University of Hertfordshire

RESEARCH APPLICATIONS

Clinical Trials Support Network (CTSN)

Standard Operating Procedure for the
Application and Maintenance of a Clinical Trial Authorisation Application (CTA) and application to the Health Research Authority for Clinical Studies, Sponsored/co-sponsored by the University of Hertfordshire

SOP Number: gSOP-13-02	**Effective Date:** 16th March 2022
Version Number: 2.0	**Review Date:** 3 years (or as required)

1.0 BACKGROUND

This is a University of Hertfordshire (UH) standard operating procedure (SOP). UH acknowledges West Hertfordshire Hospitals NHS Trust (WHHT) Research & Development (R&D) which has allowed UH to use the SOPs developed by WHHT where possible, modified for local implementation.

This document sets out the procedures to be followed by all staff who are involved in the initiation and set-up of projects sponsored/co-sponsored by UH which involve investigational medicinal products (IMPs) or non-CE marked devices which require regulatory approval from the Medicines and Healthcare Regulatory Agency (MHRA). This document also sets out how to go about obtaining Ethical and HRA approval for clinical research studies to be sponsored/co-sponsored by UH. Please refer to the Obtaining Sponsorship for research studies SOP which details how to obtain University of Herts sponsorship/co-sponsorship and the relevant reporting arrangements.

This SOP is specifically for CTIMPs, however in the absence of a documented procedure can be used as guidance for any other clinical study.

It provides guidance on how the necessary regulatory and ethical approvals should be obtained prior to commencement of the study to ensure compliance with the University's wider research policies and other applicable legislation.

It is good practice for all research projects to be registered in a publicly accessible database

to promote trial transparency and dissemination of health research outcomes. For clinical trials it is a condition of favourable ethical opinion to do so. Registration should occur before the first participant is recruited and no later than six weeks after recruitment of the first participant. The registry number should be included in the Integrated Research Application System (IRAS) when the application is prepared. The recognised registries are the International Standard Randomised Controlled Trial Number Register (ISRCTN) and Clinicaltrials.gov. For CTIMPS involving both UK and EU sites a record in the EU Clinical Trials Register (EudraCT) will exist.

2.0 PURPOSE

The purpose of this SOP is to describe the responsibilities and procedures for applying for and maintaining Clinical Trial Authorisation (CTA) and procedures for applying for Research Ethics Committee (REC)/Health Research Authority (HRA) approval for Clinical Trial involving Investigational Medicinal Products (CTIMPs) and other clinical studies sponsored/co-sponsored by UH to ensure compliance with the applicable Regulations. This responsibility is delegated to the Chief Investigator (CI) or delegated individual (DI) for UH sponsored/co-sponsored CTIMPs. This SOP is intended to provide a detailed guidance to ensure that the Sponsor maintains the quality of every aspect of the clinical trial.

A Clinical Trial Authorisation is required only in trials of medicinal products. These are substances, or combinations of substances, which either prevent or treat disease in human beings or are administered to human beings with a view to making a medical diagnosis, or to restore, correct or modify physiological functions in humans.

Any research that fulfils the definition of a clinical trial of an investigational medicinal product will require a CTA from the MHRA. A CTA will only be issued if there are no objections to the research proposal.

The definition of a clinical trial of an investigational medicinal product is:

"…any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy".

Clinical studies involving only medical devices, food supplements or other non-medicinal therapies (such as surgical interventions) may require other regulatory approvals.

For all University sponsored CTIMPs UH confirmation to commence will only be given by the Research Office following receipt of a valid CTA, REC and HRA approval.

All University co-sponsored CTIMPs require NHS R&D confirmation to commence. A valid CTA, REC and HRA approval is required.

HRA REC reviews all research projects that are CTIMPS or involve NHS patients or access to data, organs or other bodily material of past or present patients.

This SOP also describes the requirements for clinical trial registration.

3.0 APPLICABLE TO

This applies to all staff involved in clinical research sponsored/co-sponsored by UH, including: Chief Investigators, Principal Investigators, Research Fellows, Consultants, Statisticians, Clinical Trial Pharmacists, Research Managers, Research Nurses, Clinical Trial Practitioners, Allied Health Professionals, Trial Coordinators, Clinical Studies Officers, Data Managers and Research Assistants.

4.0 RESPONSIBILITIES

4.1 The **Sponsor/Co-sponsor** should risk assess the clinical trial (following gSOP-033 Risk Assessment), review study documentation and ensure that it provides approval to the study Chief Investigator of its authorisation to apply for Regulatory and REC approval. MHRA and REC approval should be sought once full funding has been secured, Sponsorship agreed in Principle and the trial protocol (related trial documents) has been finalised. Accountability for trial Registration resides with the Sponsor.

