UKCRF NETWORK

Framework for Conducting Highest Risk Phase I and Experimental Medicine Studies within NIHR Clinical Research Facilities and wider NHS acute Trusts

Version 1.0 – November 2020

Co-authors:

- Saul Faust, Chris Edwards and Kim Lee, NIHR Southampton CRF
- Richard Fitzgerald and Jennifer Gibney, NIHR Liverpool CRF

Reviewed for UKCRF Network by:

- Vincenzo Libri, NIHR UCL CRF
- Phil Chowienczyk, NIHR Guys and St Thomas' CRF
- Dave Newby and Steve Cunningham, Edinburgh WTCRF (for Scotland/Devolved Nations)

FUNDED BY NIHR | National Institute for Health Research

CHIEF SCIENTIST OFFICE

CONTENTS

LIST OF ABBREVIATIONS

BLS = Basic Life Support
CRF = Clinical Research Facility
EPSC = Early Phase Safety Committee
FIH = First in Human
ILS = Immediate Life Support
IMP = Investigational Medicinal Product

1. INTRODUCTION

Following the TGN1412 incident in March 2006 the MHRA have developed a voluntary 'Phase I Accreditation Scheme'1 for research facilities who conduct Phase I clinical trials.

Further to meetings between CRF Directors on behalf of the UKCRF network, MHRA and HRA, the UKCRF Directors have recognised that it is in the best interest of patient safety across all CRFs and the wider NHS to establish a framework for facilitating highest risk early phase and experimental studies. This framework will have a similar approach to the MHRA Phase I scheme of risk assessing studies and ensuring contingency planning to mitigate the identified risks as well as other requirements.

This document outlines areas of the formal MHRA scheme that should be adopted as best practice for all CRFs for the highest risk early phase and experimental medicine studies underpinned by other resources and tools to be shared across the network. The document also describes a governance framework, under which the highest risk studies should be managed. These principles can be applied in other NHS organisations that do not currently have a dedicated CRF.

The accompanying detailed risk assessment has been developed from the current process from NIHR CRFs in Liverpool and Southampton, which were informed by previous work undertaken in Edinburgh and shared across the network. As a minimum standard for all CRFs, the detailed risk assessment and processes are intended to apply to the highest risk studies as outlined below:

Phase 1 risk assessment level (CTIMP or locally-assessed EM high risk)	**Example participant group**	**Action required**
High	**FIH/dose escalation/age de-escalation/healthy volunteer or patients with novel IMP.** **First in patient/dose escalation with novel IMP.** **Any high risk situation (locally determined on documented case by case basis) such as new technologies (some gene therapy/ATIMP, antisense oligonucleotides by intrathecal administration, etc) agonist/stimulatory IMPs with risk of cytokine cascade.**	**UKCRF Phase 1 Framework as minimum standard. Highest standard of oversight with review of full dose escalation package by local safety assessment process.**
Moderate	Using IMP with known mechanism of action in patients where similar therapies for this indication are currently licensed in this population. Repurposing of existing IMP for patients with life-threatening disease (ie metastatic cancer)	Local process decision. For example Moderate approach with review of dose escalation decisions and safety data by local principal investigator.
Low	Other lower risk studies	Local process decision. Lighter touch approach with need to be satisfied that process is in place to ensure information collected for dose escalation with review by principal investigator.

In addition to using risk management plans, CRFs should also ensure that all studies are conducted in conjunction with GCP, Statutory Instrument 2004/1031 (and all subsequent amendments) – The Medicines for Human Use (Clinical Trials) Regulations, UK Policy Framework for Health and Social Care Research, local Trust and Research and Development Standard Operation Procedures and policies.

2. PURPOSE

The purpose of this framework is to provide a guide to the enhanced governance processes including risk assessment that will allow all CRFs to work to a minimum agreed standard for the highest risk studies.

3. RESPONSIBILITIES OF A CRF AND/OR TRUST

In line with the formal MHRA scheme that ensures CRFs (or other organisations) take responsibility for specific processes. This framework recommends that it becomes a CRF's responsibility to ensure that procedures for the highest risk studies are documented and formalised in each organisation.

