Application & Maintenance of a Clinical Trial Authorisation

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Change History			
Date	Version Number	Change details	Approved by
15 Jun 2011	2.0	Addition of Type A trials and correction of typographical and formatting errors	Jackie Powell
14 Sept 2011	3.0	Amendment of ASR to DSUR as per ICH E2 guidance	Jackie Powell
11 Nov 2013	4.0	Change of branding from JCTO to KHP-CTO and changes to MHRA fee structure	Jackie Powell
01 Dec 2016	5.0	Scheduled review, update of glossary, addition of the HRA and other clarifications	Jackie Pullen
12 May 2017	5.1	Minor amendment to remove web links, correction to references to section 7 which should have referred to section 6, removal of pre-payment	Jackie Pullen

		requirements to MHRA as no longer applicable. Update to section 4.9 as pre-payment of fees is no longer applicable. Fees will be paid on receipt of invoice.	
09 May 2018	6.0	Section 4.1 updated regarding pharmacy review and approval of IMP labels. Section 4.1.4.2 numbering corrected in Table of Contents and in section heading.	Jackie Pullen
01 Oct 2018	6.1	Minor amendment to include trials managed by KHP-CTO	Jackie Pullen
05 Jan 2021	7.0	Updated to incorporate BREXIT changes to UK Clinical Trial Authorisations	Jackie Pullen
28 May 2021	7.1	Minor updates to reflect HRA practices and website links updated	Jackie Pullen
16 June 2021	7.2	Minor update to 4.3	Jackie Pullen
20 September 2023	8.0	Updated to include process for combined review and clarify KHP-CTO responsibilities	Kirsty Hough
17 October 2025	9.0	Update to include process for final clinical study report at End of Trial	Ann-Marie Murtagh

Table of Contents

1.0 **BACKGROUND & PURPOSE**

The purpose of this SOP is to describe the procedures for applying for and maintaining a Clinical Trial Authorisation for Trials sponsored, co-sponsored or managed by King's Health Partner Organisations in order to comply with UK Regulations.

2.0 SCOPE

All clinical trials sponsored, co-sponsored or managed by one or more of King's Health Partners organisations and conducted in the United Kingdom.

3.0 PROCEDURE

3.1 Clinical Trial Authorisation application

The CTA submission package will be prepared and submitted by the KHP-CTO CRA or delegate and Chief Investigator Team as required. King's Health Partner Pharmacy Departments will review and approve the IMP label for the submission package as per their "Development and approval of labelling text for IMPs and NIMPs" SOP.

3.1.1 The CTA Application and Submission

Applications for a Clinical Trial Authorisation will be made in accordance with the EC Guidance document - '*Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial'* (see Section 6.3).

Detailed information on what to submit and how to submit the application is available on the MHRA website (https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk) (see Section 6.2).

The application is made via the Combined Review IRAS System which combines the ethics application along with an MHRA (medicines information) form.

The KHP-CTO Quality Manager or delegate will be the "contact" for the Sponsor. This is to ensure that all correspondence from the MHRA is sent to the KHP-CTO.

A copy of the submitted application form and supporting documents will be filed in the Trial Master File and the Sponsor File.

3.1.2 Competent Authority Review

3.1.2.1 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 submission to the MHRA under the notification scheme.

This will involve the sending of the standard CTA application as detailed in section 4.1.3 and accompanying documents in the usual way. A letter of acknowledgement will be sent to the KHP-CTO 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 (see Section 6. 2).

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. This includes type A trials.

3.1.2.2 Types B & C Clinical Trials

The CTA will be validated on receipt at the MHRA and an acknowledgement letter will be sent to the KHP-CTO (as "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 Sponsor "Contact" (KHP-CTO Quality Manager or delegate). The full submission package may need to be re-submitted, however the MHRA will advise.

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

Any Request for Information (RFI) required by the MHRA to the application or submitted documents must be reviewed and agreed by the KHP-CTO before resubmission.

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.

All correspondence relating to the CTA will be filed within the TMF with copies 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 Site Initiation all of the above documents will be checked by the KHP-CTO CRA (see KHP-CTO SOP 13).

The IRAS number, CTA number, protocol code and product name must be quoted in all CTA submissions, amendments and End of Trial notifications.

3.2 Substantial Amendments

The KHP-CTO Clinical CRA or delegate will prepare substantial amendments to the MHRA on behalf of the Sponsor organisation. The Investigator and trial team must inform the KHP-CTO Clinical Quality Team if they suspect that an amendment to the Protocol or the CTA is required and supply supporting information as appropriate.

