Title: UCLH SOP – Procedure for the review and approval of Early-Phase Clinical Trials at UCLH

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1	**30/04/2017**	Initial release for standardised use across UCLH	Vincenzo Libri
2	**04/07/2023**	Title change, addition of legislation referenced	Melanie Dhanaratne

ACRONYMS

AAC	Assess, Arrange and Confirm
AFC	Adoption and Feasibility Committee
ALS	Advanced Life Support
ATIMPs	Advanced Therapy Investigational Medicinal Products
BRC	Biomedical Research Centre
CI	Chief Investigator
CRF	Clinical Research Facility
CRUK	Cancer Research United Kingdom
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	Healthy Volunteers
ILS	Immediate Life Support
IMPs	Investigational Medicinal Products
JRO	UCLH/UCL Joint Research Office
LWENC	Leonard Wolfson Experimental Neurology Centre
MHRA	Medicines for Health Products Regulatory Agency
NHNN	National Hospital for Neurology and Neurosurgery
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 and Development
REC	Research Ethics Committee
SOP	Standard Operating Procedure
UCLH	University College London Hospital NHS Foundation Trust

1. PURPOSE, SCOPE AND BACKGROUND

University College London Hospital NHS Foundation Trust (UCLH) hosts a number of research studies. This includes a significant proportion of “early phase” clinical trials. “Early phase” in the context of this Standard Operating Procedure (SOP) refer to Phase I – Phase IIa Clinical Trials of Investigational Medicinal Products (CTIMPs) as defined in the Medicines for Health Products Regulatory Agency (MHRA) Good Clinical Practice Guide (2012).

This Standard Operating Procedure (SOP) describes the procedure to be followed by investigators, sponsors, and research support staff for the approval of early phase trials at UCLH, in line with MHRA expectations on the conduct of early phase trials. The scope of this SOP covers the procedure for the approval of early phase clinical trials (Phase I-IIa) at UCLH. The SOP outlines the procedure for the assessment and adoption of these trials through the National Institute for Health Research (NIHR) University College Hospitals NHS Foundation Trust (UCLH) Clinical Research Facility (CRF) Adoption and Feasibility Committee (AFC) (referred to as CRF AFC for the remainder of this SOP). This SOP applies to all UCLH investigators proposing to conduct early phase/complex trials at UCLH.

The NIHR UCLH CRF (referred to for the remaining SOP as CRF) operates at two sites, 170 Tottenham Court Road and the Leonard Wolfson Experimental Neurology Centre (LWENC) at the National Hospital for Neurology and Neurosurgery (NHNN). The CRF supports early Phase (Phase I and IIa) CTIMPs, and Advanced Therapy lnvestigational Medicinal Products (ATIMPs). These include First in Human (FIH), dose escalation and dose expansion trials in both healthy volunteers (HVs) and patients.

The CRF also undertakes some later Phase IIb and Phase III studies that have a significant experimental medicine component and mechanistic/biomarker studies. Experimental medicine can be broadly defined as investigations undertaken in humans, to identify mechanisms of pathophysiology or disease and/or demonstrate proof-of-concept evidence of the validity and importance of new discoveries or treatments. The adoption of studies later than phase IIa is not covered in this SOP.

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-lMPs 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'.*

To be compliant with the MHRA guidance, the position at UCLH is for all studies within Phase I and Phase IIa be hosted in the CRF. This is in all cases unless there is a practical or significant rationale for the study to be hosted outside of the CRF. The CRF will either confirm trial adoption of the study to take place within the CRF premises or accept a valid reason provided for the study to be hosted elsewhere at UCLH. This is referred to as an “exemption” for the study to be conducted outside the CRF.

Examples of exemptions to early-phase/complex trials that need to be conducted outside the CRF due to exceptional circumstances include trials that require the IMPs 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 myocardial infarction etc. Likewise, an exemption could be granted to early-phase trials with 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 an early-phase trial outside the CRF must obtain an exemption from the CRF, as reflected in the CRF AFC Terms of Reference (TOR). Such studies will be referred to the JRO or Cancer Clinical Trials Unit (the latter for cancer trials only) to complete the host approval procedure.

The CRF AFC reviews, risk assesses, and approves early Phase I and IIa clinical trials, including FIH and/or ATIMP trials, across a broad spectrum of diseases. The overall purpose of the CRF AFC committee, is to advise and make decisions on the adoption of such trials onto the CRF study portfolio. Should the CRF be unable, or feel it is not viable, for the study to be hosted at the CRF, the study will be referred to the JRO to advise on alternative, appropriate spaces. The purpose of the AFC is reflected in the CRF AFC TOR (see Appendix A).

