Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Clinical Research & Innovation Office

STANDARD OPERATING PROCEDURE

Risk Assessment and Sponsor Green Light Process for STH sponsored CTIMPs

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Approved by (name & role)	Dipak Patel Research Manager	**Date:**	31 October 2022
Signature:	D Patel		

Standard Operating Procedure:
Risk Assessment and Sponsor Green Light Process for STH Sponsored CTIMPs

This SOP has been produced in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004 & subsequent amendments, and the UK Policy Framework for Health and Social Care Research. 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 Medicines for Human Use (Clinical Trials) Regulations and UK Policy Framework for Health and Social Care Research require that all research projects must have a Sponsor identified and declared prior to the commencement of the project.

The Medicines for Human Use (Clinical Trials) Regulations require that the Sponsor maintains oversight for the trial and that this oversight is documented. The Sponsor must have a robust Sponsor Green Light Process which confirms that all necessary reviews and approvals have been completed before the trial opens, with commensurate processes in place for review and approval of amendments. A necessary part of these processes is risk assessment.

The current regulatory framework in the UK 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 IRAS Combined Review 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 considered from a very early stage in development of the research idea and trial design. It should be reviewed by the Sponsor and other investigators, to agree on the main risks inherent in the trial protocol. As such risk assessment should begin pre-grant application since control of risk will impact on the costs of the research. A plan to mitigate or manage these risks should be developed, documented and reviewed throughout the life of the trial. Documentation may be contained within the trial protocol and/or outlined in associated documents (such as a monitoring plan) and will be part of the documentation of the Sponsor Green Light Process.

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Acronyms

CCC	Confirmation of Capacity and Capability
cCCC	Continued Confirmation of Capacity and Capability
CI	Chief Investigator
CRF	Case Report Form
CRIO	Clinical Research & Innovation Office
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTRU	Clinical Trials Research Unit
HRA	Health Research Authority
HSC	Health and Social Care
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
PI	Principal Investigator
QA	Quality Assurance
REC	Research Ethics Committee
RMS	Research Management System
SIV	Site Initiation Visit
SGL	Sponsor Green Light

Definitions and National Context

Clinical Trial of a Medicinal Product (CTIMP)
A clinical trial of a medicinal product is an investigation in human subjects which is intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products, identify any adverse reactions or study the absorption, distribution, metabolism and excretion, with the object of ascertaining the safety and/or efficacy of those products. This definition includes pharmacokinetic studies.

The Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for advising on the Regulations and requirements for clinical trial authorisation (CTA). The MHRA provides an algorithm

to aid the decision over whether or not research is a clinical trial of an investigational medicinal product (CTIMP).

It is a criminal offence to conduct a CTIMP anywhere in the UK without CTA from the MHRA. This applies both to commercial and non-commercial research, and both to pre-licensing drug development and later phase research including research of licensed products used either off license or for their licensed indication.

Clinical studies involving only medical devices, food supplements or other non-medicinal therapies (such as surgical interventions) are **not** covered by the Medicines for Human Use Clinical Trials Regulations. The Regulations also do not apply to non-interventional trials where the medicine under study is prescribed as standard care independent of the participant's inclusion in the study and where no additional diagnostic or monitoring procedure are applied (see MHRA algorithm for detailed definition of a non-interventional trial).

Sponsor
The Sponsor is responsible for confirming arrangements to initiate, manage and finance a study, for ensuring that the proposed research respects the dignity, rights, safety, and well-being of participants and for ensuring that the research is set up and conducted in compliance with applicable regulations, guidelines and frameworks.

The Sponsor is responsible for oversight of all aspects of the trial. The Sponsor must have processes in place which enable the demonstration of Sponsor oversight for the trial.

It is essential that the Sponsor for a trial is identified and confirmed at an early stage in the development of a research idea and trial design since the Sponsor is central to the arrangements for risk assessment and Regulatory compliance. SOP C108 sets of principles for the allocation of Sponsorship.

A Sponsor can delegate responsibilities to other parties for which they remain ultimately responsible. Where there is delegation of responsibility, clear agreements describing allocation of responsibilities and rights must be reached, documented and enacted.

Clinical Trials Research Unit (CTRU) / Clinical Research Organisation (CRO)
CTRUs and CROs can provide various aspects of project management including trial design, database design, statistical support, trial monitoring and full project management. The trial Sponsor may delegate these responsibilities to a CTRU/CRO by means of a collaboration agreement or similar.

Many CTRUs are part of the UKCRC Registered CTU Network. This is a network of academic clinical trials units (CTUs) who have been assessed by an international panel of experts in clinical trials research as having expertise in centrally coordinating multicentre clinical trials, as well as in trial design, data management, and analysis.

Multicentre non-commercial CTIMPs sponsored by Sheffield Teaching Hospitals NHS Foundation Trust generally require the support of full project management by a UKCRC registered CTRU. The Chief Investigator of such a trial is responsible for identifying and approaching a suitable CTRU. STH CRIO may be able to provide advice in this area. STH CRIO will need to ensure, as trial Sponsor, that it is satisfied that the proposed project management arrangements will be appropriate to meet regulatory requirements.

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)

Risk Adaptation
The Sponsor is responsible for defining and putting in place processes to meet Regulatory needs of the trial, for justifying risk adaptations to these processes and for ensuring the documentation of this process.

Sponsor Green Light
The Sponsor is responsible for giving final green light for the initial opening of the trial (both study-wide and at each site involved in the trial) and for each amendment to the trial. The Sponsor must have a process for ensuring that all steps have been completed prior to giving green light and for documenting this process.

