Document Title: Risk-adapted Approach to the Management of Clinical Trials of Investigational Medicinal Products

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Summary of Amendments

Version:	Modification:
6.0	**FRM077 archived and reference in SOP replaced with CT004A Pharmacy IMP Risk Assessment**
5.0	**Minor administrative changes**
	Minor formatting and terminology updates throughout

Key related documents:	SOP034 Trust Approval and Research Governance SOP025 Assessment and Registration of Trust Risk Rating for Research Studies SOP072 Supply of CTIMPs Dispensing, Returns & Accountability SOP060 Version Control of Study Documents FRM024 CTIMP Risk Management Tool

	FRM028 Memorandum of understanding (MoU) for Clinical Trial Delegation of Sponsorship Responsibilities FRM040 Delegation of Sponsor Responsibilities CT004A Pharmacy IMP Risk Assessment CT015 Authorisation of IMP (Investigational Medicinal Product) storage areas outside of the Pharmacy Clinical Trials Department

Key Points of this Document

- For every Clinical Trial of an Investigational Medical Product (CTIMP) there are a core set of risks inherent to the protocol that relate to the safety of the participant and the integrity / reliability of the results. This SOP details the processes involved to identify these risks so that control measures, resources, procedures and processes can be implemented during the trial to ensure patient safety and lead to high quality results.
- The potential risks in regard to patient safety need to be balanced against the level of risk a trial participant would be exposed to outside the trial.
- This document sets out the procedures to be followed by all research staff who are involved in the assessment of the risk and preparation of a risk assessment document for Clinical Trials of an Investigational Medical Product (CTIMPs) managed by Royal Papworth Trials Unit Collaboration (PTUC) or sponsored by Royal Papworth Hospital NHS Foundation Trust.
- It provides guidance on the requirements for risk assessment.

1 Purpose and Content

a. This document defines the Trust's procedures for assessing the risk level of Clinical Trials of Investigational Medicinal Products managed by Papworth Trials Unit Collaboration (PTUC) or sponsored by Royal Papworth Hospital; preparation of a pragmatic risk assessment document; identifying what adaptations are required for the Trial; and the submission process to the MHRA.

b. The document details the requirements for pragmatic risk assessment for Clinical Trials to aid compliance with the regulatory framework and Good Clinical Practice

c. The regulatory framework in the UK provides for a simple risk categorisation based on the marketing status of the drug and standard medical care. This SOP details a range of risk-

adapted approaches that are possible to simplify the processes involved in initiating and managing a clinical trial that is low risk.

d. Further information on this approach can be found in the MRC/DH/MHRA paper 'Risk adapted approaches to the management of clinical trials of investigational medicinal products': https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf

e. The risk assessment for Research Governance is outside the scope of this SOP and is described in R&D SOP034 Trust Approval and Research Governance and R&D SOP025 Assessment and Registration of Trust Risk Rating for Research Studies.

2 Roles & Responsibilities

a. This Policy applies to all personnel that are conducting research at the Trust.

b. The trial Sponsor is responsible for the management of a clinical trial including the evaluation of the risks although they may delegate some of the actual tasks to a competent member of the study team. This delegation should be on the Sponsor / Chief Investigator delegation log/Memorandum of Understanding (refer to FRM028 and FRM040).

3 Policy

a. This SOP is mandatory and, as per the Trust's Information Governance and Records Management framework, non-compliance with may result in disciplinary procedures.

4 Procedure

4.1 Assessment of risks in Clinical Trials

a. Risk in a Clinical Trial can be defined as the likelihood of a potential hazard occurring and causing harm to the trial participant and / or an organisation, or detrimentally affecting the reliability of the trial results.

b. Risk assessment is the process of identifying the potential hazards associated with the trial and assessing the likelihood of the hazards occurring and resulting in harm.

c. The risk assessment must be customised to each individual Clinical Trial.

d. The potential risks should be balanced against the level of risk that a trial participant would be exposed to outside the trial as follows in Table A:

