Investigator Site Close-out Procedure

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Relevant regulations/legislation/guidelines	Statutory Instrument 2004 no 1031 Statutory Instrument 2006 no 1928 (*as amended from time to time)*

CHANGE HISTORY			
Date	Version Number	Change details	Approved by
24th January 2012	2.0	Change to section 4.1.5 - Deletion of requirement to notify Competent Authority if a site closes prematurely	Jackie Powell
26th January 2016	3.0	Scheduled review and minor adjustment to reflect revised practice	Jackie Pullen

31st August 2017	4.0	Addition of requirement for Investigator to sign the delegation log, update to glossary, addition of HRA requirements for end of trial notification and minor formatting changes	Jackie Pullen
1st October 2018	4.1	Minor amendment to include trials managed by KHP-CTO	Jackie Pullen
25th January 2019	5.0	Scheduled review and minor amendments to section 4.1.3 and 4.2 to reflect current practice	
5th January 2021	5.1	Minor amendment to include registering on a publicly accessible database	Jackie Pullen
22 September 2022	5.2	Scheduled review and minor adjustment to reflect revised practice	Jackie Pullen

Table of Contents

1.0 GLOSSARY

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

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

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

Clinical Research Associates (CRAs) – Part of the KHP-CTO Quality Team. Ensure compliance with the Regulations, GCP and SOPs, by monitoring clinical trials.

Close Out Report (CR) – A report written by the CRA to the Sponsor (or representative) after each site close out visit.

Competent Authority (CA) - A regulatory agency in an EU Member State with the authority to act on behalf of the government of a Member State to ensure compliance with relevant current legislation as documented in the Medicines for Human Use (clinical trial) regulations.

Contact Comment Form (CCF) – Used to record communication with a trial site that requires documentation.

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

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.

Investigator Site File (ISF) - a standard filing system which allows the effective storage and location of essential documents related to an individual trial site.

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. This 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 (or equivalent document) under the authorisation for that product, or
(c) used to gain further information about the form of that product as authorised under the authorisation

King's Health Partners – (KHP) - King's Health Partners' Academic Health Science Centre is a pioneering collaboration between one of the King's College London (University) and three of London's most successful NHS Foundation Trusts – Guy's & St Thomas', King's College Hospital and the South London & Maudsley.

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 (formerly known as JCTO).

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.

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

Quality Assurance (QA) - Systems and processes established to ensure that a trial is performed and the data are generated in compliance with GCP.

Quality Control (QC) - The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Remote Study Site Close-Out Checklist (RSSCC) – A report written by the CRA to the Sponsor (or representative) after each remote site close-out contact.

Research Ethics Committee (REC) – The REC that undertakes the review of the research protocol, including the content of the patient information sheet and consent form rather than just site specific approval for each centre.

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

Trial Master File (TMF) - a standard filing system which allows the effective storage and location of essential documents, that is the large volume of regulatory documents and approvals needed for clinical research. 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 record forms and source documentation.

The Regulations - Statutory Instrument 2004/1031 – the Medicines for Human Use (Clinical Trials) Regulations 2004 which transposed the European Union Directive 2001/20/EC for Clinical Trials into UK law effective from the 1st May 2004 and any amendments that may arise.

BACKGROUND AND PURPOSE

The purpose of this SOP is to describe close-out procedures for clinical trials monitored by the KHP-CTO in order that clinical trials sponsored by one or more King's Health Partners Organisations, or clinical trials where the sponsor responsibilities are managed by the KHP-CTO, comply with UK Regulations and European Law.

Close-out is defined as the act of ensuring that all clinical trial related activities are appropriately reconciled, recorded and reported at the end of a trial in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirement(s).

Close-out is integral to the quality assurance of a clinical trial and GCP compliance of the study according to Sponsor requirements and to ensure that all necessary documents are in place should it be necessary for the trial information to be retrieved or inspected in the future.

2.0 SCOPE

All clinical trials sponsored by one or more King's Health Partners Organisations, or clinical trials where the sponsor responsibilities are managed by the KHP-CTO, will be closed-out as described in this SOP.