Site Initiation Visit
A Site Initiation Visit (SIV) is a meeting (which may be conducted remotely or by phone) between representative(s) of the Sponsor and Site staff before the opening of a study at the site to ensure that the site fully understands its responsibilities and that the Sponsor representative is satisfied that the site is able to deliver these responsibilities and that arrangements being put in place are satisfactory

Amendments
An amendment requiring submission to the HRA and/or REC/MHRA is any change to the original study application during the life of the study. This includes but is not limited to: protocol amendments, updated study documentation, duration of the study, changes in study management (including Sponsorship or funding) or changes to the leads of the research team (CI/PI). All such amendments also require review and approval by the trial Sponsor and subsequent implementation via Sponsor Green Light. SOP C105 will be followed for all amendments but additional procedures for documentation of risk review and Sponsor Green Light are set out in this SOP.

'Sponsor Only' Amendments
A clinical trial involves the creation and use of many other documents besides those included in the study application to HRA/MHRA. Examples include study specific SOPs, case report forms, study specific prescriptions and drug accountability logs. It is essential that these documents fully reflect the requirements of the trial protocol and risk assessment. It is therefore essential that the Sponsor reviews and approves these documents and also reviews and approves amendments to these documents during the life of the trial. Such amendments to documents which do not require submission and review outside of the Sponsor organisation (ie do not require HRA/MHRA approval) are referred to in this SOP as 'Sponsor Only' amendments. The process for review and approval of these amendments is set out in this SOP.

STH Sponsorship
Where STH is identified as the appropriate study Sponsor and where STH is able to accept sponsorship as set out in the below procedure and in SOP C108, sponsorship responsibilities will be exercised by the Clinical Research & Innovation Office (CRIO). The CRIO Risk Assessment Lead will lead the process of Sponsor review of study documents, study set up and risk assessment, delegating reviews as appropriate as described in this SOP. The CRIO QA Lead will lead Sponsor Quality Assurance processes including review of risk assessment and study team management arrangements and drafting of Sponsor monitoring arrangements, delegating responsibilities as appropriate as described in this SOP.

Version Control Tracking Sheet
STH CRIO uses a Version Control Tracking Sheet to record Sponsor approval for each study document involved in an STH sponsored CTIMP (where trial project management is not delegated to a CTRU/CRO). The Version Control Tracking Sheet also records all the required approvals for each study document, lists each amendment, links each study document to its relevant submission and approval and defines the current document set. The appendix records the additional documents

involved in the completion of the Sponsor Green Light process during study set up. The Version Control Tracking Sheet is also used to record the presence of each document in the TMF/ISF and Sponsor R&D file and as such serves as a monitoring tool.

Procedure

1. The CRIO 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 CRIO 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 CRIO Coordinator is in any doubt about whether a study will be classed as a CTIMP the CRIO Coordinator will consult with the Risk Assessment Lead, or Pharmacovigilance Leads.

2. If the study is confirmed as a CTIMP the CRIO 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 requests further information to provide an initial assessment based on the type of study, IMP involved and expertise within the study team.

4. The Risk Assessment Lead or Delegate provides feedback based on an initial assessment of likely risks to the CRIO Coordinator on whether STH is able to accept sponsorship responsibilities and the terms under which this responsibility can be accepted.t[1, 2]; this is relayed to the CI or delegate, The CI or delegate is also provided with the STH CTIMP Pre-application considerations for cost and support document for information.

5. The Risk Assessment Lead and/or CRIO Coordinator or delegate work with the CI or delegate(s) to define areas requiring costing and the appropriate levels of and sources of support to be costed using the STH CTIMP Pre-application considerations for cost and support document and table as a guide.

   5.1. The Risk Assessment Lead or Delegate ensures that the level of activity requiring costing, including that of third-party vendors, is appropriate for the trial, providing further advice on funding for study management in any grant application as necessary and involving CRIO Leads for Databases and Laboratory Assessments as necessary based on the requirements of the trial.
   5.2. The Risk Assessment Lead or delegate the STH CTIMP Pre-application considerations for cost and support table to document decisions over the levels of and sources of support required to be costed as appropriate for the trial.
   5.3. The CRIO Coordinator liaises with the CI team and with Research Finance colleagues to obtain actual costs for the grant submission.

6. Further study set up will not proceed until available funding which meets the needs identified for the trial is confirmed. When funding is confirmed further set up will proceed according to either section 7 or section 9 depending on whether a CTRU/CRO is providing full project management for the trial

7. **Studies not using a CTRU/CRO for full project management.** (Note: except in exceptional circumstances these studies will be single centre studies)
   7.1. The CI or delegate writes the protocol using the HRA CTIMP protocol template. The CI or delegate may liaise with the CRIO Coordinator and/or Risk Assessment Lead for advice as

[1] Due to limited resources STH is unlikely to be able to agree to Sponsor multi-centre UK-based IMP clinical trials regardless of the risk classification of the trial without full project management and monitoring by an STH approved Clinical Research Organisation (CRO) or Clinical Trials Research Unit (CTRU); STH will delegate responsibilities to the CRO or CTU as defined in an agreement. The CRO or CTU will require full funding for these responsibilities.

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

necessary. The CI or delegate should also obtain advice from the relevant STH Pharmacy Clinical Trials Manager and from a statistician.

7.2. The CI submits the protocol to the CRIO Coordinator for review.

7.3. The CRIO Coordinator confirms whether ISR is required (SOP A109/B103) and follows SOP B103 if ISR is required.

7.4. When ISR is confirmed as complete the CRIO Coordinator forwards the protocol to the Risk Assessment Lead or delegate.

