Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Research Department

STANDARD OPERATING PROCEDURE

Risk Assessment of STH sponsored CTIMPs

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Standard Operating Procedure:
Risk Assessment of STH Sponsored CTIMPs

This SOP has been produced in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004 & subsequent amendments, and the Department of Health's Research Governance Framework 2005. This SOP will outline the procedure for acceptance of STH sponsorship of a non-commercial CTIMP, study risk assessment and the review of study management arrangements. This SOP applies to all CTIMP studies sponsored by Sheffield Teaching Hospitals NHS Foundation Trust (STH).

Background

The current regulatory framework in the UK/EU allows for a range of risk-adapted approaches that may simplify the processes for initiating and conducting some clinical trials. These adaptations are largely related to how much is known about the investigational medicinal product (IMP) and therefore the risk to the participant in relation to the IMP.

These potential risks should be assessed relative to the standard of care for the relevant clinical condition and the level of clinical experience with the intervention rather than the patients' underlying illness or the recognised adverse effects of the intervention. The potential risks should be balanced against the level of risk that a trial participant would be exposed to outside of the trial.

The MHRA has published guidance in October 2011 on risk adapted approaches proposing a three-level categorisation:

- Type A = No higher than the risk of standard medical care
- Type B = Somewhat higher than the risk of standard medical care
- Type C = Markedly higher than the risk of standard medical care

Using a simple categorisation of three risk types it is possible to highlight, particularly for lower risk trials, where simplification is possible, resulting in a more risk proportionate approach. These include:

- the need for authorisation by the competent authority
- the content of the Clinical Trials Authorisation (CTA) application
- IMP management
- safety surveillance
- trial documentation
- GCP Inspection

The other aspects of clinical trial design and methodology which should be included in the overall risk assessment of the trial include:

- the clinical trials experience within the team proposing to conduct and manage the research
- safety risks from clinical procedures specified by the protocol
- risks related to participant rights
- risks to the reliability of trial results.

The design of a study has a major impact on the quality of the results; the more robust the design the less dependence there is on quality control and assurance measures for reliable results. Of critical importance is the identification of areas of potential vulnerability in trial design and planned methodology, which may require mitigation activities to ensure the reliability of the trial results and to protect participants' rights.

Risk assessment should be initiated by the chief investigator/protocol author at an early stage in protocol development. It should be reviewed by the sponsor and other investigators, to agree on the main risks inherent in the trial protocol. A plan to mitigate or manage these risks should be developed, either as part of the trial protocol or outlined in associated documents (such as a monitoring plan).

Definition

Risk in clinical trials
This can be defined as the likelihood of a potential hazard occurring and resulting in harm to the participant and/or an organisation, or to the reliability of the results.

For every trial there is a core set of risks inherent to the protocol that relate to the safety of the participants and the integrity/reliability of the results. All organisations involved need to understand these risks so that the control measures, resources, procedures and processes implemented during the trial ensure the safety of the trial participants, and lead to high-quality results.

Risk Assessment
This is essentially a process of identifying the potential hazards associated with that trial, and assessing the likelihood of those hazards occurring and resulting in harm. This risk assessment will include:

- the risks to participant safety in relation to the IMP
- all other risks related to the design and methods of the trial (including risks to participant safety and rights, as well as reliability of results)

Procedure

1. The R&D Coordinator identifies a registered study as a potential CTIMP where STH is the lead NHS institution and therefore potentially the study sponsor.
   1.1. The R&D Coordinator makes further enquiries as necessary to establish whether the project will be classed as a CTIMP and to obtain a protocol outline or research proposal. If the R&D Coordinator is in any doubt about whether a study will be classed as a CTIMP the R&D Coordinator will consult with the Risk Assessment Lead, or Pharmacovigilance Leads

2. If the study is confirmed as a CTIMP the R&D Coordinator alerts the Risk Assessment Lead and Research Manager to the study immediately regardless of the stage of set-up of the study.

3. The Risk Assessment Lead or Delegate performs an initial risk assessment based on the type of study and expertise within the study team using the preliminary risk assessment tool.

4. The Risk Assessment Lead or Delegate provides feedback to the R&D Coordinator on whether STH is likely to be able to accept sponsorship responsibilities and the terms under which this responsibility can be accepted based on the outcome of the initial risk assessment[1, 2].

5. The R&D Coordinator arranges a feasibility meeting with the CI to discuss the outcome of the initial risk assessment and how to take the study forward. The Risk Assessment Lead or Delegate attends the meeting where appropriate.

6. The Risk Assessment Lead or Delegate provides further advice on the inclusion of funding for study management in any grant application as necessary.

7. When available funding is confirmed the Risk Assessment Lead or Research Manager makes a final decision on whether the terms under which STH can accept sponsorship have been met. The Risk Assessment Lead or Research Manager provides feedback on the sponsorship decision to the CI/PI and R&D Coordinator.

