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This page details the version history and the main changes made for each new version.
The new changes are in red font.

Version Log		
Version number and date	**Author**	**Details of significant changes**
Version 1, 08.08.12	J H Pacynko & J Illingworth	Original SOP approved by R&D Committee on 01.08.12
Version 2, 29.01.14	J H Pacynko	- Internet links up-dated - Page 7 & 10 – The sponsor has 10 days to review sponsorship deleted. - Page 9 – A copy of the completed Delegation Log and signed off Monitoring Plan added to list of QA checks before R&D approval. - Science review of protocol added to Sponsorship Request Form
Version 3, 07.02.18	J H Pacynko	HRA approval added More detail on Risk Assessment and Sponsor greenlight process added Regulatory greenlight process added
Version 4, 12.02.19	J H Pacynko	- Added requirement for external auditing of trial. - Risk Assessment to be circulated to the CI/PI and all support service departments involved for their review and input. - Added Type A Notification Scheme. - Added, for single/double-blind trials, prior to Sponsor Green-light; ➢ to identify staff who should be blind/unblind to trial medication, ➢ to test un-blinding processes prior to Sponsor Green-light. -Added requirement for vendor assessments for 3rd party organisations. - Added requirement, for mult-site trial run by a CTU, that Sponsor green-light tasks and checks done by both the CTU and the Sponsor are to be documented, version controlled and signed off by both parties.
Version 5, 18.02.21	S Moffat	2.1 EU Directive replaced by UK Clinical Trials regs. 2.5 Clarification about the sponsor following the UK exit from the EU. 4.5.2 Addition of new process for seeking advice from MHRA whether trial is a CTIMP. 4.5.6 Addition of “Protocol guides are available from the R&D QA staff.” 4.7.5 Replacement of R&D Director to Sponsor Oversight Group will make the final decision whether to sponsor the trial. 4.7.6 Addition of paragraph about feedback to the applicant of sponsorship decision. 4.7.7 Addition of note explaining the circumstances where the UoH may have to be considered for sponsorship rather than HUTH. 4.7.8 Addition of “Costs for third party vendors will have to be included in any funding applications.”

Please note for definitions of acronyms refer to Appendix 1 of Management of SOPs. Refer to Appendix 2 of Management of SOPs for the standards to which clinical trials that investigate the safety and/or efficacy of a medicinal product are conducted.

All the HUTH R&D GCP SOPs are available at:
https://www.hey.nhs.uk/research/researchers/gcp-sops-for-hey-sponsored-ctimps/

1 Purpose and who should use this SOP

1.1 This SOP describes the procedures for investigators to follow when applying for sponsorship by Hull University Teaching Hospitals NHS Trust (HUTH) for a clinical trial of an investigational medicinal product (CTIMP).

1.2 The SOP also sets out the procedures that HUTH Research and Development Department (R&D) QA staff are required to follow when an investigator applies for sponsorship.

1.3 This SOP also sets out the Sponsor green-light process. This is the final green-light needed before recruitment to the trial can start.

1.4 Following these procedures will ensure compliance with the UK clinical trial regulations (Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments) and ICH GCP (International Conference on Harmonisation Good Clinical Practice for clinical research).

1.5 This SOP should be used by:

- All research staff involved with HUTH-sponsored CTIMPs – Chief/Principal Investigator, co-investigators, research nurses, clinical trial assistants, project managers, clinical trial co-ordinators, data managers, administrators etc.
- Clinical trials pharmacy staff – technicians and pharmacists.
- All HUTH R&D staff who manage the sponsorship of HUTH-sponsored CTIMPs.
- Research staff involved with clinical trials sponsored by an external organisation where the sponsor has no SOP for safety reporting. HUTH R&D SOPs are defaulted to in this case.

2 Background

2.1 An investigational medicinal product (IMP) is defined as follows:

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 authorization 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 authorization,
(b) used for an indication not included in the summary of product characteristics under the authorization for that product, or
(c) used to gain further information about the form of that product as authorised under the authorisation ***The Medicines for Human Use (Clinical Trial) Regulations 2004(SI 1031)*** *as amended.*

2.2 Medicinal products with a marketing authorization are IMPs when they are to be used as the test substance, reference substance or comparator in a clinical trial.