7.5. The Risk Assessment Lead or delegate reviews the protocol against the HRA CTIMP protocol template, MHRA Risk Adapted Approaches document and STH CTIMP Protocol Review Checklist. If the Risk Assessment Lead or delegate judges that the protocol is not yet ready for formal CTIMP review the Risk Assessment lead or delegate will provide the CI or delegate with informal feedback and invite the CI or delegate to revise the protocol and resubmit. The Risk Assessment Lead or delegate will meet with the CI or delegate as necessary to discuss areas where the protocol needs more work in order for the protocol to be ready for formal review.

7.6. The CI or delegate requests review of the protocol by a statistician. Statistical advice can be requested from the STH CRIO Statistics Clinic. Once statistical review is complete the CI or delegate requests that the statistician involved completes the Statistical Review Checklist to provide confirmation that the trial design, power calculation and outline statistical analysis plan included in the protocol are suitable to meet the needs of the trial. The CI or delegate submits the completed Statistical Review Checklist to the CRIO Coordinator.

7.7. If the protocol is judged as ready for formal review the Risk Assessment Lead or delegate completes the STH CTIMP Protocol Review Checklist. The Risk Assessment Lead or delegate will detail in the checklist where the protocol requires revision for the purposes of risk mitigation, clarity of process, confirmation of risk adapted approach or other reason.

7.8. The Risk Assessment Lead or delegate sends the completed checklist to the CI or delegate and requests a revised protocol together with the addition of comments on the revisions made in the STH CTIMP Protocol Review Checklist. The Risk Assessment Lead or delegate will also identify which other study documents require their formal review within the checklist. These will normally be the main participant information sheet and consent form and participant identification card but may also include other documents.

7.9. The CI updates the protocol using tracked changes according to the comments in the STH CTIMP Protocol Review Checklist, detailing the revisions made in the checklist and re-submits the updated protocol and annotated checklist and other documents required as specified in the checklist to the Risk Assessment Lead or delegate.

7.10. The Risk Assessment Lead or delegate reviews the updated protocol and other requested documents and adds comments to the checklist to either confirm that the revision has resolved the identified issue or to request further revision.

7.11. If further revision is required steps 7.8-7.10 are repeated until all identified issues are resolved.

7.12. When the Risk Assessment Lead or delegate is satisfied that the protocol addresses the identified risks and that all outstanding identified issues are resolved and that the statistical review has been returned, the Risk Assessment Lead or delegate signs off the STH CTIMP Protocol Review Checklist as complete and circulates this signed off document and protocol to the CI and to the relevant STH Pharmacy Clinical Trials Manager

7.13. The STH Pharmacy Clinical Trials Manager reviews the relevant sections of the protocol to confirm that the arrangements detailed in the protocol which are relevant to the IMP management for the trial are compliant with the relevant regulations, are feasible and are in line with the discussions which the CI team has previously had with the Pharmacy Clinical Trials Manager and with any costing which the Pharmacy Clinical Trials team may have already provided.

7.13.1. The STH Pharmacy Clinical Trials Manager confirms by email that the protocol is satisfactory as per the review outlined in 7.13 or requests revision as necessary.

7.14. The Risk Assessment Lead or delegate completes the STH CTIMP Sponsor Green Light Checklist to indicate the expected full set of study documents and requirements for Sponsor Green Light, liaising with the CI or delegate and CRIO Coordinator as necessary to confirm the expected full document set and the expected necessary agreements.

7.14.1. Potential formal agreements with collaborators from outside STH, may include but are 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 CRIO Coordinator and/or Risk Assessment Lead consult with appropriate members of STH CRIO (eg Research Manager) as necessary if it is unclear whether an agreement is required.

7.14.2. Where a technical agreement for IMP supply is required the CRIO Coordinator ensures that an appropriate member of STH CRIO (eg Research Manager, Risk Assessment Lead or QA Lead) and an appropriate individual(s) from STH Pharmacy review the agreement to agree the necessary content.

7.15. The CI or delegate submits the full set of documents required for HRA and MHRA applications to the CRIO Coordinator, including a draft of the IRAS Combined Review form.

7.16. The CRIO Coordinator reviews the draft IRAS Combined Review form and the document set against each other, against relevant guidelines and legislation and the STH CTIMP Sponsor Green Light Checklist. The CRIO Coordinator provides feedback to the CI or delegate as necessary to revise the documents until they are ready for submission.

7.17. The CRIO Coordinator confirms when the trial is ready for submission to the relevant study team member(s) and to the relevant CRIO IRAS signatory, circulating the updated STH CTIMP Sponsor Green Light Checklist to confirm the final document set. The relevant study team member submits the trial to the Combine Review system and the relevant CRIO IRAS signatory confirms the submission on behalf of the Sponsor in the Combined Review system.

7.18. The CRIO Coordinator files the updated version of the STH CTIMP Sponsor Green Light Checklist in Alf 5.5 and files submitted versions of the IRAS Combined Review forms in Alf 4.1.3.

7.19. The Risk Assessment Lead or CRIO coordinator or delegate drafts the STH CTIMP Risk Assessment for Risk Adapted Monitoring table to detail all the identified risks for the trial, the measures taken in the protocol and other study documents to limit these risks and the potential measures which could be taken in the monitoring plan to further limit the identified risks.

7.19.1. Where drafted by the CRIO coordinator, the Risk Assessment Lead or delegate reviews the drafted STH CTIMP Risk Assessment for Risk Adapted Monitoring table and updates as necessary to complete a final first draft

7.20. The Risk Assessment Lead or delegate circulates the completed STH CTIMP Risk Assessment for Risk Adapted Monitoring table to the CI, STH Pharmacy Clinical Trials Manager and STH CRIO QA Lead for review and comment.

