirm submission of the amendment is sent to the applicant.

Note: Mental Capacity Act (MCA) section 30 (pertinent to intrusive research involving people without capacity) amendments and modified amendments follow a different process.

The process for amendments, and link to the amendment tool and online submission are provided on IRAS Help, and this guidance should be followed.

For further guidance about procedures for submitting substantial amendments to the MHRA, please see guidance on the MHRA website.

5.7.4.4 Categorisation of Amendments

Amendments have been grouped into three different categories for the purpose of handling them in a manner appropriate to the amendment:

- Category A – Amendment to a research study that ALL participating NHS organisations are expected to consider;
- Category B – Amendment to a research study that only those participating NHS organisations affected by the amendment are expected to consider
- Category C – Amendment to a research study that participating NHS organisations are not expected to consider

Further guidance available on the HRA website and IRAS Help.

5.7.4.5 Adding additional sites

If a site is added that is in a nation not previously involved in the project, this should be indicated at the relevant question of the Amendment Tool and make this clear in the covering letter when submitting the amendment to the lead nation.

The Organisation Information Document(s) and the UK Local Information Pack should be prepared and used with the new participating NHS/HSC organisations.

5.7.5 After submission of amendments

Upon submission the amendment will be shared with REC and/or NHS/HSC as applicable. For substantial amendments notified to the REC, you should await communication from the REC with the outcome of their review, and relevant information on how to provide additional information, or resubmit an application.

MHRA performs their assessments within 35 days. Healthy volunteer trials and sponsor-determined phase I trials in non-oncology patients may qualify for a shorter assessment time

(average 14 days). If an application does not meet the requirements, it will not be assessed. MHRA will provide the reasons why an application is invalid and how to resubmit an application.

The following points apply to NHS/HSC organisations in all nations:

- Sponsors should not expect to receive a letter or email of confirmation from NHS/HSC organisations before implementing the amendment. If all relevant regulatory approvals are in place and there has been no objection from site, the amendment can be implemented after 35 days (see below).
- Category A and B amendments may be implemented sooner than 35 days in cases where all regulatory approvals have been issued and where the NHS/HSC organisation has confirmed that the amendment may be implemented prior to this date.
- Upon receipt of the amendment, the coordinating function of the lead nation will share the amendment with the coordinating function of any other participating nation(s). There is no need to separately submit to each nation.

5.7.6 Implementing amendments at participating NHS/HSC organisations

After submission, the completed Amendment Tool with confirmation of amendment category and, if applicable, amended documents, should be shared with relevant participating NHS organisations in England and/or Wales, including the NHS R&D Office, LCRN (where applicable) and the local research team.

The HRA provides template emails which should be used to notify participating NHS organisations in England and/or Wales.

Participating NHS organisations in England and/or Wales should then prepare to implement the amendment. An amendment may be implemented at all participating NHS organisations in England and/or Wales 35 calendar days from the day on which you provide the organisation(s) with the amendment and any amended documents so long as:

- HRA and HCRW approval has been issued for the amendment where this is required.
- A participating NHS organisation does not request additional time to assess.
- A participating NHS organisation does not decline to implement the amendment.

For multicentre studies with sites in Northern Ireland and/or Scotland the National Coordinating Function will pass the amendment to the relevant R&D offices along with any amended documents on your behalf. You should share these documents with the research teams at these NHS/HSC organisations who should prepare to implement the amendment as described above, provided that all relevant regulatory approvals necessary for the amendment have been issued.

Single centre study amendments should be sent directly to the R&D office and research team at the participating site.

With the exception of urgent safety measures, if an amendment requires approval the changes cannot be implemented until the relevant approvals are in place.

5.7.7 Amendments to contracts/agreements

5.7.7.1 Changes to contracts between the funder and the host institution

The two main types of amendments to contracts are cost and no cost extensions.

Cost extensions include requests for additional funds and time to complete contracted work. No cost extensions do not request additional funds but may propose to use budget underspend to fund extra time to complete contracted work.

The funder will usually require the study team to complete a document providing details of the extension, justification for this and the financial information. Make sure you check with the relevant funder what the processes are for extensions as cost extension processes may differ from no cost extensions in what forms are required and how these are submitted.

Cost extensions will require contact with the applicable finance department to complete an interim financial reconciliation spreadsheet as well as identifying the new, additional costs required.

The organisation holding the grant has the overall responsibility for the process of applying for a contract amendment. However, this can be delegated to the CI, but still ensuring that the host organisation is informed of the details of the request.

Any proposed extension should be notified to the BTC Head of Operations and the BTC Business Manager. Extensions must be approved by the BTC (BTC resources required and associated costs) before submission to the funder. This is so that the BTC is aware of the proposed changes and potential cost implications on BTC resources. This will ensure the BTC are able to continue to support the study.

