RESEARCH APPLICATIONS

Research & Development

Standard Operating Procedure for the Production and Maintenance of a Clinical Trial Authorisation Application (CTA) and Application to the Health Research Authority for West Hertfordshire Hospitals NHS Trust Sponsored CTIMPs

SOP Number: SOP-13-05	**Effective Date:** October 2021
Version Number: v05	**Review Date:** 2 - 3 years

1.0 BACKGROUND

This document sets out the procedures to be followed by all West Hertfordshire Hospitals Trust (WHHT) staff who are involved in the initiation and set-up of projects sponsored by WHHT which involve Investigational Medicinal Products (IMPs) or medical devices which require regulatory approval from the Medicines and Healthcare products Regulatory Agency (MHRA). This document also sets out how to go about obtaining Ethical and Health Research Authority (HRA) approval for research studies to be sponsored by WHHT.

2.0 PURPOSE

The purpose of this SOP is to describe the responsibilities and procedures for applying for and maintaining a Clinical Trials Authorisation (CTA) and procedures for applying for Research Ethics Committee (REC)/HRA approval for Clinical Trials of an Investigational Medicinal Product (CTIMPs) sponsored by WHHT to ensure compliance with the applicable regulations. This responsibility is delegated to the Chief Investigator (CI) or delegated individual (DI) for WHHT 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 CTA 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 will require a CTA from the MHRA. A CTA will only be issued if there are no objections to the research proposal.

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

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

All WHHT sponsored CTIMPs will not receive R&D confirmation to commence unless REC approval is received by the trial investigator.

3.0 APPLICABLE TO

Any Trust employee involved with CTIMPs sponsored by WHHT including, but not limited to, Unit Heads, Chief Investigators (CI), Principal Investigators (PI), Consultants, Co-investigators, Research Fellows, Clinical Trial Pharmacists, Research Managers, Statisticians, Research nurses, Allied Health Professionals, Trial Coordinators, the Research & Development Steering Group (RDSG) & Data Managers.

4.0 RESPONSIBILITIES

4.1 The Sponsor

The Sponsor should risk assess the clinical trial and ensure approval is provided to the CI so they can apply for regulatory and REC approval. MHRA and REC approval should be sought once funding has been secured, sponsorship agreed in principle and the trial protocol (related trial documents) has been finalised.

4.2 The Chief Investigator

The CI/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/DI must ensure that the draft CTA is reviewed by the Clinical Trial Pharmacist before the application is submitted and ensure that pharmacy reviews subsequent amendments relating to the management of the IMP(s) before they are submitted.

4.3 The Research and Development Department

The R&D Office is responsible for ensuring that the applicable research governance checks are completed prior to the provision of the 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. (see SOP-09).

4.4 Pharmacy

The 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:
Appendix 2: Algorithm to determine whether it's a clinical trial of a medicinal product

If, after working through the algorithm, there is still uncertainty, the R&D Department will advise and assist investigators in contacting the MHRA Clinical Trial Helpline. A copy of the protocol or protocol proposal should be emailed to the MHRA alongside the request.

5.1.1 **Clinical trials involving only medical devices, non interventional trials and clinical trials involving food supplements**

- Clinical trials involving only medical devices or non-medicinal therapies (such as surgical interventions) are not covered by clinical trial regulations. Please refer to the following

webpage for the latest guidance resulting from EU exit; Regulating medical devices in the UK.

- In addition the regulations do not apply to non-interventional trials
- Clinical trials with food supplements are also not covered by clinical trials regulations; however, where a food supplement is presented as a pharmaceutical form, and is being evaluated for a medicinal purpose, then it will be considered a medicine and the requirements of the regulations will apply

5.1.2 **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 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. Please refer to the following webpage for the latest guidance resulting from the EU exit; Regulating medical devices in the UK.

5.1.3 **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 subject, 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

5.2 Clinical Trial Authorisation Application

Once a clinical trial has been classified as a CTIMP, the CTA submission package will be prepared and submitted by the CI/I for WHHT sponsored CTIMPs.

