Portsmouth Hospitals NHS
NHS Trust

Standard Operating Procedure (SOP) for the Risk Assessment of Studies Sponsored by PHT

For Completion by SOP Author	
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If you are reading this SOP in printed form then you are reading an uncontrolled document. You must therefore verify that the version number and date given below are the most recent, by cross-checking with the Trust research website before proceeding with implementation.

Portsmouth Hospitals NHS Trust is committed to ensuring that, as far as is reasonably practicable, the way we provide services to the public and the way we treat our staff reflects their individual needs and does not discriminate against individuals or groups on any grounds. This SOP has been assessed accordingly

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1. INTRODUCTION

Sponsors have a duty to provide oversight of research studies to ensure there is adequate protection of participant's safety and rights and data integrity however, there are inherent risks. The purpose of a risk assessment is to identify potential hazards and assess the likelihood of those hazards occurring and resulting in harm. Identified risks will be assessed and either tolerated or treated with mitigating actions or monitoring.

The Medicines for Human Use (Clinical Trials) Regulations 2004 allow for risk adapted approaches to the management of clinical trials of investigational medicinal products (CTIMPs). Portsmouth Hospitals NHS Trust (PHT) has adopted the same risk-adaptive approach for all research studies it sponsors.

Different, proportionate, approaches to risk mitigation and management can be taken at each step of the study lifecycle. Using a simple categorisation of three risk types, low, medium and high, it is possible to highlight where risk based adaptations should be focused. Low risk studies could tolerate a reduction in management strategies whereas medium/high risk studies will likely need additional attention. Focused attention will result in more proportionate and resource efficient study management.

2. PURPOSE

The purpose of this document is to describe the standard operating procedures (SOP) for conducting a risk assessment of studies sponsored by PHT. It is recommended a risk assessment is conducted on all studies to identify potential risks that will impact on participants or the study results.

The risk assessment should consider the study fully and take a pragmatic and proportionate approach when addressing each risk identified. It will then describe suitable strategies or procedures to mitigate or manage the risks. The risk assessment will be used to inform the monitoring plan.

Continuous review of the risk assessment and subsequent monitoring plan, throughout the lifecycle of the study, will ensure necessary adjustments are made to maintain the safe and successful delivery of the study.

3. SCOPE

This SOP is designed to be used by the members of the Research & Innovation (R&I) Office, the Study Teams delivering the research studies and any applicable support departments, e.g. Pharmacy, Pathology and Radiology.

This SOP describes the process by which a risk assessment will be carried out on the research study in order to identify risks that have the potential to impact participant safety or the reliability of results.

The Trust recognizes that some external sponsors, networks, funders and employers may require the use of their own SOPs for the good governance of research. In such cases it is the responsibility of the Portsmouth Hospitals Trust user (including those individuals contracted to work on behalf of the Trust), to ensure that the external SOP is compatible with the procedure outlined below. If the external SOP contradicts the Trust's procedure then approval must be sought in writing from the Research and Quality Manager.

In the event of an infection outbreak, flu pandemic or major incident, the Trust recognizes that it may not be possible to adhere to all aspects of this document. In such circumstances, staff should take advice from their manager and all possible action must be taken to maintain ongoing patient and staff safety

4. ABBREVIATIONS & DEFINITIONS

Term	Definition
PHT Sponsored Studies	Studies which PHT have ultimate responsibility for the initiation, management of and financing for. They take primary responsibility for ensuring that the design of the study meets appropriate standards and that arrangements are in place to ensure appropriate conduct and reporting.
Study Team	The people involved in the conduct of a research project. There may be different research teams for the project at different sites.
Risk in Research Studies	The likelihood of a potential hazard occurring and resulting in harm to the participant and/or organisation, or to the reliability of the results.
Risk mitigation	Strategies or procedures that reduce either the impact or the probability of an adverse consequence of a hazard

Abbreviation	**Meaning**
CI	Chief Investigator
CTA	Clinical Trial Assistant
CTIMP	Clinical Trial of Investigational Medicinal Product
MHRA	Medicines and Health products Regulatory Agency
PHT	Portsmouth Hospitals NHS Trust
PI	Principal Investigator
RF	Research Facilitator
R&I	Research & Innovation (Office)
SOP	Standard Operating Procedure
TMF	Trial Master File