Studies referred for adoption (see UCLHCRF-OP01 Trial Application & Adoption) at the CRF will undergo the following full assessments at CRF AFC:

- 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 requirements in compliance with CRF's relevant SOPs

The CRF AFC also recommends 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 clinical, laboratory and operational SOPs, to which investigators must adhere, have been developed to define and underpin the conduct of these trials at the CRF to ensure stringent patient safety during experimental drug administration and monitoring.

2. PROCEDURE

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

If any applications for early phase studies are received by the UCLH JRO or another unit at UCLH, the JRO or unit should refer the application to the CRF Clinical Studies Manager (CSM) who will advise the researcher on the procedure for submission of an application to the CRF AFC.

Investigators applying for a CRF exemption should submit a completed CRF Exemption Form (see Appendix B) to the CRF CSM for review. Early phase studies applying for a CRF exemption will need to demonstrate a clear rationale of the safety and logistical considerations for the conduct of the trial outside for the CRF.

Any studies applying for an exemption from the CRF will be reviewed in the first instance by the CRF Director, CRF General Manager, CRG Lead Nurse, CRF Quality Assurance Manager and CRF Clinical Studies Manager. If an exemption is accepted, studies will be referred to the JRO for AAC. If further feedback is required to make a decision, this may be discussed, and minutes recorded at AFC. If an exemption is not accepted, applicants will have the option to appeal the decision as reflected below.

The CRF AFC will:

- Include approved and adopted trials in the CRF portfolio.
- Record the decision in minutes, i.e. approval, approval with exemptions or non-acceptance, and notify the latter to CI/PIs and the JRO.
- Maintain oversight of regulatory compliance for studies approved to be carried out within the CRF.
- State whether the CRF or JRO will be responsible for completing the Assess, Arrange, Confirm activities for any CRF adopted trials. This will be confirmed in the CRF AFC Adoption Letter.
- For studies that have applied for an exemption and considered ineligible to take place within a UCLH site outside the CRF, AFC will consider appeals from investigators. In the event of an appeal being unsuccessful, investigators will have the option of referring the matter to the Director of Research at UCLH who will issue a final decision.

Studies will not be able to go ahead until the CRF assessments are completed and the JRO have been informed of the decision taken by AFC.

3. IMPLEMENTATION & TRAINING

This SOP is relevant across all research conducted at UCLH and targets all investigators and research teams who plan to conduct research studies which falls within the above categories and CRF remits.

All relevant investigators and study teams will be required to read, understand and familiarise themselves with this SOP on the UCLH JRO website and via JRO/Research Directorate communication bulletins & CRF bulletins.

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

4. PUBLICATION & COMMUNICATION

This SOP is authorised and published on the JRO website: http://www.ucl.ac.uk/joint-research-office. The latest version of the SOP will be made available on the JRO website.

The original fully signed master copy is stored in a designated folders within the JRO and maintained by the JRO Research Quality & Safety Manager (or Research Unit QA Manager if a Departmental SOP).

5. TEMPLATES ASSOCIATED WITH THIS DOCUMENT

N/A

6. REFERENCES

This SOP should be read in conjunction with:

CRF Adoption and Feasibility Committee Terms of References

UCLHCRF-OP01 Study application and adoption

UCLHCRF-OP02 CRF SOP for Study Start

UCLHCRF-OP05 Assess Arrange Confirm

UCLHCRF-CL01 Clinical Cover in the NIHR UCLH CRF

MHRA Good Clinical Practice Guide (2012)

All the above SOPs can be obtained via the CRF Quality Assurance & Governance Manager via uclh.referrals.clinicalresearchfacility@nhs.net

7. APPENDICES

APPENDIX A:

NIHR UCLH CRF AFC Terms of Reference is attached to UCLHCRF-OP01 Study application and adoption.

Please check with the CRF Quality Assurance & Governance Manager for an updated version of the Terms of Reference (where applicable) via uclh.referrals.clinicalresearchfacility@nhs.net

APPENDIX B:

EXEMPTION APPLICATION FORM - SOP 11

Please check with the CRF Clinical Studies Manager if there are any questions pertaining to any CRF Exemptions: via uclh.referrals.clinicalresearchfacility@nhs.net