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 trial participants;
- the scientific value of the trial;
- the conduct or management of the trial
- the quality, safety, or data integrity 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 (see KHP-CTO PV Policy)
- Temporary halt of a trial
- End of Trial (see Section 4.6)

. On behalf of the Sponsor(s) the KHP-CTO Quality Manager or delegate will review each amendment for Substantiality to the MHRA in comparison with the above criteria and complete a KHP-CTO Amendment assessment form (see Section 5). Once completed this form will be filed in the trial Sponsor File.

If there are any changes to the RSI the updated RSI must be submitted to the regulatory licensing authority for approval before it can be used for the purposes of expedited reporting. If an update to the RSI occurs mid DSUR period, and after a risk assessment the changes to the RSI are deemed minimal or not relevant to the study population, the submission to the licensing authority can be delayed to be in line with the next DSUR submission.
If updates are important to patient safety, submit a substantial amendment immediately, but state the RSI will not be implemented until start of next reporting period.

3.2.1 Submission of a Substantial amendment to the MHRA

Amendments to a Clinical Trial Authorisation will be made in accordance with the requirements as set out in the EC Guidance Document (see Section 6.3). A fee is payable to the MHRA for all substantial amendments (see Section 4.9).

Detailed information on how to submit substantial amendments is available on the MHRA website (see Section 6.4).

3.2.2 Submission of a Substantial Amendment to the REC/HRA

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 Chief Investigator is responsible for the submission of all amendments to the REC.

The Chief Investigator is also responsible for submission of amendments to the HRA, this includes amendments sent for notification only.

3.2.3 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, approval letter from the REC, HRA approval and local R&D continued confirmation of capacity and capability *(if required)*. Once all approvals are in place the trial CRA or delegate will notify site(s) and ensure that the correct documentation is in place to implement the amendment.

NB Urgent Safety Measures may be implemented immediately without submissions or approvals as detailed in the current version of the KHP-CTO Pharmacovigilance Policy.

3.3 Non-Substantial amendments

Amendments to the protocol that do not significantly affect the conduct of the trial or change the initial application form in any way are known as non-substantial amendments.
e.g.:

- Administrative changes to the protocol, such as contact details of trial staff
- Change of central technical facility.

Non-substantial amendments do not need to be submitted to the MHRA or REC. Please note that some non-substantial amendments may need to be submitted to the HRA for review or notification only. These will still require review and sign off by the KHP-CTO prior to submission.

Non-substantial amendments will be documented locally and submitted to the MHRA and REC as part of the next substantial amendment to be submitted for the trial.

Amendments that make changes to patient facing documents such as the Patient Information Sheet or Consent Form, are substantial amendments to the REC but not the MHRA and therefore do not need to be reviewed by the MHRA.

Amendments that make significant changes to the initial CTA but not the protocol and do not significantly affect the conduct of the trial, will be submitted as substantial amendments to the MHRA – however, these are not required to be submitted to the REC - e.g. – change of IMP supplier or brand of IMP.

3.4 Temporary Halt of a Trial

If a trial is halted temporarily, the MHRA, REC and R&D dept. must be notified immediately and no later than 15 days from when the trial is temporarily halted. The notification must be

made as a substantial amendment using the Notification of Amendment form detailing the reasons for the temporary halt.

It is the responsibility of the CI to inform the REC, R&D Depts and participating Investigator sites of the temporary halt, the KHP-CTO Clinical Quality Team will submit notification to the MHRA.

To restart a trial that has been temporarily halted, a separate substantial amendment is required. Dependent upon the reason for the temporary halt, evidence that it is safe to restart the trial may be required. The CI is responsible for informing the REC, R&D Departments and participating Investigator sites and the KHP-CTO will submit notification to the MHRA.

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 Study Declaration form. The KHP-CTO is responsible for the MHRA notification, the CI for the REC.

3.5 Development Safety Update Report

The KHP-CTO will ensure that a DSUR is sent to the MHRA and REC within 60 days of the Data Lock Point.

A copy of the DSUR will be filed in the TMF and Sponsor file.

3.6 End of a Trial

The end of the trial will be defined in the protocol and original CTA application. It is recommended this is the date of database lock. 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 EC guidance (see Section 7.1). If the trial terminates early the signed End of Trial form will be submitted within 15 days of the end of the trial to the MHRA and REC.

Detailed information on how to submit and End of Trial Notification can be found on the MHRA website (see Section 6.7).

The CI or delegate is responsible for completing the HRA End of Trial Form.

The KHP-CTO CRA will submit the End of Trial Form to the MHRA, and copies will be filed in the TMF and Sponsor file.

If the trial has gone through the Combined Review process, then the end of trial declaration will be submitted via IRAS.

