UNIVERSITY OF SUSSEX

Standard Operating Procedures for Risk Assessment – CTIMPs

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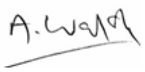
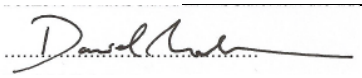
Author: Antony Walsh **Designation:** RES Research Governance Officer	*Signature* 	*Date* 26 May 2021
Authorised by: Dr Daniel Michelson **Designation:** SSC Chair		11 June 2021

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Acknowledgement , University of Keele

[1] http://www.sussex.ac.uk/staff/research/governance

1. Purpose & Scope

1.1 The EU Good Clinical Practice (GCP) Directive 2001/20/EC was introduced to establish standardisation of research activity in Clinical Trials throughout the European Union. It was transposed into UK law as the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) which came into force on 1st May 2004. The Medicines for Human Use (Clinical Trials) Regulations together with subsequent amendments will be referred to as the Regulations in the rest of this document[2].

1.2 This SOP describes the processes that are involved for risk assessment of a Clinical Trial of an Investigational or Medicinal Product (CTIMP) at an individual study or trial level.

1.3 The scope of the document is for all schools at the University of Sussex, all members of staff with substantive employment and students registered at the University (including Brighton and Sussex Medical School).

2. Introduction

2.1 Risk assessment is a systematic process of evaluating the potential hazards associated with a study / trial and assessing the likelihood of those hazards occurring and resulting in harm. All studies contain a level of risk inherent to the protocol that relate to safety and rights of the participants and the credibility of results.

2.2 Risk assessment is an ongoing process that must be continually assessed and managed at each stage of a study to ensure the safety, rights and wellbeing of participants and research staff and the integrity of data is considered for the successful completion of the study.

2.3 It is recommended that a full study-specific risk assessment is conducted for every study and that this is clearly documented, minimally evidenced through the study protocol, although ideally as a separate document in its own right (***RGRA1:*** is a suggested template for this) and stored in the Trial Study Master File.

2.4 During the Sponsorship review process, risk assessment is conducted and recorded in accordance with the processes outlined in ***SOPRG01a Sponsorship Approval – CTIMPs*****.**

2.5 The Chief Investigator (CI) is responsible for ensuring an in-depth assessment of the risks involved is completed prior to commencing recruitment in a study, and ensuring any measures put in place to mitigate identified risks are also documented.

2.6 The duty of documenting risk assessment is usually delegated to the Trial Manager; however, the CI is responsible for approving this document.

3. Responsibilities

Chief Investigator

3.1 The Chief Investigator has responsibility for:

- Content and approval of the completed risk assessment document.
- Review of the risk assessment document.
- The CI may delegate the development and review of the risk assessment document to appropriate members of their study team.

The Sponsor

3.2 The Sponsor has responsibility for undertaking a risk assessment to inform the decision to provide sponsorship to research and developing risk mitigation actions as appropriate.

4. Procedure

4.1 The regulatory framework in the UK provides a range of risk adapted approaches that simplify the processes involved in initiating and managing CTIMPs that meet certain risk criteria. The guidance from the MHRA (Medicines and Healthcare products Regulatory Agency) must be followed alongside any other relevant guidance or regulations.

4.2 The MHRA document *Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products* must be followed to categorise a trial based on the risk to participant safety in relation to the IMP (Investigational Medicinal Product), as follows:

- 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

4.3 Examples of types of clinical trials that are covered under these categories are described in more detail within the guidance document (*Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products*).

Development of Risk Assessment Document

4.4 Assessment of risk in CTIMPs should commence during grant development.

4.5 Following confirmation of award (where applicable), the study-specific risk assessment documentation) should be developed by the CI (or delegate) alongside the protocol. Identifying risks associated with a study at an early stage in study development will allow for any necessary modifications to be made to the study design in order to minimise associated risk.

4.6 Risk based decisions must also be made when developing study documents, procedures and working instructions. These decisions should also be captured within the risk assessment.

4.7 When mitigations are complete, this should be documented. In many cases, the risk identified can be managed via the design of the trial as captured in the protocol, training made available to the study/site teams, use of external service providers (e.g. randomisation) or via internal and on-site monitoring.

4.8 The CI must approve the final version of the initial risk assessment.

4.9 The risk assessment should guide the monitoring of the whole study process, with the oversight of the trial/study management group, trial steering committee and data monitoring committee. Based on the risk assessment, a trial specific monitoring plan should be developed .

Ongoing Risk Assessment Review

4.10 The study/trial risk assessment should be reviewed regularly by the CI / delegate to ensure the risk assessment document is still current and the implementation of mitigations have been conducted as necessary. This should include, but not be exclusive to, review as part of study management group meetings.

