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MRC Clinical Trials Unit

Smarter studies
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UCL

RISK ASSESSMENT SOP

VERSION 4.0

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All appropriate approvals must have been completed prior to uploading to SOPbox.

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RISK ASSESSMENT SOP

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The following symbols may be used in this SOP:

Indicates a link to a related document

Indicates instructions to document trial-specific processes elsewhere

Throughout this document the MRC Clinical Trials Unit at UCL, will either be referred to as ‘MRC CTU or ‘the unit’. In instances where neither read well in the sentence, ‘the CTU’ may be used.

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1 PURPOSE

The purpose of this SOP is to:

- Define the MRC CTU roles and responsibilities involved in preparing, presenting, reviewing and approving risk assessments for projects undertaken by MRC CTU, whoever the sponsor.
- Outline the procedures involved in completing and reviewing risk assessments for MRC CTU projects to ensure that all Sponsor national and/or international standards are met.
- Describe the elements of risk which the MRC CTU will evaluate for each project in order to determine appropriate quality management strategies based on risk-adapted approaches to project management.

Definition of risk: Any hazards or uncertainties integral to, or relevant to, a project which may put at risk the safety and rights of participants, the successful achievement of the project objectives or the reputation or resources of MRC CTU or UCL.

The aim of the risk assessment is to ensure that MRC CTU projects are conducted to the highest quality with controls which are relevant and proportionate to the risks identified. Therefore it is a requirement for all MRC CTU projects to complete a risk assessment.

This SOP should be used in association with other MRC CTU templates and working instructions. These include:

- Trial Summary and Review Form (initial or annual/additional)
- Risk Register
- Risk Assessment Form (**only to** be used by older on-going trials UNLESS they have been advised to move across to a Risk Register)
- Guidance for Completion of the Risk Assessment Documents
- Snapshot template
- Guide to creating a word version (snapshot) of the Risk register

It is expected that all trials will complete the relevant Trial Summary and Review Form template (either initial or annual version) for their submission to the Quality Management Advisory Group (QMAG) and the Research Governance Committee (RGC). All new trials following the release of version 3.0 of this SOP(released on 17-Jun-2020), should use the Risk Register for their risk assessment. Ongoing or existing trials will be advised by QMAG which Risk Assessment document should be used moving forward. The Risk Assessment Form and Risk Register will be referred to as the Risk Assessment documents throughout this SOP.

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2 RESPONSIBILITY AND ROLES

The following table lists the roles relevant to this SOP and a brief description of their responsibilities.

This SOP will be circulated to be Read and Understood to all appropriate roles identified in the training matrix.

ROLE	RESPONSIBILITIES
MRC CTU Scientific Strategy Group (SSG)	• Reviews all new projects, whether stand alone or part of an existing project prior to submission of a funding application. Although this review is primarily scientific and strategic, high level key risks are raised by the trial team at this stage on the Project proposal form. • May request formal review of the risk assessment by the Research Governance Committee.
Research Governance Committee (RGC)	• Reviews project risk assessments for clinical projects carried out by MRC CTU staff. RGC will review the initial Risk assessment before UCL sponsorship is agreed and submission for approvals made. Risk Assessment documents for all studies managed by the MRCCTU will be reviewed in full again before the study opens to recruitment and then s annually and at the time of any substantial change during the course of a project. • Approves the review form for each submission • Information on the selection and experience of RGC members is provided in the Quality Management Policy.
• Trial Management Team (TMT)	• Undertaking project risk assessments and f development of the related risk-based quality management documents in conjunction with relevant members of the TMG. • During the project development stage, the risk assessment process primarily involves the Programme Leader and/or Project Lead, Chief Investigator, Clinical Project Manager (CPM) Statistician and Trial Manager(s). Other expertise will be requested depending on the nature of the project. This may include statistics, Data Management Systems (DMS) and clinical sciences. • If and when they are appointed to the project, the Trial and Data Manager should be involved in the development of the risk assessment; other expertise may be requested by the Programme/Project Lead or CPM depending on the nature of the project. • Ongoing review and oversight of the Risk Assessment documents and procedures for annual submission to QMAG and RGC and as issue arise to ensure any significant changes are communicated to the RGC and QMAG. • Complete the relevant section in STOPOver.
Trial Management Group (TMG)	Advising TMT on likelihood impact and mitigation strategies of identified trial risks and associated input into the development of the relevant quality management documents

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Project lead or CPM)	• Submission and presentation of the study risk assessment to the RGC for their review and approval. • Clinical Project lead and/or trial statistician and CPM should present the initial Risk Assessment to RGC and any annual updates where there is a major impact on safety or delivery of the trial as planned.