3.7 Final Clinical Study Report

When a Clinical Trial of an Investigational Medicinal Product (CTIMP) is completed, or prematurely terminated, the Clinical Study Report (CSR) or summary report must be sent to the appropriate Research Ethics Committee(s) (REC) and the Sponsor within 12 months of the 'end of the trial'. In addition, for CTIMP studies, the end of trial summary results must be uploaded to the publicly available database eg ISRCTN registry within 12 months of the 'end of trial' for trials involving adults and within 6 months of the 'end of trial' for paediatric trials.

Prior to submission, the Chief Investigator will submit the clinical study report to the KHP-CTO for final review/CRA reconciliation.

CRA Reconciliation process

- The purpose of the sponsor review is to ensure that the study data is appropriately represented; it is not an additional scientific review. It is meant to be a check that ensures all issues are appropriately discussed (e.g. serious breaches, significant deviations etc.) and that the data being presented can be traced back to the source data.
- CRAs to review all SAEs/SARs/SUSARS/IMEs listed in the CSR and ensure the number or events reported is consistent with the safety data reported throughout the study as listed in the final DSUR and eCRF at time of Database lock.
- CRA to review the actual recruitment number matches the sample size, or that any discrepancies are justified.
- CRA to review any tables/figures that may include safety data. This is not a statistical analysis review.
- CRA to contact CI with any comments and final draft to be obtained for submission.

The KHP-CTO or delegate will submit the report and lay summary to EudraCT, ISRCTN or other publicly accessible database on behalf of the Sponsor.

A copy of the final clinical study report will be filed within the TMF.

The clinical trial summary report does not need to be submitted to the MHRA. A short confirmatory email to CT.Submission@mhra.gov.uk once the result-related information has been uploaded to the public register is sufficient. If the clinical trial is not on a public register, summary results should be submitted to the MHRA. No acknowledgment email or letter from the MHRA is necessary.

The Chief Investigator should also submit the final report to the Research Ethics Committee within the same timeframe for reporting the summary of results.

3.7.1 Publication

KHPCTO must be acknowledged on all publications resulting from a KHPCTO sponsored study. The KHPCTO must be notified of any outputs of the research such as guidelines, publications, presentation, changes in service delivery etc. prior to external submission or presentation. All publications must comply with funder and collaborator publication agreements/terms.

Some journals only publish primary results that have not appeared in the public domain. Check the publication guidelines of the journal where you intend to publish the primary paper and plan the timing of the Final Report submission accordingly

Research Integrity

In the event that research misconduct or data integrity concerns have been raised, the CTO, as sponsor along with the senior management of the affected organisation, reserves the right to review, request a hold on publication submission, or refuse permission to publish in discussion. The KHPCTO as sponsor representative retains the right to review, or request a hold on publication submission, or to refuse permission to publish if there are research misconduct concerns raised, or under investigation, regarding data integrity. This is in addition to any action taken under SOP 6 Notification of a Serious Breach.

3.8 Other activities

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

- Reporting of serious unexpected adverse reactions (SUSARs) to the MHRA and relevant Ethics Committee within the required time frames (KHP-CTO PV policy)
- Providing the MHRA and relevant Ethics Committee with a Development Safety Update Report. (SOP 17 Development Safety Update Reports)
- Permit inspection of any trial premises by MHRA inspectors as appropriate.

3.9 MHRA Fees

The MHRA charge an initial submission fee for all Type B & C trials. A charge is also made for all substantial amendments and DSUR review. All fees must be paid upon receipt of invoice. The CI or delegate is responsible for ensuring the MHRA invoices are paid.

Details of current fees may be found on the MHRA website.

4.0 RELATED TEMPLATES

4.1 HRA Amendment Tool

4.2 Declaration of the End of a Clinical Trial Form

4.3 Development Safety Update Report Template for MHRA

4.4 KHP-CTO Amendment Assessment form

5.0 RELATED DOCUMENTS

5.1 Guidance, Clinical trials for medicines: apply for authorisation in the UK

https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk

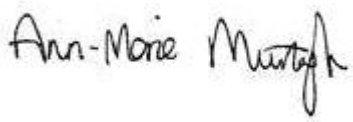
5.2 European Commission guidance, Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial

https://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2010:082:0001:0019:en:PDF

5.3 Guidance: Clinical trials for medicines: manage your authorisation report safety issues

https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues

6.0 APPROVAL and SIGNATURE



17th October 2025

Ann-Marie Murtagh
Director
King's Health Partners Clinical Trials Office

Appendix 1

GLOSSARY

Chief Investigator (CI) – The overall lead researcher for a research project (Outside the UK the term Coordinating Investigator or Investigator may be used). In addition to their responsibilities if they are members of a research team, chief investigators are responsible for the overall conduct of a research project.

Clinical Trial - Any investigation in human trial participants, other than a non-interventional trial intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal product and/or to identify any adverse reactions to one or more such products and to study absorption, distribution, metabolism and excretion of one or more such products with the object of ascertaining the safety and/or efficacy of those products.