5.3 Registering with Appropriate Registry

In order for a clinical trial to be considered for authorisation, it must be registered on a public registry as a part of the transparency requirements. The recognised registries include:

- International Standard Randomised Controlled Trial Number (ISRCTN) which accepts all clinical research studies. Prospective and retrospective registrations are accepted. ISRCTN is the preferred partner of the Department of Health and Social Care (UK)
- ClinicalTrials.gov which accepts the registration of medical studies in human volunteers. Prospective and retrospective registrations are accepted
- EU Clinical Trials Register which consists of information from the EU Clinical Trial Database, EudraCT. (It accepts interventional clinical trials that are conducted in the European Union (EU) and the European Economic Area (EEA) as well as clinical trials

conducted outside the EU / EEA that are linked to European paediatric-medicine development. For clinical trials (other than adult Phase 1 studies) involving both UK and EU sites a record in the EU Clinical Trials Register will satisfy the REC favourable opinion condition for registration.)

The HRA recognise that commercial sensitivity may be a concern in some sectors and so it is possible for applicants and sponsors to submit a request to defer registration of clinical trials on a publicly accessible database. Such requests should be made in writing to study.registration@hra.nhs.uk as soon as possible after REC review, and include the following:

- identification of the research that is the subject of the request (IRAS ID and REC reference as a minimum)
- clear justification for the request (whilst there is not a single reason for automatic deferral, the HRA does note the potential commercial confidentiality issues around research)
- the timeframe for the deferral (N.B. 12 months is the maximum allowed time)

The request to defer registration may also include a request to defer publication of the HRA Research Summary.

5.4 The CTA application and submission

Detailed information on what to submit and how to submit the application is available on the HRA website: Combined review - Health Research Authority (hra.nhs.uk).The application may be completed via the new part of the Integrated Research Application System (**IRAS**) system.

The CI/DI must send the draft version of the IRAS form to the Clinical Trial Pharmacist to allow the Pharmacist to review the IMP section of the form. The 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 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/DI and R&D Department.

Although the CI will sign the application form as the “Applicant” the Associate Director of R&D/DI will be the “contact” for the CI and Sponsor. This is to ensure that all correspondence from the MHRA is sent to the Sponsor.

Prior to submission to the MHRA the CI/DI should liaise with the Associate Director of R&D 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.

An electronic signature of the submitted application form and supporting documents will be filed in the Trial Master File (TMF) and R&D file. 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/DI should communicate any IMP related outstanding actions requested by the MHRA as part the approval to the Pharmacist, who will work with the CI/DI to ensure these actions are completed. The 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.

Some acceptance letters state conditions or remarks. The remarks must be responded to prior to the start of the study. If there are grounds for non-acceptance, the CI/DI should reply within 14 days (30 days for gene therapy, somatic cell therapy or products containing genetically modified organisms) to submit an amended request for authorisation. These periods may be extended in certain circumstances.

The amended request is assessed within a total of 60 days from receipt of the initial application (90 days for gene therapy products) and there are two possible outcomes:

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

5.4.2 **Terms and conditions of approval**

For a multicentre trial, the MHRA must be notified of each additional investigator using the amendment process detailed in SOP-09. Ethics approval for each additional investigator should also be obtained.

In accordance with regulation 27, you 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 however, the majority of Type A trials conducted in the UK will only require to be notified to the MHRA.

This will involve the sending of the standard EudraCT application form as detailed in section 5.4 and accompanying documents in the usual way. A letter of acknowledgement will be sent to the CI/DI 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. 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**

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/DI contact.

The full submission package may need to be re-submitted, however the MHRA should advise on the requirements for resubmission. The CI/DI 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 CTA these must be responded to and a confirmation of satisfactory resolution received from the MHRA for the approval to be valid. The R&D Department 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 R&D File.