4.2 The **Chief Investigator (CI) (or delegated individual (DI))** is responsible for ensuring that the Regulatory and HRA/REC applications are completed, and approval obtained as delegated by the study sponsor. The CI (or DI) must ensure that the draft CTA is reviewed by the Trust Clinical Trial Pharmacist before the application is submitted and ensure that pharmacy review subsequent amendments relating to the management of the IMP(s) before they are submitted. Responsibility for timely trial Registration resides with the CI in receipt of NIHR funds.

4.3 For co-sponsored studies the **NHS Trust study Co-sponsor is** responsible for ensuring that the applicable research governance checks are completed prior to the provision of the NHS R&D confirmation letter. They are also responsible for ensuring that any subsequent amendments receive review by the applicable staff and regulatory and/or HRA/REC approval prior to implementation.

4.4 For UH sponsored studies the research office are responsible for provision of confirmation to commence and continuation following any HRA approved subsequent amendments.

4.5 The Trust **Clinical Trial Pharmacist** is responsible for reviewing and providing oversight for CTA applications and subsequent substantial amendments which impact the management of the trial IMP(s) thereafter.

5.0 PROCEDURES

5.1 Classification of Clinical Trials of an Investigational Medicinal Product (CTIMPs)

To find out whether a clinical trial is covered by the Clinical Trials Directive 2001/20/EC, an algorithm 'Is it a clinical trial of a medicinal product' available from the MHRA website can be used:

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/317952/Algothrithm.pdf

After working through the algorithm, please contact the CTSN/R&D department for advice. The MHRA Clinical Trial Helpline can be contacted if required. A copy of the protocol or protocol proposal should be emailed to the MHRA alongside the request.

5.1.1 Clinical Trials involving medical devices and medicines

- Clinical trials involving a medicine and a medical device will be subject to clinical trials regulations and may also be subject to medical device regulations depending on the purpose of the trial.
- In such cases, the CTSN/R&D department will advise and assist Investigators in contacting the MHRA to check the regulatory position.
- Advice from the MHRA Devices Division should be sought for clinical trials involving non-CE marked devices or CE marked devices used outside the conditions of the CE marking.
- If the medical device is to be used in an NHS Trust, please contact the Trust medical devices department. Devices cannot be used in NHS Trust without their approval.

5.1.2 Clinical Trials of non-investigational medicinal products (nIMPs)

- Some clinical trials also involve medicinal products which are classified as non-investigational medicinal products (nIMPs). Standard of care medicines that are already being administered to a participant but are continued during the clinical trial are generally considered to be nIMPs.
- If further clarification is required as to whether a product is an IMP or nIMP, further information is available from the MHRA website/helpline.

5.2 Clinical Trial Authorisation application

Once a Clinical Trial has been classified as a CTIMP, the CTA submission package will be prepared by the CI/Delegated individual for UH Sponsored/Co-sponsored CTIMPs and can be submitted following sponsor approval.

5.3 Registering with EudraCT

In order for a Clinical Trial to be considered for authorisation, it must be registered on the European Clinical Trials Database – EudraCT. This is done by obtaining a unique reference number for each clinical trial.

Guidance is available on the EudraCT website and IRAS.

5.4 The CTA Application and Submission

Detailed information on what to submit and how to submit the application is available on the MHRA website. The trial application form is on the Integrated Research Application System (IRAS).

Your submission package must include:

- a covering letter (when applicable, the subject line should state that the submission is for a Phase I trial and is eligible for a shortened assessment time, or if it is submitted as part of the notification scheme);
- a clinical trial application form in PDF and XML versions;
- a protocol document;
- an investigator's brochure (IB) or document replacing the IB;
- an investigational medical product dossier (IMPD) or a simplified IMPD;
- a non-investigational medicinal product dossier (if required);
- a summary of scientific advice from the MHRA or any other regulatory authority, if available;
- manufacturer's authorisation, including the importer's authorisation and Qualified Person declaration on good manufacturing practice for each manufacturing site if the product is manufactured outside the EU;
- a copy of the UK or EMA's decision on the paediatric investigation plan and the opinion of the paediatric committee, if applicable;
- the content of the labelling of the investigational medicinal product (IMP) (or justification for its absence).

The investigator must ensure consistency between all the submitted documents.

