Study Set-Up and Initiation of an Investigator Site

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CHANGE HISTORY			
Date	Version Number	Change details	Approved by
22nd February 2013	2.0	Re-branding of JCTO Addition and removal of glossary terms. CRA responsibilities section amended and addition of further CRA requirements.	Jackie Powell
10th February 2016	3.0	Scheduled review and minor adjustment to reflect revised practice including	Jackie Pullen

		addition of CRA responsibilities.	
17 Aug 2018	4.0	SOP amended to include study set up activities. Glossary updated to include HRA definition.	Jackie Pullen
01 Oct 2018	4.1	Minor amendment to include trials managed by KHP-CTO	Jackie Pullen
05 Nov 2021	4.2	Amended to include changes in internal processes due to remote SIVs	Jackie Pullen

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1.0 GLOSSARY

Blinding - A procedure in which one or more parties involved in the conduct of a clinical trial are unaware of the treatment assignment(s).

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

Case Record Form (CRF) - a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject`.

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

Clinical Trial - Any investigation in human subjects, 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.

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. Co-Sponsors should decide which organisation will assume responsibility for carrying out the Sponsor functions of that trial and document this accordingly.

Curriculum Vitae (CV) - A summary of a person's education, professional history, and job qualifications.

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

Health Research Authority (HRA) – Government body set up in 2011 to protect and promote the interests of patients and the public in health and social care research. Specifically tasked with streamlining research in the UK and now responsible for issuing a single NHS approval which includes the REC ethical opinion.

Informed Consent Form (ICF) – The document which is signed by the participant/legal representative as well as the person who conducted the informed consent discussion confirming the volunteers willingness to participate in the particular trial, having been informed of all aspects of the trial that are relevant to their decision.

Investigator Brochure (IB) – is a compilation of the clinical and non-clinical data on the investigational product(s) that are relevant to the study of the product(s) in humans.

Once an investigational product has a marketing approval, the IB is superseded by the **Summary of Product Characteristics (SmPC),** unless an IMP has been developed, licensed and manufactured by King's Health Partners.

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 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 Center 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 Foundation Trust to provide a streamlined approach for all aspects of trial administration.

MATTS – MedSciNet's Active Trial Tracking System. An electronic Clinical Trial Portfolio Management System.

Monitoring Plan (MP) – A document written by the CRA detailing how all the monitoring activities for the trial will be carried out based upon the trial risk assessment.

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

Participant Information Sheet (PIS) - explains all relevant study information to assist the trial participant in understanding the expectations and requirements of participation in a clinical trial.

Pharmacovigilance (PV) – the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

Reference Safety Information (RSI) – relates to the IMP and will be either in an Investigator Brochure for non-licensed IMPs or in the Summary of Product Characteristics for IMPs with a marketing authorisation.

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

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.

Sponsor - The organisation who takes responsibility for the initiation, management and financing (or arranging the financing) in relation to a clinical trial. The Sponsor organisation has responsibility for carrying out the sponsor functions of that trial (as defined in the Regulations).

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.

Summary of Product Characteristics (SmPC) – this reference document is produced for health professionals and details how to use a medicinal product safely and effectively.

The Regulations - –The Medicines for Human Use (Clinical Trials) Regulations 2004, transposed the EU Clinical Trials Directive into UK legislation, as Statutory Instrument 2004 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.

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

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 report forms and source documentation.

2.0 BACKGROUND AND PURPOSE

The purpose of this SOP is to describe the study set-up and initiation procedures prior to, during and following the initiation visit for clinical trials supported by the KHP-CTO, in order that clinical trials sponsored by one or more of King's Health Partners Organisations, or clinical trials where the sponsor responsibilities are managed by the KHP-CTO, comply with UK Regulations and when applicable European Law.

Initiation of a trial site ensures that all required trial authorisations and documentation are in place, and that the protocol and trial procedures are reviewed with the Investigator and the Investigator's trial staff in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirement(s).

Initiation is integral to the QC of a clinical trial and is designed to ensure quality of the trial according to Sponsor requirements and to ensure that all necessary documents are in place to facilitate appropriate conduct and ongoing documentation of the trial.

3.0 SCOPE

All clinical trials sponsored by one or more of King's Health Partners Organisations, or clinical trials where the sponsor responsibilities are managed by the KHP-CTO, will be set-up and initiated as described in this SOP. An initiation visit must be performed for all clinical trials prior to the Sponsor Green Light being confirmed.

Kick-off meetings and initiation visits will be conducted by the KHP-CTO CRAs and overseen by the Quality Manager or delegate. From time to time as required, initiation visits may be contracted out to external organisations/CRAs, but oversight will be retained by the KHP-CTO.

All trial sites will be initiated in both single and multi-centre trials.