The close-out process will be conducted by the KHP-CTO CRAs and overseen by the Quality Manager or delegate. From time to time as required, the close-out process may be contracted out to external organisations/CRAs, but oversight will be retained by the KHP-CTO.

3.0 PROCEDURE

For clinical studies sponsored by one or more King's Health Partners Organisations, or clinical trials where the sponsor responsibilities are managed by the KHP-CTO, the Monitoring Team from the KHP-CTO is the main line of communication between the KHP-CTO (on behalf of the Sponsor) and the Investigator. The KHP-CTO ensures that the Investigator site conducts the clinical study in compliance with the final protocol and subsequent protocol amendments, if any, as well as GCP and applicable safety reporting and regulatory requirements. The trial close-out procedures will be performed as soon as practicable after the end of the trial as defined in the protocol or premature termination and after KHP-CTO monitoring activities have been completed. However, site close-out activities may be performed earlier, for example, if a site fails to recruit or requests early closure. The procedures may span several days; however, one final Close-out Report or Remote Study Site Close-out Checklist should be

completed for each site. Once close-out has been completed all further contact with the site(s) should be documented appropriately.

3.1 CRA Responsibilities

4.1.1 Study Status

The CRA will act as the main line of communication between the KHP-CTO (on behalf of the Sponsor) and the Investigator. The specific timelines and scheduling for study close-out will be defined in the Monitoring Plan.

1. The CRA will ensure that all documents needed to conduct close-out of the trial/site, and to comply with the applicable regulatory requirements, are available.
2. The CRA will confirm recruitment status at the end or premature end of the trial. If the site is to be closed prior to the end of the trial a reason for early closure should be clearly documented.
3. The CRA will ensure that all Serious Adverse Events (SAEs) have been reported by the Investigator to the Sponsor and that the Investigator is aware of any future reporting requirements and follow-up of any ongoing SAEs. A line listing of all SAE/SUSARs that have occurred at the site should be filed in the ISF. In a multicentre trial a line listing for all SAEs/SUSARS at each site should be filed in the TMF.
4. The CRA will ensure that all outstanding data queries at the time of site close-out are resolved and that there are clear systems in place for continuing data entry and query resolution after the close-out procedures have been completed.
5. All outstanding issues from previous monitoring visits will be resolved or appropriately documented.
6. The CRA will ensure that the Delegation of Duties and Authorised Signature log has been fully completed and signed by the Principal Investigator.
7. The CRA will ensure that a provisional timeline for database lock has been determined by the Chief Investigator.

4.1.2 Investigational Medicinal Product and Pharmacy

1. The CRA will verify that final drug accountability is complete.
2. The CRA will give authorisation for IMP destruction and ensure that the destruction or return of unused, partially used or returned Investigational

Medicinal Product is appropriately completed and documented in the Pharmacy File.

3. The CRA will verify that (if applicable) Code Break Documentation is still intact and any code that has been broken or lost during the study has been appropriately documented. Details and remaining documentation will be filed in the Pharmacy File.
4. The CRA or appropriate delegate will review Pharmacy File documentation for completeness to ensure that it has been maintained throughout the trial. Documentation will be filed in a coherent manner ensuring a clear audit trail of study conduct at the site. If applicable, the CRA will oversee reconciliation of the Pharmacy File with the ISF according to local requirements.

4.1.3 Laboratory, Biological Samples other study supplies

1. The CRA will ensure that all unused trial supplies are returned or destroyed according to trial requirements.
2. If applicable, the CRA will ensure that the Sponsor(s) and CI are aware that all samples are processed within the timeframe of the ethical approval for the trial or moved to a HTA licensed tissue bank for storage, if the patients have consented to further storage of their samples.
3. If applicable, the CRA will ensure that arrangements are in place for the destruction of retained biological samples and diagnostic material.

4.1.4 Ethics, Regulatory and Research and Development

For single centre trials both “End of Trial” and “Closure of a Site” activities listed below should be completed. For multicentre trials, if a participating site is to be closed then only “Closure of Site” activities need to be completed. If all sites are to be closed due to study end/premature termination then “Closure of a Site” activities should be completed for each participating site and “End of Trial” and “Closure of Site” activities should be completed at the lead site.