The CI (or delegated individual) must send the draft version of the IRAS form to the Trust CT Pharmacist to allow the CT Pharmacist to review the IMP section of the form. The CT Pharmacist should review and authorise/provide guidance on the following aspects of the CTA submission to the MHRA;

- Review the application for each IMP identified in the trial.

- Sample Label(s) to be used for the trial IMP(s) - The CT Pharmacist must approve any labels submitted or design the label to be used. Notification of this approval should be documented and provided to the CI/delegated individual and CTSN. For co-sponsored studies notification of approval should also be sent to the R&D department.

A draft version of the completed Clinical Trial Application should be sent to the CTSNMG for review.

Although the CI will sign the application form as the "Applicant", the DI (Research Sponsorship (research-sponsorhip@herts.ac.uk), Project Manager, Trial Manager, Clinical Research Scientist or Study Coordinator)) will be the "contact" and will receive all correspondence relating to applications for this project in addition to the Chief Investigator. This is to ensure that all correspondence from the MHRA is sent to the Sponsor.

For co-sponsored CTIMPS, prior to submission to the MHRA, the CI or delegated individual should liaise with the relevant R & D department to authorise and arrange the payment (by

bacs transfer) of the required fee to the MHRA as detailed on the MHRA website. The EudraCT number must be included with the payment.

Proof of payment of the fee must be sent with the submission package to the MHRA to ensure the validity of the application.

The Clinical Trial Application should be submitted via the MHRA submissions. The CI should liaise with the CTSN to gain access to the portal.

An electronic signature of the submitted application form and supporting documents will be filed in the Trial Master File and for co-sponsored studies sent to R&D. A copy of the signed CTA and applicable approvals should be maintained in the trial specific pharmacy file.

Upon receipt of the MHRA approval letter, the CI or delegated individual should communicate any IMP related outstanding actions requested by the MHRA as part of the approval to the Trust CT Pharmacist, who will work with the CI or delegated individual to ensure these actions are completed. For co-sponsored studies the CTSN and R&D department must be informed when these actions are completed and documented.

5.4.1 What are the possible outcomes?

There are two possible outcomes:

- Acceptance (with or without conditions).
- Grounds for non-acceptance.

The initial assessment will be completed within 30 days of being submitted. Applications for healthy volunteer trials and sponsor-determined phase 1 trials in non-oncology patients may qualify for a shortened assessment time (average 14 days).

If the submission is not accepted, information as to why will be provided and the application will need to be amended and resubmitted. The amended request is assessed within 60 days from the MHRA receiving the original valid application (90 days for gene therapy, somatic cell therapy (including xenogenic cell therapy)).

5.4.2 Terms and conditions of approval

For a single and multicentre CTIMPs, the MHRA must be notified of each additional investigator using the Amendment Tool. Ethics approval for each additional investigator should also be obtained.

In accordance with regulation 27, the Sponsor /CI must notify the MHRA within 90 days of the conclusion of the trial.

The MHRA may suspend or terminate a clinical trial where it feels the conditions for authorisation are not being met.

5.5 MHRA

5.5.1 Type A Clinical Trials

All interventional trials of an IMP conducted in the UK require an approved CTA from the MHRA before they may commence. The majority of Clinical Trials categorised as type A (no

higher than the risk of standard medical care) conducted in the UK can be submitted under the Notification Scheme.
These are trials involving medicinal products licensed in any EU Member state if:

- The trial relates to the licensed range of indications, dosage and form of the product, or;
- The trial involves off-label use (such as in paediatrics and oncology) that is established practice and supported by enough published evidence and/or guidelines.

Applications under the notification scheme must include:

- Covering letter which includes the statement that this is a submission under the notification scheme;
- Clinical Trial Authorisation application form + valid xml;
- Protocol;
- Summary of Product Characteristics (SmPC);
- Justification for absence of labelling (or the content of trial-specific labelling if this will be used);
- Justification for the absence of a manufacturer's authorisation (or a copy of the authorisation for each manufacturing site involved in repackaging of the marketed product, where this site is not a hospital or health centre).

A letter of acknowledgement will be sent to the CI or delegated individual by the MHRA with an accompanying note to say that the trial may go ahead after 14 days from receipt of notification, if the MHRA has not raised any objections. Therefore, the acknowledgement letter will act as the authorisation.

If no Notification Objection letter is received from the MHRA the clinical trial authorisation becomes valid. The applicant will also receive email confirmation, from the clinical trial helpline, that no objection to the notification has been raised.
If the MHRA raises an objection to the notification, the submission is treated as a standard request for authorisation and an assessment of the submission is carried out.
Further details are provided on the MHRA website.

