COMBINED RISK ASSESSMENT

DOCUMENT NO.:	**GS002 v6.0**
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1 INTRODUCTION

1.1 The Academic & Clinical Central Office for Research & Development (ACCORD) is a joint office comprising clinical research management staff from NHS Lothian (NHSL) and the University of Edinburgh (UoE).

1.2 ICH Q9 Quality Risk Management Guidelines define quality risk management as the systematic application of quality management policies, procedures and practices to the tasks of "assessing, controlling, communicating and reviewing risk".

2 PURPOSE

2.1 To describe the processes of risk assessment to be applied to each Clinical Trial of an Investigational Medicinal Product (CTIMP), Clinical Investigation of a Medical Device (CIMD) and other selected studies sponsored by NHSL and/or UoE as determined by the process described in Standard Operating Procedure (SOP) GS003 Sponsorship Approval.

3 SCOPE

3.1 This SOP applies to ACCORD Quality Assurance (QA) personnel, Clinical Trials Monitors, NHSL and UoE Sponsor Representatives (including Heads of Research Governance, Research Governance Manager, Clinical Research Facilitators and Research Governance Coordinators).

3.2 This SOP also applies to any members of the research team or support areas (e.g. Pharmacy) asked to contribute to the ACCORD risk assessment process.

4 RESPONSIBILITIES

4.1 The assigned Sponsor Reviewer, as defined by GS003 (Sponsorship Approval), is responsible for;

- Asking the QA Manager, or designee, to arrange a risk assessment meeting, when sufficient study information and documents are available,
- Attending the risk assessment meeting,
- Providing input into the draft Combined Risk Assessment report,
- Providing the Investigator, and support areas with feedback from the risk assessment meeting, and informing QA when actions are complete,
- Implementing and documenting Sponsor outcome strategies documented in the draft and final Risk Assessment report.

4.2 The QA Manager, or designee, is responsible for;

- Arranging and attending the risk assessment meeting,
- Drafting the Combined Risk Assessment report following the risk assessment meeting, with input from the Senior Clinical Trials Monitor(s), or designee, and Sponsor Reviewer,
- Finalising and circulating the Combined Risk Assessment report to those involved in the process,
- Following up on completion of outstanding management strategies,
- Implementing outcome strategies documented in the draft and final Risk Assessment report i.e. the audit plan (QA003 Risk Analysis Used to Develop Annual Audit Schedules),
- Assessing and performing a computer systems validation (CSV) review where appropriate.

4.3 The Senior Clinical Trials Monitor(s), or designee, is responsible for;

- Attending the risk assessment meeting,
- Providing input into the draft Combined Risk Assessment report,
- Implementing outcome strategies documented in the draft and final Risk Assessment report i.e. the monitoring plan (CM004 Developing a Monitoring and SDV Plan).

4.4 The Pharmacovigilance (PhV) Manager or designee, is responsible for;

- Attending the risk assessment meeting,
- Providing input into the draft Combined Risk Assessment report,
- Implementing PhV outcome strategies documented in the draft and final Risk Assessment report.

4.5 The Investigator team are responsible for agreeing a suitable date for risk assessment with the Sponsor Representative and for providing the draft study documentation at least two weeks prior to the scheduled risk assessment.

4.6 The Heads of Research Governance (NHSL and UoE), or designees, are responsible for attending the risk assessment meeting and providing input to the risk assessment process and report, as required.

4.7 Other meeting attendees (e.g. Sponsor representatives, representatives from experts in the field, including members of the research team, or appointed individuals from support areas, are responsible for providing input to the risk assessment process and report as required.

5 PROCEDURE

5.1 New Study

5.1.1 The decision for a study to undergo a combined risk assessment will be documented during the sponsorship review (GS003-F01 Sponsorship Checklist). All clinical research for which a Combined Risk Assessment is

deemed appropriate (e.g. CTIMPs, CIMDs, Performance Evaluations and other invasive, experimental, or complex research involving one or more research sites) will be collectively known as 'Facilitated Studies' (FA001 Facilitating a Regulated or Complex Research Project).

5.1.2 During the sponsorship review (GS003), or at the earliest opportunity the Sponsor Reviewer, or designee, will set a provisional date for the risk assessment with the Investigator team and ask the QA Manager, or designee, to arrange a risk assessment meeting as close to the provisional date as possible.