Table A

Trial categories	Examples
Type A No higher than the risk of standard medical care	Examples: Trials involving Investigational Medicinal Products (IMPs) authorised in any EU Member State if: They relate to the authorised range of indications, dosage and form, or They involve off-label use if this off-label use is established practice (such as in paediatrics, oncology etc) and supported by sufficient published evidence and / or guidelines
Type B Somewhat higher than the risk of standard medical care	Examples: Trials involving IMPs authorised in any EU Member State if: Such products are used for a new indication (different patient population / disease group), or Substantial dosage modifications are made from the licensed indication, or If they are used in combinations for which

	interactions are suspected Trials involving medicinal products not authorised in any EU Member State if the active substance is part of a licensed medicinal product authorised in the EU. (A grading of Type A may be justified if there is extensive clinical experience with the product and no reason to suspect a different safety profile in the trial population[a].)
Type C Markedly higher than the risk of standard medical care	Examples: Trials involving IMPs not authorised in any EU Member State: (A grading of other than Type C may be justified if there are extensive class data or non-clinical and clinical evidence[a].)

[a] *If a grading other than those indicated is felt to be justified, the rationale and evidence should be presented in the application to the MHRA (CTA).*

4.1.1 Risk Assessment Process

a. The risk assessment process should be undertaken by a multi-disciplinary team able to consider all the various aspects of the trial. This should include as a minimum: Chief Investigator (or delegated Medical Colleague); Pharmacist and the Clinical Project Manager. Other personnel such as specialist clinical departments, a Statistician, Data Managers, and Research Nurses may be required depending on the complexity of the study. Pharmacy also completes a local risk assessment for each CTIMP (see Imp Risk Assessment Form CT004A and also refer to SOP072 and CT015).

b. The management of a Clinical Trial should be based on the risk adapted approach carried out above. The risk assessment should identify any potential risks in the trial that need to be mitigated by monitoring and management activities. The risk assessment process must be initiated prior to the finalisation of the protocol as the risk assessment and mitigation may influence the trial design and trial procedures.

c. The nature and extent of possible adaptations should be determined during the protocol development phase so that they can be incorporated into the trial design as necessary, detailed in the Risk Assessment documents and stored in the Sponsor File. The template

(FRM024 CTIMP Risk Management Tool) should be used for this process. The risk assessment process must document:

1. Justification as to the chosen risk level (Type A, B or C) including reference to current care, evidence of drug's current license / established use and quoting any appropriate established guidelines
2. The potential risks to trial subjects and to the reliability of trial results and the actions necessary to mitigate them. The risk assessment must include IMP and non-IMP risks. Consideration should be given to follow-up of female partners of male subjects depending on the safety profile of the drug (e.g., if it is known to have an effect on spermatogenesis).
3. The potential risks to the reliability of the results and actions necessary to mitigate against them.
4. In addition the following aspects should be considered:
   a Which key trial documents are required
   b The input required from the members of the trial team or external experts
   c Trial management requirements, including the planning and resource aspects of the trial (e.g., trial monitoring requirements)
   d Selection of site/s and the type of site assessment that is appropriate for the trial and site (e.g., pre-qualification questionnaire vs on-site visit)
   e The need to sub-contract any study activities
   f Adverse event reporting
   g Type and frequency of monitoring
   h IMP storage and documentation requirements
   I The planned randomisation process including back-up and emergency randomisation procedures
   J The requirement for a Data Monitoring Committee (DMC) as part of the oversight and management of the trial

4.1.2 Possible risk adaptations

a. Once the risk level has been identified the possible adaptations can be considered to the management of the Clinical Trial. Table B details the types of adaptations that may be possible and further information can be found in the MRC/DH/MHRA Joint Project document: 'Risk adapted approaches to the management of clinical trials of investigational medicinal products'.

b. Once developed the risk assessment and associated management and monitoring plans should facilitate a risk-proportionate approach to the trial activities.

c. The risk assessment form must be sent to the key members involved in the trial to request confirmation that they are in agreement before the form can be finalised. The form must be signed-off by the Chief Investigator, before the Site Initiation Visit at the first site. Evidence of team review (e.g., meeting minutes and/or email correspondence) and the risk assessment form must be stored in the Sponsor File.

d. The risk assessment form must be version controlled in accordance with PTUC SOP060 Version Control of Study Documents and signed and dated by the Chief Investigator.

e. The Chief Investigator or delegated member of the project team is responsible for overseeing the mitigations or actions planned from the risk assessment. This must be documented in the Sponsor / Chief Investigator delegation log/Memorandum of Understanding (refer to FRM028 and FRM040).