2.3 The Sponsor is the organisation that is responsible for ensuring that there are proper arrangements in place for the initiation, management, monitoring and financing (or arranging the financing) of a study.

2.4 A Sponsor can delegate any or all of its functions but cannot delegate responsibility for the study. Overall responsibility for the study always remains with the Sponsor.

2.5 It is a statutory requirement that all CTIMPs have a named Sponsor. For trials being conducted in the UK, the MHRA will continue to accept the Sponsor/Legal Representative being located in the UK or a country on the approved list of EU/EEA countries (this list may vary, please check at https://www.gov.uk/government/publications/importing-investigational-medicinal-products-into-great-britain-from-approved-countries).

2.6 It is important to identify a Sponsor as early as possible. Many funding bodies require a Sponsor to be agreed in principle prior to accepting a funding application.

2.7 The procedures described in this SOP enable HUTH to fulfil its statutory requirements as Sponsor under the UK Clinical Trial Regulations and to have appropriate control over the sponsorship process.

2.8 Adhering to these procedures will avoid unnecessary work and delays for investigators.

3 Responsibilities of HUTH as Sponsor

3.1 Hull University Teaching Hospitals NHS Trust (HUTH) as a Sponsor for clinical research must be in a position to ensure the following requirements are met (list not exhaustive):

- The dignity, rights, safety and well-being of participants are given priority at all times by research teams.
- Research protocols are worthwhile, of high scientific quality and represent good value for money.
- Research trials meet all relevant standards.
- Arrangements are put and kept in place for adequate management, monitoring and reporting of trials.
- Trials are conducted in accordance with appropriate regulatory approvals; MHRA clinical trial authorization, Research Ethics Committee (REC) favourable opinion, HRA approval, R&D confirmation of capacity and capability and Sponsor Green-light.
- Amendments to the study or protocol are reported according to the regulatory requirements.
- Notification of the end of trial is in accordance with the regulatory requirements.
- HUTH puts and keeps in place arrangements to adhere to the UK CT regulations and GCP.
- HUTH keeps records of all serious adverse events reported by investigators.
- HUTH ensures the recording and prompt reporting of suspected unexpected serious adverse reactions (SUSARS) to the MHRA and REC.
- HUTH ensures that serious adverse events (SAEs), serious adverse reactions (SARs) and SUSARs are reported annually in a Developmental Safety Update Report (DSUR) to the MHRA and REC.
- HUTH takes appropriate urgent safety measures with the Chief/Principal Investigator, if necessary.

3.2 HUTH R&D department acts on behalf of HUTH Trust to ensure that the above requirements are met.

4 Procedure

4.1 Sponsorship of CTIMPs represents a significant risk, cost and responsibility to HUTH and therefore requires appropriate planning at the earliest opportunity. The protocol and all documentation and procedures associated with it must be developed in detail. Monitoring must be arranged and the monitor involved in the trial set-up. For large multi-site trials, external auditing of the trial systems must be arranged. All investigators must be trained and there must be sufficient financial and staff resources available for safe and effective conduct of the trial. Investigator teams will need to work with the R&D Office on all these matters (see R&D GCP SOP 04 -Trial set-up).

4.2 External auditing is an MHRA expectation. Auditors must be independent of Sponsor delivery staff (R&D QA staff). A risk-based audit plan should be developed to identify specific systems or areas and studies to focus on.

4.3 The following points lay out the process of requesting sponsorship and obtaining the Sponsor Green-light to start the trial. This is summarised in the flowchart in Appendix 1.

4.4 Contact the R&D Office

4.4.1 HUTH requests that the Chief/Principal Investigator (CI/PI) alerts the R&D office as early as possible to prevent unnecessary delays in the request for sponsorship. The CI/PI should contact the R&D Office **when the protocol is in an early stage of development,** either by email using research.development@hey.nhs.uk or telephone 01482 461883. If by email please put in the subject line – Request for HUTH sponsorship.