5.7.7.2 Changes to site agreements

The model Non-Commercial Agreement (mNCA) template should be used without modification or negotiation, therefore there should not be any amendments during the study to the clauses of the agreement. Any other changes to study-specific text (e.g. to the Schedules), or amendments to bespoke site agreements, should be managed between the sponsor and the research site.

5.7.7.3 Changes to collaboration agreements

Once the funder has approved the proposed change, the host organisation will need to sign the revised contract. Please liaise with the contracts department for updates on when this is likely to be completed.

For the relevant collaborators, the host organisation contracts department drafts a new collaborator agreement to include the changes approved by the revised contract between the host organisation and funder. This is circulated to all relevant collaborators for comments. The final contract is then shared to the relevant collaborators for sign-off.

5.7.8 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.

It may be necessary to update the risk assessment form prior to study initiation or at any point during the study if for any reason there is a change in:

- Study design
- Responsibilities and procedures
- The conduct of the trial, including significant changes to sites or participant numbers
- New information becomes available about the intervention, the population or study implementation.

The risk assessment should be reviewed each time a substantial amendment is made to the study and after any significant event or deviation. On-going risk assessment and documentation review should also be completed after monitoring events (visits or other review processes).

All additional mitigating actions identified must be implemented by the responsible parties.

All revisions should be version controlled and superseded versions must be clearly identified as such.

5.8 Progress Reports

5.8.1 Annual Progress Reports to REC

Progress reports should be submitted to the REC which gave the favourable opinion 12 months after the date on which the favourable opinion was given, using specific forms. Safety information also needs to be included in the annual progress reports.

For non-CTIMP studies the 'Annual progress report form (non-CTIMPs)' available from the HRA website should be used.

For CTIMPs the 'Annual progress report form for CTIMPs' should be submitted to REC using the form available on the HRA website.

Annual reports to the REC are a condition of REC approval and should be completed every year until the study is closed.

5.8.2 Progress reports to funders

Most funders require regular, interim and final reports on the activity of the funded project. Some funders provide a specific form to fill in, whilst others may ask for a report. The specific requirements (frequency, format) are usually detailed in the terms and conditions of funding or other agreements relevant to the project. Some funders impose financial penalties if final reports are not submitted by the deadline given.

NIHR-funded researchers are required to provide regular progress reports to the NIHR. The nature and frequency of reporting varies according to research programme, project stage, and key milestones, but progress reports are generally due every six months. When a project starts, the NIHR will advise the grant holder of the dates or milestones when progress reports need to be submitted, and provide feedback.

5.8.3 Updating trial records and registries

Registries must be kept up to date during the study. All relevant study registry information (such as recruitment start and end dates, participating sites, study summaries, etc) should be updated regularly as appropriate and in line with instructions from the funder and relevant registry (ISRCTN, ClinicalTrials.gov) guidelines, including any changes to recruitment data and key outcomes.

For an NIHR research project, Clinical Trial registry records should be updated as necessary to include final enrolment numbers achieved, and the date of Primary Study Completion (defined as the last data collection time point for the last subject for the Primary Outcome measure).

5.9 Study Monitoring

5.9.1 Introduction

The GCP guidelines state that the purposes of study monitoring are to verify that:

- The rights and well-being of study participants are protected
- The reported study data are accurate, complete, and verifiable from source documents
- The conduct of the study is in compliance with the currently approved protocol, with GCP and with the applicable regulatory requirement(s).

5.9.2 Extent of monitoring

The extent and nature of monitoring should be agreed with the Sponsor and be based on a risk assessment.

The Sponsor may have a monitoring plan, documenting if and when the study will be monitored by the sponsor or delegate (e.g. BTC). In the absence of a Sponsor monitoring plan, or if the Sponsor monitoring plan is not comprehensive, a BTC monitoring plan should be developed. Where it is the delegated responsibility of the research team to monitor sites, the research team should be involved in determining the level and nature of monitoring required for any particular study in conjunction with the Sponsor with reference to the risk assessment (see BTC SOP-TM-001 Study Start Up).

5.9.3 Types of monitoring

There are many types of monitoring and the appropriate procedure should be decided upon as the study is developed. Some or all of the following may be employed:

5.9.3.1 Central monitoring

This refers to the monitoring of any participating site for any BTC adopted study using data held centrally.

Data held on the database may be validated or monitored/reviewed centrally in order to ensure that the data are complete and accurate. Data held outside of the study database may be validated or monitored/reviewed centrally or by specific research teams, e.g. the qualitative lead for the study would be responsible for checking, monitoring and reviewing qualitative data.

5.9.3.2 On-site monitoring

This refers to monitoring characterised by individual site visits.

Arrangements may vary from routine visits to all sites, visits to only a selection of sites or targeted visits to specific sites. Targeted visits may be appropriate if a monitor has concerns about a site or if a site has less experience or has highlighted problems.