5.1.3 In order for the risk assessment meeting to take place, the following personnel must be in attendance; the assigned Sponsor Reviewer or designee, a representative from QA, Monitoring and Pharmacovigilance, and at least 1 representative from each of the Sponsor organisations (NHSL and UoE), and the Trial Manager where applicable.

5.1.4 Depending on involvement and the nature of the study, the Sponsor Reviewer will flag to the QA Manager, or designee, the appointed individuals from support areas and/or experts in the field involved e.g. representatives from the Clinical Research Facility (CRF), Pharmacy, Medical Physics, Qualified Person (QP).

5.1.5 The QA Manager, or designee, will invite the appropriate personnel to attend or contribute to the meeting (if available).

5.1.6 The QA Manager, or designee, will advise the Investigator of the meeting date/time. The Investigator will be invited to attend and/or contribute to the meeting (if available).

5.1.7 The Investigator team will provide the Sponsor Reviewer with the finalised draft study documentation at least two weeks prior to the scheduled risk assessment meeting.

5.1.8 The Sponsor Reviewer will review the finalised draft documentation and provide feedback to the Investigator team. The documents must be updated by the Investigator Team based on this feedback, prior to the document submission deadline.

5.1.9 The Sponsor Reviewer will confirm to the QA Manager that all essential documentation has been received, as per the Essential Document Checklist (GS002-WI01), and the draft documentation is appropriate for the risk assessment meeting to proceed as scheduled.

5.1.10 The essential documents required for the combined risk assessment meeting are detailed in GS002-WI01 (Essential Document Checklist).

5.1.11 If the 2 week deadline is not met, or the Sponsor Reviewer determines the documents are not at a sufficiently advanced stage suitable for risk assessment

review by the committee, then the risk assessment meeting will be rescheduled by the QA Manager, or designee.

5.1.12 The QA Manager, or designee, will circulate or advise on the location of draft study documentation in advance of the meeting e.g. protocol, Informed Consent form, Participant Information Sheet, Investigators Brochure/Summary of Product Characteristics (SPC) etc.

5.1.13 In advance of the meeting, the QA Manager, or designee, will circulate the risk assessment tool (GS002-T01) to the following representatives attending the meeting; Sponsor Reviewer, Monitoring, Pharmacovigilance, and R&D. Each representative will complete their assigned section as directed by the QA Manager, or designee.

5.1.14 The QA Manager, or designee, will collate comments from ACCORD personnel and provide a draft copy of the risk assessment tool (GS002-T01) to the CI, or designee (e.g. Trial Manager) at least two working days in advance of the risk assessment meeting.

5.2 Risk Assessment Meeting

5.2.1 The QA Manager, or designee, will chair the risk assessment meeting using the draft Combined Risk Assessment Tool/Report (GS002-T01) as a guide.

5.2.2 Risks will be discussed at the meeting , and the risk assessment team will determine if any additional mitigation is necessary to reduce the risk or discuss and agree how the risk will be managed. Following discussion , risks will by scored by the QA Manager (low, moderate, high) in relation to the likelihood of occurrence and impact of risk. The assessment of risk score will be reviewed by the risk assessment group following section 5.3.

5.2.3 Responsibilities for management strategies will be defined in the Combined Risk Assessment Report (GS002-T01).

5.2.4 When reviewing the experience of the Investigator and the clinical team, the following will be considered, and the associated risks, mitigation and necessary sponsor support documented;

- Does the Investigator have previous CTIMP/CIMD experience?
    - If not, consider the involvement of experienced research staff in the study team
- Has the trial protocol been subject to peer review e.g. by funder?
    - If not, consider independent review e.g. Clinical Pharmacologist
- Does the trial have the support of a Trial Manager, experienced Research Nurse and/or Clinical Trial Unit involvement?
    - If not, consider the assignment of appropriate support staff/facilities.

5.2.5 If the study is a CTIMP, the risk assessment attendees will agree on the study type during the meeting i.e. A, B or C (section 1 of GS002-T01).

5.2.6 Support departments (e.g. Pharmacy) and the Investigator or members of the research team will be invited to provide input into the risk assessment process. This can be during the meeting, if in attendance, or prior to the meeting at the request of the QA Manager, or designee.