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3 PROCEDURES

For each project, potential risks and the consequences of those risks, need to be assessed for risk i.e:

- Liklihood: How likely is it that the adverse consequences will occur and
- Impact: If the risks occur, what impact would they have on the participant, study and /or reputation of the MRC CTU, UCL and/or Sponsor.
- Detectability: how will the CTU detect whether the risk has happened

For most projects all risks will be documented in a single trial register. However in some cases, for example in complicated MAMs studies it may be approriate to prepare a separate risk register for each arm/comparison. This may help clarify which risks are related to which IMP /intervention and to be completed once the comparison/arm closes.

For each risk identified, all risk reduction strategies implemented should be listed.

While all projects will have elements of risk, the MRC CTU is experienced in the design and conduct of trials and studies and the SOPs and Policies in place are designed to manage the standard risks. The risk assessment should detail only those risks where their mitigation requires quality management procedures that are in addition to the normal controls described in MRC CTU SOPs and Policies. The impact, likelihood and detectability of all the potential risks identified should be categorised according to the relevant risk assessment template. The focus should be on those risks that have a greater than “low” impact.

Any risk reduction strategies proposed should be feasible, appropriate and proportionate. They should be reflected in the protocol (where possible) and quality management documents. The submitted Risk Assessment documents should have sufficient information on risk reduction strategies to enable the QMAG and RGC to assess their appropriateness.

QMAG should always review the Risk Assessment document prior to RGC however this is not required if the initial submission to RGC is to formally assign UCL sponsorship (please refer to section 3.2.1). When the quality management documents have been drafted, QMAG will review the risk assessment documents in conjunction with their review of the quality management documents to ensure that the project risks and risk reduction strategies are adequately addressed in the documents.

The completed Risk Assessment documents should be submitted to the QMAG via the QMAG Secretariat initially and once any comments have been addressed should be submitted to RGC via the RGC Secretariat. Each submission of the Risk Assessment documents to the RGC and QMAG should be in draft versions. and include the Trial Summary and Review Form (either initial or annual). This form should not be signed prior to submission. Signatures are obtained following RGC review by the RGC Secretariat from the author, reviewers, and a representative of the RGC.

The risk assessment documents (Risk assessment form and Risk Register) must not be signed. This is because these documents are dynamic living documents that should be continually updated throughout the course of the trial and as situations change. Risk assessment should be a regular item on TMT and TMG agendas. New risks, potential issues may be identified across the TMT and TMG for example concerns may arise from central, remote, or on-site monitoring and these should be added to the risk assessment documents with details of the implemented mitigation plans and notified to RGC as appropriate. Risk assessment is an ongoing process across a trial duration and formal unit review is performed only at specific timepoints of the trial lifestyle. The live document will show the

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progress of the trial and the evolution of the risks as the trial progresses, it **should not** be only updated prior to submission to QMAG or RGC.

See Risk Assessment documents templates on SOPbox

For more information, please refer to Quality Management Advisory Group (QMAG) Procedures SOP (MRC_CTU_SOP_065); Guidance Document for Risk assessment Documentation (MRC_CTU_WI_0452) and

3.1 ELEMENTS OF RISK TO BE CONSIDERED

Risks should be considered and identified within the following categories:

i. The safety and rights of participants
ii. Project design and reliability of results
iii Project management and governance
iii. Sponsor
iv. Other considerations (including COVID19 and other pandemic risks, economic and political instability concerns)

Any additional risks identified which do not fall within one of the first four categories should be addressed in the Other Considerations sections in the relevant template.

The topics to be considered within the categories listed above include but are not limited to the elements described below. They are for guidance only and do not have to be noted as a risk unless there is a project-specific risk that would not be controlled by MRC CTU standard procedures.