(NB - Ethics Committee role: All interventional trials of an IMP conducted in the UK will continue to require a positive opinion from a Research Ethics Committee before they may commence.)

5.5.2 Types B & C Clinical Trials

For Type B (somewhat higher than the risk of standard medical care) and Type C (markedly higher than the risk of standard medical care) the CTA will be validated on receipt at the MHRA and an acknowledgement letter will be sent to the Sponsor Contact. If the application is valid then the assessment period will begin. This starts from the date of receipt of a valid application.

If the application is not valid the MHRA will inform the CI or delegated individual "Contact". The full submission package may need to be re-submitted, however the MHRA should advise on the requirements for resubmission. The CI or delegated individual should contact the Sponsor contact for further advice in such circumstances if required.

Each application will be assessed by the MHRA within 30 days from the date of validation of the application. They will provide an initial response to all *valid* applications within 30 days of receipt.

If the Notice of Acceptance letter from the MHRA places any conditions on the Clinical Trial Authorisation these must be responded to and a confirmation of satisfactory resolution received from the MHRA for the approval to be valid. The Sponsor should verify that the CTA authorisation letter including any such remarks is responded to prior to Sponsor activation of the trial/ Sponsor approval of amendment.

All correspondence relating to the CTA will be filed within the TMF with copies of relevant applications and approvals in the Sponsor File.

It is a requirement of the CTA that a favourable opinion of a REC is sought and maintained.

The Chief Investigator is responsible for the submission of the initial application to the REC to obtain favourable opinion.

Prior to the activation of the study/ approval of substantial amendments the Research office and CTSN for sponsored studies and the R&D department for co-sponsored studies will verify the governance requirements as part of the initiation visit (see gSOP-18).

N.B - The EudraCT number, CTA number and product name must be quoted in all CTA submissions, amendments, Development Update Safety Reports and End Of Trial notifications.

5.5.3 End Trial Report

Within 12 months from the End of Trial Declaration the Final Trial Report is required to be submitted to the MHRA. Prior to submission to the MHRA, the Chief Investigator will submit the report to the Sponsor/Co-sponsor/CTSN for final review and Sponsor approval. This final report will be sent to the MHRA within one year of the end of the trial and a copy filed within the TMF and for co-sponsored studies will be sent to R&D (see gSOP-22 End of Trial reports).