4.11 The risk assessment must be reviewed when any significant changes are made within the study/trial, for example:

- Substantial Amendment to the protocol or Patient Information Sheet/Informed Consent Form
- Change to organisation of the trial (e.g. governance, funding, personnel)
- An event which may impact participant safety or scientific integrity (e.g. a serious breach)
- Significant change to Summary of Product Characteristics/Investigator Brochure
- Change in risk identified during interim analysis by Trial oversight committees

4.12 The outcome of the review should be documented as evidence that it was assessed, even when no changes result.

5. Training

5.1 This is a 'read and understand' SOP. Please note that the Research Ethics and Integrity Team discourages the retention of hard copies of SOPs and can only guarantee that the most up-to-date version is on the University website.

6. Abbreviations

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational or Medicinal Product
CTU	Clinical Trials Unit
CV	Curriculum Vitae
DSC	Data Steering Committee
EU	European Union
EUDRACT	European Union Drug Regulating Authorities Clinical Trials Database
GCP	Good Clinical Practice

GMP	Good Manufacturing Practice
HRA	Health Research Authority
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational or Medicinal Product
ISF	Investigative Site File
ISO	International Standards Organisation
IVD	In Vitro Diagnostic
MHRA	Medicine and Healthcare Products Regulatory Agency
PI	Principal Investigator
PIS	Patient Information Sheet
PPI	Patient and Public Involvement
REC	Research Ethics Committee
REIGO	Research Ethics and Integrity Office
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions)
TSC	Trial Steering Committee
TMF	Trial Master File
TMG	Trial Management Group
US	University of Sussex

6. Cross Referenced SOPs

SOPRG01a	Sponsorship approval – CTIMPs
SOPRG03	Notifications of serious breach of GCP or trial protocol
SOPRG17	CTIMP Data Management
SOPRG21	Adverse Events in CTIMPs

7. References

Clinical Trials Regulations 2004 (SI 2004/1031)
http://www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf

MHRA (2011) Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Riskadapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicin al_products.pdf

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

ICH E3 – structure and content of clinical study reports (1993)
https://database.ich.org/sites/default/files/E3_Guideline.pdf

ICH E6 – Guideline for Good Clinical Practice (1996)
https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

Medicines and Healthcare products Regulatory Agency (MHRA) (2014, updated 2019
https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials

MHRA Good Clinical Practice Guide, The Stationery Office: London, 2012

Risk proportionate approaches in clinical trials, Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No. 536/2014 on clinical trials on medicinal products for human use, 25 April 2017

https://ec.europa.eu/health/sites/default/files/files/clinicaltrials/2016_06_pc_guidelines/gl_4_resp_contributor_6.pdf

Risk Assessment Tool

Study Title:	
Sponsor (if not US):	
Sponsor Reference Number:	
IRAS Reference:	
EudraCT Number:	☐ Not Available
REC Number:	☐ Not Available
Is the study commercially funded?	☐ Yes ☐ No

Research Category:	**Check box if unknown** ☐
☐ Clinical trial of an investigational medicinal product (CTIMP)	
☐ Clinical investigation or other study of a medical device (CMD)	
☐ Clinical trial involving both an investigational medicinal product (IMP) and a medical device	
☐ Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice	
☐ Basic science study involving procedures with human participants	
☐ Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology	
☐ Study involving qualitative methods only	
☐ Study limited to working with human tissue samples (or other human biological samples) and / or data	

☐ Study limited to working with data (specific project only)
☐ Research tissue bank
☐ Research database
☐ Other research *Provide details:*

Staff Present:
List the names of staff present during the risk assessment and feasibility discussion/meeting. If staff have been involved in earlier/separate discussions/meetings document this below

Study Summary:
Include a summary of relevance and importance of this research and how this research will benefit NUH and/or it's staff and patients

Section 1 - Risk Assessment of the Investigational Medical Product or Intervention

If this study does not involve an IMP check box ☐ and proceed to section 2

Where risks associated with the IMP/intervention are somewhat or markedly higher than those of standard medical care (i.e. Type B or Type C trials) details regarding specific risks to body systems and proposed methods for clinical monitoring of such risks should be described. The drug risk assessment should be based on available information (e.g. SmPC, Investigator Brochure, British National Formulary other publications)

Risks associated with IMP / intervention: ☐ Type A: risk *comparable* to that of standard medical care ☐ Type B: risk *somewhat higher* than that of standard medical care ☐ Type C: risk *markedly higher* than that of standard medical care	**Justification** *Please give reasons why Type A/B/C was applied for this study*

IMP/Intervention	**Body System** ***(i.e. System Organ Class)***	**Hazard**	**Risk Likelihood** L = Low M = Medium H = High	**Mitigation**	**Comments**
e.g. ABC123	*Metabolic*	*Hyperglycaemia*	*L*	*Blood glucose monitoring*	*X hourly*

Section 1 - Risk Assessment of the Investigational Medical Product or Intervention (continued)