4. PROCEDURES

a) CLINICAL TRIAL DESIGN AND SET-UP

i) Safety information availability and Insurance

A study sponsor must provide "any ongoing safety and toxicology data updates to the CRF and local principal investigator (PI) immediately, to ensure the safety of the subjects in these early phase trials"2. The sponsor must also ensure that appropriate indemnity insurance is in place.

It is the responsibility of the local R&D office to ensure that the above requirement is written in the Clinical Trial Agreement for all studies. HRA processes (R&D in Scotland) will take responsibility for specifically checking there are no exclusions in the Sponsor insurance policy that put Trusts or patients at risk.

ii) Early Phase Safety Committees (EPSC) or other local process.

A CRF/Trust EPSC should have specific terms of reference (see appendix 1 for example) and expertise to allow appropriate risk assessment of all highest risk phase 1 and experimental medicine studies. The committee (or process) should ideally consist of a wide range of expertise to ensure all aspects of the trial have been reviewed

iii) Risk Assessment/ Risk Management/ Mitigation

CRFs should implement a process of formal risk assessment of phase I/ or highest risk experiment medicine studies to ensure that an appropriate contingency plan is in place to mitigate any known or possible risks.

The completed risk assessment should be reviewed by a EPSC (of the CRF or organisation) before the trial begins and that all necessary measures are in place. In future, the UKCRF network envisages being able to simplify and create a pathway similar to the unified HRA process whereby CRFs will share risk assessment processes and be able to accept risk assessments from other sites for multi-centre studies.

CRFs/Trusts should embed the risk assessment process in local R&D pathways to ensure that *prior to study approval/opening*, all appropriate studies have completed the risk assessment (including minimum staff requirements) and been submitted for review by the EPSC with a contingency plan that is then circulated to relevant staff.

CRFs have responsibility to ensure processes include oversight of:

- study/document amendments (also important for EPSC to have oversight of amendments that may affect the risk assessment)
- staff changes (particularly the PI/co-investigators conducting the study)
- file notes relating to the study conduct
- monitoring reports and audit findings

iv) Dose Escalation overview

Issues to be considered for safe dose escalation should be highlighted at the very start of every study including dose escalation. The trial design and decisions on the number of participants, starting doses, dose increments and maximum dose should be based on a detailed evaluation of predicted and possible risks related to the nature of the agent, its target in vivo and the intended recipients, and take into account the available pre-clinical and clinical data. The protocol/ charter/study-specific plan (see below) should include the specific data to be included in dose escalation decisions and to what time post-dose these data should be collected and reviewed. Other information to be included should be set out, for example minimum datasets required, escalation criteria, potential requirement for sentinel dosing, membership of the DMC or equivalent, and PI Qualifications etc.

Where the PI and DMC have oversight of dose escalation, the EPSC role is to ensure dose escalation decision documentation in TMFs and QA/QC as explained in section vi). For less experienced local researchers, a EPSC role is also to ensure local oversight of the dose escalation event (that is formally overseen by the trial DMCs), and to document that it is at minimum GCP compliant as outlined in the dose escalation decision tree in appendix 2.

v) Dose escalation process

CRFs should ensure a study-specific dose escalation process is outlined in the protocol or separate document. This can be a SOP, Charter or Study-specific plan. If required, a separate form may be needed to outline the dose escalation process, including how the required data is source data verified and how it is communicated to PIs/EPSC. Full MHRA accreditation does require PIs review of the whole dataset.

vi) Dose escalation data

Dose escalation decisions made on an unvalidated dataset puts the patient and organisation at a high risk. For a multi-centre study, the EPSC and local PI need a process to document the certainty that data generated at other sites are robust and of high quality. For the MHRA scheme, oversight requires CRFs to ensure appropriate (often 100% for high risk studies) source data verification at all sites prior to dose escalation: although this may not be feasible or practical for all studies, CRFs and PIs need to be certain of data quality prior to dose escalation in the highest risk studies. Ideally, an agreement between the CRF/Trust and sponsor should state that it is the Sponsor's responsibility to ensure that appropriate QA/QC procedures prior to dose escalation have been conducted as per protocol.

vii) Dose escalation decision

Study PIs must be satisfied with, and document their satisfaction with, the Sponsor's decision to dose escalate, and of the accuracy of the data on which the dose escalation decision is based.