7.20.1. The CI or delegate is required to confirm acceptance or otherwise of the content of the first draft of the STH CTIMP Risk Assessment for Risk Adapted Monitoring table.

7.20.2. Where the trial will involve independent committees (e.g. Trial Steering Committee and/or Data Monitoring Committee) the CI or delegate forwards the STH CTIMP Risk Assessment for Risk Adapted Monitoring table to the members of the committee for review or tables the document at the first meeting of the committee. The independent committee provides feedback on the STH CTIMP Risk Assessment for Risk Adapted Monitoring table before Sponsor Green Light for the study is issued.

7.20.3. The STH CTIMP Risk Assessment for Risk Adapted Monitoring table will be reviewed and finalised by the QA Lead or delegate before Sponsor Green Light for the trial is issued.

7.21. The CRIO Coordinator takes forward the negotiation and execution of the identified necessary agreements with third party institutions involved in the study. Agreements with all external institutions involved will generally be required. The CRIO Coordinator consults with appropriate member(s) of the CRIO team and/or Research Manager as necessary regarding the need for and content of agreements. The agreements must clearly describe the division of responsibilities between the Sponsor and the external institution.

7.22. The CRIO Coordinator reviews the arrangements for the trial database, laboratories and any other third-party vendor and refers the CI or delegate to the relevant CRIO Lead for further evaluation, as necessary.

7.23. The CRIO Coordinator requests a copy of the study Case Report Form (CRF) from the CI or delegate.

7.24. The CI or delegate drafts the CRF according to SOP C128 and submits the draft to the CRIO Coordinator for review.

7.25. The CRIO Coordinator and Risk Assessment Lead review the CRF according to SOP C128 and, when completed, record the CRF versions approved in the STH CTIMP Sponsor Green

Light Checklist. The CRIO Coordinator sends the CI or delegate the CI Team Management and Monitoring Arrangements form.

7.26. The CI or delegate drafts the study specific SOPs and/or study manuals as identified on the Sponsor Green Light checklist and submits these to the CRIO coordinator for review. The CRIO coordinator forwards these to the Risk Assessment Lead or delegate for review.
  7.26.1. The Risk Assessment Lead or delegate reviews the study specific SOPs and/or study manuals and either requests revisions as necessary or confirms Sponsor approval by email.

7.27. The CI or delegate drafts the study specific logs and forms as identified on the Sponsor Green Light Checklist and submits these to the CRIO coordinator for review. The CRIO coordinator forwards these to the Risk Assessment Lead or delegate for review.
  7.27.1. The Risk Assessment Lead or delegate reviews the study specific logs and forms and either requests revisions as necessary or confirms Sponsor approval by email

7.28. The CI or delegate completes the CI Team Management and Monitoring Arrangements form and returns it to the CRIO Coordinator.
  7.28.1. The CRIO Coordinator forwards the CI Team Management and Monitoring Arrangements form to the Risk Assessment Lead or Delegate for review.
  7.28.2. The Risk Assessment Lead or delegate reviews the CI Team Management and Monitoring Arrangements form and either requests revision or confirms to the CI or delegate the content is fit for purpose. The Risk Assessment lead or delegate copies the QA Lead or delegate into correspondence and discusses the proposed arrangements with the QA Lead or delegate as necessary
  7.28.3. When the Risk Assessment Lead confirms that the content of the CI Team Management and Monitoring Arrangements form is satisfactory, the CI signs the completed document and sends a signed copy to the CRIO Coordinator

7.29. The QA Lead or delegate reviews the CI Team Management and Monitoring Arrangements form and the STH CTIMP Risk Assessment for Risk Adapted Monitoring table for the trial in conjunction with the trial protocol and CRF. The QA Lead or delegate updates the STH CTIMP Risk Assessment for Risk Adapted Monitoring table to reflect any further risks or any changes to identified risks.

7.30. The QA Lead or delegate takes forward completion of the Sponsor Management and Monitoring Arrangements form, agreeing the content with the Risk Assessment Lead and/or CRIO Coordinator as necessary.

7.31. The CRIO Coordinator arranges sign-off for the Sponsor Management and Monitoring Arrangements form.

7.32. The QA Lead takes forward development of study specific monitoring tools as necessary

7.33. Steps 7.28-7.30 may be completed either before or after issue of Sponsor Green Light for the trial, provided they are completed before the first monitoring visit for the trial..

7.34. The CRIO Coordinator sends the PI the Responsibilities of Investigators form
  7.34.1. The PI signs and returns the Responsibilities of Investigators form.

7.35. The CRIO Coordinator checks GCP training of the CI, PI and other key research staff.

7.36. The CRIO Coordinator agrees a date for the Sponsor Site Initiation Visit (SIV) and sends out an Agenda.
  7.36.1. The CRIO Coordinator agrees the Agenda with the Risk Assessment Lead or delegate. The agenda will be based on the STH CRIO SIV Agenda template.

7.37. The CI team ensure that a draft TMF/ISF, compiled using the STH TMF/ISF Contents Page, is available for review at the SIV.

7.38. The CRIO Coordinator or Risk Assessment Lead or delegate leads the Sponsor SIV.

7.39. The CRIO Coordinator or Risk Assessment Lead or delegate writes a report of the Sponsor SIV identifying in the report all outstanding issues identified at the SIV and the steps required for their resolution. Any outstanding issues preventing Sponsor Green Light are highlighted.
  7.39.1. The CI or delegate responds to the report confirming the actions taken and supplying any necessary documentation.
  7.39.2. The CRIO Coordinator and Risk Assessment Lead work together as necessary to confirm whether the CI or delegate response is satisfactory, updating the STH CTIMP Sponsor Green Light Checklist accordingly.

