STANDARD OPERATING PROCEDURE 18

Risk Assessment and Monitoring

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Revision Chronology:	Effective date:	Reason for change:
Version 2.0	13 July 2022	Biennial review. To update text to be relevant to remote monitoring; DPIA reference change. Addition of training resource. Review to reduce repetition and excess text.
Version 1.7	28 January 2020	Review to update in accordance with the revised approach to conducting risk assessments; to review and update in accordance with requirements following NHS Digital audit.
Version 1.6	25 July 2019	Review by QA Team to ensure activities are compliant with SOP. To ensure SOP reflects additional activities in place as a result of an expanded QA team. To ensure SOP reflects the updated addendum in ICH GCP E6(R2). Addition of co-monitoring section.
Version 1.5	25 July 2016	Minor text amends; change to review/approval process, escalation process added. Change to new format.
Version 1.4	9 December 2013	Addition of process for undertaking triggered on-site visits, plus addition of process to review and approve risk assessments and monitoring plans
Version 1.3	25 May 2012	Renamed as includes risk assessment information. RSS web link updated. Minor text amends in section 3. Templates added.
Version 1.2	29 January 2010	Biennial review: RSS web page link updated.
Version 1.1	31 January 2008	Biennial review Format change.
Version 1.0	March 2006	

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Risk Assessment and Monitoring

1. Purpose and Scope

To describe the process for undertaking a Risk Assessment (RA), and to produce a Monitoring Plan (MP) based on the determined levels of risk. It is applicable to all research studies sponsored by the University of Warwick and for externally sponsored studies where the risk assessment and monitoring has been delegated to Warwick Clinical Trials Unit (WCTU).

For WCTU studies, read in conjunction with G06 RAMP Guidance.

2. Definitions

Risk Assessment	A systematic process of organising information to support decisions made within a risk management process. It consists of the identification of hazards and the evaluation of the likelihood of harm caused by exposure to those hazards. The assessment should identify and document control measures to reduce the hazards/risks and reduce the likelihood of harm.
Monitoring	Quality control function to oversee the progress of a clinical trial, to verify that the rights and well-being of participants are protected; data are accurate, and to ensure it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

3. Background

Considerations for a study RA should include all aspects of the study from protocol design to study report and archiving. The MP should be based on the level of risk associated with the study.

N.B. Before University of Warwick agree to sponsor a study, the University's Sponsorship & Oversight Committee will review a separate sponsorship RA.

Monitoring activities for each study will vary and should be proportionate to the relative risks highlighted in the RA. The level of monitoring required will be based upon considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study. ICH GCP states that in general there is a need for on-site monitoring, however, central monitoring in conjunction with procedures such as investigators' training and meetings, and written guidance can assure appropriate conduct of the study. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

4. Procedure

4.1 Responsibilities

Sponsor	▪ Ensure RA is undertaken and documented. ▪ Liaise with research teams to allocate monitoring responsibilities*.
Chief Investigator (CI)	▪ Production and approval of study specific RA/MP. ▪ Periodic review of RA/MP. Ensure actions are completed and documented.
WCTU QA team	▪ Organise and lead initial RA/MP meeting

	▪ Support study team to develop RA/MP to ensure in place in a timely manner, and seek relevant approvals. ▪ Review final document. Oversight of RA/MPs via dashboard to ensure documents are being reviewed at regular intervals to maintain status as live and dynamic process.
Trial Manager/Study Co-ordinator	▪ Obtain approvals for RA/MP. ▪ Upload of initial, approved version of the RA/MP to Q-Pulse (WCTU studies only). ▪ Update RA/MP following changes to trial processes. ▪ Arrange meetings with relevant personnel to ensure periodic review of RA/MP, contributing to and documenting decisions.

*For WCTU managed studies, the responsibility for undertaking the RA/MP is delegated to WCTU.

4.2 When?

The RA/MP process should start during the study set-up phase. The RA is a live, dynamic document which should be approved prior to opening to recruitment, reviewed periodically and revised accordingly to ensure that the risk control measures and mitigation remain effective and consider emerging knowledge and experience. This may be on an annual basis, but high-risk or time-dependent items should be reviewed earlier if necessary, and a review should be considered in response to study amendments, non-compliances or significant changes to study resources. It is recommended that a review date and owner is allocated to each item on the RA to facilitate review meetings and to focus on areas to concentrate resource. If the RA is updated this would also prompt a review of the MP. Review and approval of the RA/MP should be documented.

4.3 How?

4.3.1 Generation, review and approval of risk assessments and monitoring plans

For non-WCTU managed studies, appropriately experienced staff should undertake and document the RA/MP and ensure it has been approved by the study lead. Consider involving a multi-disciplinary team in the development (e.g. statistician, clinician, QA, pharmacy/lab expert).

It can be beneficial at the protocol development stage to schedule a scoping meeting between a QA representative, the clinical team and the study management team to discuss the study pathway in preparation for the formal RA/MP meetings.