4.5 Confirmation of CTIMP/non-CTIMP and protocol guides

4.5.1 Investigators will be requested to email their draft protocol to R&D.

4.5.2 If there is any ambiguity as to whether the study is a CTIMP or non-CTIMP, investigators will be asked to email the MHRA to obtain an opinion on whether a study involving a medicinal product falls within the scope of the clinical trial regulations and therefore requires a clinical trial authorisation (CTA).
The investigator will complete the "Request for an opinion on whether a study is a clinical trial of an investigational medicinal product under The Medicines for Human Use (Clinical Trials) Regulations 2004" form, found at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/949147/Scope_-_request_form.docx and email it with a copy of the protocol (the document describing the objectives, design and methodology) to clintrialhelpline@mhra.gov.uk , with 'Scope - protocol review' followed by the study title (shortened)' as the subject line. Please ensure R&D is copied into this email.
Investigators will be required to forward a copy of the response to R&D QA to confirm if the study is a CTIMP or non-CTIMP.

4.5.3 The MHRA has an algorithm to ascertain the classification of the study as CTIMP or non-CTIMP which is available from R&D or on the MHRA website at:
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/317952/Algothrim.pdf

4.5.4 In areas of doubt the R&D office reserves the right to request confirmation from the MHRA. The algorithm will not be relied upon alone.

4.5.5 Investigators must ensure that all correspondence to and from the MHRA is kept safe as it will need to be filed in the Trial Master File (TMF) (see see R&D GCP SOP 04 -Trial set-up). R&D QA will create the eTMF during the set-up of the trial.

4.5.6 R&D will send to investigators the CTIMP or non-CTIMP protocol guide for HUTH-sponsored trials in order to finalize the protocol. The aim of these guides is to ensure that the protocols reach the standard required by the regulations and GCP. Using the guides will reduce the number of queries raised by the REC and MHRA during their review of the study and hence reduce the time taken to obtain REC and MHRA approvals. This is the expected standard for HUTH Sponsor Green-light. Protocol guides are available from the R&D QA staff.

4.6 Completion of the Sponsorship Request Form

4.6.1 If the study is a CTIMP, R&D will send to investigators a Sponsorship Request Form for completion. The form requires a complete breakdown of the financial cost of the study.

4.6.2 The investigator must approach all the support services involved in the trial (pharmacy, HUTH labs, University of Hull labs, radiology, medical physics etc) and agree any costs. The early alert of all support departments will speed up the time to start the study.

4.6.3 **If funding will be via a grant, then R&D will need to review and advise on sponsorship and potential monitoring and auditing costs before sponsorship is given.**

4.6.4 The completed Sponsorship Request Form will need to be emailed to the R&D Manager or QA Manager together with the latest version of the protocol.

4.7 Protocol review and Risk Assessment

4.7.1 The QA Manager (Clinical Trials Monitor or R&D Manager) will review the protocol and Sponsorship Request Form.

4.7.2 A Sponsor Risk Assessment will be started by the QA Manager or Monitor. The perceived risks associated with delivering the trial will be assessed and documented. Risks will be evaluated such as whether the research question is likely to be answered, whether there are adequate resources and whether the trial is safe and fully funded.

4.7.3 The Risk Assessment will also be circulated to the CI/PI and all support service departments involved for their review and input. Where possible, the Risk Assessment will be conducted face-to-face with the CI/PI and support services and will be documented by the QA Manager or Monitor.

4.7.4 Part of the Risk Assessment will involve the Sponsor and CI/PI deciding whether the trial is a Type A, B or C trial based on the type of IMP used.

- Type A trial is comparable to the risk of standard medical care.
- Type B trial is somewhat higher than the risk of standard medical care.
- Type C is markedly higher than the risk of standard medical care.

More detail on how to categorise the trial is given in the MRC/DH/MHRA's document 'Risk-adapted approaches to the management of CTIMPs'.