4.0 STUDY SET UP PROCEDURE

For clinical trials covered by the scope of this SOP, the CRA is the main line of communication between the KHP-CTO (on behalf of the Sponsor(s)) and the Investigator. The KHP-CTO Quality Team ensures that the Investigator conducts the clinical trial in compliance with the final protocol and subsequent protocol amendments if any, as well as GCP, applicable safety reporting and regulatory requirements and SOPs. All CTIMP trials will have a kick-off meeting once there has been confirmation of funding, sponsorship in principle and a CRA has been allocated to work on the trial.

The CRA will arrange the kick-off meeting. Attendees include but are not limited to the CI, research nurse, contracts negotiator, pharmacy representative and an R&D representative.

The following list is an example of the information that will be discussed during the meeting:

- IMP supply
- Data management
- Database provider
- Emergency unblinding (if applicable)
- Randomisation (if applicable)
- Essential documents
- Data monitoring committee and trial steering committee
- Obtaining regulatory approvals
- Obtaining sponsorship
- Site visits and monitoring
- Sample analysis and processing
- Trial master file
- Vendor oversight and contracts
- Statistical analysis
- Final study report and publications

After the kick-off meeting a summary of the meeting will be produced by the R&D contract manager, or delegated individual, which will be circulated to all attendees and other relevant stakeholders.

Activity on the study set-up will continue until all the required approvals are in place in order for the initiation visit to take place as detailed in section 5.0.

5.0 INITIATION PROCEDURE

All sites that are in a position to obtain/receive IMP will be initiated. Sites that will not be involved in handling or administering IMP will be assessed on a case-by-case basis by a Senior CRA or delegate. The initiation visit will be performed as soon as all required approvals, documentation and procedural information is in place at the study site. The visit may span several days; however, a final Investigator and Site Initiation Visit report must be completed for each site. Recruitment at the site must not commence until the initiation process is completed and the Site Initiation Checklist is signed by the Quality Manager or delegate. A trial Investigator Meeting is not an alternative to a Site Initiation Visit (SIV) but is an additional opportunity for trial-specific training to be delivered to Investigators.

5.1 CRA Responsibilities

1. The CRA or delegate will act as the main line of communication between the KHP-CTO (on behalf of the Sponsor(s)) and the Investigator.

Prior to the Initiation Visit

2. The CRA will facilitate collection of all approvals and essential documentation according to the Site Initiation Visit Checklist and verify that applicable items are in place at site in order for initiation to take place.

3. The CRA will verify that all Chief/Principal Investigators (CI/PI) and all other relevant trial staff have had up-to-date training in relevant areas. In addition to GCP training, the CRA will verify that the CI has completed all mandatory training as required by the KHP-CTO and UK Regulations.

4. The CRA will ensure that the Investigator and Study Site Staff including the Pharmacist (if applicable), involved with the study have been advised of the meeting and are able to attend. It is mandatory for the CI/PI to be present at the Site Initiation meeting.

5. The CRA will confirm availability of all documents needed to conduct initiation of the trial properly, and to comply with the applicable regulatory requirements.

6. The CRA will ensure that the trial is entered into the MATTS database and that it is regularly updated.

7. The CRA will ensure that the contracts have been fully executed.

8. The CRA will ensure other associated documents are finalised and sent to the site for localisation e.g. patient emergency contact cards, having been reviewed for accuracy and consistency.

9. The CRA will ensure that the trial-specific risk assessment has been finalised.

10. The CRA will prepare the SIV presentation and collate any documents that may need completing during the meeting.

During the Initiation Visit

11. If the Investigator has attended an Investigator Meeting for the trial, the CRA will review what training was given and ensure that copies of any minutes/certificates are filed in the Trial Master File/Investigator Site File (TMF/ISF). In some rare circumstances i.e. the site is a control site with no investigational medicinal product (IMP), site initiation may be performed for these sites during the Investigator meeting if all aspects of the

initiation visit checklist can be completed with the exception of the Pharmacy Visit section. This must be agreed in advance by the Quality Manager or delegate and fully documented in the monitoring plan (MP). Dependent upon the trial risk assessment and trial type, sites using IMP may require a full site initiation visit to be performed in order to confirm the IMP storage conditions and accountability are satisfactory.

12. The CRA or delegate will review the current version of the protocol with the Investigator ensuring that they are aware of the current version and date of the document to be followed.

13. The CRA will verify that all approvals and essential documentation are available for filing in the TMF/ISF according to the Site Initiation Visit Checklist.

14. The CRA will discuss recruitment methods for the trial. The current versions of the PIS and ICF will be reviewed and the CRA will discuss GCP compliant informed consent procedures with the Investigator and relevant personnel.

15. The CRA will ensure that the CI/PI has completed the delegation of duties and authorised signature log. Where possible, the CRA will also verify that all duties delegated by the CI/PI to other site staff have been documented on the Delegation of Duties and Authorised Signature Log. However, this may be an ongoing process completed throughout the trial.