For WCTU managed studies, a meeting with a member of the QA team, senior project manager, trial manager/coordinator/statistician and any other relevant staff (e.g. health economist, pharmacist, radiologist) associated with the study should be arranged to work through the RA/MP template, discuss areas of risk/hazards and document the outcome of the discussion, including considerations to reduce any risks identified. Ideally, the Chief Investigator should be present at this initial meeting. Additional advice may be sought from relevant advisors outside of the meeting.

See *WCTU Risk Assessment and Monitoring Plan: Guidance* for further detail and use of the standard tool.

For WCTU managed studies, the initial RA/MP should detail names of all reviewers present during the meeting and uploaded to Q-Pulse for sign off by the reviewers and the Chief Investigator (CI) or delegate to approve. This should be filed in the study/trial master file and communicated with others involved in the trial to ensure that everyone is aware of the risks, expectations and mitigating actions. Subsequent amendments to RA/MP should be documented.

4.3.2 Risk Assessment

It should be decided which risks to reduce and which to accept, proportionate to the significance of the risk or the impact of the hazard occurring. Risk control and mitigation strategies may be incorporated into the study protocol, and into documents defining study roles, responsibilities and training requirements.

The likelihood of a risk occurring is often not known until the study commences. Emerging knowledge and experience may increase or decrease the level of risk and will inform monitoring activities accordingly. Priority should be given to any items that would impact the safety of participants, the integrity of the data, or the efficient conduct of the study. Allocating a review date to individual risk items (rather than a single over-arching review date for the study), enables a proportionate approach to be taken, with resource and mitigation activities focused appropriately.

4.3.3 Monitoring Plan

The MP should take a systematic, prioritised, risk-based approach, based on the study design to inform the methods used for each study.

The monitoring procedures for each study should be documented and retained in the Study/Trial Master File (S/TMF), to include:

- The extent, nature and frequency of monitoring activities to be employed
- The responsibilities of those involved
- The procedures for creating monitoring reports and escalation strategies

The MP should be generated and reviewed by staff with an appropriate level of knowledge about the study. Consideration should be made to include review of critical data items and aspects of the study outside of standard processes.

Quality tolerance limits should be established to identify systematic issues that can impact participant safety or reliability of trial results. Deviations from these limits should trigger an evaluation to determine if further action is needed.

For WCTU managed studies, the monitoring activities should be approved by the CI, a member of the QA team and those involved in the process via Q-Pulse.

For Clinical Trials of Investigational Medicinal Products (CTIMPS), the protocol should include details of the monitoring processes to be undertaken.

4.3.4 Types of monitoring

Various approaches may be used e.g. trial oversight committees, central monitoring, remote monitoring, on-site monitoring, triggered on-site monitoring and site self-monitoring checks. The MP should demonstrate the monitoring strategy adopted for the trial.

Central Monitoring
Performed away from the investigator research site, usually at the CTU/Sponsor's office. It involves an evaluation of accumulating data, performed in a timely manner. These data are examined by qualified and trained persons such as the data entry clerk, study manager/co-ordinator or statistician, to identify anomalies, outliers or deviations and inconsistencies. All activities should be clearly defined and documented upon completion, with evidence of any findings and escalation.

On-site Monitoring
Performed at researcher sites where the study is being conducted. It requires access to medical records and other source documents of study participants for the purpose of source data review (SDR) - to ensure compliance with the protocol and GCP, and source data verification (SDV) - to

confirm the accuracy of data transcription and to verify the existence of participants. On-site visits may be routine or triggered.

Remote Monitoring
Follows the same principles as on-site monitoring but performed at a location away from the Investigator site. This may be in the form of a telephone or MS Teams video call with the site, via a self-monitoring checklist or through requesting copies of trial documents/redacted source data. This may also include direct access to electronic healthcare records, if appropriate security measures are in place. This may be the initial approach for a routine or a triggered monitoring visit and has the potential to be escalated to an on-site visit if required.

4.3.5 Responsibilities and training of monitoring staff

Monitoring procedures should make clear the responsibilities of the staff involved, the arrangements for central monitoring, the frequency of site visits and how the results of monitoring inform other activities (e.g. training of personnel at study sites, updating central processes, feedback to the RA/MP).

Successful trial monitoring requires appropriate and relevant scientific and/or clinical knowledge, and appropriate training. On the job training, SOP training and study specific training should be provided and documented.

Free to access monitoring-specific training resources are available from the UKCRC Registered Clinical Trial Units Network. Four recorded modules can be accessed at any time and are accompanied by a complementary handbook UKCRC Monitoring Resources

For remote and on-site visits, the monitor should have a pre-determined remit for the visit, agreed with the trial team. Communication between the team and the monitor prior to the visit is essential to ensure the available information is provided and the visit can be conducted effectively. For WCTU managed studies, read-only access to the trial database for the monitor can assist with the process and resolution of findings.

Sites should have clear expectations of the process, usually communicated at the site initiation visit. Guidance may be given to sites to facilitate documentation in source data. This is irrespective of whether there is planned SDV during on-site monitoring visits. Template documents to assist with this (Source Data Guidance; Source Data Location log) are available. See Available Templates/Associated Documents at the end of the text.