Where on-site monitoring requires access to participant medical records, appropriate access will need to be arranged.

5.9.3.3 Remote monitoring

For some studies, individual sites will be required to monitor themselves if deemed appropriate in the risk assessment and quality management plan. In this instance, a self-assessment questionnaire / checklist will be designed to allow assurance that the study is being conducted at the site in accordance with the protocol.

5.9.4 Items to be monitored

The following aspects may need to be monitored (not an exhaustive list):

- That data collected are consistent with adherence to the study protocol;
- That CRFs are only being completed by authorised persons;
- That SAE recording and reporting procedures are being followed correctly;
- That no key data are missing;
- That data are valid;
- Review of recruitment rates, withdrawals and losses to follow up to educate staff about the study and to review understanding of the protocol and study procedures e.g. through presentation and discussion;
- To verify that staff at the site have access to the necessary documents to conduct the study e.g. by checking site file content and availability of study documents;
- To ensure that the required local arrangements and resources (e.g. pharmacy or laboratories) are adequate; e.g. this can be assessed by meeting department members and visiting the facilities;
- To check adherence to the protocol and GCP e.g. by reviewing participants' signed Informed Consent Forms (ICFs) and eligibility for entry to the study;
- To verify selected data items and SAEs recorded on the CRFs and compare with data in the clinical records to identify errors of omission as well as inaccuracies;
- Compliance with intervention;
- For CTIMPs:
    - IMP supply, storage and accountability;
    - An additional 'close out' visit is often performed at the end of the study; during such a visit, final product accountability can be performed, and the monitor can ensure that all site file documents are complete and up-to-date.

5.9.5 Monitoring Report

Monitoring activities and outcomes should be recorded.

If visits are conducted, visit reports would typically include the date, site, name of the monitor, name of the investigator(s) or other individuals contacted and a summary of what was reviewed during the monitoring visit. The monitor should record significant findings and deficiencies, conclusions and any recommended actions in the monitoring report.

The site should be asked to record that the outstanding monitoring actions were followed up. Monitoring reports should be sent to the Sponsor, the CI/PI, the study coordinator and if applicable, the study pharmacist. The final report should be filed in the TMF with a copy in the Investigator Site File (ISF) kept at site.

Any protocol breaches or suspicions of serious misconduct (e.g. missing signed ICFs, recruitment of ineligible participants) should be reported to the CI/PI at the earliest opportunity. (Also see section 5.8 below.)

Records should be kept of any central monitoring that has been performed. This can take a variety of formats, such as Study update meeting minutes (e.g. when central monitoring reports at reviewed at a study update meeting) or can be recorded within central monitor reports or on the study database. It needs to be clear what was checked and any actions that arise, and resolution of these actions.

5.9.6 Monitoring outcomes

There are several potential monitoring outcomes which may include the need for amendments to study procedures or documentation, temporary halt of the site/study or even the early termination of a site/study (though exceptionally rare).

Actions identified in the monitoring report should be followed up and it is the Monitor's responsibility to ensure that the outstanding action points are being followed-up until resolution.

All documentation relating to monitoring of the study should be filled in the TMF with a copy in the ISF kept at site if appropriate.

5.10 CRF completion

5.10.1 General principles for completing CRFs

Data reported on the CRF must be extracted from, and be consistent with, documented source data, unless the CRF is source data.

Instructions should be given to all participating sites on how to complete the CRFs to ensure data is collected in a standardised fashion. A CRF completion guide may be produced.

In general, CRFs must only be completed by authorised personnel who have received study-specific training and are competent in CRF completion. They should also have completed and signed the site's study Delegation Log with the respective task assigned to them. There are times when this might not be the case, such as completion of small amounts of data as part of their normal practice.

The version of the CRF form must be current when the form is completed.

All CRF pages must be clear, legible (if on paper) and all fields need to be completed unless otherwise stated.

It is acceptable to include an explanation if data are not available, e.g. not known, not applicable, not done, as appropriate. This will either be on the paper CRF, or recorded as a reason why a query for missing data needs to be excluded on an eCRF or database.

On paper CRFs, any mistakes should be crossed through, but NOT scribbled over so that the initial text remains visible. Typing correction fluid should NOT be used. The correction should be written clearly next to the original text, and all changes must be initialled and dated. If it is not clear why a change has been made, an explanation should be written next to the change. Data queries should be treated in the same way as mistakes. The original text should still be visible, but should be crossed through, initialled and dated, with the amendment written alongside.

For electronic CRFs and databases, an audit trail should be available to record any changes made to the CRF.

The timely completion, legibility and accuracy of the CRFs remain the responsibility of the PI.

5.10.2 Transfer of CRFs

Where CRFs need to be sent to the central research team to permit data entry or trial monitoring, they should not contain any participant-identifiable information unless specified in the protocol and/or approved by the REC, and the participant consent has been obtained for sharing their data in this way.