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

The CI/DI 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 R&D Department will verify the governance requirements as part of the initiation visit (see SOP-18)

N.B- The EudraCT number, CTA number, protocol code 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 CI/DI will submit the report to the RDSG 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 R&D File (see SOP-22)

5.5.4 **Other activities**

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

- Adverse Events (see SOP-02)
- Development Safety Update Reports (see SOP-16)

5.5.5 **How and where to apply for CTA?**

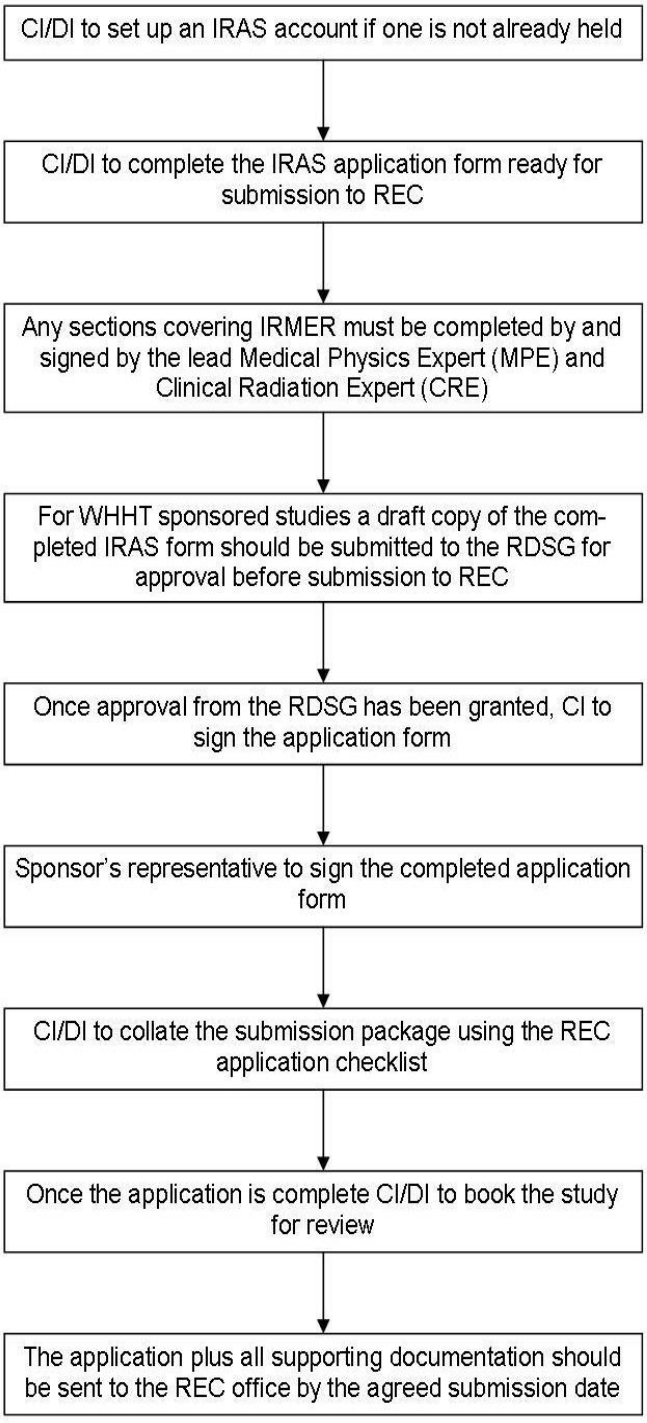
Please see the guidance outlined on the HRA website following changes to the regulations and the introduction of the combined review. Combined review - Health Research Authority (hra.nhs.uk)

5.5.6 **MHRA Fees**

The MHRA charge an initial submission fee and an annual service fee for all open CTA's. Details of current fees may be found on the **MHRA website**

5.6 Application to the HRA/REC

5.6.1 **HRA/REC Application Process**



5.6.2 **The REC Application and Submission**

- All the data required to complete the application to for authorisation of a clinical trial can be completed within **IRAS**
- The IRAS form should be completed by the CI/DI
- 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/DI and approved by the R&D Department before submission. An electronic signature should be completed for all WHHT sponsored CTIMPs
- The application should also be signed by the Sponsor's representative
- Submissions should be completed according to the REC application checklist
- Once the application is complete and ready for submission, the application should be booked for review

5.6.3 **What are the possible outcomes?**

Once the application is received by REC they will check that it is valid and send a validation letter confirming this.

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/DI will need to address all the conditions and remarks and submit their response back to the REC for their final opinion. The CI/DI must provide a copy of this documentation to the R&D Department 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/DI will ensure all documentation submitted to the REC and all correspondence received from the REC is sent to the R&D Department and a copy maintained in the TMF.