5.3 Combined Risk Assessment Report

5.3.1 Following the meeting, the QA Manager, or designee, will finalise the Combined Risk Assessment report using GS002-T01. Based on discussion of risks at the meeting (e.g. likelihood of occurrence and impact of risk), the QA Manager, or designee, will score risks (e.g. low, moderate, high). In addition, the QA Manager, or designee, will include the QA strategy i.e. the preparation of a study audit plan based on the outcome of the risk assessment (QA003).

5.3.2 The QA Manager, or designee, will circulate the finalised Combined Risk Assessment to ACCORD personnel who attended the risk assessment meeting for input as required.

5.3.3 The Sponsor Reviewer, or designee, will follow up with the Investigator and the research team, if possible in person, regarding updates to study documentation required to further mitigate/manage identified risks.

5.3.4 If there have been any updates to documents e.g. change to protocol, the Sponsor Reviewer will consider impact on the Risk Assessment and seek input from appropriate individuals (e.g. Monitoring / Pharmacovigilance). Any update to documents impacting the risk assessment will be communicated to the QA Manager and documented in the Combined Risk Assessment report by the Sponsor Reviewer.

5.3.5 The Sponsor Reviewer will inform the QA Manager, or designee, when all Investigator actions have been addressed.

5.3.6 The Sponsor Reviewer will complete any Facilitation/Sponsorship strategies and risk adaption in the outcomes section of the Combined Risk Assessment report, with reference to GS002-T01 (Appendix 1), and return the report to the QA Manager, or designee.

5.3.7 The Senior Clinical Trials Monitor(s), or designee, will complete the monitoring strategies in the outcomes section of the Combined Risk Assessment report, with reference to the GS002-T01 (Appendix 2), and return the report to the QA Manager, or designee.

5.3.8 The Pharmacovigilance Manager, or designee, will complete any pharmacovigilance strategies in the outcomes section of the Combined Risk

Assessment report, with reference to the GS002-T01 (Appendix 2), and return the report to the QA Manager, or designee.

5.3.9 The QA Manager, or designee, will update the Combined Risk Assessment report with comments from the Investigator team, Pharmacovigilance Manager Senior Clinical Trials Monitor(s), Sponsor Reviewer and representatives of contributing areas if applicable, and retain the updated draft Combined Risk Assessment report in the ACCORD QA files and on the ACCORD SharePoint.

5.3.10 Finalisation of the Combined Risk Assessment report will usually occur at the point of submission to the competent authority and/or the Research Ethics Committee (REC).

5.3.11 The QA Manager, or designee, will finalise the Combined Risk Assessment report and circulate for signatures. The report will be signed by Sponsor Representatives (NHSL and UoE), representatives from the Pharmacovigilance, QA and Monitoring teams and representatives of contributing areas if applicable.

5.3.12 The completed/signed Combined Risk Assessment report will be stored at the ACCORD offices in the study Trial Master File (TMF) or Sponsor File. A electronic copy will be retained in ACCORD QA files and the appropriate study folder on the ACCORD SharePoint.

5.3.13 The QA Manager, or designee, will e-mail the completed/signed Combined Risk Assessment report to the Chief Investigator (CI)/Trial Manager and support departments (as considered appropriate).

5.3.14 The QA Manager, or designee, will add all outstanding management strategies to the Risk Assessment Status tracker on the ACCORD SharePoint. The QA Manager, or designee, will follow-up every 4 weeks (+/- 2 weeks) with the appropriate ACCORD personnel for confirmation of the completion of management strategies.

5.3.15 A new study, forwarded for Combined Risk Assessment, may not commence recruitment until the Combined Risk Assessment report has been completed and signed (see CM001 Site Initiation and Sponsor Authorisation).

5.4 Appraisal of Risk Assessment

5.4.1 The need to appraise the completed Combined Risk Assessment report may be raised by QA, the Monitoring team or Research Governance (NHSL or UoE).

5.4.2 The Combined Risk Assessment report should be appraised in response to significant changes to the study (e.g. certain substantial amendments) and significant developments (e.g. serious breach, changes to the Reference Safety Information (RSI), where appropriate).

5.4.3 The Sponsorship Reviewer will consider the impact of any changes on the risk assessment (following ACCORD SOP GS011 Sponsor Approval of Amendments) and prompt the QA Manager, or designee, to organise a combined re-risk assessment meeting if required following section 5.3. If a meeting is not considered necessary by the QA Manager, or designee, updates to the combined risk assessment can be communicated via e-mail to the same individuals who attended the initial risk assessment meeting.