Potential source of harm	**Risk Factor Identified** Provide details of study-specific considerations/risk concerns	**Risk Likelihood** L = Low M = Medium H = High	**Mitigation** Address all concerns identified	**FOR RGO USE ONLY** **Monitoring/audit methods**
Manufacture and distribution - IMP sourcing/manufacture/supply - Licence status, QP release - IMP ordering/delivery - Temp control for delivery				
Drug labelling - IMP packaging - IMP labelling - blinding				
Storage - pharmacy/ward - temperature controlled				
Drug accountability				
Application method - dose calculation/strength - duration/regimen of administration - dosing procedure - drug interactions - dosing follow up				
Pharmacovigilance -Dose limiting toxicity - AE/SUSAR reporting - urgent safety measures - out of hours cover - stopping criteria - data monitoring committee				
Other				

Section 2 - Risk Assessment of the Medical Device or In vitro Diagnostic (IVD)

If this study does not involve a medical device check box ☐ and proceed to section 3

Where risks associated with device are higher than normal (i.e. device used outside of CE marking, or device without CE marking) details regarding specific risks to body systems and proposed methods for clinical monitoring of such risks should be described. The device risk assessment should be based on available information (e.g. Investigator Brochure, Device Technical Specification)

Use of the medical device:	**Class of Device**	**Justification for classification**
☐ CE marked device used within its intended purpose(s) ☐ CE marked device which has been modified or will be used outside its intended purpose(s) ☐ Non-CE marked device ☐ In vitro Diagnostic (IVD)	☐ Class I or A (IVD) B ☐ Class IIa or VD) ☐ Class IIb or (IVD) ☐ Class III or D (IVD)	

Device	**Body System** ***(i.e. System Organ Class)***	**Hazard**	**Risk Likelihood** L = Low M= Medium H = High	**Mitigation**	**Comments**

Section 3 – Research Risk Assessment

Mark risk as "N/A" if not relevant for this study. List any other risks identified for this study in "Other" **A. Participants' Rights and Safety**

Potential source of harm	**Risk Factor Identified** Provide details of study-specific considerations/risk concerns	**Risk Likelihood** L = Low M = Medium H = High	**Mitigation** Address all concerns identified	**FOR RGO USE ONLY** **Monitoring/audit methods**
Participant population -healthy volunteer/patient -age/vulnerable group -rare disease/illness - non-adherence to study intervention				
Enrolment - eligibility criteria (restrictive inclusion/exclusion) - withdrawal - recruitment period - competitive recruitment - enrolment target justified				
Consent - verbal/written - emergency situation - proxy/legal representative/ professional legal representative				
Participant confidentiality - data access - collect personal identifiable data - collect sensitive information - data sharing/transfer outside UK/EU - information governance				
Study assessment methods - samples/tests/biopsies/procedures and sample storage - visit schedule vs. standard care				

Other - Phase I considerations - Emergency procedures				

B. Facilities, Equipment and Resources

Potential source of harm	**Risk Factor Identified** Provide details of study-specific considerations/risk concerns	**Risk Likelihood** L = Low M = Medium H = High	**Mitigation** Address all concerns identified	**FOR RGO USE ONLY** **Monitoring/audit methods**
Study staff experience - appropriate qualifications - research experience - ICH-GCP, ISO14155 trained - protocol training - sponsor SOP awareness - time allocation - back-up co-Investigator				
Partner organisations - additional sites, external service provider/third party - geography - language - international regulations				
Study management - CTU managed - Research team size and setup				
Resource availability - support departments/clinics/wards - (special) equipment - equipment servicing/maintenance				
Other				

C. Study Design and Reliability of Results

Potential source of harm	**Risk Factor Identified** Provide details of study-specific considerations/risk concerns	**Risk Likelihood** L = Low M = Medium H = High	**Mitigation** Address all concerns identified	**FOR RGO USE ONLY** **Monitoring/audit methods**
Data collection/management - source data - (e)CRF design and completion - database design and entry - quality control/verification checks - objective vs. subjective				
Study recruitment power - number feasible - participant withdrawal - loss to follow up				
Blinding and/or randomisation - blinded allocation - single/double blind - unblinding procedures				
Complexity of study design - intervention - treatment arms/groups - visit schedule and follow up - crossover, dose escalation/adjustment, MTD				
Other - PPI/E				

D. Documentation, Governance and Compliance

Potential source of harm	**Risk Factor Identified** Provide details of study-specific considerations/risk concerns	**Risk Likelihood** L = Low M = Medium H = High	**Mitigation** Address all concerns identified	**FOR RGO USE ONLY** **Monitoring/audit methods**

Trial master file maintenance				
Is a Vendor(s) licence/certification required? - GMP licence - ISO 9001/13485 - HTA licence				*Is a vendor questionnaire or audit is required?* *Confirm with the RGO HRC/QA manager.*
Insurance/indemnity arrangements				
Funding - Funding arrangments - Milestones				
Suitability of proposed trial steering committees (TSC, DMC, TMG)				
Other				
Reference Material:				
List any documentation used as a reference to complete this risk assessment				

[Chief Investigator] [Signature] [Date]

Risk Assessment Tool

Completed by:

[Sponsor Representative] [Signature] [Date]