The investigator site should always retain a copy of each completed form.

5.10.3 Amendments to CRF

Revisions to the CRF may be required during the course of the study. The trial manager, study statistician and database manager should review the amendment to assess the impact on CRF design, study database and study analyses. The CI (and TMG if applicable) should be advised of any potential changes required to a CRF and study database.

All changes should be documented, together with the reason for the change. The implementation date should also be documented.

The new version of the CRF must be approved as described in BTC-SOP-TM-001 Start Up. Standard version control should be followed (see BTC-SOP-QM-002).

5.10.4 Storage of CRFs

Paper CRFs are classified as essential documents and should be stored in a secure location accessible to authorised staff during the course of the study and archived when the study has finished. For details on archiving see BTC-SOP-TM-003 Study Closedown.

5.11 Non-Compliance

5.11.1 Introduction

The principles of GCP state that all information relating to a clinical research study shall be recorded, handled, and stored in such a way that allows its accurate reporting, interpretation and verification. Sponsors are expected to implement procedures that assure the quality of every aspect of the study.

In addition, it is a legal requirement for CTMPs that serious breaches of GCP or the trial protocol are notified to the MHRA.

When conducting a research study, it is important to have procedures in place for identifying, documenting and reporting non-compliance, as well as investigating and assessing such occurrences, and determining corrective and preventative actions, as required.

Episodes of non-compliance can consist of:

- Poor data quality;
- Protocol deviations;
- Serious breaches of:
    - the study protocol and associated documents (e.g. SOPs/study manual, data management plan, statistical analysis plan);
    - the principles of GCP;
    - any applicable regulatory requirements;
- Misconduct.

5.11.2 General principles

Issues may be identified through several means, e.g. central or on-site monitoring procedures or independent audits.

On becoming aware of an issue, the research team/BTC will support prompt and appropriate action to determine whether the issue is one of poor data quality, research misconduct, a protocol deviation, or a serious breach of the trial protocol and/or GCP that warrants further action and onward reporting.

A breach can be classified as serious or non-serious depending on whether participant safety or the integrity of the study are immediately compromised.

Issues which may compromise the safety of participants and/or the integrity of the study should be classified immediately, and the appropriate action taken (NB these events are likely to be classified as serious breaches). Other issues can be discussed at a later date such as during a TMG meeting.

The categories of poor data quality, research misconduct, a protocol deviation, or a serious breach are not mutually exclusive. If the issue fits more than one category, e.g. a protocol deviation that is found to be research misconduct, each procedure must be followed.

In all cases appropriate corrective and preventative measures need to be employed to safeguard the conduct of the study as appropriate. These may include staff training, protocol amendments and/or implementing urgent safety measures.

Investigators at participating sites should be given every opportunity to provide an explanation for the suspect data or protocol non-compliance or serious breach of GCP and/or the protocol.

5.11.3 Poor data quality

Examples of types of poor data quality include:

- Persistent missing key data in the CRFs for a number of research participants;
- Inadequate source documents; examples include persistent lack of recording of study information in the medical records, or persistent errors in documentation of informed consent.

Poor data quality should be dealt with through data management procedures. Where the extent of poor data quality may jeopardise the safety of research participants and the integrity of the research study, it may be classified as research misconduct, deviation or a serious breach.

Appropriate oversight of study data management must be put in place to ensure such instances are detected. Data quality should be discussed at Study Update /TMG/TSC meetings.

Concerns should be discussed with staff responsible for data collection or data entry within the research group and/or at the participating site, and the local PI may need to be involved. Issues that are not or cannot be resolved (e.g. missing data that cannot be retrieved) should be escalated to the TMG, CI or Sponsor, as required.

5.11.4 Protocol deviations

Examples of a deviation are as follows:

- Treatment outside of a specified treatment window that does not compromise the safety of the recipient;
- Non-compliance with procedure(s) specified in the protocol that does not compromise patient safety (e.g. omission of tests or assessments that are research related and not required for the clinical management of the patient) or inclusion of study participants who fail to comply with eligibility criteria;
- Non-compliance with GCP; examples include late reporting of serious adverse events, no evidence of study team training or delegation of tasks.

Deviations may be identified by routine quality control procedures or may be reported directly from the local PI or other staff at the research site. All such deviations should be documented and reviewed on a regular basis with the CI and/or TMG, to ensure that recurring issues are dealt with appropriately.

Deviations may be recorded in a number of ways including on the CRF, in study update/TMG meeting minutes or as part of a monitoring report. If it is necessary to generate a separate deviation report because the event is not captured elsewhere, the report should include:

- full title of the clinical study
- name of the CI and the PI at the research site where the deviation occurred
- brief explanation of how the deviation was identified and the nature of the deviation
- details of initial corrective actions
- an assessment of the impact on the study participants, including safety.