4.1.5 Closure of Site

Close-out processes will be defined in the trial monitoring plan and will be conducted either on site or remotely according to the risk assessment for the trial.

1. In the case of closure of a participating site prior to end of the study, the CRA will ensure that the Chief Investigator is aware of their responsibility to notify the REC of the closure of the participating site.
2. The CRA will ensure that the Investigator at the participating site is aware of their responsibility to notify the local R&D Department of the closure of the site and provide copies of required documentation.

4.1.6 End of the Trial

1. The CRA or delegate will be responsible for submitting the End of Trial Notification to the Competent Authority within required timelines from the “end of trial” as defined in the protocol or clinical trial authorisation application or at premature trial end. The CRA or delegate will ensure that the Chief Investigator is aware of their responsibility to notify the REC, and their local R&D Department. Where a project has HRA Approval and has been reviewed by a REC there is no requirement to notify the HRA of the end of trial.

2. The CRA will remind the Chief Investigator of their regulatory obligation to submit a Clinical Study Report to the REC and KHP-CTO within 12 months of the End of Trial Notification. The KHP-CTO will upload the Clinical Study Report to the publicly accessible database where the trial was originally registered on behalf of the Sponsor and notify the Competent Authority by email that this has been done. For CTIMPS registered on EudraCT which began after 01 January 2021, the KHPCTO are not required to upload the Clinical Study Report to EudraCT.

3. The CRA will ensure that the Principal Investigator is aware of their responsibility to notify their Research and Development Department of the end of the study.

4.1.7 Sponsor File, Trial Master File and Investigator Site File

1. The CRA or appropriate delegate will review all Sponsor, Trial Master File and Investigator Site File (as applicable) documentation for completeness. Documentation will be filed in a coherent manner ensuring a clear audit trail of study conduct at the site.

4.1.8 General Considerations

1. If commercial / external funding was obtained for the study the CRA will ensure that the Investigator is aware of all contractual reporting obligations that must be fulfilled.

2. All Investigators will be reminded that all essential documentation must be retained for the required length of time according to the protocol and current regulations. Trial Master File documentation will be archived according to the KHP-CTO Archiving SOP. If necessary, the CRA may assist in the archiving process in collaboration with the KHP-CTO Archivist.

3. The CRA will remind the Investigator of their obligation to inform the Sponsor and the KHP-CTO if they are notified of an intent to conduct a regulatory inspection.

4. The CRA will inform the Investigator of their obligation to immediately inform the Sponsor/KHP-CTO (on behalf of the Sponsor) of any change in circumstances that may affect their ability to retain study material.

The CRA will immediately notify the Quality Manager or KHP-CTO Director in the event of any suspicion of scientific misconduct, fraud or breach of GCP. This will be dealt with according to appropriate local organisational policy and the KHP-CTO Notification of a Serious Breach SOP.

4.2 Close-out Documentation

Following close-out activities, the CRA will promptly submit a written report to the KHP-CTO. This will be done using the either the Close-out Visit Report template (see Section 5.1) or the Remote Study Site Close out Checklist template (see Section 5.4) (as applicable). Any other communication with the site after the close-out which requires documentation will be recorded appropriately.

The protocol deviation log (see section 5.5), and if applicable a Note to File (see Section 5.3), will be used to document any deviations from the protocol or other issues and these should be filed in the ISF and/or TMF with copies submitted to the KHP-CTO.

The close-out process documents will be reviewed by an authorised KHP-CTO individual promptly after the visit or communication. Documentation of the close-out process will be filed in the Trial Master File.

The Investigator will be informed in writing of discussions that took place during the close out procedures and of any follow-up items that were identified. These items will be followed up until completion. If there is evidence of systematic failure to comply with GCP the Sponsor will be informed.

Once all outstanding actions and data queries are resolved and the Clinical Study Report is complete the trial may be archived.

5.0 RELATED TEMPLATES

5.1 Close-out Visit Report Form template

5.2 Contact Comment Form template

5.3 Note to file template

5.4 Remote Study Site Close-out Checklist template

5.5 Protocol Deviation Log Template

6.0 APPROVAL AND SIGNATURE

27 September 2022

Jackie Pullen
Director
King's Health Partners Clinical Trials Office

Date