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Table B: Possible adaptations depending on the risk of the study

() = maybe possible on a case by case basis

	Type A	Type B	Type C
Reduced MHRA role in approvals	Yes (notification only)	No	No
Adverse Event/Reaction Recording & Reporting	Yes	(Yes)	(Yes)
SAE/SAR Event Reporting	(Yes)	(Yes)	(Yes)
SUSAR reporting to MHRA/REC/Concerned Investigators	No	No	No
Annual Safety Report	No	No	No
Requirement for Trial Level IMP Accountability	Yes	(Yes)	No
Requirement for Subject Level IMP Accountability	Yes	(Yes)	No
Storage Conditions Records	(Yes)	(Yes)	No
Protocol Deviation Impact Assessment	(Yes)	(Yes)	No
Requirement for Investigators Brochure (IB)	Yes	(Yes)	No
Requirement for IB annual Update	No	No	No
Requirement for a Sample Label	Yes	(Yes)	No
Requirement for Certificate(s) of Analysis	Yes	(Yes)	No
Investigational Medicinal Product (IMP) Shipment(s)	Yes	Yes	No
Instructions for Handling IMP(s)	Yes	(Yes)	No
Master Randomisation List	No	No	No

Decoding Procedures for Blinded Trials	No	No	No
IMP Accountability at Site	Yes	(Yes)	No
IMP Return &/or Destruction	Yes	(Yes)	No
Investigational Medicinal Product Dossier	Yes	(Yes)	No
Manufacturer's Authorisation for Investigational Medicinal Product (MIA (IMP)	Yes	(Yes)	No
Manufacturer's Authorisation (MA)	(Yes)	No	No
Authorisation for IMP Importation	No	No	No
Qualified Person Certification (where required)	Not Applicable	(Yes)	No
Statement of EU GMP or EU GMP Equivalence	Yes	(Yes)	No
Safety Monitoring Plan	No	No	No
Yes – possible; (Yes) – may be possible on case by case basis; No – little, if any flexibility in requirements			

4.1.3 Ongoing review

a. The risk assessment form must be reviewed at least annually, or earlier if new information becomes available. For example after patient walk through (dummy run), a protocol amendment, or when the summary of product characteristics / investigator brochure is updated.

b. Evidence of the review (e.g., meeting minutes and/or email correspondence), must be documented in the Sponsor File, even if no changes are required.

5 Risk Management / Liability / Monitoring & Audit

a. The R&D SOP Committee will ensure that this SOP and any future changes to this document are adequately disseminated.

b. The R&D Department will monitor adherence to this SOP via the routine audit and monitoring of individual clinical trials and the Trust's auditors will monitor this SOP as part of their audit of Research Governance. From time to time, the SOP may also be inspected by external regulatory agencies (e.g. Care Quality Commission, Medicines and Healthcare Regulatory Agency).

c. In exceptional circumstances it might be necessary to deviate from this SOP for which written approval of the Senior R&D Manager should be gained before any action is taken. SOP deviations should be recorded including details of alternative procedures followed and filed in the Site and Sponsor Files.

d. The Research and Development Directorate is responsible for the ratification of this procedure.

Further Document Information

Approved by: *Managment/Clinical Directorate Group*	Research and Development Directorate
Approval date: *(this version)*	
Ratified by Board of Directors/ Committee of the Board of Directors:	STET
Date:	N/A
This document supports: *Standards and legislation*	Medicines for Human Use (Clinical Trials) Regulations 2004 and all associated amendments. UK Policy Framework for Health and Social Care Research (2023)

Equality Impact Assessment: Does this document impact on any of the following groups? If YES, state positive or negative, complete Equality Impact Assessment Form available in Disability Equality Scheme document DN192 and attach.

Groups	Disability	Race	Gender	Age	Sexual orientation	Religious & belief	Other
Yes/No	No	No	No	No	No	No	No
Positive/Negative							

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