Title: Procedure for the review and approval of Early-Phase 1/2a Clinical Trials or research studies with an Experimental Medicine Component at UCLH.

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Author:
Name: Dr Vincenzo Libri
Position: Director of NIHR UCLH Clinical Research Facility

Signature Date 27/3/17

Approved by:
Name: Nick McNally
Position: Director of Research Support

Signature 27/3/17 Date

Authorised by:
Name: Professor Bryan Williams
Position: Director of R&D and BRC

Signature 28/3/17 Date

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ACRONYMS

AAC	Assess, Arrange and Confirm
AFC	Adoption and Feasibility Committee
ALS	Advanced Life Support
ATIMPs	Advanced Therapeutic Investigational Medicinal Products
BRC	Biomedical Research Centre
CI	Chief Investigator
CRF	Clinical Research Facility
CRUK	Cancer Research UK
CSM	Clinical Studies Manager
CTIMP	Clinical Trials of Investigational Medicinal Product
EIA	Equality Impact Assessment
FIH	First In Human
GCP	Good Clinical Practice
HRA	Health Research Authority
HV	Health Volunteers
ILS	Immediate Life Support
IMPs	Investigational Medicinal Products
JRO	Joint Research Office
LWENC	Leonard Wolfson Experimental Neurology Centre
MHRA	Medicines for Health Products Regulatory Agency
NHS	National Health Service
NIHR	National Institute for Health Research
PI	Principal Investigator
PK	Pharmacokinetics blood sampling analysis
QAM	Quality Assurance Manager
R&D	Research & Development
REC	Research Ethics Committee
SOP	Standard Operating Procedures
UCLH	University College London Hospitals NHS Foundation Trust

BACKGROUND

The National Institute for Health Research (NIHR) University College Hospitals NHS Foundation Trust (UCLH) Clinical Research Facility (CRF) and the Leonard Wolfson Experimental Neurology Centre (LWENC) support and accommodate early Phase (Phase I and IIa) Clinical Trials of Investigational Medicinal Products (CTIMPs), and Advanced Therapeutic Investigational Medicinal Products (ATIMPs). These include First in Human (FIH), dose escalation and dose expansion trials in both healthy volunteers (HVs) and patients.

The NIHR UCLH CRF and LWENC also host some later Phase IIb and Phase III studies that have a significant experimental medicine component and complex mechanistic/biomarker studies that require intense patient monitoring, significant infrastructural support and adherence to comprehensive document maintenance and record keeping.

The UCLH R&D requests that all studies in the categories above are managed within a UCLH CRF, when possible.

The NIHR UCLH CRF and LWENC are committed to providing the highest standards of safety and care for trial participants as well as delivering high quality clinical research and best practice for investigators and sponsors. The strong track record of both CRFs has been recognised by recent awards from the NIHR and CRUK for infrastructure support.

For the purposes of this SOP, the term 'CRF' or 'CRFs' will herein refer to both the NIHR UCLH CRF and the LWENC.

The MHRA guidance on Serious Adverse drug reactions emphasise that such reactions *'may occur in any trial, regardless of the perceived 'higher risk' of certain compounds and molecules. There are also risks associated with trial procedures and the possibility of reactions to marketed drugs used as comparators and non-IMPs used as challenge agents. It is therefore vital that all units conducting Phase I studies have adequate staff and facilities for dealing with any such emergencies'.*

It is therefore vital that all units conducting phase I and IIa studies have the appropriate staff and facilities for resolving any such emergencies. To be compliant with the MHRA guidance, the CRFs have an established Adoption and Feasibility Committee (AFC) for the review, risk assessment and approval of such early Phase I and IIa clinical trials, including FIH and/or ATIMP trials, across a broad spectrum of diseases. The overall purpose of the AFC committee is to advise and make decisions on the adoption of such trials onto the CRF study portfolio.

The AFC is also instrumental in recommending additional safety measures, necessary training for investigators, and contingency plans for patient safety which must be in place before the research commences. Likewise, a comprehensive set of Standard Operating Procedures (SOPs), to which Investigators must adhere to, have been developed to define and underpin the conduct of these trials at the CRFs to ensure stringent patient safety during experimental drug administration and monitoring.

As part of new Health Research Authority (HRA) approval process introduced in 2016 which replaced the former Trust-specific NHS permission, investigational research sites are expected to focus their resources on assessing, arranging and confirming their capacity and capability to deliver these clinical research studies.

In conjunction with this, the UCLH Joint Research Office, (JRO) has devolved the responsibility for conducting these feasibility assessments to its local CRFs, who review all study related

documentation and confirm a favourable or unfavourable opinion prior to the JRO's decision to deliver the study within the Trust.