This report should be filed in the TMF, unless it contains confidential information, in which case it should be filed separately.

An impact assessment to determine whether the deviation is deemed to be serious will be undertaken by the CI and/or TMG and/or Sponsor. The assessment of seriousness should include the following considerations:

- Is the deviation likely to affect participant safety, participant confidentiality, or data integrity?
- Is the deviation relating to significant GCP non-compliance?
- Are there minor but persistent GCP non-compliances suggesting a systematic quality assurance failure?
- Does the deviation show failure to comply with the regulations?

Deviations that are considered to be serious should be reported to the Sponsor. The Sponsor will decide if the event should be classified as a serious breach or research misconduct and if further action is to be taken.

Other actions may include the following:

- Alerting the investigator (the PI and/or CI) and asking for further explanation or data verification
- A triggered/for-cause audit of a participating site or the clinical study database as applicable
- Examination of data from the site by the study statistician, as a central monitoring procedure, to estimate the likelihood that any anomalies could have occurred by chance
- Review of other data from the respective site
- Involvement of the DMSC or TSC.

Findings should be agreed and documented and in the case of serious deviations a final assessment should be agreed in conjunction with the Sponsor.

The findings and outcome decisions should be notified as applicable to relevant members of the research team, TMG, TSC and, where appropriate, local site staff, to ensure that appropriate actions can be taken in the conduct of the study. This report may be provided to the DMSC and REC as applicable, and to the study statistician(s) for assessment on any impact on the data analysis.

If the deviation was discussed initially as a potential issue of research misconduct or a serious breach but it is decided that this is not the case, details of the enquiries and an explanation of the reasons for the finding should be recorded.

5.11.5 Serious breaches

A “serious breach” is defined as a breach of the protocol or of the principles of GCP which is likely to affect to a significant degree the safety or physical or mental integrity of the research participants, or the scientific value of the research.

Examples of a serious breach are as follows:

- A breach of GCP or the protocol leading to the death, hospitalisation or permanent disability of a study participant;
- Proof of research misconduct relating to study records or data, if the fraud is likely to have a significant impact on the integrity of research participants or the scientific value of the study;
- Persistent or systematic non-compliance with GCP or the protocol that has a significant impact on the integrity of study participants or the scientific value of the study. This might include widespread inclusion of participants who do not meet the trial eligibility criteria, or failing to stop or reduce a dose of an IMP in response to a trigger defined in the protocol;
- Failure to control IMPs such that study participants or the public are put at significant risk or the scientific value of the study is compromised;
- Failure to report AEs, SAEs or SUSARs such that study participants or the public are put at significant risk.

The Sponsor should decide if an issue is to be classified as a serious breach.

The Sponsor should notify the REC of a serious breach within 7 days of becoming aware of that breach. Reports of serious breaches should give details of when the breach occurred, the location, who was involved, the outcome and any information given to participants. An explanation should be given, and the REC informed what further action the Sponsor plans to take.

In the case of a CTIMP, the sponsor must notify the MHRA of a serious breach within the same timescale. Initial contact with the MHRA inspectorate may be by telephone to discuss the breach, with follow up written information being submitted within 7 days of the sponsor first becoming aware of the breach. The report form prescribed on the MHRA website should be used and e-mailed to the MHRA GCP serious breach team, and a copy provided to the REC.

There is no requirement to notify minor breaches of GCP or the protocol.

The research team should ensure prompt notification of a serious breach to the Sponsor to facilitate reporting within the required time frame.

Identifying and investigating a serious breach will require the sponsor, the CI, local PI and BTC if delegated to work together to identify the extent of the breach and to initiate any urgent safety measures or additional training that may be required (see section 5.5 Urgent Safety Measures).

A written report documenting the investigations, an explanation of the findings and subsequent recommendations should be issued by the Sponsor or delegate to all relevant parties including the Sponsor (if not the author), CI, local PI and BTC.

The Sponsor or delegate should track the outstanding actions until resolution.

If a critical non-compliance is identified, the study may need to be suspended and recommendations made. Recommendations may include some or all of the following:

- A triggered/for-cause audit of a research site or the study database, as applicable;
- Termination of the investigator site (by protocol substantial amendment if CTIMP);
- Re-training of the investigator and/or site staff;
- Re-analysis or exclusion of censored data (NB. no use will be made of any fraudulent data, although this will be retained in the database);
- Suspension or termination of the study by protocol substantial amendment;
- Determination of how to deal with participants still participating in the trial;
- Increase in monitoring procedures until satisfied that the site is fully compliant;
- Notifications to the MHRA, REC and any third party organisations as appropriate;
- The taking of appropriate corrective and preventative measures, and the defining of further oversight procedures.

All documentation will be retained in the TMF, with the exception of confidential and/or unblinded information which will be filed separately and made available to the MHRA during any subsequent GCP inspection.