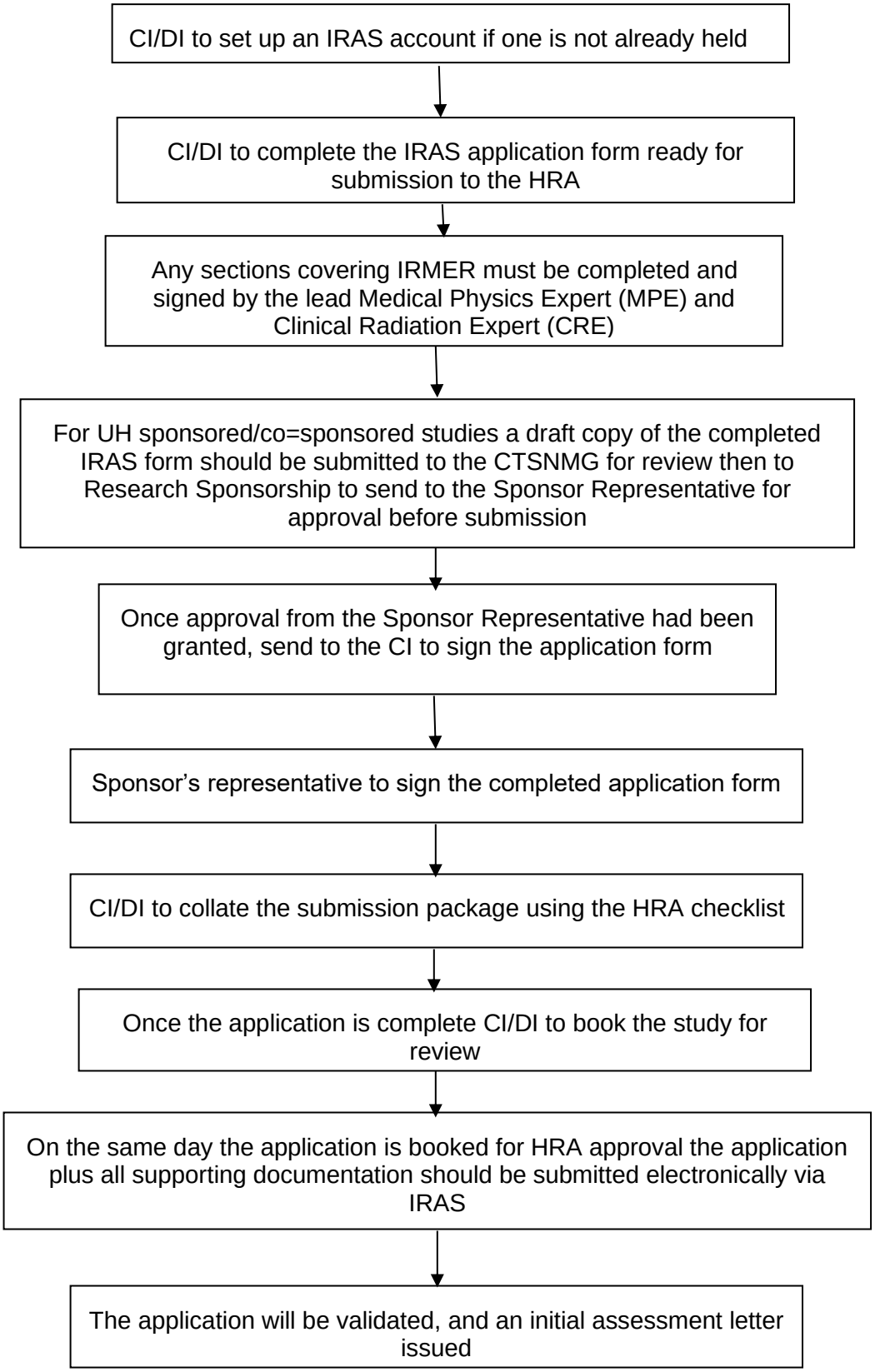
5.5.4 Other activities

The following also contribute to the maintenance of the CTA but are outside the scope of this SOP:

- Adverse Event Reporting (gSOP-02)
- Development Safety Update Reports (gSOP-16)

6.0 APPLICATIONS TO THE HRA/REC

6.1 HRA/REC Application Process



6.2 The HRA Application and Submission

- Application for authorisation of a clinical trial should be completed within IRAS
- The IRAS form should be completed by the CI or delegated individual.
- Sections covering the Ionising Radiation (Medical Exposures) Regulations 2000 (IRMER) must be completed by and signed by the lead Medical Physics Expert (MPE) and lead Clinical Radiation Expert (CRE).
- The Application must be signed by the CI and approved by the Sponsor before submission. An electronic signature should be completed for all Sponsored/Co-sponsored CTIMPs.
- The Application should also be signed by the Sponsor's Representative.
- Applications should be completed according to the HRA application checklist.
- Once the application is complete, the application should be booked for review.
- The application should be submitted electronically via IRAS on the same day it is booked for review.
- The HRA will validate the application for REC review and issue an Initial Assessment Letter.

6.2.1 What are the possible outcomes?

If the application submitted is valid, the application will be assessed and discussed at the REC meeting and the applicant will be sent a letter informing them of:

- Favourable opinion
- Provisional opinion
- Rejection

If the letter states a provisional opinion, the CI will need to address all the conditions and remarks and submit their response back to the REC for their final opinion. The CI must provide a copy of this documentation to the Sponsor/Co-Sponsor/R&D and CTSN and maintain a copy in the TMF.

The RECs are required to give an opinion within 60 days of receipt of a valid application. However, the clock stops if further information is requested and restarts when this information is received by the REC.

The CI will ensure all documentation submitted to the REC and all correspondence received from the REC is sent to the Sponsor/Co-sponsor/R&D and CTSN and a copy maintained in the TMF.

When NHS sites are to be used, in addition to completing the IRAS forms A "Statement of activities" may be required for each "site type" in place of an agreement. A "Schedule of Events" may also need to be completed as part of the HRA submission. The templates for these are available on the HRA website. These forms should be included in a local information pack and sent to the R&D/CRN.

The HRA Initial Assessment Letter will clarify if any site types do not need to confirm capacity and capability.

6.2.2 Conditions of approval

Favourable ethical opinion letters will also list conditions of that favourable opinion including:

- HRA approval
- NHS R&D confirmation being obtained, where NHS sites are involved
- Obtaining a CTA for CTIMPs
- Other specified conditions

Following favourable ethical opinion, the HRA will assess all study documentation prior to HRA approval. Notification of HRA approval must be forwarded to NHS R+D sites for confirmation of green light to commence being granted.