7.40. The CRIO Coordinator or delegate drafts the Version Control Tracking Sheet from the document set on Alfresco, using the Sponsor Green Light Checklist as a guide and checking the final document set against REC, HRA and MHRA approval letters. The CRIO Coordinator takes forward necessary actions where any missing, incomplete or unreviewed documents

are identified. The CRIO Coordinator or delegate files the completed Sponsor Green Light Checklist in Alfresco 5.5

7.41. The CRIO Coordinator or delegate puts together a hard copy R&D file using the STH R&D Master File template.

7.42. The CRIO Coordinator drafts the Confirmation of Capability and Capacity (CCC) / Sponsor Green Light email and updates RMS as necessary ready for CCC.

7.43. A second member of the CRIO Coordinator team completes the STH CTIMP CRIO QA Review Checklist, fully reviewing the Version Control Tracking Sheet, the drafted CCC and key fields on RMS against the study documents in Alfresco. The reviewer confirms to the CRIO Coordinator that the drafts are correct or details any discrepancies to resolve these. The CRIO Coordinator files this completed Checklist and the confirmatory email in Alf 5.5 and makes a diary entry to confirm completion.

7.44. The CRIO Coordinator forwards the verified CCC/SGL email to the Research Manager requesting authorisation to open the trial. If the Research Manager is expected to be unavailable, a pre-authorised delegate (eg QA Lead) will be arranged.

7.45. The Research Manager or pre-authorised delegate confirms to the CRIO Coordinator that the trial is ready to open by email. The CRIO coordinator files the confirmatory email in Alfresco 5.5.

7.46. The CRIO Coordinator issues the CCC/SGL email to the CI team, copying in support services as necessary. The CRIO coordinator attaches the finalised Version Control Tracking Sheet, as a pdf copy of the ongoing working document to the email. This serves to show the documents approved at this stage.

7.47. The CRIO Coordinator updates RMS as necessary to change the study status to authorised and files the CCC/SGL email and finalised Version Control Tracking Sheet at Site level (section 00) in Alfresco and both at the front of the R&D file (working copy) and with the CCC/SGL email in section 5.1.

7.48. The CI team update the TMF/ISF with the CCC/SGL email and attachments and take forward opening the trial as appropriate.

8. Studies not using a CTRU/CRO for full project management. Process for Amendments.

Amendments will be reviewed and approved according to SOP C105. The processes set out here are in addition to the processes contained in SOP C105. The amendments process will apply to all amendments required for the trial including 'Sponsor Only' amendments as defined in the Definitions section of this SOP. Processes for Urgent Safety Measures are defined in SOP C117.

8.1. The CI or delegate prepares the amendment as per SOP C105.

8.2. The CRIO coordinator reviews the amendment to confirm the classification with the CI or delegate as per SOP C105 and then forwards the drafted amendment to the Risk Assessment Lead if the amendment consists of a substantial amendment to the protocol, a change to the IMP or handling of IMP, or is otherwise of concern to the CRIO Coordinator. If the amendment is a Sponsor Only amendment and consists of a major change to a CRF or a major change to processes in an SOP, the CRIO Coordinator will forward the suggested changes to the Risk Assessment Lead.

8.3. The Risk Assessment Lead or delegate and/or CRIO Coordinator assess the amendment to determine whether the documents are consistent with each other, whether the amendment has any implications for the risks and regulatory compliance of the trial and whether the amendment will require update to any other study documents (eg CRFs, SOPs).

8.3.1. The Risk Assessment Lead or delegate or CRIO Coordinator feeds back to the CI or delegate as appropriate on the above points, requesting revisions if required and noting any updates to further internal study documents expected as a result of the amendment prior to Sponsor Green Light being issued.

8.3.2. Significant amendments which result in material effect on the risk assessment for the trial may require further review (e.g. by the trial DMC or by further ISR). The Risk Assessment Lead or delegate will discuss any potential need for further review with the Research Manager and/or CI as necessary and take forward as appropriate. The STH CTIMP Risk Assessment for Risk Adapted Monitoring table for the study may also need updating as a result of the amendment. Monitoring tools may also need updating as a result of the amendment.

8.4. Where the amendment requires submission to regulatory bodies (i.e. it is not 'Sponsor Only'), once the amendment is agreed as ready for submission the CRIO Coordinator and/or CI team take forward sign off and submission of the amendment as per SOP C105.

8.4.1. The CRIO Coordinator will be responsible for making any required submission to MHRA.

8.4.2. The 'Sponsor pre-submission Approval of Amendment' email, generated by the CRIO Coordinator or delegate, along with the locked PDF of the Amendment Tool serves as documentation that the Sponsor agrees the content of the amendment submission.

8.5. The CRIO Coordinator takes forward local review of continued capability and capacity as necessary according to SOP C105.

8.6. The CI team draft updates to CRFs and other internal documents as identified in 8.3 and submits these to the CRIO Coordinator and Risk Assessment Lead as required.

8.7. The CRIO Coordinator and/or Risk Assessment Lead or delegate review updated documents to verify that these are consistent with the submitted amendment, requesting further amendment from the CI team if required.

8.8. When the necessary external approvals for the amendment are received and any local review required by SOP C105 is complete the CRIO Coordinator updates the Version Control Tracking Sheet and issues continued CCC and Sponsor Green Light for the amendment using the appropriate email template, attaching a pdf copy of the updated Version Control Tracking Sheet in addition to the relevant approvals.