5.4.4 The Senior Clinical Trials Monitor(s), or designee, will consider whether significant changes affect the monitoring strategies detailed in the risk assessment and update the Monitoring Plan accordingly.

5.4.5 The QA Manager, or designee, will also consider whether any significant changes affect the QA strategies in terms of audits.

5.4.6 If new risks are identified or if any of the existing risks or associated mitigation are altered as a result of the appraisal, the outcome strategies will be revised and the Combined Risk Assessment report revised following the procedures detailed in section 5.3.

5.4.7 A tracked changed version of the Combined Risk Assessment will be maintained and retained in the QA files on the ACCORD SharePoint. The QA Manager, or designee, will record changes to the Combined Risk Assessment report in the risk assessment appraisal history table (GS002-T01, Section 8).

5.4.8 The QA Manager, or designee, will mark the previous Combined Risk Assessment report as superseded, and the updated completed/signed Combined Risk Assessment report will be stored in the study TMF or Sponsor File and an electronic copy retained in the QA files and the appropriate study folder on the ACCORD SharePoint.

5.4.9 The QA Manager, or designee, will e-mail the updated completed/signed Combined Risk Assessment report to the CI/Trial Manager and support departments (as considered appropriate).

6 REFERENCES AND RELATED DOCUMENTS

- ICH Q9 Guidelines for Quality Risk Management
- MRC/DH/MHRA Joint Project: Risk-Adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products
- GS002-T01 Combined Risk Assessment Tool/Report
- GS002-WI01 Essential Document Checklist
- CM001 Site Initiation and Sponsor Authorisation
- CM004 Developing a Monitoring and SDV Plan
- QA002 Audit Preparation, Conduct and Reporting
- QA003 Risk Analysis Used to Develop Annual Audit Schedules

- QA003-T05 Audit Schedule Study Management
- QA009 Vendor Assessment
- GS011 Sponsor Approval of Amendments
- GS003-F01 Sponsorship Checklist
- FA001 Facilitating a Regulated or Complex Research Project).

7 DOCUMENT HISTORY

Version Number	Effective Date	Reason for Change
1.0 – 3.0	09 Nov 2012 – 18 Aug 2017	Reason for version change available from QA@accord.scot on request.
4.0	07 NOV 2019	Responsibility for Research Governance Manager added to process. Arrangement of risk assessment meeting updated at 5.1.1 and 5.1.5. Section 5.3.10 updated to state finalisation of risk assessment will occur prior to submission to competent authority/REC. Section 5.3.13 added detailing responsibility for QA to track completion of management strategies. Section 5.4.2 updated to allow risk assessment appraisal meetings to take place virtually across email, if appropriate. Section 5.4.6 added detailing that where possible a tracked changed version of the combined risk assessment will be retained. GS002-T01 section 8 added capturing a document history table.
5.0	16 FEB 2021	Further clarity provided at section 5.3.1 regarding what comprises the QA strategy. This includes reference to SOP QA002 and QA009. Minor updates made to GS002-T02
6.0	04 MAR 2024	Essential Document Checklist (GS002-WI01) created. Sections 5.1.8 - 5.1.10 of the SOP updated to outline process for document review and submission of required documentation to the Sponsor Reviewer. Sections 5.1.13 - 5.1.14 outline completion of the combined risk assessment tool/report by ACCORD representatives and collation of comments, prior to being circulated to the CI, or designee, in advance of the meeting date. Computer System Validation Checklist (GS002-T02) has been moved to new ACCORD SOP QA010 (Use of Computerised Systems in Research). GS002-T01 updated to v9.0. Minor administrative changes throughout.

8 APPROVALS

Sign	Date
AUTHOR: Lorn Mackenzie, QA Manager, NHS Lothian, ACCORD	Feb 15, 2024
Heather Charles Heather Charles (Feb 15, 2024 10:11 GMT) APPROVED: Heather Charles, Head of Research Governance, NHS Lothian, ACCORD	Feb 15, 2024
Gavin Robertson (Feb 15, 2024 12:07 GMT) AUTHORISED: Gavin Robertson, QA Coordinator, NHS Lothian, ACCORD	Feb 15, 2024

GS002 Combined Risk Assessment v6.0

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