5.11.6 Research misconduct

Anyone with concerns over the conduct or quality of a research study should report these concerns immediately (within 24 hours) to their line manager or BTC Senior Management in the first instance, preferably in writing together with relevant associated documentation generated through routine monitoring or quality assurance processes. Allegations will be dealt with in confidence in the appropriate manner.

The monitor, auditor or other study related staff must not take independent action. All written material is to be confined to factual observations and must not include opinions and preliminary conclusions.

The line manager, or BTC Senior Management will in turn escalate this to the CI, TMG, BTC, Sponsor or BTC Senior Management as appropriate.

False accusations of research misconduct will place BTC/UoB at risk of litigation. Whilst this should not inhibit the reporting of suspicions and thorough investigation, it should limit the number of people involved in the assessment.

The staff member reporting the suspicion of research misconduct will only be involved further if directly included by those investigating the suspicion. Investigations will be conducted according to national procedures as detailed by the UK Research Integrity Office (UKRIO) Procedure for the Investigation of Misconduct in Research.

In very exceptional circumstances, where a member of staff does not consider it appropriate to report their suspicions through the normal reporting lines, they may directly contact the relevant oversight committee, the REC or the MHRA.

The decision for reporting to other third party organisations e.g. professional body or employing organisation will be determined and undertaken jointly by the staff investigating the misconduct.

5.12 Management of IMPs and medical devices under investigation

Investigational Medicinal Products

The risks associated with an IMP will vary between trials and should be assessed and categorised as Type A, B or C in line with MHRA guidance on risk adapted approaches to CTIMPs.

Once the category has been determined then a full risk assessment of the trial can be carried out. The trial risk assessment and this SOP should inform the trial specific documentation relating to the management of the IMP.

5.12.1 Receipt of IMP supplies at the participating research site or other facility storing and/or administering the IMP

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(s) will normally be released to the relevant local pharmacy (or other facility) from the supplier responsible for the providing the IMP.

The Trials Pharmacist (or equivalent) from the relevant pharmacy (or other facility) will be responsible for managing and documenting the receipt of the IMP, code-break envelopes (which may be used for emergency unblinded) 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.

On receipt of an IMP the trial pharmacist or equivalent should ensure that:

- supplies are correctly addressed;
- all packaging is intact;
- the quantity, batch/serial numbers, correspond with any shipment paperwork;
- suitable transport conditions have been maintained (e.g. no temperature breaches in transit) in accordance with those outlined by the manufacturer or as detailed in the study manual.

If there are any breaches, such as temperature breaches, or the packaging is damaged the BTC (and manufacturer, if applicable) should be contacted to determine what course of action should be taken and this should be followed and documented. This role may be performed by the courier responsible for IMP transportation.

The person who receives the IMP must complete a drug receipt log, which may be paper based or electronic and held as part of the study database.

All paper-based documents relating to the accountability of the IMP should be kept in the site/pharmacy file as appropriate.

5.12.2 Storage of IMP supplies prior to use

If a research site is in receipt of IMP, if possible, the IMP should be stored in the local hospital pharmacy in a designated IMP storage area. It may be stored elsewhere on site provided that the location has been approved by the trial pharmacist.

Sites must clearly document where the IMP is stored. In order for a site to store an IMP, the following procedures must be in place:

- The IMP should be inspected before it is used, to ensure it is fit for purpose;
- For any trials where the storage of the IMP(s) must be temperature controlled, temperature logs of the IMP(s) should be kept or there should be evidence that temperature is monitored, and breaches can be identified (e.g. electronic temperature monitoring system);
- The site should be able to conform to any handling/storage guidelines found in the SmPC, IB or study/Pharmacy manual;
- The site should keep documentation relating to how the IMP is accessed, including who has access to the IMP and how access is controlled.

If the IMP is to be stored outside local pharmacy (e.g. if required by the trial protocol, or if the IMP is to be administered outside of the pharmacy's working hours), it must be stored in a secure location/facility appropriate for the defined storage conditions (fridge, freezer or appropriate drug cupboard) which is accessible only to authorised staff. The temperature may need to be recorded for IMPs which are stored in a drug cupboard and this should be done according to the trial-specific instructions in the pharmacy manual and/or protocol. The frequency and method of temperature monitoring required should be determined and documented in the risk assessment. The MHRA Good Clinical Practice Guide contains guidance on the different frequency and method of temperature monitoring.

If temperature parameters are breached, this must be documented and reported to the CI/PI, Sponsor or delegate (and pharmacy if appropriate) as soon as possible, and the affected stock quarantined until further instruction is provided by the Sponsor (or pharmacy if appropriate). All quarantined IMP should be labelled clearly as such and stored in a separate area from any remaining stock. It can be returned to pharmacy if required.

The storage of the IMP may be delegated to a Sponsor-approved third party if the IMP is not handled by the research sites.