8.9. Where the amendment is 'Sponsor Only', the amendment will involve a one-stage submission and approval process. For these amendments, the only columns completed in the Amendment section of the Version Control Tracking Sheet will be the 'CRIO Sponsor Approval' columns, the 'submission documents' will be 'NA'. The documents reviewed as part of the amendment will be entered onto Section B2 of the Version Control Tracking Sheet. The CRIO Coordinator will issue continued CCC and Sponsor Green Light for the amendment using the appropriate email template, attaching a pdf copy of the updated Version Control Tracking Sheet.

8.10. The CRIO Coordinator or delegate updates RMS and files the documents associated with the amendment on Alfresco and in the hard copy R&D file. The Version Control Tracking Sheet is filed in section 00 on alfresco, superseding the previous version. The CRIO Coordinator or delegate prints two copies of the Version Control Tracking Sheet, one of which is filed with the CCC/SGL email in section 5.2, the other being filed at the front of the R&D file, discarding the copy previously filed in this location.

8.11. The CI team files the documents associated with the amendment in the TMF/ISF, superseding previous versions of study documents as appropriate, and implements the amendment accordingly.

8.12. If appropriate the Risk Assessment Lead or QA Lead or delegate updates the STH CTIMP Risk Assessment for Risk Adapted Monitoring table, the 'Sponsor Management and Monitoring Arrangements' and/or the Sponsor monitoring tools as required to accommodate the amendment. This step may be completed and after issue of Sponsor Green Light for the amendment, provided that where update is required it is completed before the next monitoring visit for the trial is required.

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

9.1. The CI writes the study protocol in collaboration with the CTRU/CRO according to CTRU/CRO working practices, SOPs and templates. Following preliminary reviews within the CTRU/CRO the Project Manager forwards a draft to the CRIO Coordinator for review.

9.2. The CRIO Coordinator confirm whether ISR is required (SOP A109/B103) and follows SOP B103 if ISR is required.

9.3. When ISR is confirmed as complete the CRIO Coordinator forwards the protocol to the Risk Assessment Lead or delegate

9.4. The Risk Assessment Lead or delegate reviews the protocol against the HRA CTIMP protocol template and MHRA Risk Adapted Approaches document and returns comments on identified areas of risk, inconsistency or missing information to the Project Manager, copying in the CRIO Coordinator.

9.4.1. The Project Manager amends the protocol as necessary and returns it for further review by the Risk Assessment Lead or delegate.

9.5. When the protocol is confirmed as ready for submission the CRIO Coordinator reviews the associated study documents and draft IRAS Combined Review forms, returning comments and queries to the Project Manager as necessary until the documents and forms are ready for submission.

9.6. The CRIO Coordinator confirms when the trial is ready for submission to the relevant study team member(s) and to the relevant CRIO IRAS signatory. The relevant study team member submits the trial to the Combine Review system and the relevant CRIO IRAS signatory confirms the submission on behalf of the Sponsor in the Combined Review system. The CRIO Coordinator files the IRAS Combined Review forms in Alf 4.1.3.

9.7. The CRIO Coordinator completes the STH CTIMP Sponsor Green Light Checklist to indicate the expected full set of study documents and requirements for Sponsor Green Light, liaising with the CI or delegate as necessary to confirm the expected full document set and the expected necessary agreements

9.7.1. The Risk Assessment Lead or delegate reviews the drafted Sponsor Green Light checklist for completeness with regard to the expected set of documents based on their protocol review

9.8. The CRIO 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, consulting with relevant members of the CRIO team and/or the Research Manager as necessary to agree the necessary content.

9.9. The CRIO 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 CRIO Coordinator consults with relevant members of the CRIO team and/or the Research Manager 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.

9.9.1. The CRIO Coordinator works with the CTRU/CRO Project Manager to negotiate these agreements consulting with relevant members of the CRIO team and/or the Research Manager as necessary to agree the necessary content.

9.9.2. Where a technical agreement for IMP supply is required the CRIO Coordinator ensures that an appropriate member of STH CRIO (eg Research Manager, Risk Assessment Lead or QA Lead) and an appropriate individual(s) from STH Pharmacy review the agreement to agree the necessary content.

9.9.3. The CRIO Coordinator works with the CTRU/CRO Project Manager to execute these agreements.

9.10. The CRIO Coordinator works with the CTRU/CRO Project Manager to prepare a template agreement (mNCA preferred) for participating sites. The CRIO Coordinator and CTRU/CRO Project Manager work with the relevant member of the Research Finance team to prepare and agree the financial appendix. The CTRU/CRO Project Manager negotiates the agreement with participating sites. The CRIO Coordinator facilitates this process as required, including the collection of Sponsor signature. The CRIO Coordinator files copies of all signed agreements in Alfresco and the hard-copy R&D Master File.

9.11. The CTRU/CRO arranges for the study protocol to undergo risk assessment according to its own SOPs and forwards a copy to the CRIO Coordinator.

9.11.1. The CRIO Coordinator reviews the risk assessment with the Risk Assessment Lead to confirm whether the risk assessment is satisfactory. The CRIO Coordinator files a copy of the agreed risk assessment document in Alfresco and in the hard copy R&D file.

9.11.2. Where the CTRU/CRO does not have its own procedures for protocol risk assessment the CRIO Coordinator follows the STH process detailed above in Section 7.

9.12. The CTRU/CRO Project Manager sends draft study specific SOPs and manuals to the CRIO Coordinator. The CRIO Coordinator reviews the documents with the Risk Assessment Lead to confirm whether the documents are satisfactory, updating the Sponsor Green Light form when documents are agreed as final.