7.0 CLINICAL TRIAL REGISTRATION

All clinical trials are to be registered on a clinical trial registry. Trials should be registered on the ISRCTN registry or ClinicalTrials.gov. For CTIMPS involving both UH and EU sites a record in the EU Clinical Trials register will exist. Non-CTIMP research does not require a EudraCT number.
The NIHR's registry of choice is the International Standard Randomised Controlled Trial Number Register (ISRCTN). In some cases, other recognised registries may be appropriate or required for the primary registry; e.g. where there is a regulatory requirement. In such cases, NIHR will only require registration once, and will therefore waive the requirement for Registration in ISRCTN. Registration advice is provided in the documentation supplied by NIHR programmes as part of the application, contracting and start-up processes. All studies eligible for Clinical Trial Network (CRN) support which have a study identifier are able to register for an ISRCTN using the Central Portfolio Management System (CPMS).

Registration must occur prior to the start of an intervention as part of the Clinical Trial.

8.0 SUBSTANTIAL AMENDMENTS

The CI or delegated individual should prepare, submit and manage the maintenance of the CTA on behalf of the Sponsor. The investigator and trial team must inform the Sponsor and R&D Department/CTSN if an amendment to the Protocol or the CTA is required and supply supporting information as appropriate as detailed in the amendment SOP (gSOP-09).

An amendment is considered to be substantial when it changes the terms of the request for clinical trial authorisation or the ethics committee application, or to the accompanying particulars or documents and is likely to have a significant impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial;
- the quality or safety of any IMP used in the trial.

Therefore, substantial amendments may include, but are not limited to: Amendments to the trial protocol or investigator's brochure, including: -

- Changes to dose
- Change of IMP supplier
- Eligibility criteria
- Statistical review or analysis (including sample size)
- Amendments to change the sponsor or sponsor name
- Urgent safety measures
- Temporary halt of a trial
- End of Trial (See Section 8.9).

The addition of a new NHS/HSC site, and the addition or change of a Principal Investigator (PI) in the NHS/HSC for CTIMP studies, is now classified as non-substantial changes. (Note changes should still continue to be classed as substantial when relating to non-NHS/HSC settings).

The completed Amendment Tool will output the recommended amendment category automatically based on the question responses. It is the responsibility of the Sponsor to review the categorisation and authorise the Amendment Tool.

8.1 Submission of a Substantial amendment to the MHRA

Substantial amendments to a Clinical Trial of an investigational medicinal product (CTIMP) must be notified using the Amendment Tool to both the MHRA and the ethics committee before it is implemented, unless it is an urgent safety measure (see gSOP 29-01).

Once the Amendment Tool has been completed, this needs to be submitted alongside any other appropriate documentation to the MHRA. Alternatively, for 'bulk' amendments to MHRA only, where the same change affects a large number of trials (e.g. change to the reference safety information in an investigators brochure), the Annex 2 form which is available on the MHRA website, can still be completed and submitted to the MHRA.

When notifying the MHRA of a substantial amendment to a CTIMP, the following must be included in the submission:

- Covering letter outlining the substantial and any non-substantial changes.
- A pdf copy of the locked amendment tool. You should ensure that the amendment tool contains a clear description of the amendment and reasons for the proposed changes. Alternatively, for 'bulk' amendments to MHRA (where the same change affects many trials), the Annex 2 form can still be completed and submitted to the MHRA. The form is available on the MHRA website.
- An updated XML and PDF file of the Clinical Trial Application Form (Annex 1) with changes highlighted, if the amendment affects the information previously submitted. **Please Note:** The original clinical trial application form can be updated in IRAS by following the instructions under the submission tab. Alternatively, if your application was prepared in EudraCT you may wish to import the full EudraCT dataset into your existing project in IRAS following the instructions in Section 3 above. The imported data can then be edited in IRAS as usual. Please be aware that using this option will overwrite any existing data in IRAS.
- Copy of the proposed changes to the protocol or any other documents (e.g. IMPD), showing previous and new wording where applicable supporting data for the amendment, including as applicable:
    - Summaries of data,
    - Updated overall risk benefit assessment,
    - Possible consequences for participants already in the trial,

- Possible consequences for the evaluation of results.

For detailed amendment submission guidance, please see the MHRA website.

The CI or designated individual must liaise with the Trust CT Pharmacist regarding all amendments to the protocol of any CTIMPs and ensure the Pharmacy Clinical Trials Team are fully up to date and working to the most recent version of the protocol.

For any pharmacy related amendments, the Trust CT Pharmacist must review and approve the amendment, including any changes to the protocol and if resubmission to the MHRA is required, associated applications and regulatory documents.

The Trust CT Pharmacist will send amendment approvals (if applicable) to the CI/designee and Sponsor/R&D department/CTSN/Research Office (See gSOP-09).