4.7.5 The Sponsorship Request Form and the Risk Assessment will be reviewed and discussed by the R&D Manager, QA Manager and R&D Monitor. The Sponsor Oversight Group

(SOG) will make the final decision whether to sponsor the trial. The SOG can be emailed for a decision to sponsor a trial, this will not have the wait for the next planned meeting.

4.7.6 The applicant will be informed of the SOG outcome. In the event that sponsorship is declined feedback will be given with an opportunity for the applicant to discuss further with the R&D QA team and SOG.

4.7.7 Please note:

- In the event that sponsorship is declined the CI/PI may be required to engage the University of Hull to sponsor the trial.
- In the event of capacity issues, priority is given to the investigators principally employed by HUTH. Those employed by the University of Hull may need to have discussions with their employer about sponsorship.

4.7.8 At this point, it will also be discussed if vendor assessments are required for third party organisations such as a Clinical Trials Unit (CTU) who is managing a multi-site trial, an IMP manufacturing/preparation unit, a laboratory or randomisation service external to the Trust. Costs for third party vendors will have to be included in any funding applications.

4.7.9 The CI/PI will be notified by email of any concerns, vendor assessments and changes required.

4.7.10 The Sponsor Risk Assessment Form is Working Instruction 12 which is saved on the ClinicalGov Y drive in Y:\GCP SOPs & forms\Working Instructions.

4.8 Regulatory submissions

4.7.1 Regulatory submissions are all the documents submitted to the; REC for REC favourable opinion, the MHRA for the clinical trial authorisation and the HRA for approval.

4.7.2 If the trial is considered by the Sponsor and CI/PI to fall into the category of a Type A trial and as such involves an IMP or IMPs;

- licensed in the UK or any EU member state to be used according to the licensed indication, dosage and form
- or to be used off-label if the off-label use is established practice and supported by sufficient published evidence and/or guidelines.

Then the trial can be submitted under the MHRA's Notification Scheme. The Notification Scheme has the advantages that a response will be received from the MHRA within 14 days of submission and there is no fee.

4.7.3 If sponsorship is agreed, the R&D QA Manager or Monitor will need to review all the documents for REC submission before the R&D Manager will confirm sponsorship by electronically signing the IRAS form.

4.7.4 R&D QA staff will supply templates to the investigator for the PIS, ICF and GP letter.

4.7.5 Likewise all the documents for MHRA submission must be reviewed by R&D QA before submission.

4.7.6 Investigators must work closely with pharmacy to ensure that the correct labels and Summary of Product Characteristics or Investigator Brochures are submitted for each IMP.

4.7.7 Electronic copies of all documents submitted to the MHRA, REC and HRA and all subsequent correspondence must be emailed to the R&D QA staff upon request in order to be saved in the eTMF.

4.8 Sponsor Green-light process

4.8.1 **The trial cannot start recruiting before the Sponsor Green-light is sent to the CI/PI.**

4.8.2 The following documents and reviews are required before the Sponsor Green-light is issued, the list is not exhaustive and there may be additional requirements for each trial:

- Protocol review and all actions addressed
- PIS, ICF, GP letter, patient invitation letter, advert review and all actions addressed
- Fully completed Sponsorship Request Form
- Fully completed Risk Assessment
- Fully signed Finance Agreement if required
- R&D finance review and sign off
- Approval of all service support departments involved
- Copy of REC, HRA and MHRA submission documents and correspondence received
- CRF and spreadsheet/database review
- Site initiation visit performed by R&D Monitor and all actions addressed
- Fully signed Protocol
- Fully signed CI/PI Sponsor Agreement
- Fully signed Contracts/Agreements with third party organisations (e.g. Lab Agreement with University of Hull labs, Funder Agreement, CTU Contract)
- Finalised Data Management Plan
- Finalised Monitoring Plan
- Fully completed Training and Delegation Log
- Current GCP certificates, CVs and Honorary Contracts (if applicable) received for the research team
- Study-specific SAE forms QA checked
- Copies of finalised pharmacy dispensing procedure, prescription and drug accountability log
- REC favourable opinion
- MHRA clinical trial authorisation (CTA)
- HRA approval
- All conditions of approvals completed
- Regulatory Greenlight if required
- R&D confirmation of capacity and capability (R&D C&C)
- Insurance/indemnity in place
- For double-blind trials, un-blinding procedures tested
- Pharmacy in receipt of all regulatory approvals and MHRA letter of non-acceptance and PI response (if applicable)
- Pharmacy Green-light
- Pharmacy final confirmation IMP checked and ready to dispense if not part of green-light.
- Final review of Risk Assessment
- **Sponsor Green-light**