The Sponsor or delegate (e.g., BTC) should make sure that adequate monitoring of storage conditions is in place.

5.12.3 IMP prescribing and administration

Adequately trained and qualified prescribers should be named on the delegation log. Only qualified and registered doctors and health care professionals who meet certain conditions (supplementary prescribers) can prescribe IMPs. It is not defined in the clinical trial regulations that dispensing of IMP must be on a prescription form as long as record is made in the participant medical notes, trial specific prescription, CRF, trial worksheets or database. Sites may insist that a prescription form is used to assist tracking and audit. Hospital standard or research specific prescriptions can be used. Research specific prescriptions should follow BNF guidance, which can be found on the BNF website.

Responsibility for IMP administration must be stated on the Delegation Log for the trial.

IMPs will be administered to or by participants as detailed in the trial protocol, prescription (where applicable) and any relevant Sponsor instructions/study manual.

Deviation to the IMP administration procedures (as defined in the protocol) must be reported to the CI/PI, pharmacy and Sponsor as soon as possible. The deviation may also have to be reported as a clinical incident in accordance with the local policies. The Sponsor will assess whether or not a serious breach of GCP or of the trial protocol has occurred as a result of a deviation of IMP administration, and, if necessary, will report it to the MHRA within the required timelines.

5.12.4 Transfer of IMP between investigational sites

Transfer of IMP between participating sites should be avoided unless other arrangements cannot be put in place. If transfer is required then this should be discussed with the IMP supplier and Sponsor (or delegate) as it may need to go back to the IMP supplier for inspection and QP release prior to transfer. If it becomes necessary to transfer IMP between participating sites in exceptional cases (e.g. a participant safety will be compromised if supplies are not provided from another site), this should be managed by the Sponsor (or delegate) and the research team. The process must be documented.

5.12.5 IMP accountability

IMP accountability records/logs should be kept for all CTIMPs, either on paper or as a part of the study database. These logs may include:

- Trial identifiers (Name, IRAS number, CI and PI name, Sponsor),
- IMP name, strength, form, expiry date;
- Participant identification;
- Date dispensed;
- Visit number (if applicable)
- Dose
- Kit/bottle/pack number (if applicable)
- Quantity dispensed;
- Batch/serial numbers;
- Date returned (if applicable);
- Quantity returned;
- Date of destruction or return to Sponsor
- Pharmacist/delegate name and date of completion

The exact accountability process for a particular IMP in a particular study should be described in a study manual or equivalent.

If there are any breaches, such as temperature breaches, or the packaging is damaged, details of how to manage this will be described in the study manual or equivalent.

For Type A category trials and some Type B category trials (on a case by case basis) a risk adapted approach for the IMP management may be adopted. If an IMP accountability log is not used, this should be justified in the risk assessment, completed in collaboration with the sponsor.

5.12.6 Returned IMP supply and IMP recall and destruction

Study specific documentation will describe the process for the return of any unused IMP and/or IMP packaging and must be in accordance with local policies. If the packaging of used IMPs is required to be kept after the IMP is administered for drug accountability, this process must be described in the study manual or equivalent. In these circumstances the number of unused and returned products will be monitored.

In the event that an IMP needs to be recalled for any purpose, the Sponsor or research team should follow the manufacturer/supplier's SOP. If the dispensing pharmacy also has a SOP for IMP recall, the manufacturer/supplier's SOP takes precedence.

Once all supplies have been accounted for and the research team have confirmed that this has taken place, unused IMP and/or IMP packaging can be destroyed as per pharmacy SOPs. In some cases, the IMP may be destroyed by the local pharmacy where the IMP is stored or may be returned to the manufacturing pharmacy or the Sponsor. These arrangements should be described in the study manual or equivalent.

5.12.7 Emergency unblinding

Unblinding is the process by which the allocation code is broken so that the CI, PI and/or other designated member(s) of the research team (e.g. the study statistician) becomes aware of the intervention.

If applicable to the trial, the Sponsor or delegate must have a written procedure in place for unblinding of trial participants. The procedure must be tested and documentation of testing kept before use, secure, readily available at all times during the trial, and not allow breaks of the blinding to go undetected.

The delegation log must include names of research staff that will have access to the treatment randomisation codes for purposes of unblinding.

Local research staff must follow instructions detailed in the trial protocol or study manual in the event of an emergency situation occurring at site which requires a participant to be unblinded. All care shall be taken to ensure that the study team are kept blinded.

The unblinding system should be tested on a regular basis during the conduct of the trial to ensure unblinding procedures remain fit for purpose.

Investigational Medical Devices

The risks associated with each device trial will vary. The trial risk assessment and this SOP should inform the trial specific documentation relating to the management of the device.