It should be the responsibility of the PI or delegated CRF individuals / site study team to ensure the Sponsor's decision to dose escalate and the PI's oversight of the data used is documented in the site file.

b) MEDICAL EMERGENCIES AND FACILITIES

i) Emergency trolley

There must be an appropriate number of emergency trolleys (or acceptable alternative, such as a grab bag) to ensure they are easily and rapidly accessible. The emergency trolley contents should reflect the current Resuscitation Council (UK) guidelines. If there is local deviation from Resuscitation Council (UK) guidance, this should be documented and documents accessible for transparency. Emergency trolleys should be stocked and checked accordingly. CRFs may refer to the local Trust process if it meets the above criteria.

ii) Medical Emergency Rehearsal/ scenario

As part of the formal Phase I Accreditation Scheme, the MHRA state that "periodic all staff testing of emergency scenarios should occur within the unit and be documented"1. The UKCRF Network agrees that all CRFs should deliver clinical emergency scenario training, and has highlighted the need for robust planning and management of these scenarios7. Please refer to the 2015 UKCRF Network Education and Training group UKCRF Network Emergency Scenario Training Guidance Document. CRFs should identify the staff members responsible for arranging the appropriate number of announced and unannounced scenarios at least annually. CRFs that prioritise FIH/phase I trials should conduct emergency simulations more often (set local SOP) and ensure that all core clinical staff are exposed to different scenarios. Staff training records should reflect the number and frequency of simulations attended by all staff members

The scope of the emergency training should cover all core CRF clinical staff. For non-core CRF clinical staff using the CRF, the individual study risk assessment should determine which staff require sign off for specific training. Regardless of the decision, non-core CRF staff must be trained to the standard required by local Trust policy.

Consideration should be given by CRFs/Trusts to also implement study specific emergency scenario testing and training for the highest risk IMPs, for example the treatment of a cytokine release phenomenon. All CRFs should have a management of emergencies SOP detailing the working relationships with emergency response and resuscitation teams, intensive care units locally and where applicable the ambulance service. A detailed risk register and mitigation plan should also be in place and this should be reviewed monthly.

C) STAFF

i) Principal Investigators

CRFs and Trusts should establish local requirements for PI expertise (Qualification, training and experience including relevant post-graduate qualification for FIH trials)

For FIH studies, the MHRA require that study PIs are authorised to undertake this role. PIs undertaking FIH studies in formally accredited CRFs must meet the following criteria1,2:

- Hold a suitable post graduate qualification, such as a Diploma in Pharmaceutical Medicine, Diploma in Human Pharmacology, MSc in Clinical Pharmacology or equivalent.

or

- Have received approval from the MHRA to act as a PI on FIH studies following submission of the application form 'Request for Acceptance as Phase I Principal Investigator for FIH Trials' and documented rationale for their exemption.

This UKCRF framework recommends that CRFs or Trusts have a written policy regarding the expertise requirements of PIs conducting the highest risk studies, acknowledging that training and inexperienced "first time" PI risk is mitigated by;

- Site in NHS University Hospital with full medical back up
- EPSC, CRF Director, colleagues and/or clinical pharmacology partnerships and supervision

ii) Medical staff
CRFs should ensure that there is a written local policy and study-specific documentation regarding the level and nature of medical cover for the studies of different risk levels and location of study delivery, including the minimum details of location on or off site, time in attendance after dosing (by bedside or in building).

iii) Clinical staff requiring ILS
All clinical nursing staff working in the CRF should have as a minimum Immediate Life Support (ILS) training with annual updates, or local Trust equivalent. For medical staff, they must have the minimum of the Trust Statutory and Mandatory Resuscitation training to attend patient visits in the CRF. Some particularly high risk studies may require ALS trained staff to be in attendance, but this is not usually required for units with access to hospital emergency response teams".

iv) Minimum Staffing Levels:
Minimum staffing levels in the CRF should be established studies of different risk levels. For the higher/highest risk studies these will be all visits not just dosing days and overnight stays[1].

v) Staff Qualifications and Training:
All Core and non-core CRF staff who conduct EPSC approved Phase I studies within the facility must be qualified and trained appropriately in order to perform

their roles. CRFs should have formalised procedures for identifying and tracking staff training needs (i.e. example, via training courses, written procedures and competency assessments) to ensure these are kept up to date. Many units use training matrices and tracking spreadsheets which are available to relevant personnel for scheduling training (such as life support training) and resource planning.