For the remainder of this SOP, trials that are relevant to this procedure i.e. early phase clinical trials (Phases I-IIa, including ATIMP trials), later Phase IIb and Phase III studies with a significant experimental medicine component, and complex mechanistic/biomarker studies that require intense patient monitoring, significant infrastructural support and adherence to comprehensive document maintenance, and record keeping are herein termed **'early-phase/complex trials'.**

PURPOSE

The aim and key objective of this SOP is to ensure that early-phase/complex trials are reviewed and adopted by the CRF Adoption and Feasibility Committee and are implemented within their premises.

For early-phase/complex trials at UCLH, the JRO requests that CRFs either confirm trial adoption with trial activities taking place within their premises or provide a valid reason and justification for the exemption of the study to be conducted outside a UCLH CRF.

Studies adopted onto the CRF portfolio are monitored robustly to i) safeguard high standards of patient safety; ii) ensure appropriate regulatory and governance systems and processes in place and iii) ensure stringent internal Trust wide policies and procedures are followed.

This SOP is not relevant to early-phase/complex trials that need to be conducted outside the CRFs due to exceptional circumstances, e.g. trials that require the IMP to be administered in an operating theatre in parallel with surgical procedures, or in patients who are severely ill requiring intensive in-patient care and/or in acute life threatening situations such as acute stroke, acute MI etc. Likewise, this SOP is not relevant to early-phase/complex trials involving IMP administration in patients involved in emergency situations during which they may have impaired consciousness e.g. patients with head injuries, major trauma or cardiac arrest.

UCLH investigators proposing to conduct their early-phase complex trials outside a CRF must obtain an exemption from the CRF.

If a study is required to be conducted outside a CRF, the UCLH JRO will undertake the formal review and approval process and the oversight of regulatory compliance will fall under the responsibility of the PI and the alternative investigational site.

This SOP applies to all UCLH investigators proposing to conduct early-phase/complex trials at UCLH.

PROCEDURE

Investigators planning to conduct an early-phase/complex trial at UCLH must submit an application to the CRF AFC for their review and approval in order to use the CRF and its resources.

If any applications for early-phase/complex trials are received by the UCLH JRO in the first instance, these will be referred to the CRF Clinical Study Manager (CSM) who will conduct an early feasiblity assessment, seeking further opinion from the CRF Director, if required. Studies considered suitable for the CRF will be referred to the AFC for full review, whilst unsuitable studies will be referred back to the JRO offices for full review and approval at a UCLH alternative site.

Studies referred to the CRF AFC will undergo the following full assessments:

- Study specific risk assessment and risk mitigation plans;

- Level of investigator's experience in conducting highly risky and complex trials;
- Staff training requirements;
- Study complexity and intensity;
- Blinding and emergency un-blinding procedures;
- Medical and Nursing cover requirement in compliance with CRF's relevant SOPs.

The CRF AFC will:

- Record the decision in minutes, i.e. approval, approval with exemptions or non-acceptance, and notify the latter to CI/PIs and the JRO;
- Include approved and adopted trials in the CRF portfolio;
- Maintain oversight of Regulatory Compliance for studies approved to be carried out within the CRF;
- Consider appeals from investigators for studies that have been considered ineligible to take place within a UCLH site outside the CRF. In the event an appeal being unsucessful, investigators will have the option of referring the matter to the Director of Research at UCLH who will issue a final decision.

The UCLH JRO will issue a decision to deliver the study at a UCLH investigational site (either at the CRF or elsewhere within UCLH) based on the outcomes of the CSM and/or AFC feasibility assessments. Studies will not be able to go ahead until all CRF assessments are completed and all JRO/regulatory approvals are in place.

IMPLEMENTATION

This SOP is intended to be implemented across all research active departments at UCLH and targets all investigators and research teams who plan to conduct research studies which fall within the above categories and CRF remits.

DISSEMINATION AND TRAINING

All relevant investigators and study teams will be required to read, understand and familiarise themselves with this SOP on the UCLH JRO, CRF and BRC websites and via JRO/R&D communication bulletins disseminated and circulated through heads/leads of relevant UCLH departments for distribution to all relevant investigative teams.

Training of this UCLH JRO/R&D SOP will not be formally documented.

REFERENCES

This SOP should be read in conjunction with the CRF Adoption and Feasibility Committee Terms of References.

CRF SOP for Set up Activities conducted by the NIHR UCLH Clinical Research Facility SOP 31

CRF Study Risk Assessment SOP 12

CRF internal audits SOP 26

CRF Trial Adoption Committee SOP 4

All the above SOPs can be obtained via the NIHR UCLH CRF Quality Assurance Manager contact number 0203 447 72904

APPENDICES

APPENDIX A:

A link to the Terms and References of UCLH CRF AFC can be found by clicking on the following link:

G:\Share\Shared Folder\Adoption Committee\Adoption Committee meetings\Terms of reference

Please check with Head of Operations, at the CRF for an updated version of the Terms of Reference (where applicable): *0203 447 72901*

Appendix B: The procedure for the review and approval of early phase clinical trials to be supported by the Clinical Research Facilities at UCLH:

Early Phase Clinical Trials Process