9.13. The CTRU/CRO Project Manager sends the trial Monitoring Plan to the CRIO Coordinator for review. The CRIO Coordinator checks the adequacy of the Monitoring Plan, consulting with the Risk Assessment Lead and/or QA Lead where necessary and updating the Sponsor Green Light form when the plan is agreed as final.

9.14. The CTRU/CRO Project Manager is responsible for site SIVs and for collecting all documentation required from sites to satisfy the CTRU/CRO's own site green light process. The CRIO Coordinator receives only a copy of the fully executed site agreement for filing in Alfresco and in the hard copy R&D file

9.15. The CRIO Coordinator or delegate puts together a hard copy R&D file using the STH R&D File template.
9.16. The CRIO Coordinator then proceeds according to section 10 or section 11 depending on whether Sponsor Green Light needs to be issued separately to local Confirmation of Capacity and Capability or not.

10. CTRU studies for which STH is required to give Sponsor Green Light only, or are providing Sponsor Green Light in advance of local Confirmation of Capacity and Capability

10.1 The CRIO Coordinator checks the Sponsor Green Light Checklist against Alfresco, adding in any additional study specific documents which have been identified as necessary following the initial draft. The CRIO Coordinator finalises the STH CTIMP Sponsor Green Light Checklist by entering either a final version and date of a document or signatory and date of a document in the final column. 'Not Applicable' must be entered where a document is not relevant to the study, there must be no blank spaces.
10.2 The CRIO Coordinator drafts the Sponsor Green Light email using the 'STH CTIMP SGL only email' template and updates RMS as necessary ready for SGL.
10.3 A second member of the CRIO team completes section 1.2, 2 and 3.1 of the STH CTIMP CRIO QA Review Checklist to review the STH CTIMP Sponsor Green Light Checklist, key fields on RMS and the drafted SGL email and against the study documents in Alfresco. The reviewer confirms to the CRIO Coordinator that the drafts are correct or details any discrepancies to resolve these. The CRIO Coordinator files this completed QA Checklist and the confirmatory email in Alf 5.5 and makes a diary entry to confirm completion.
10.4 The CRIO Coordinator forwards the verified SGL email to the Research Manager requesting authorisation to open the trial. If the Research Manager is expected to be unavailable, a pre-authorised delegate (eg QA Lead) will be arranged. The Research Manager or pre-authorised delegate confirms to the CRIO Coordinator that the trial is ready to open by email. The CRIO coordinator files the confirmatory email in Alfresco 5.5.
10.5 The CRIO Coordinator issues the SGL email to the CI team, copying in support services as necessary. The CRIO coordinator attaches the finalised STH CTIMP Sponsor Green Light Checklist, as a pdf copy to the email, this serves to show the documents approved.
10.6 The CRIO Coordinator files the SGL email and finalised STH CTIMP Sponsor Green Light Checklist in Alfresco 5.1 and in the R&D file
10.7 If STH are not a site for the trial, the CRIO Coordinator updates RMS as necessary to change the study status to 'Governance Exempt – active'
10.8 If STH are a site for the trial, and the study requires subsequent CCC for STH, the 'Template CCC email – STH Sponsor CTIMP' must be used once appropriate. The CRIO Coordinator drafts the Confirmation of Capability and Capacity (CCC) email using the 'STH CTIMP CCC email' template and updates RMS as necessary ready for CCC.
10.9 A second member of the CRIO team updates the STH CTIMP CRIO QA Review Checklist, completing section 3.2, to review the drafted CCC email and confirms to the CRIO Coordinator that the draft is correct or details any discrepancies to resolve these. The CRIO Coordinator files this updated QA Checklist and the confirmatory email in Alf 5.5 and makes a diary entry to confirm completion.
10.10 The CRIO Coordinator updates RMS as necessary, changing the study status to 'Governance Exempt, Active' if STH is not expected to become a site, and files the SGL email in Alfresco 5.1 and in the R&D file.

11. CTRU studies for which STH is required to give Sponsor Green Light at the same time as local Confirmation of Capacity and Capability

11.1 The CRIO Coordinator finalises the STH CTIMP Sponsor Green Light Checklist by entering a final version and date of a document or signatory and date of a document in the final column. 'Not Applicable' must be entered where a document is not relevant to the study, there must be no blank spaces.
11.2 The CRIO Coordinator drafts the Confirmation of Capability and Capacity (CCC) email using the 'STH CTIMP CCC email' template and updates RMS as necessary ready for CCC/SGL.
11.3 A second member of the CRIO team completes section 1.2, 2 and 3.2 of the STH CTIMP CRIO QA Review Checklist to review the STH CTIMP Sponsor Green Light Checklist, the key fields on RMS and the drafted CCC email and against the study documents in Alfresco. The reviewer confirms to the CRIO Coordinator that the drafts are correct or details any

discrepancies to resolve these. The CRIO Coordinator files this completed QA Checklist and the confirmatory email in Alf 5.5 and makes a diary entry to confirm completion.

11.4 The CRIO Coordinator forwards the verified CCC email to the Research Manager requesting authorisation to open the trial. If the Research Manager is expected to be unavailable, a pre-authorised delegate (eg QA Lead) will be arranged.

11.5 The Research Manager or pre-authorised delegate confirms to the CRIO Coordinator that the trial is ready to open by email. The CRIO coordinator files the confirmatory email in Alfresco 5.5.

11.6 The CRIO Coordinator issues the CCC/SGL email to the CI team, copying in support services as necessary. The CRIO coordinator attaches the finalised STH CTIMP Sponsor Green Light Checklist, as a pdf copy to the email, this serves to show the documents approved.