D) SUBJECT RECRUITMENT IDENTIFICATION

i) Prevention of over-volunteering

CRFs should implement a formal procedure to minimise the risk of over-volunteering for healthy volunteers and in some cases volunteer patients (e.g. diabetic or asthma studies). There is no single mechanism to combat this risk but there are a variety of different activities that when combined can reduce the risk of over-volunteering.

Below are two recommended methods of oversight to reduce over-volunteering, which need to be run in tandem.

TOPS database

The Over-Volunteering Prevent System (TOPS) is a database, free to all UK organisations undertaking Phase I trials in healthy volunteers, that aims to prevent participants from taking part too frequently in trials of new medicines. More information and a template consent form can be found at:

https://www.hra.nhs.uk/about-us/committees-and-services/the-over-volunteering-prevention-system/

Local Healthy Volunteer Database

Units should have a robust database of all the healthy volunteers that have participated in any clinical trials in order to identify the last time the unit has dosed the volunteer. The database will need to hold the following information:

- Patient details
- Participated trials details
- Record of SAEs experienced
- Record of other “significant events that might impact on volunteer suitability to participate in future trials on the CRF

The database can be in any format that follows UK and Trust data protection regulation requirements.

It is the responsibility of the CRF to implement and formalise the process through a written SOP.

ii) Photographic Identification

CRFs should have a formal procedure to address how subjects will be identified to ensure that it is the same person that attends all the trial visits in the highest risk trials and healthy volunteer studies. This must be done using a valid form of photographic ID (i.e. photo driving licence or passport).

It is the responsibility of the CRF to ensure there is a formalised process in place to check the participant ID before the study visit.

iii) Confirmation of subjects' past medical history

CRFs should have a process in place so that all highest risk trial subjects (whether healthy volunteers or patients), have their medical histories confirmed1,2. This is in order to provide assurance that a subject meets the eligibility criteria to participate in a trial. Confirmation of medical history may be sought from the GP (for most trials) and/or a hospital consultant to supplement information for studies involving patients. In some specialities (e.g. oncology) and/or other specific situations it may be appropriate to gather only hospital-based information.

E) QUALITY MANAGEMANENT/QUALITY SYSTEM

There must be CRF and/or Trust Quality Control (QC) and Quality Assurance (QA) systems in place, to ensure that study processes are reliable and that no major system failures are expected to occur that would expose participants to unnecessary risk, violate their legal or ethical rights or result in unreliable data. Minimum requirements for formal QA Procedures need to cover generic unit requirements and consider having formal processes to manage:

- **The CRF** should ensure that continuous monitoring equipment is available and that the beds which can be titled and adjusted for height are available for patients who are being dosed.

- **Pharmacy and IMP management**, including storage. temperature monitoring, local ATIMP guidelines and/or committee oversight, dosing instructions and worksheets. In future it may be possible for CRFs to share study dosing instructions and pharmacy worksheets (national discussions in process).

- **Emergency Unblinding procedure is** in place and has been tested before the start of the study.

- **Communication of Phase I / High Risk experimental medicine activity to ICU or equivalent**: ICU, or equivalent, and Resuscitation services need to be aware of the study and the dosing date(s) as appropriate.

- Out of Hours Medical Cover: subjects are provided with a 24 hour emergency contact number which they can use when they are not present in the CRF to contact the study team[1,2]. Subjects must be given a subject card or equivalent which contains out of hours contact numbers for the study team. The contact system should be tested by CRFs routinely in a specified time interval (eg monthly). Should out of hours cover not be provided by the CRF for a trial (i.e. it is an investigator team providing OOH cover) then study documentation should specify (a) how this is tested and (b) whether and cover arrangements for annual leave, travel etc.

- **Any emergency related procedures** (for example, emergency unblinding, emergency alarm buttons, out of hours/emergency phone numbers etc.) should encompass routine testing, how this is documented, the frequency and any CAPA in the event of failures/issues.

- **Medical Emergencies: CRFs should ensure formal, documented** agreement with the Trust for supporting emergencies arising from high risk studies and to demonstrate communication and notification of trial information with the hospital emergency team. For local medical emergencies, standard Trust practice should be followed, and the local Emergency Response Team used as necessary.