Further details on the assessment, categorisation and documentation of risks are provided in the Risk Assessment documents and Guidance Notes. Further guidance is also available from multiple sources including the MRC/DH/MHRA Joint Project on Risk-adapted Approaches to the Management of CTIMPs or medical devices; although particularly relevant to CTIMPs and medical devices being conducted in the UK, the guidance is also applicable to other clinical trials.

See Risk Assessment Documents and Guidance for Completion of the Risk Assessment Documents on SOPbox

3.1.1 THE SAFETY AND RIGHTS OF THE PARTICIPANTS

This includes:

- What are the risks to the participants from being in the study compared to their Standard of care?:
    - What is the nature of the intervention. Is the intervention invasive or non -invasive; an IMP or medicaldevice or other . If an IMP/medical device what is the assigned category assigned to the research type (A,B,C) ? is the safety profile of the IMP well known? What additional procedures, including pharmacovigilance procedures will be needed.
    - Are there invasive clinical procedures in the project?

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- How vulnerable are the patient/study group involved? e.g. children, elderly, prison populations, advanced stages of disease, patients with mental health problems, including the ability of potential study participants to give fully informed consent.
- Are there additional data protection and security measures to be implemented ? e.g. are directly identifable or particularly sensitive data items collected ? If so what security measures are in place for collection, storage and transfer of data?

For more information please refer to Management of Participant Personal Data SOP (MRC_CTU_SOP_058)

3.1.2 PROJECT DESIGN AND RELIABILITY OF RESULTS

- Are there aspects of the study design that may impact the reliability of results? e.g.:

the complexity or ambiguity of the eligibility criteria (for example could lead to the admission of ineligible participants), method of randomisation or other potential recruitment difficulties that may result in low recruitment numbers and have implications for the power of the study.

- Potential for error in applying the intervention for example in the blinding and use of placebos.
- Objectivity of the outcome measures.
- Potential use of the data for product licensing and the implications for trial monitoring.
- Implications of data collection methods, including choice/validation of database system and data entry methods (double, remote, EDC).
- Other competing trials, ongoing or in planning, whose results may impact the trial

3.1.3 PROJECT MANAGEMENT AND GOVERNANCE

This includes:

- Sponsorship arrangements, including requirements of the sponsor if not UCL.
- Project governance and oversight arrangements, e.g. the need for a Steering Committee and/or an Independent Data Monitoring Committee
- Any organisational complexities in any of the proposed study collaborations, for example complicated saftey reporting requirements where multiple partners and /or counbtries are involved.
- Extent of industry involvement and contractual arrangements.
- Project site selection e.g. site experience with respect to the interventions and procedures, and GCP responsibilities; MRC CTU experience in working with the site across the whole portfolio of MRC CTU studies.
- International sites and the coordination and oversight arrangements.
- Project logistics and systems, including: drug supply and management systems; source, quality standards and validation of the database and any IT systems; purchasing and ownership of trial-related equipment; Quality Assurance (QA) and Quality Control (QC)systems.
- Project Agreements and Financing, including source and level of funding for project conduct, financial, reputational and legal issues (e.g. intellectual property, indemnity, insurance, liability, breach, misconduct, fraud and bribery). Are there translational projects running as part of the main study? What are the plans when the main study finishes to oversee the sample management and custodianship of these projects

3.1.4 OTHER CONSIDERATIONS

The risk categories above are not exhaustive as the MRC CTU performs a wide range of research activities. Additional risks relevant to particular projects, which do not fit into the categories listed above should be assessed and documented under this category (Other Considerations). This will include any particular risks associated with the COVID19 pandemic but may included risks to other

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pandemics or local epidemics in particpating countries or political and/ or economic instabilities that may arise which may cause additional risks..

3.2 DEVELOPMENT PROCESS

There should be a high-level risk assessment of all clinical research projects included in the submission to SSG in the Project Proposal form.

For more information please refer to Project Initiation and Development SOP (MRC_CTU_SOP_036)

It is expected that a risk assessment will be undertaken as early as possible in the development of a project so that measures required to manage the risks, particularly those required in addition to the normal controls described in MRC CTU SOPs and Policies, can be built into the grant application and expanded on in the protocol and quality management documents. It is also expected that the risk assessment documentation will be reviewed regularly throughout the life of a project (at least annually), and whenever substantial changes in risks are identified.