11.7 The CRIO Coordinator updates RMS as necessary to change the study status to 'Authorised' and files the CCC/SGL email and finalised STH CTIMP Sponsor Green Light Checklist in Alfresco 5.1 and in the R&D file.

12. Studies using a CTRU/CRO for full project management. Process for Amendments.

12.1. Amendments will be reviewed and approved according to SOP C105. The processes set out here are in addition to the processes contained in SOP C105. Processes for Urgent Safety Measures are defined in SOP C117.

12.2. The CTRU/CRO Project Manager prepares the amendment as per SOP C105.

12.3. The CRIO coordinator reviews the amendment to confirm the classification with the CI or delegate as per SOP C105.

12.4. If the amendment consists of a substantial amendment to the protocol, a change to the IMP or handling of IMP, or is otherwise of concern to the CRIO Coordinator and the CRIO Coordinator forwards the drafted amendment to the Risk Assessment Lead for review.

12.5. The Risk Assessment Lead or delegate and/or CRIO Coordinator assess the amendment to determine whether the amendment documents are consistent with each other and whether the amendment has any implications for the risks and regulatory compliance of the trial.

12.6. The Risk Assessment Lead or delegate or CRIO Coordinator feeds back to the CTRU/CRO Project Manager as appropriate on the above points, requesting revisions if required.

12.7. The CRIO Coordinator confirms when the amendment is ready for submission by locking the amendment tool and issuing Sponsor pre-approval according to SOP C105.

12.8. The CRIO Coordinator takes forward local review of continued capability and capacity as necessary according to SOP C105

12.9. When the necessary external approvals for the amendment are received and any local review required by SOP C105 is complete the CRIO Coordinator issues continued CCC and Sponsor Green Light for the amendment using the appropriate email template.

12.10. The CRIO Coordinator or delegate updates RMS and files the documents associated with the amendment on Alfresco and in the hard copy R&D file

Appendix 1
STH Related Documents

	Document	CRIO Network Location	Website	Database	Created by
National Documents					
	MHRA Risk Adapted Approaches document				
	MHRA algorithm				
	HRA CTIMP protocol template				
Local Documents					
	STH CTIMP Pre-application considerations for cost and support	S:\General\Research Governance\Monitoring documents\STH Sponsored CTIMPS\Risk assessment	No	No	EW/AC
	Statistical Review Checklist	S:\General\Research Governance\Monitoring	No	No	EW

		documents\STH Sponsored CTIMPS\Risk assessment			
	STH CTIMP Protocol Review Checklist	S:\General\Research Governance\Monitoring documents\STH Sponsored CTIMPS\Risk assessment	No	No	EW
	STH CTIMP Risk Assessment for Risk Adapted Monitoring	S:\General\Research Governance\Monitoring documents\STH Sponsored CTIMPS\Risk assessment	No	No	EW
	STH CTIMP Sponsor Green Light Checklist	S:\General\Research Governance\Monitoring documents\STH Sponsored CTIMPS\Risk assessment	No	No	EW
	STH CTIMP CRIO QA Review Checklist	S:\General\Research Governance\Monitoring documents\STH Sponsored CTIMPS\Monitoring and QA	No	No	AC
	STH CTIMP CRF Review Checklist	S:\General\Research Governance\Monitoring documents\STH Sponsored CTIMPS\Risk assessment	No	No	EW
	CI Team Management and Monitoring Arrangements	S:\General\Research Governance\Monitoring documents\STH Sponsored CTIMPS\Monitoring and QA	No	No	EW
	Sponsor Management and Monitoring Arrangements	S:\General\Research Governance\Monitoring documents\STH Sponsored CTIMPS\Monitoring and QA	No	No	AC
	STH CRIO SIV Agenda template	S:\General\Research Governance\Monitoring documents\STH Sponsored CTIMPS\Site Initiation and Training	No	No	EW
	STH ISF/TMF Contents Page template	S:\General\Research Governance\Project Authorisation\Templates\Site file index	Yes	No	AC
	STH R&D Master File Contents Page template	S:\General\Research Governance\Project Authorisation\Templates\Site file index	No	No	AC
	STH CTIMP Version Control Tracking Sheet	S:\General\Research Governance\Monitoring documents\STH Sponsored CTIMPS\Monitoring and QA	No	No	AC
	STH Responsibilities of Investigator's Declaration	S:\General\Research Governance\Monitoring documents\STH Sponsored CTIMPS\Risk Assessment	Yes	No	BZ
	STH CTIMP SGL only email template	S:\General\Research Governance\Monitoring documents\STH Sponsored CTIMPS\Risk assessment	No	No	AC
	STH CTIMP CCC email template	S:\General\Research Governance\Monitoring documents\STH Sponsored CTIMPS\Risk assessment	No	No	AC

	STH CTIMP amendment email template	S:\General\Research Governance\Monitoring documents\STH Sponsored CTIMPS\Risk assessment	No	No	AC

Appendix 2 SOP revisions and history

SOP number	Effective date	Reason for change	Author
THIS SOP			
C118 V2.0	01 Dec 2022	Revision of risk assessment process to reflect the addition of the STH CTIMP Risk Assessment for Risk Adapted Monitoring table and study specific monitoring plan. Revision of the review process for risk assessments Addition of Sponsor Green Light processes Addition of processes for risk assessment and Sponsor Green Light for amendments Addition of processes for risk assessment of grant applications Revision of review processes for CTIMPs led by CTRU/CROs	EW/AC
PREVIOUS SOPs			
C118 V1.1	12 Dec 2013		EW