Clinical Trial Authorisation (CTA) – Authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) to conduct a Clinical trial of an investigational medicinal product (CTIMP). No CTIMP can commence in the UK without both a CTA and a favourable ethical opinion. Applications to the MHRA and the Research Ethics Committee (REC) may be made in parallel

Co-Sponsors – Where two or more organisations take responsibility for the initiation, management and financing (or arranging the financing in relation to a clinical trial, those organisations will allocate responsibility for carrying out the sponsor functions of that trial and document this accordingly.

Data Lock Point – Day prior to the DIBD. The Sponsor can designate this as the last day of the month prior to the month of the DIBD.

Development International Birth Date (DIBD) – Date of the first authorisation to conduct a clinical trial of a specific investigational medicinal product in any country worldwide.

Development Safety Update Report (DSUR) - A common standard for periodic reporting on drugs under development (including marketed drugs that are under further study) among the ICH regions. In the EU it replaces the annual safety report.

Good Clinical Practice (GCP) – an international ethical and scientific quality standard for designing, conducting, recording, and reporting clinical trials. GCP emphasizes participant well-being, proportionality, quality by design, risk-based quality management, and comprehensive data governance across the lifecycle. It ensures the safety, well-being, and rights of trial participants are protected while maintaining the credibility and accuracy of trial data. GCP is crucial for safeguarding trial participants and ensuring clinical trials produce reliable, scientifically valid results.

Health Research Authority (HRA) – An authority in England established in 2011. The authority exercises functions in connection with the facilitation and promotion of research and the establishment of research ethics committees

Investigational Medicinal Products (IMP) – a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial. This includes products with marketing authorisation when used in a way different from the approved form, for an unapproved indication, or to gain further information about an approved use.

Integrated Research Application System (IRAS) - the online application system used to apply for most permissions and approvals for research in health and social care in the UK.

King's Health Partners (KHP) - King's Health Partners brings together research, education and clinical practice across three NHS Foundation Trusts - Guy's and St Thomas', King's College Hospital and South London and Maudsley - and a world-leading university, King's College London

King's Health Partners Clinical Trials Office (KHP-CTO) – Established in 2006 by King's College London, Guy's & St Thomas' NHS Foundation Trust, South London and Maudsley NHS Foundation Trust and King's College Hospital NHS Foundation Trust to provide a streamlined approach for all aspects of trial administration. The King's Health Partners CTO has two sections: the Commercial Team which provides a single interface for those wishing to conduct trials sponsored by the pharmaceutical industries and the Quality Team that supports investigators at King's Health Partners institutions who undertake CTiMP trials where King's Health Partners are the sponsor or co-sponsor

KHP-CTO Quality Team - Comprises the Quality Manager, Clinical Research Associate(s), Clinical Trial Administrator(s), Systems Executive, Training Executive(s) and Training Assistant.

KHP-CTO Standard Operating Procedures (SOPs) - Detailed, written instructions to achieve uniformity of the performance of a specific function, SOPs are the base on which Quality Systems and Processes are conducted and monitored against.

Licensing Authority The licensing authority is responsible for the grant, renewal, variation, suspension and revocation of licences, authorisations, certificates and registrations under the Clinical Trial Regulations. The MHRA is the UK licensing authority.

Medicines & Healthcare products Regulatory Agency (MHRA) – the UK's regulatory body responsible for ensuring the safety and effectiveness of medicines, medical devices, and blood components for transfusion. It operates as an executive agency sponsored by the Department of Health and Social Care

Research & Development Dept (R&D) – NHS department responsible for confirmation of capacity and capability for all clinical research.

Research Ethics Committee (REC) – An independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility is to protect the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent.

Sponsor - The person or body who takes on ultimate responsibility for the initiation, management and financing (or arranging the financing) of a clinical trial. Note: The Clinical Trials Regulations allow for two or more persons to take responsibility for the functions

The Regulations – The Medicines for Human Use (Clinical Trial) Regulations 2004 which transposed the EU Clinical Trials Directive into UK legislation, as Statutory Instrument 2004 no 1031**.** An amendment to implement Directive 2005/28/EC was made to the Regulations as Statutory Instrument 2006 no 1928. As amended from time to time.

Trial Master File (TMF) - a standard filing system which contains all essential documents which individually and collectively permits the evaluation of the conduct of a trial and the quality of the data produced. The filing system can be in the form of a single project file or a

number of files/filing cabinets, depending on what is deemed most appropriate for a particular clinical trial given its size and complexity. The regulatory documents and approvals within the TMF will be maintained alongside case report forms and source documentation.

Type A Clinical Trial – A clinical trial 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 – A clinical trial 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 - A clinical trial 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.