[1] Due to limited resources STH is unlikely to be able to agree to Sponsor multi-centre UK-based IMP clinical trials without project management and monitoring by an STH approved Clinical Research Organisation (CRO) or Clinical Trials Unit (CTU); STH may delegate responsibilities to the CRO or CTU as defined in an agreement.

[2] Due to limited resources STH is unlikely to be able to agree to Sponsor multi-centre international IMP clinical trials with external sites outside the UK

8. **Studies not using a CTRU/CRO for full project management.** (Note: except in exceptional circumstances these studies will be single centre studies)
   - 8.1. The CI writes the protocol using the STH protocol template and STH guidance on writing protocols. The CI incorporates risk assessment of the study into the study protocol as directed by the STH guidance on writing protocols.
   - 8.2. The CI submits the protocol to the R&D Coordinator for review.
     - 8.2.1. The R&D Coordinator forwards the protocol to the ISR Lead, indicating that this study requires ISR for CTIMP risk assessment purposes.
     - 8.2.2. The ISR Lead forwards the protocol to the Risk Assessment Lead or Deputy. The ISR Lead also conducts a first pass review of the protocol according to the ISR SOP(s).
     - 8.2.3. The Risk Assessment Lead or delegate reviews the protocol against the guidance on writing protocols and the template for full risk assessment of STH sponsored CTIMPs.
     - 8.2.4. The Risk Assessment Lead or delegate provides feedback to the CI advising where any risks need further addressing in the protocol.
     - 8.2.5. The CI updates the protocol according to the advice of the Risk Assessment Lead or delegate and re-submits the updated protocol to the Risk Assessment Lead or Delegate.
     - 8.2.6. When the Risk Assessment Lead or Delegate is satisfied that the protocol addresses the identified risks the Risk Assessment Lead or Delegate advises the CI and ISR Lead that the protocol can proceed to Independent Scientific Review (ISR).
     - 8.2.7. The ISR Lead arranges for the protocol to be reviewed independently to confirm the adequacy of the risk assessment (see Independent Scientific Review SOP(s)) and forwards the result of this review to the Risk Assessment Lead and Delegate.
     - 8.2.8. When the process of risk assessment and scientific review is completed the Risk Assessment Lead or Research Manager confirms that the study is ready to proceed to ethics, EUDRACT and MHRA applications.
   - 8.3. On confirmation of STH sponsorship and satisfactory risk assessment, the R&D Coordinator applies for study EUDRACT registration and MHRA CTA as Sponsor on behalf of the CI according to the Clinical Trial Authorisation SOP. The CI is responsible for providing all study information and documentation required for these applications.
   - 8.4. The R&D Coordinator identifies whether any other external institutions are involved in the study (other than in the capacity of a participating site). Agreements with all external institutions involved will generally be required. The R&D Coordinator consults with a senior member of the Research Department if it is unclear whether an agreement should be required. The R&D Coordinator negotiates and executes these agreements as described in the Execution of Agreements SOP.
   - 8.5. The R&D Coordinator sends the CI the Single Site Internal Study Management Arrangements Form.
   - 8.6. The CI completes, signs, and returns the Single Site Internal Study Management Arrangements Form to the R&D Coordinator.
     - 8.6.1. The R&D Coordinator forwards the Single Site Internal Study Management Arrangements Form to the Risk Assessment Lead or Delegate for review.
     - 8.6.2. The Risk Assessment Lead or Delegate reviews the Single Site Internal Study Management Arrangements Form and either requests revision or confirms to the CI they are fit for purpose.
   - 8.7. The R&D Coordinator sends the PI the Responsibilities of Investigators form
     - 8.7.1. The PI signs and returns the Responsibilities of Investigators form
   - 8.8. The R&D Coordinator requests a copy of the study Case Report Form (CRF) from the CI.
     - 8.8.1. The R&D Coordinator forwards the CRF to the Risk Assessment Lead or Pharmacovigilance Lead/Deputy for review.
     - 8.8.2. The Risk Assessment Lead or Pharmacovigilance Lead/Deputy reviews the CRF and either requests revision or confirms to the CI it is fit for purpose.
   - 8.9. The R&D Coordinator checks GCP training of the CI, PI and other key research staff.
   - 8.10. The R&D Coordinator reviews the need for formal agreements with collaborators from outside STH, including but not limited to funder, IMP supplier, clinical trials unit or contract research organisation, central laboratories and participating sites. Agreements with all external institutions involved will generally be required. The R&D Coordinator consults with a senior member of the Research Department if it is unclear whether an agreement should be required. The agreement must clearly describe the division of responsibilities between the

sponsor and the external institution. The R&D Coordinator negotiates and executes these agreements as described in the Execution of Agreements SOP.

8.11. The R&D Coordinator files evidence of satisfactory initial risk assessment, independent scientific review, study management arrangements review and CRF review in the R&D Master File.