This should be reviewed and further developed by the Trial team including the Project Lead and Clinical Project Manager and/or Trial Manager and statisican, clincial lead and DMS (where applicable) prior to submission of a funding application. At this stage it should be in sufficient detail to ensure that the funding application requests the necessary resources for the project to be conducted to MRC CTU standards.

3.2.1 UCL SPONSORED STUDIES

For proposed UCL sponsored studies, the RGC will review the first Risk Assessment document (for new studies started since 20-Jun-2020, the Risk Register) post grant award pre regulatory and/or ethical submission to formally assign sponsorship to UCL. This will be accepted with high level or major risks documented.

For more information please refer to Sponsorship of Studies conducted by MRC CTU at UCL SOP (MRC_CTU_SOP_081)

3.2.2 FOR ALL STUDIES MANAGED AT THE UNIT

The Risk Assesment document should be developed along side the protocol and take into consideration the type, complexity and setting of the trial. This must be submitted to QMAG, with the supporting quality management documents for review in time to allow full RGC approval before the first participant is enrolled (unless a UCL sponsored study see section 3.2.1). Details of submissions and approvals from RGC should be entered into the relevant section of STOPOver.

For more information please refer to Quality Management Advisory Group (QMAG) Procedures SOP (MRC_CTU_SOP_065)

For more information please refer to Completion of RGC section in STOPOver SOP (MRC_CTU_SOP_066)

3.3 RISK ASSESSMENT REVIEW

The risk assessment for each project is a dynamic living document and should be kept under constant review by the Trial team and continually updated with documentaion and correspondence saved in

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the TMF. At least annually, but more frequently if there is a change to the risk profile before the annual review date, completed Risk Assessment documentation should be submitted to the RGC following submission and feedback from QMAG. This review process will continue until the study is closed with the ethical and /or regulatory authorities.

See Risk Assessment Documents and Guidance for Completion of the Risk Assessment Documents on SOPbox

The date of annual review of the risk assessment will remain as a year after submission of the first full QMAG/RGC risk assessment review, submitted before the opening of the study. Where a risk assessment is updated and submitted due to a significant change of risk, or where there has been an agreed delay in submission, the annual review date will move to year after the submission date of the updated Risk Assessment documents. The QMAG secretariat will remind trial teams of their expected date of annual review with two months notice.

When reviewing the risk assessment, changes to risks already highlighted should be considered as well as any additional risks that have been identified since the last review. Significant changes may include safety issues as identified by the Independent Data Monitoring Committee, addition of a new arm or comparison, changes to SmPC/IB, safety alert or TMG, or changes to the protocol which impact on the safety, data management, operational or monitoring activities of the project.As a trial progresses and mitigation strategies mature, the liklihood and/or impact of a risk may change. Risks that are no longer relevant should be noted as closed on the Risk Register. If using the risk assessment form, closed risks should be marked as being no longer applicable on a tracked version and may be deleted from the clean new version of the risk assessment form.

Many projects undertaken within the unit have associated projects or sub-studies which may or may not require a separate risk assessment, depending on the extent of the differences between them and the main study. This decision as to whether to submit separate risk assessments or to incorportate the additional risks in the main risk assessment should be made by the TMT with advice from QMAG if required.

Further review is on an annual basis from the date of submission or at the point of substantial change to the protocol or risk of the trial.

Detail on how to complete the documentation and versioning can be found in Guidance for Completion of the Risk Assessment Documents on SOPbox

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4 RELATED DOCUMENTS

For further information on this topic, see also:

- Management of Participant Personal Data SOP (MRC_CTU_SOP_058)
- Project Initiation and Development SOP (MRC_CTU_SOP_036)
- Sponsorship of Studies conducted by MRC CTU at UCL SOP (MRC_CTU_SOP_081)
- Quality Management Advisory Group (QMAG) Procedures SOP (MRC_CTU_SOP_065)
- Quality Management Policy (MRC_CTU_POL_01)
- Document Management and Version control Policy (MRC_CTU_POL_04)
- Risk assessment Form Template
- Risk register template
- Trial Summary and Review Form Template (initial and annual)
- Guidance for Completion of the Risk Assessment Documents
- Guide to creating a word version (Snapshot) of the Risk Register
- Risk Register Snapshot template

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