5. DUTIES AND RESPONSIBILITIES

Role	Responsibilities
Sponsor	▪ The duties of the Sponsor will be carried out by a member of the Research & Innovation (R&I) Office; in most cases this will be the Research Facilitator (RF) or Research Coordinator (RC) ▪ The RF/RC will facilitate the completion of the risk assessment form ▪ The RF/RC will work closely with the Chief Investigator and their Study Team to identify study risks and agree mitigating and monitoring actions ▪ Manage the risk assessment, including reviewing and updating as necessary
Chief Investigator (CI)	▪ The CI and their Study Team will complete the risk assessment and where necessary involve other staff with expertise in different fields ▪ The CI will have primary responsibility for ensuring any actions arising from the risk assessment are carried out as necessary (this will be supported, where applicable, by the RF/RC ▪ Manage the risk assessment, including reviewing and updating as necessary

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6. PROCESS

6.1. Risk Assessment Process

The risk assessment can be initiated by either the RF/RC or a member of the Study Team using the risk assessment form (refer to section 8).

Ideally, the risk assessment should be carried out in parallel with the development of the protocol to give an opportunity for adjustments or adaptations to be made to the protocol before it is finalised.

If the study is complex, it is recommended the Study Team and the RF/RC arranges a meeting to discuss the detail of the risk assessment. Input into the risk assessment could also be given by the data management team, statistician and any applicable support departments.

Study risks should be considered at both a system level (e.g. facilities, SOPs, computerized systems, personnel and vendors) and the study level (e.g. study intervention, study design, data collection and recording).

Apply a risk rating of low, medium or high to each identified risk. The risk rating should be proportionate to the type of study being set up. For example an inexperienced research team would be identified as a risk however that risk is low if the team is running a qualitative study compared to a complex interventional study.

Once the study risks have been classified (low, medium and high) a risk-adaptive approach can be applied to mitigate the risks (e.g. using oversight groups, central or on-site monitoring). In some cases it could be agreed that the risk can be accepted or even eliminated (e.g. by adapting the study design). Guidance on risk adaptive approaches can be found in appendix 1.

It is important to document any risk mitigating decisions made, in order for it to be possible to reconstruct the risk assessment process.

Any risks that cannot be mitigate or suitably managed should be escalated and discussed with an appropriate oversight group. If a solution cannot be agreed then sponsorship of the study, by PHT, may be reconsidered.

The initial risk assessment should be completed before the study starts.

Once finalised, the risk assessment will inform the monitoring plan, which will describe any monitoring activities that will be employed to manage the study risks (refer to PHTRD/SOP019 Monitoring Plan SOP)

When the risk assessment and it's corresponding monitoring plan has been agreed by the R&I office and the Study Team it will be signed by both parties and filed in the TMF and an electronic copy saved in the study folder on the R&I G-Drive.

It will be the responsibility of the Chief Investigator or delegated Principal Investigator to ensure that any actions resulting from the risk assessment are implemented and undertaken. Where applicable, for example where there is a dedicated Trial Manager, the assigned member of the R&I Office will also maintain oversight of any requirements raised by the risk assessment.

The risk assessment should be reviewed throughout the study lifecycle to confirm risk management activities remain effective and relevant. In particular it should be reviewed after monitoring has taken place to take into account any monitoring findings. The risk assessment may then be updated as necessary.

Revisions of the risk assessment will be agreed and signed by both the Study Team and the R&I office before filing with the original risk assessment.

6.2. The Risk Assessment Form

The Risk assessment form is divided into two parts.

- Part 1 – describes the risks to participant safety in relation to the specific study intervention/s
- Part 2 – describes all other study related risks

6.2.1 Risks to participant safety (Part 1)

Risks to the participant should be assessed relative to the standard of care for the relevant clinical condition and the level of clinical knowledge about the intervention rather than the patients' underlying illness or the recognised adverse effects of the intervention.

Any potential risks should be balanced against the level of risk that the participant would normally be exposed to outside of the study.

A three level risk categorisation is used for the study intervention:

- 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

The risk category of the intervention will guide the nature and extent of patient safety monitoring that will be required. In general a Type A study will involve a low intensity of safety monitoring, Type B will involve moderate intensity and Type C will have a high intensity of monitoring.