5.6.4 **Conditions of approval**

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

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

These must be reviewed, actions taken, responses made (where necessary) and all related documentation retained in the TMF and R&D file to prove these conditions have been met.

5.7 Substantial Amendments

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

An amendment is considered to be substantial when it 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's name
- Urgent Safety Measures (USMs)
- Temporary halt of a trial
- End of Trial (See section 5.8.8)

It is the responsibility of the Sponsor to decide whether an amendment is deemed to be substantial. The R&D Department will review the proposed amendment.

5.7.1 **Submission of a Substantial amendment**

Detailed information on how to amend a CTA is available on the IRAS Help - Maintaining your approvals - Amendments (myresearchproject.org.uk)

The CI/DI must liaise with the Clinical Trials Pharmacist regarding all amendments to the protocol of any WHHT sponsored 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 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 Pharmacist will send amendment approvals (if applicable) to the CI/DI and R&D Department (see SOP-09).

5.7.2 **Submission of a Substantial Amendment 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 CI/DI is responsible for the submission of all amendments to the REC (see SOP-09).

5.7.3 **Submission of a Substantial Amendment to R&D**

All amendments and required approvals will be submitted for approval to the R&D Department electronically. In multicentre trials it may be a requirement of the R&D approval at the participating sites to submit a copy of the amendment and relevant approvals. This will be coordinated by the CI/DI.

5.7.4 **Implementation of Substantial amendments**

The changes listed in a substantial amendment may NOT be implemented before receipt of the Notice of Acceptance of Amendment from the MHRA (if required), approval letter from the REC and local R&D confirmation; with the exception of USMs where the changes may be implemented immediately. Once all approvals are in place the R&D Department will notify the CI/DI and ensure that the correct documentation is in place to implement the amendment.

5.7.5 **Non-Substantial amendments**

These are defined as a non-substantial administrative 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 ethics approval. However, they should still be submitted for notification.

For further guidance please also refer to the HRA website.

5.7.6 **Temporary Halt of a Trial**

If an WHHT sponsored CTIMP is halted temporarily, the Sponsor must be notified immediately by the CI/DI in writing. If a CTIMP is halted due to request from the Sponsor through the RDSG or trial specific Oversight Committee, the MHRA and REC should be notified no later than 15 days from when the trial is temporarily halted.

The notification must be made as a substantial amendment using the Amendment Tool detailing the reasons for the temporary halt.

It is the responsibility of the CI/DI to inform the participating Investigator sites of the temporary halt.

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 **Declaration of the End of Trial Form**

If an USM is implemented on trial or a serious breach of Good Clinical Practice (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 SOP-10)

5.7.7 **Development Safety Update Report (DSUR)**

The R&D Department alongside the CI/DI and 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** (see SOP-16). A copy of the completed DSUR report will be retained in the TMF and a study specific Quality Assurance folder.

5.7.8 **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 European Commission guidance (see SOP-21)

6.0 RELATED DOCUMENTS

- SOP-02- SAEs (Sponsored)
- SOP-04-Informed Consent
- SOP-06- TMF

- SOP-07- Research Training
- SOP-08- Role of Pharmacy, Nuclear Medicine and R&D
- SOP-09- Amendments
- SOP-10- Serious Breaches (Sponsored)
- SOP-11- Organisational Oversight
- SOP-14- Writing Research Protocols
- SOP-15- CRF and Data Management
- SOP-16- DSURS
- SOP-17- Archiving
- SOP-21- Trial Closure
- SOP-22- End of Trial Reports
- SOP-28- Source Data
- ICH GCP (1996), Section 1.8, 5.18 and 5.5.2
- Research Governance Framework Second edition April 2005
- The Medicines for Human Use (Clinical Trials) Regulations 2004 SI 1031/200 1928/2006 (as amended from time to time)
- EUCTD 2001/20/EC and GCP Directive 2005/28/EC

Useful Web links for detailed guidance on procedures described in this SOP;
Clinical trials for medicines: apply for authorisation in the UK - GOV.UK (www.gov.uk) (includes details of the notification scheme)
WebPages for Submitting a CTA Application
WebPages for Amendments to CTA and End of Trial Notifications