8.2 Submission of Amendments to the REC

It is a requirement of the CTA that a favourable opinion of the REC is sought and maintained, if the amendment is considered substantial for ethical review. The HRA must be notified of both substantial and non-substantial amendments. The Chief Investigator or delegated individual is responsible for the submission of all amendments to the REC. Both non-substantial and substantial amendments should be submitted online through the Integrated Research Authority System (IRAS) using the Amendment Tool (see gSOP-09). Upon submission the amendment will be shared with REC and/or NHS/HSC as applicable.

After submission of amendment the completed Amendment Tool with confirmation of amendment category and amended documents should be shared with relevant participating NHS organisations. The NHS R&D Office as well as the local research team should also be included. Templates for notification can be found on the HRA website.

For detailed guidance on submission of amendments please see (gSOP-09)

8.3 Implementation of Substantial amendments

If all relevant regulatory approvals are in place and there has been no objection from site, the amendment can be implemented after 35 days. Once participating NHS organisations have been notified of the amendment, they should prepare to implement the amendment. The amendment may be implemented at all participating NHS organisations in NHS organisations in England and/or Wales 35 days from the day on which the organisation(s) were provided with the amendment and supporting documentation provided that:

a. HRA Approval has been issued for the amendment where this is required;
b. A participating NHS organisation does not request additional time to assess;
c. A participating NHS organisation does not decline to implement the amendment.

In some cases, amendments may be implemented before 35 days if all approvals are in place.

8.4 Non-Substantial amendments

These are defined as a non-substantial amendment that will have no significant implications for participants or for the conduct, management or scientific value of the study. Except for device studies, non-substantial amendments do not require MHRA or REC approval. However, they should still be submitted for notification.

For further guidance please also refer to the HRA website.

8.5 Temporary Halt of a Trial

If the decision is made to suspend a trial temporarily, the Sponsor, MHRA and REC must be notified within 15 days. The notification should be made as a substantial amendment, clearly explaining what has been stopped and the reason(s) for the suspension. A notification of substantial amendment should be submitted alongside declaration of early termination where necessary.

The notification must be made as a substantial amendment using Amendment Tool.

It is the responsibility of the CI (or delegated individual) to inform the participating Investigator sites of the temporary halt. The CI (or delegated individual) should request confirmation of receipt from Investigator sites that they have understood the instruction for the temporary halt (why it has been imposed, when it is to be effective from, what it means, what and how to communicate with enrolled participants).

All information pertaining to a temporary halt should be retained in the Trial Master File and at site in the Investigator Site File.

If it is decided not to recommence a temporarily halted trial, the MHRA and REC must be notified within 15 days of this decision, using the End of Trial Declaration form.

If an Urgent safety measure (gSOP-29-01 implemented on trial or a serious breach of GCP and/or the trial protocol is identified which requires expedited reporting to the MHRA and REC procedures detailed in the Sponsor's SOP on serious Breaches should be followed (see gSOP-10).

8.6 Development Safety Update Report

The Sponsor alongside the CI (or delegated individual) and Trust clinical trial pharmacist (where required) will ensure that a DSUR is sent to the MHRA and REC no later than 60 days after the **data lock date** (gSOP-16). A copy of the completed DSUR report will be retained in the TMF and a study specific QA folder.

8.7 End of a Trial

The end of the trial is defined as the last patient, last visit, unless described differently in the trial protocol and original CTA application. The signed End of Trial form will be submitted within 90 days of the end of the trial to the MHRA and REC as detailed in the HRA guidance (see gSOP-21).

9.0 RELATED DOCUMENTS

- gSOP-02- Adverse Event Reporting (Sponsored/Co-sponsored)
- gSOP-04- Informed Consent
- gSOP-06- TMF/Site File
- gSOP-07- Research Training
- gSOP-09- Amendments
- gSOP-10- Serious Breaches

- gSOP-29-01- Urgent Safety Measures
- gSOP-11- Organisational Oversight
- gSOP-14- Writing Research Protocols
- gSOP-15- CRF Design
- gSOP-16- DSURS
- gSOP-17- Archiving
- gSOP-21- Trial Closure
- gSOP-22- End of Trial Reports
- gSOP-28- Management of Source Data
- ICH GCP
- UK Policy Framework for Health and Social Care Research
- The Medicines for Human Use (Clinical Trials) Regulations 2004 SI 1031/200
- EUCTD 2001/20/EC and GCP Directive 2005/28/EC

Useful Web links for detailed guidance on procedures described in this

SOP;