6.2.2 All other study related risks (Part 2)

These risks should be assessed independent of the risk categorisation of the study intervention. I.e. a study categorised as type A does not mean all other risks will be considered low.

Other study related risks would be those that arise from the protocol and study procedures other than those associated with the intervention namely:

- Risks to participants associated with
  - *The clinical procedures specified by the protocol* – risks should be assessed relative to standard investigations and procedures for the clinical condition of the participant in the study. For example an invasive procedure in the protocol that is usually carried out as part of standard care would not be considered an additional risk. Whereas if the same procedure is not normally part of standard care then it would pose an additional risk.
  - *Failure to obtain appropriate, fully informed consent* – consideration should be given to the competency of the participant to give consent, whether consent is being given for a study that is very similar to standard care and whether the window of opportunity for consent to be given is very short. For example in acute emergency situations
  - *Failure to protect personal data* – it is essential personal data, collected during the study, is held securely and only accessed by authorised staff. Where data is transferred to another site there may by increased risk.
- Risks to the reliability of results

- It is important to recognise that it is the reliability of the study results rather than the data *per se* that is paramount. So quality control and assurance methods should focus on the quality of data required to meet the study objectives and obtain reliable results rather than simply on data accuracy.
- It may be appropriate to undertake targeted quality control of key items (e.g. end point data) and to tolerate some variability in the quality of some other data items
- Consideration should be given to the data collection and handling methods. Well designed systems may help improve data quality.

7. TRAINING REQUIREMENTS

The following must evidence training in this SOP:

- Members of the R&I Office staff who are developing the risk assessment for PHT sponsored studies.
- Chief Investigators and delegated members of their Study Team who are developing PHT Sponsored Studies.
- Any staff, from support departments, involved in the development of a risk assessment.

"The Research Dept., will endeavour to notify staff of SOP developments that may be relevant to them. SOPs are available on the Research department website. Updates on SOPs will feature in Research newsletters and communications and disseminate at local research meetings. It is the responsibility of all research active staff to ensure that they read the issued updates that may be relevant to them.

When a new SOP is authorised, or when an existing SOP is revised, self directed training must be carried out by all staff to which the SOP is relevant and this training documented in their training record. A template is provided to support this process. A study specific SOP training plan will be developed for investigators on high risk PHT Sponsored studies.

Staff should take time to read and fully understand the SOP and relevant documents, ensuring that they are able to implement the SOP when required. If clarification is needed then the trainee should approach their line manager and the SOP Controller who will arrange additional training. All staff should complete their training prior to the published implementation date which will normally be between 2-6 weeks after publication.

All staff are responsible for maintaining their own SOP Training Records and copies must be made available to line managers, the SOP Controller or study monitors on request."

8. REFERENCES AND ASSOCIATED DOCUMENTATION

Associated Documents

- Template – Risk Assessment Form
- PHTRD/SOP019 SOP for developing a monitoring plan for studies sponsored by PHT

References

- The Medicines for Human Use (Clinical Trials) Regulations 2004
- MRC/DH/MHRA Joint Project – Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products, 6th October 2011

- Risk Adaption in Clinical Trials of Investigational Medicinal Products (CTIMPS) – MHRA Blog, 16th November 2017
- ICH Guideline for GCP E6 (R2), Step 4, 9th November 2016
- Risk Proportionate Approaches in Clinical Trials, 25th April 2017

9. VERSION HISTORY LOG

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Details of Significant Changes
1.0	16 Jan 2020	New document