7.0 APPENDICES

Appendix 1.0 - Definitions

8.0 VERSION HISTORY

Revision Chronology:		
Version Number	**Effective Date**	**Reason for Change**
SOP-13-05	**October 2021**	1. Change from general Standard Operating Procedures (gSOP) to SOP 2. Removal of the '10.0 Agreement' from the template - all agreement signatures will be collated on a new 'SOP Signature Sheet Document' 3. Update to registration of Clinical Trials, CTA application and submission 4. Addition of reference to new Medical Device guidance 5. Minor amendments following review including reference to the new amendment application process and clarifications of terms
gSOP-13-04	**October 2017**	Minor amendments following review
gSOP-13-03	**07/05/2014**	Minor amendments following review
gSOP-13-02		SOP modified for implementation at ENHT/WHHT
gSOP-13-01 (MVCC)		SOP modified for implementation at MVCC

9.0 AUTHORSHIP & APPROVAL

Author

Signature  **Date** 28/10/2021

R & D Steering Group Approval

Signature  **Date** 28/10/2021

Appendix 1: Definitions

Adverse Event (AE)
An unfavourable outcome that occurs during or after the use of a drug or other intervention, but is not necessarily caused by it.

Adverse Reaction (AR)
Any untoward and unintended response to an investigational medicinal product related to any dose administered. Comment: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product would qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship.

Chief Investigator (CI)
The investigator with overall responsibility for the research. In a multi-site study, the CI has coordinating responsibility for research at all sites. All applications for ethical review should be submitted by the CI. For Trust sponsored trials, the CI had been delegated the pharmacovigilance responsibility for identification, recording and reporting of safety events, including submission of Development Safety Update Reports (DSURs) to the MHRA and REC.

Clinical Trial
A clinical study in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions. A Study Type.

Data Lock Point
This should be the last day of the one year reporting period and the Development Update Safety Report (DSUR) should be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC) no later than 60 days after the data lock date.

Delegated Individual (DI)
An individual delegated by a person of responsibility to carry out their task(s).

Development International Birth Date (DIBD)
The date that the Sponsor received the first Clinical Trial Authorisation (CTA) for that IMP. This date will determine the annual reporting period for the DSUR.

Development Safety Update Report (DSUR)
The common format for annual safety reports on investigational drugs in the ICH regions under ICH guideline E2F. These:

- Summarise the current understanding and management of identified and potential risks;
- describe new safety issues that could have an impact on the protection of clinical trial subjects;
- Examine whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the product's safety;
- Provide an update on the status of the clinical investigation/development programme

Good Clinical Practice (GCP)
Good Clinical Practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.

Investigational Medicinal Products (IMP)

A pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a Clinical Trial, and includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial - a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation, b) used for an indication not included in the summary of product characteristics under the authorisation for that product, or c) used to gain further information about the form of that product as authorised under the authorisation.

MHRA Clinical Trial Authorisation (CTA)
The MHRA is the competent authority for the UK in relation to the Directive 2001/20/EC and the Clinical Trials Regulations, and for Medical Devices, the competent authority in relation to the Medical Devices Regulations 2002.

Principal Investigator (PI)
The investigator responsible for the research site. There should be one PI for each research site. In the case of a single-site study, the chief investigator and the PI will normally be the same person.

The Medicines & Healthcare products Regulatory Agency (MHRA)
The MHRA is the competent authority for the UK in relation to the Directive 2001/20/EC and the Clinical Trials Regulations, and for Medical Devices, the competent authority in relation to the Medical Devices Regulations 2002.

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 contains all essential documents held by the sponsor/Chief Investigator which individually and collectively permits the evaluation of the conduct of a trial and the quality of the data produced.

Type A Clinical Trial
Trials with no higher risk than that of standard medical care.
Trials involving medicinal products licensed in any EU Member State if:

- They relate to the licensed range of indications, dosage and form.
- Or, they involve off-label use (such as in paediatrics and in oncology etc) if this off-label use is established practice and supported by sufficient published evidence and/or guidelines.

Type B Clinical Trial
Trials with somewhat higher risk than that of standard medical care
Trials 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
  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
Trials with markedly higher risk than that of standard medical care.
Trials involving a medicinal product not licensed in any EU Member State.