8.12. The R&D Coordinator files the signed Responsibilities of Investigators form, PI CV, evidence of PI GCP training and sample CRF in the R&D Master File.

8.13. Where any other participating sites are involved the R&D Coordinator follows clauses 9.8 to 9.11 below.

9. Studies using a CTRU/CRO for full project management

9.1. The CI writes the study protocol in collaboration with the CTRU/CRO using the STH protocol outline and guidance for writing protocols. This outline and guidance can be replaced by the CTRU/CRO's own templates and guidance where these exist.

9.2. The R&D Coordinator negotiates an agreement between STH and the CTRU/CRO which details the work to be undertaken by the CTRU/CRO and the division of sponsorship responsibilities between STH and the CTRU/CRO. The R&D Coordinator negotiates and executes this agreement as described in the Execution of Agreements SOP.

9.3. The R&D Coordinator identifies whether any other external institutions are involved in the study (other than in the capacity of a participating site). An agreement with the CTRU/CRO will always be required. Agreements with all other external institutions involved will generally be required. The R&D Coordinator consults with a senior member of the Research Department if it is unclear whether an agreement should be required. The agreement must describe the division of responsibilities between the sponsor and the external institution.

9.3.1. The R&D Coordinator negotiates these agreements as described in the Execution of Agreements SOP.

9.3.2. The R&D Coordinator forwards the proposed division of responsibilities between STH and the CTRU/CRO to the Risk Assessment Lead or Delegate for review.

9.3.3. The Risk Assessment Lead or Delegate reviews the proposed division of responsibility and either requests revision or confirms to the R&D Coordinator that they are fit for purpose.

9.3.4. The R&D Coordinator executes these agreements as described in the Execution of Agreements SOP .

9.4. The CTRU/CRO arranges for the study protocol to undergo risk assessment according to its own SOPs.

9.4.1. The R&D Coordinator confirms that this has taken place and files a copy of the risk assessment document in Alfresco.

9.4.2. Where by the CTRU/CRO does not have its own procedures for protocol risk assessment the R&D Coordinator follows the process detailed above in clause 8.2.

9.5. The CTRU/CRO or R&D Coordinator applies for study EUDRACT registration and MHRA CTA on behalf of the Sponsor. The CI is responsible for providing all study information and documentation required for these applications.

9.6. Where the CTRU/CRO is not registered with the UKCRC Clinical Trials Unit Network, STH Research Department requires further confirmation of the adequacy of the study management and monitoring arrangements. The CTRU/CRO forwards their study management and monitoring arrangements to the R&D Coordinator.

9.6.1. Where the CTRU/CRO does not already have a prepared study management and monitoring arrangements document the Research Coordinator forwards the Multi-Centre Study Management Arrangements form to the CTRU/CRO for completion..

9.6.2. The R&D Coordinator forwards the CTRU/CRO study management and monitoring arrangements to the QA Lead or Delegate for review.

9.7. The QA Lead or Delegate reviews the study management and monitoring arrangements and either requests revision or confirms to the R&D Coordinator that they are fit for purpose. The CTRU/CRO forwards a copy of the study case report form to the R&D Coordinator. The R&D Coordinator files a copy of the case report form in the R&D Master File

9.8. The R&D Coordinator prepares a template agreement (mNCA preferred) for participating sites and follows the Sponsorship SOP and the Execution of Agreements SOP to negotiate agreement and sign off by participating sites. The CTRU/CRO study manager may facilitate this process. The R&D Coordinator files copies of all signed agreements in the R&D Master File.

9.9. The CTRU/CRO Coordinator collects PI CVs and evidence of GCP training and signed copies of the responsibilities of investigators document from each PI.

9.10. The CTRU/CRO or R&D Coordinator receives NHS permission letters from the participating sites

Appendix 1
STH Related Documents

	Document	Research Department Network Location	Website	Database	Created by
3	Preliminary risk assessment for proposed STH sponsored CTIMPs	Directory\!_Working Drafts\Research Governance\Monitoring documents\STH sponsored CTIMPS\Risk assessment process	No	No	EW
4	Protocol Guidance Notes	Directory\Research Governance\Independent Scientific Review\STH_internal_review\Current_Documents\Current ISR documents	Yes	No	EW
5	Risk Assessment Checklist	Directory\!_Working Drafts\Research Governance\Monitoring documents\STH sponsored CTIMPS\Risk assessment process	No	No	EW
6	STH Guidelines and Template for Single Centre Internal Management and Monitoring of CTIMPs	Directory\!_Working Drafts\Research Governance\Monitoring documents	No	No	EW
7	Multi-centre Study Management Arrangements template	Directory\!_Working Drafts\Research Governance\Monitoring documents\Research Department Monitoring Requirements	Yes	No	BZ
8	Investigator's Responsibilities Declaration	Directory\!_Working Drafts\Research Governance\Sponsorship	Yes	No	BZ