10. APPENDICES

10.1. Appendix 1. A guide to potential risk adaptations

Regulatory Approvals	The MHRA regulates CTIMPS and studies involving medical devices. Clinical Trial Authorisation is required for all CTIMPS before they commence however there is a reduced MHRA role for approval: 1. Type A studies may proceed upon receipt of an acknowledgement letter from the MHRA if they raise no objections. 2. Amendments to the study protocol will be treated in the same way.
IMP Management	IMPs require accountability and traceability. The extent of accountability may vary depending on the authorisation status of the IMP. 1. An IMP used within its authorised indication it may be sourced from normal stock or re-labelled if provided by another site. 2. For low-intervention clinical studies, where medicinal products are used as IMPs routinely maintained pharmacy documentation on receipt, storage and handling may be sufficient if: a. Normal prescribing and documentation applies b. Prescriptions and doses are available in the patient's medical records or other source documents. 3. Unlicensed IMPs will require full accountability records of receipt, use and return/destruction unless justified in the risk assessment with mitigating actions. Risk adaptations performed on drug accountability should take into account the impact of not performing drug accountability on the reliability of the results of that particular study.
Device Management	Risk adaptations can be made on studies involving medical devices. Considerations should include whether the device is CE marked or not and whether it is to be used within the conditions of the CE marking. A study using a device as it is intended will pose far less risks that one using a non-CE marked device. 1. A device used within its indication may be sourced from normal stock or procured from an external supplier 2. Non CE marked devices will require full accountability records to be kept including receipt, use and return/destruction unless justified in the risk assessment
Safety Reporting	The level of detail of recording and reporting adverse events can be adapted in the protocol in line with the scope and type of study and the level of knowledge on the safety profile of the intervention and disease profile of the study subject. 1. The protocol may select only certain adverse events to be recorded in the CRF and reported to the sponsor. In particular marketed products with a known safety profile tested within the framework of low-interventional study. Safety reporting can be targeted based on the study specific risks identified in the risk assessment. 2. Where there are anticipated disease or population related adverse events, these can be waived from be recorded and reported. This risk adaptation should be described in the protocol 3. In a study, for example of high morbidity or high mortality, which safety or efficacy endpoints meet the criteria of SAEs these outcome

	events may be exempt from immediate reporting to the sponsor. The safety data should be promptly evaluated by an independent data safety monitoring board (DSMB) who may deem an outcome to be classified as an SAE which should then be reported without delay.
Monitoring	In defining the monitoring strategy based on the study specific risk assessment, the intensity and focus of the monitoring may vary. The level of on-site monitoring activities may range from frequent and/or detailed monitoring to lower levels of activity and less frequent on-site visits to targeted visit of certain sites or of a particular activity. The type and combination of monitoring activities should be adapted to suit the study: 1. On site monitoring 2. Remote monitoring – telephone contact, web enables training 3. Centralised monitoring of study data supported by an appropriately qualified and trained person 4. Central medical review of study data 5. Centralised monitoring of pre-defined operational metrics critical to quality (e.g. turnaround time of central lab results to the investigators)
TMF	All studies should maintain a TMF containing relevant documentation. ICH GCP offers guidance on the essential documents and states these should be supplemented or reduced where justified. This justification should be based on the risk assessment. Examples include: 1. Replacement by a document that serves a similar function e.g. replace Investigator Brochure when the Summary of Product Characteristics is being used instead. 2. Combining documents so that one document serves a number of purposes, e.g. screening and recruitment logs or signature and delegation logs 3. Absence of documents as a result of other risk proportionate measures: a. Clinical study report may be absent if it is replaced by a medical journal publication. b. Hospital laboratory accreditation certificates and reference ranges (when the lab is not providing information critical to the reliability of the study) c. IMPs with marketing authorisation and supplied to the patient via routine medicines supply chain (i.e. from pharmacy based on a prescription) may not require any additional accountability records or only limited recording of consumption e.g. in the CRF or patient diary. Therefore may not need IMP handling, storage and analysis records, temperature logs or destruction documentation.

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CONFIRMATION OF SOP TRAINING RECORD

A copy of this record may be kept in your personal training file to confirm your training in a specific SOP. If required by a study Sponsor a record may also need to be kept in the Trial Master Files (TMF) or Investigator Site Files (ISF)

SOP Details: To be completed by the SOP Controller	
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Personnel Details	
Name	
Job Title & Research Role	
Date of Training	
Nature of Training	Self Directed/Delivered by etc
Records of any meetings to clarify details in SOP	

Signatures
I confirm that I have read and consider myself to be sufficiently trained in the above Standard Operating Procedure with regards to my individual roles and responsibilities Signature of Trainee …… Date ……
I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities Signature of Trainer …… Date ……

Additional Notes & Signatures
Signature of Trainer (where appropriate) I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities Signature of Trainer …… Date …….