4.8.3 If the trial is single or double-blind, it will be necessary to identify and document which trial staff should remain blind to trial medication and which trial staff unblind. This will need to be circulated amongst all trial staff including pharmacy and statisticians prior to Sponsor Green-light. Testing of un-blinding processes will need to occur prior to Sponsor Green-light.

4.8.4 There may be other checks required depending on the trial. A green-light checklist is prepared by R&D QA staff and updated as documents and reviews are completed. The checklist template is Working Instruction 05 saved on the ClinicalGov Y drive in Y:\Research\GCP SOPs & forms\Working instructions.

4.8.5 If the trial is multi-site run by a CTU, for the Sponsor green-light process, the tasks and checks done by both the CTU and the Sponsor should be documented, version controlled and signed off by both parties.

4.8.6 The R&D Office will prepare and negotiate appropriate Contracts/Agreements with any external organisations. Contracts/Agreements should not be signed by the Chief or Principal Investigator prior to review by R&D. Agreement signatories should be parties (institutions or organisations) rather than individuals.

4.8.7 A site initiation visit (SIV) will be carried out by the R&D Monitor with the research staff involved with the trial. A separate SIV will be performed by the Monitor with the clinical trials pharmacy staff. The Monitor prepares the Investigator Site File and Pharmacy Site File ahead of the visits. The purpose of the SIV is to check that all essential study documents are in place and research/pharmacy staff are trained in study procedures before the study starts. All actions as a result of the SIVs will need to be dealt with. More details on the SIV are in the R&D GCP SOP 15 - Monitoring.

4.8.8 Should the trial involve labs, then a lab monitoring visit will be performed by the R&D Monitor.

4.8.9 If the IMP is supplied by a third party organization, the Regulatory Green-light process described below will be followed, unless otherwise advised by the third party. If the IMP is obtained from pharmacy stock or pharmacy sourced the Regulatory Green-light is not required.

4.9 Regulatory Green-light process

1. 'Technical release' - Sponsor to ensure that a QP certifies that IMP has been manufactured to EU GMP and the CTA. This is **not needed** if the IMP is unaltered and marketed in the UK or EU.
2. 'Regulatory release' – MHRA CTA, REC favourable opinion and HRA approval obtained.
3. All contracts/agreements have been signed
4. All approvals are in place
5. Insurance/indemnity is in place

4.8.10 The Regulatory Green-light checklist template is Working Instruction 06 saved on the ClinicalGov Y drive in Y:\Research\GCP SOPs & forms\Working instructions.

4.8.11 The Sponsor Green-light will be issued when R&D are happy that all the green-light checks have been completed.

4.8.12 Sponsor Green-light will be emailed to the CI/PI with the research team, statistician and all service support departments on copy.

4.8.13 If the trial is multi-site, the Sponsor must green-light each site before the site can start recruiting. The Sponsor Green-light process is given in the R&D GCP SOP 18 -Site Initiation of Multi-centre HUTH-sponsored CTIMPs.

4.8.14 Any significant issues arising from this process that cannot be resolved with the R&D QA staff and Manager will be referred to SOG for for discussion and action. Ultimately decisions where disputes cannot be resolved in this way will reside with the R&D Director (or Chief Medical Officer, as required).

5 Implementation

Implementation of this SOP will conform to the process outlined in R&D SOP 01 Management of SOPs.

Appendix 1:

Flowchart showing the process for requesting sponsorship and Sponsor Green-light for HUTH-sponsored clinical trials with investigational medicinal products