Detailed guidance for the notification of a type A clinical trial

Detailed guidance for the request for authorisation of a clinical trial

MHRA Web Page for Submitting a CTA Application

MHRA Web Page for Amendments to CTA

MHRA Web Page for End of Trial Notifications

10.0 APPENDICES

Appendix 1.0 – Definitions

11.0 VERSION HISTORY

Revision Chronology:		
Version Number	**Effective Date**	**Reason for Change**
V1.0	**26th April 2018**	**HRA updated submission of amendments on the 2nd June 2020. Amendments are now submitted online, and the amendment tool has replaced the previous Notice of Substantial Amendment (NOSA) Form and the non-substantial amendment form.**

12.0 AUTHORSHIP & APPROVAL

Author Megan Smith

Signature  **Date** 08/03/2022

Pro-Vice Chancellor (Research & Enterprise)

Approval Signature  **Date 01/03/22**

13.0 AGREEMENT

Please detach and retain within <u>your training files</u>

I have read and understood the contents and requirements of this SOP (ref gSOP-13-01) and accept to follow University policies implementing it.

Recipient
Signature: ……Date: ……..
Name & Position: ……

Please retain copy of the signed form for your reference in your training file

Appendix 1: Definitions

Adverse Event (AE)
Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)
Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Chief Investigator (CI) - A Registered Physician, Dentist, Pharmacist or Registered Nurse who has overall responsibility for the conduct of the study

Clinical Trial – A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or control) to evaluate the effects of those interventions on health outcomes.

Clinical Trial of Investigational Medicinal Product (CTIMP) - A study that looks at the safety or efficacy of a medicine/food stuff/placebo in humans as defined by the Medicines for Human Use Regulations (2004). Clinical Trials are categorised as Type A, B or C.

Type A Clinical Trial - as above but with no higher risk than standard medical care. The medicinal product must be licensed in an EU Member State and the trial relates to the licensed range of indications, dosage and form or, the trial involves off-label use (such as in paediatrics and in oncology), if this off-label use is established practice and supported by sufficient published evidence and/or guidelines

Type B Clinical Trial – as clinical trial above but with somewhat higher risk than standard medical care and involving medicinal products licensed in any EU Member State if such products are used for a new indication (different patient population/disease group), or substantial dosage modifications are made for the licensed indication or if they are used in combinations for which interactions are suspected. Also, trials involving medicinal products not licensed in any EU Member State if the active substance is part of a medicinal product licensed in the EU

Type C Clinical Trial - as clinical trial above but with markedly higher risk than standard medical care and involving a medicinal product not licensed in any EU Member State A grading other than TYPE C may be justified if there is extensive class data or pre-clinical and clinical evidence.

Clinical Trial Authorisation (CTA) – Regulatory approval issued by a Competent Authority to conduct a clinical trial within a Member State.

Development Safety Update Report – (DSUR)

Development International Birth Date - (DIBD) this is the date that the Sponsor received the first CTA for that IMP and this will determine the annual reporting period for the DSUR.

Data Lock Point – This should be the last day of the one-year reporting period and the DSUR should be submitted to the MHRA and the REC no later than 60 days after the data lock date.

Delegated Individual (DI)
An individual delegated by the PI to carry out their task(s).

Good Clinical Practice (GCP) - as defined in the Regulations.

Investigational Medicinal Products (IMP) - means a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial.

Principal Investigator (PI)
A Registered Physician, Dentist, Pharmacist or Registered Nurse who has responsibility for the conduct of the trial at a host site.

Sponsor's Representative
The Pro-Vice Chancellor (Research & Enterprise) will act as the Sponsor's Representative.

The Medicines & Healthcare products Regulatory Agency (MHRA)
UK Competent Authority responsible for regulation of clinical trials.

The Regulations
Medicines for Human Use (Clinical Trial) Regulations 2004 transposed the EU Clinical Trials Directive into UK legislation, as Statutory Instrument 2004 no 1031. This became effective on the 1st May 2004. An amendment to implement Directive 2005/28/EC was made to the Regulations as Statutory Instrument 2006 no 1928.

Trial Master File
The Trial Master File (TMF) will be held at the principal site by the sponsor, Chief Investigator or at the co-ordinating Centre. The TMF should contain all essential documents defined as documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. A Trial Master File should be set up at the beginning of a trial and maintained up to date throughout the trial until trial conclusion.

For trials currently running, it is recommended that Section 8 of the ICH-GCP Guideline is followed as guidance in order to meet statutory requirements. However, some of the documents listed may not be available or applicable in many non-commercial trials. The appropriate documentation will vary according to the trial and sponsor requirements.