APPENDIX 1: EXAMPLE EPSC COMPSITION AND TERMS OF REFERENCE

CRF Early Phase Safety Committee (EPSC) Terms of Reference

Purpose:
The Early Phase Safety Committee (EPSC) will convene to support the scientific review and clinical risk assessment of all Phase I and First in Human (FIH) studies that will be conducted within the XXXXXXNIHR Clinical Research Facility (CRF). Where the need is identified by the CRF Directors, the EPSC will also provide support for the scientific review and clinical risk assessment of other early phase studies.

The EPSC will share experience and expertise in the field of early phase studies to ensure that all Phase I and FIH studies that are conducted within the CRF have been risk assessed and associated contingency planning implemented.

Composition of the EPSC:
The EPSC will comprise individuals from both the Trust and UNVERSITY PARTNER, and when needed external bodies with appropriate expertise in early phase studies, statistics, clinical pharmacology, toxicology and/or pharmacy.

Chair: CRF Director, Associate Director or Consultant/Clinical Academic in Clinical Pharmacology
Member: RG&QA Manager
Member: QA Lead
Member: Clinical Pharmacologist
Member: Appropriate representation from local scientific community
Member: Appropriate representation from Trust Clinical Trials Pharmacy
Member: Statistician
Member: Other expertise as required

Representation from other areas of the Trust or University may be called to the EPSC with agreement of the group to discuss specific matters.

The committee members assessing a study must not have any involvement in the study under review or have any other conflicts of interest.

Terms of Reference:
For FIH studies (and any high risk early phase studies in that have been identified as requiring EPSC support), the risk assessment (with associated contingency plan) will be reviewed by the committee and signed off by the chair. The decision

as to what constitutes 'high risk' will be made by the EPSC Chair or the study sponsor.

All other Phase I studies (and any early phase studies that have been identified as requiring EPSC support) will have the risk assessment (and associated contingency plan) reviewed by the CRF Director or CRF Associate Director. Advice will be sought from other members of the EPSC as appropriate, and 'Chairman's Action' will be used to sign off the risk assessment.

The EPSC will facilitate the following, as required:

- Provide a forum for members to share knowledge and expertise relating to investigational medicinal products (IMPs) proposed for specific early phase studies that will take place in the CRF.
- Review the curriculum vitae of the study Principal Investigator (PI) and any co-investigators for evidence of appropriate qualifications, relevant experience and the competency to supervise and conduct the study under review.
- Review and risk assess pre-clinical data of proposed Phase I studies from a technical and clinical risk perspective on a case by case basis.
- Risk assess all aspects of the IMP, including: class, novelty, species specificity, mode of action, potency, dose and concentration response relationship for efficacy and toxicity, and route of administration.
- Assess whether the trial should be submitted for review by the Expert Advisory Group (EAG) to the Committee of Human Medicines (CHM).
- Consider the probability and severity of adverse reactions relating to study drugs, and consider the availability of specific antidotes and appropriate supportive treatment.
- Assess procedures and any non-IMP used in the specific Phase I study under review.
- Consider whether the trial should involve healthy subjects or patients.
- Provide a decision on whether proposed studies are approved to take place in the CRF from a technical, scientific and clinical perspective.
- Establish and document necessary contingency plans for all aspects of the study that must be in place prior to the initiation of Phase I studies in the CRF. For example, starting dose, dose escalation, administration of doses, facilities and staff, procedures, and subject type.
- Review the impact of any protocol amendments and/or any new safety information during the study. Provide a decision on the acceptability of the changes within the context of the original risk assessment and contingency plan.

Quorum:
For FIH studies (and any high risk early phase studies in experimental medicine that have been identified as requiring EPSC support), the committee requires five members to be quorate. The quorum must include a Pharmacologist, (or other appropriately qualified individual) the CRF Director / Associate Director and the Trust RG&QA Manager / QA Lead.

Secretariat:
Secretarial support (minutes) for face to face meetings will be provided by XXXXX. Minutes will be distributed to all EPSC members following a meeting, and the minutes will be distributed to other individuals as necessary.

APPENDIX 2: DOSE ESCALATION DECISION TREE