16. The CRA will verify that a signed and dated Curriculum Vitae (CV) has been provided by the CI/PI. Where possible the CRA will also ensure that signed and dated CVs have been filed for other site staff listed on the Delegation Log.

17. The CRA will verify that all identified trial staff have been appropriately trained in both GCP and the trial protocol. Attendance at the visit will be recorded appropriately.

18. The CRA will ensure that the Investigator has defined what will be considered as source data and that this has been accurately documented on the Source Document Location List.

19. The CRA will discuss with the Investigator their responsibility to provide direct access to the source data for each participant and how this will be achieved.

20. The CRA or delegate will give Case Record Form (CRF or electronic (e) CRF) completion and correction training to all applicable personnel present at the Initiation meeting.

21. The CRA will ensure that, for trials using an eCRF, trial personnel are aware of the process for obtaining their usernames and passwords.

22. The CRA will ensure that there is a Database Plan in place for the trial, if applicable.

23. During the visit the CRA/delegate will verify that the relevant study staff have been trained on the KHP-CTO Pharmacovigilance (PV) Policy and will detail basic requirements for safety reporting (this is in addition to and not in place of formal KHP-CTO Chief Investigator's Responsibilities training).

24. If applicable the CRA will ensure that the Investigator and relevant site staff are aware of the emergency code-break and un-blinding procedures for the study.

25. The CRA will ensure that the Investigator is aware of their responsibility to communicate with the REC and R&D Dept on an ongoing basis.

26. The CRA will review the safety profile for the IMP within the Investigator Brochure (IB) or Summary of Product Characteristics (SmPC) and verify that the current Reference Safety Information is available at site.

27. Dependent upon the trial type, the CRA may review all IMP procedures including but not limited to receipt, storage, dispensing, accountability, return and destruction.

28. The CRA will check the storage conditions for the IMP even if it has not been received at site at the time of the visit.

29. The CRA, if applicable, will check that adequate facilities and supplies are in place to ensure that the laboratory requirements for the trial can be fulfilled according to any applicable Laboratory Manual.

30. The CRA will ensure that procedures for allocation of participant numbers and, if applicable, randomisation have been reviewed.

31. The CRA will check that the site has all staff, facilities, and equipment to perform the trial according to the study protocol and that all protocol-specific procedures (including handling of any samples) have been explained.

32. The CRA will ensure that the Investigator is aware of the monitoring requirements for the trial. This will include the requirements for each visit and the estimated frequency of visits. The level of monitoring required is defined according to risk assessment performed by the Quality Manager (or delegate) and will be detailed in the trial-specific Monitoring Plan.

33. The CRA will make Investigator sites aware that they should notify the KHP-CTO immediately if they are informed of any upcoming (regulatory or internal) inspections or audits.

34. The CRA will ensure that the Investigator is aware of their responsibility for the ongoing maintenance of trial documentation including correspondence in the TMF / ISF.

35. The CRA will ensure that correspondence pertaining to the SIV is filed accordingly in the TMF/ISF.

36. The CRA will ensure that the Investigator is aware of all contractual reporting obligations to external parties.

37. Archiving arrangements and retention of pertinent documentation for the trial will be discussed during the SIV.

38. The CRA will ensure that the Investigator is aware of their responsibility to ensure adequate cover during absences and of their obligation to have ongoing oversight of the trial.

39. The CRA will ensure that the Investigator is aware that assessment of patient eligibility and inclusion into the trial is a medical decision which must be clearly documented by an appropriately delegated medical professional.

5.2 Investigator and Site Initiation Visit Report

Following the Site Initiation Visit, the CRA will promptly complete the SIV Checklist and submit a written report to the KHP-CTO. This will be done using the SIV Checklist and Investigator and SIV Report templates.

The report will be reviewed promptly after the visit or communication and signed by an authorised individual within the KHP-CTO (Quality Manager, Senior CRA or delegate), the CRA and the Investigator. Any original copy will then be filed in the TMF and a copy retained for the Sponsor files. Recruitment of participants will not be able to commence until the SIV Checklist has been signed by the Quality Manager or delegate.

The Investigator will be informed in writing of discussions that took place during the visit and any follow-up items that were identified. These items will be followed up until completion. **Sponsor Green Light will only be given when KHP-CTO is satisfied that relevant queries raised during the Site Initiation Visit have been resolved.** If there is evidence of systematic failure to comply with GCP, the Sponsor will be informed and procedures outlined in KHP-CTO SOP 6.0 Notification of Serious Breach of GCP will be followed.

6.0 RELATED TEMPLATES

6.1 Investigator and Site Initiation Visit Report

6.2 Site Initiation Visit Checklist

6.3 Monitoring Plan

6.4 Source Document Location List

6.5 Authorised Signature and Delegation Log

6.6 Site Initiation Visit Attendance Log

6.7 Kick Off Meeting Checklist

7.0 APPROVAL AND SIGNATURE

23 November 2021

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Director
King's Health Partners Clinical Trials Office

Date