5.12.8 Receipt and storage of the medical device

The local research team should be familiar with the processes at the site for the receipt, storage, dispensing, reconciliation and return or authorised destruction of the investigational device, and any arrangements should be clearly documented and available. Training should be provided to the local team, usually during site initiation but ongoing/periodic training may be required and should be scheduled.

On receipt at site, the responsible personnel should:

- Check that the correct product, complete with Instructions for use, certificates, usage and maintenance information etc. and any relevant accessories, have been supplied;
- Check for any damage apparent to the device on inspection;
- If applicable, ensure that the randomisation code has been received;
- Record device information as required, including (not an exhaustive list): amount, batch details, asset number / serial number, model identification codes, integrity of the packaging seal, protocol number, etc.;
- Record who carried out the checks.

Any discrepancies should be promptly brought to the attention of the Sponsor or delegate/ manufacturer.

The medical device should be stored in a specific, well identified, secure location, with access limited to authorised personnel, and in accordance with the storage requirements detailed in the protocol, study manual or supplied by the Sponsor or manufacturer. A storage area temperature log should be maintained, if appropriate.

5.12.9 Maintenance of the device

The site personnel should be aware, at any time during the trial, where the medical device under study is located (both used and unused devices, if applicable).

Local research team members should be provided with training and relevant information on setup of the equipment for use with a study participant and any pre-use checks that may be required.

In cases where the manufacturer's instructions specify specialist assembly or manipulation, training should be undertaken to ensure familiarity with the functions of the device and its components and accessories, as required.

Any testing, calibration or adjustment required should be carried out before the device is used for the first time, and at any other time points specified, and recorded as specified in the instructions/manual.

Details of training for users (both healthcare professionals and participants) should be available to all members of the local research team.

5.12.10 Dispensing of device and accountability

Each time the trial device is dispensed or employed, a record/accountability form should be completed. Documentation may include: name of individual dispensing the device, participant study ID number (other identifiers may be utilized as per protocol), date (and time if appropriate) of dispensing, date study device returned, if appropriate.

5.12.11 Emergency unblinding

If emergency unblinding is medically necessary the local research team should follow the study specific unblinding procedures as per the protocol or study manual and document all circumstances appropriately.

5.12.12 Return/destruction/dispensation of device

Transfer of medical devices under investigation between participating sites should be avoided unless other arrangements cannot be put in place. Should transfer become necessary, this should be managed by the Sponsor or delegate and the local team and proper documentation and communication must be maintained.

The local team should ensure that all documentation regarding dispensing and return of the device is complete and accurate. A record of the return or destruction of the device should be maintained and stored in the TMF and ISF.

5.13 Study closing to recruitment

A study is said to be ‘closed to recruitment’ when it has recruited its target number of participants as detailed in the protocol or is terminated early. If the study is multicentre this must mean that no further participants can be recruited at any of the participating sites.

Participants may still be on treatment/intervention when the study is closed to recruitment.

The end to recruitment should be clearly communicated and subsequently documented at each site. It is the PI’s responsibility to ensure that the participating site’s R&D Office is informed about the change in status and that evidence of this is kept in the ISF.

Once the study is ready to close, as defined in the protocol, the research team should start closedown procedures as detailed in the BTC-SOP-TM-003 Study Closedown. The end of study definition should be detailed in the protocol.

6. SUPPORTING DOCUMENTS TO BE USED

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-001	Study Start Up SOP
BTC-SOP-TM-003	Study Closedown SOP
BTC-SOP-QM-002	Quality Management Systems SOP
BTC-SOP-ST-001	Statistics SOP

7. CHANGE HISTORY

Previous version and date	New version and date	Brief summary of review
NIL		New document
V1, 2 July 2021	V2, 9 February 2022	Clarifications regarding processes mandated by external review bodies (HRA/MHRA) and requirement to follow the applicable guidance from HRA/MHRA Clarifications of confirmation of participant eligibility Minor clarifications on obtaining and recording informed consent and competency of minors to give consent Update to replace “withdrawal of consent” with “change in participant study participation” and clarification on related procedures in accordance with internal processes and national workstreams Clarification on where RSI can be found Mention of the shortened DSUR for ‘Type A’ trials
V2, 9 February 2022	V3, 26 February 202426	Reference to the BTC Sharepoint was removed and replaced with BTC Teams site. Updated with new HRA and MHRA processes CTIMPs submitted via combined ways of working. Clarification added on process for obtaining consent and completing consent forms Appendix removed and replaced with reference to the MHRA Good Clinical Practice. Clarification added on when emergency unblinding should take place. Clarification added on safety reporting definitions and reporting processes. Information added on the implementation of a urgent safety measure.

		Clarification added about the types of amendments to contracts (cost and no cost extensions). Information about regarding MHRA guidance on risk adapted approaches to CTIMPs. Information added regarding delegation and documentation of IMP prescription Information about regarding IMP accountability and transfer between sites