Not all data items must be supported by a source document or checked. Where there are original documents, the study data should be consistent with the information they contain. Where the Case Report Form (CRF) is the source document (e.g. information collected directly from the participant and not recorded elsewhere) then the training of the persons collecting and recording those data and having clearly documented procedures in place are crucial.

4.3.6 Monitoring Report

All monitoring activity should be recorded and made available to the sponsor (and appropriate staff responsible for the study and its oversight) in a timely manner for review and follow up. For University of Warwick sponsored studies, reports should be sent to sponsorship@warwick.ac.uk

On-site visit reports would typically include the author, date, site, name of the monitor, and name of the investigator(s) or other individuals present, as well as a summary of what was reviewed.

The monitor should record significant findings, conclusions and any recommended actions (including timelines stipulated for response, and person responsible for each action).

For WCTU managed studies, reports to be sent to sites should be reviewed and approved by a QA Manager prior to sending. This is completed via Q-Pulse where possible.

A Monitoring Visit Checklist/Report template and a visit report letter template are available via the WCTU web pages. Study specific versions should be in place, developed by the study team and monitor.

4.3.7 Dealing with issues raised by monitors

It should be clear by whom monitoring reports have been written, and who is involved in the review process.

Any required actions detailed in the monitoring report should be dealt with in a timely manner by the member of staff identified in the report, within specified timelines. The PI will maintain oversight of these actions until completion for each action.

If the required actions are not completed in an acceptable timeframe, the study team will contact the person to whom the report was addressed to flag non-responses. This escalation should then be followed up until all concerned are satisfied that the required actions have been completed. For WCTU managed studies, the QA Team can support these escalation strategies with support from the Governance Committee. If no satisfactory response is received and the site remains unresponsive, the issue should be discussed with the Chief Investigator to agree the subsequent actions. This may include the CI discussing the issue with the site's PI. Consideration should be given to closing the site to recruitment, if it is considered a risk to the study for the site to remain recruiting. In such instances, this should be discussed with the TMG and the sponsor to agree a plan and implement any actions within agreed timeframes. Any required escalation guidance should be detailed in the MP.

If there is a non-compliance raised during a site monitoring visit, follow the procedures outlined in SOP 31 'Deviations, Violations, Misconduct and Serious Breaches of GCP and/or Protocol'.

4.3.8 Triggered on-site/remote monitoring visits

Where information comes to light regarding allegations or suspicions of non-compliance, or where issues have been raised from central monitoring activities, a monitoring visit may be instigated. Examples of this include sites with data anomalies or a higher frequency of errors, protocol violations or withdrawals relative to other sites, persistently late reporting of SAEs.

The procedure will follow that of routine monitoring visits, but with a particular focus on the activity or issue causing concern. The relevant site must be notified of the visit with sufficient notice to enable the site to have relevant personnel and documentation present. If the site refuses to host a visit or do not respond to the request, this should be discussed with the CI and sponsor to agree an action plan.

A report should be written and distributed, and responses required as per routine visits. If an issue persists or an unsatisfactory response to the report is received, this may constitute a serious breach. For more information on serious breaches see SOP 31 'Deviations, Violations, Misconduct and Serious Breaches of GCP and/or Trial Protocol'.

4.3.9 Joint monitoring visit to study site

Visits involving more than one member of study staff may be undertaken, for example:

- When a site has a large number of participants, and the monitoring plan requirements can be more efficiently achieved with an additional staff member.
- To add expertise (e.g. statistician, pharmacy advisor, trial manager) where necessary to advise on specific issues.

- To provide support where challenging issues are anticipated.
- To provide training to a staff member who will be undertaking onsite monitoring as part of their role.
- To assist with continuing professional development of staff involved in the study.

NB Visits for staff training and development may be referred to as co-monitoring or accompanied monitoring. Documentation of these visits should be retained in the individual's personal development folders to show evidence of training.

For on-site visits, the site should be informed who will be attending, along with their role/job title to ensure there is sufficient space available. The remit of each staff member attending the visit should be clearly determined and communicated to the site team as appropriate.

List of Abbreviations

RA	Risk Assessment
CRF	Case Report Form
GCP	Good Clinical Practice
UK GDPR	UK General Data Protection Regulation
ICH	International Conference on Harmonisation
MP	Monitoring Plan
PI	Principal Investigator
QA	Quality Assurance
SAE	Serious Adverse Event
SDR	Source Data Review
SDV	Source Data Verification
SOP	Standard Operating Procedure
S/TMF	Study/Trial Master File
SMG	Study Management Group
TMG	Trial Management Group
WCTU	Warwick Clinical Trials Unit

Available templates/associated documents

T19	RA/MP Template [Available from QA Team on request]
T58	Trial Monitoring Checklist
T11	Lone worker RA
T12	Lone worker visit details
G16	Source Data
T25	Source Data location log