CLINICAL GOVERNANCE - STANDARD OPERATING PROCEDURE

PROTOCOL DEVELOPMENT

CG-QMS SOP CG04

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Approved by: Signature:	UREC See original

Version History	**Reason for change**

NOTE: All SOPs are subject to regular review.

Please ensure that the version of this SOP is the most up-to-date.

OUT OF DATE DOCUMENTS MUST NOT BE USED AND HARD COPIES SHOULD BE DESTROYED

1. PURPOSE

To outline the process for developing a clinical trial or clinical study protocol. The aim is to develop a protocol document of sufficient quality to satisfy the requirements for formal University of Lincoln sponsorship and for submission to the ethics and regulatory bodies.

2. SCOPE

This SOP applies to any researcher conducting research falling under the remit of the Secretary of State for Health where a declaration of research sponsor is required. Where the University of Lincoln is sponsor.

3. BACKGROUND

3.1 The definition of a protocol as given in the Medicines for Human Use (Clinical Trials) Regulations, SI 1031, 2004, shall be adopted for all clinical trial/study protocols:

3.2 "protocol" means a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial'

3.3 It is the responsibility of the Chief Investigator (CI) or delegated nominee to ensure development of the protocol / supporting documents, to seek appropriate advice and consultation (including Public, Patient Involvement (PPI) where necessary) and to secure all necessary permissions.

3.4 Development of study documentation shall coincide with a request for Sponsorship from the University of Lincoln as per SOP CG02 Sponsorship

3.5 In line with University of Lincoln Health and Safety policy, a risk assessment must be carried undertaken, and the outcomes taken into consideration within the protocol. Potential risks associated with clinical research may be found in appendix A

3.6 The PIS and consent form should provide brief and clear information, using non-technical language (with technical terms explained), and follow the current HRA guidance on the design of information sheets and consent forms. UoL participant information sheet and consent form templates may be found at: https://lncn.ac/clinical_res

3.7 If the study is a Clinical Trial of an Investigational Medicinal Product (CTIMP) all ICH 'Elements of Informed Consent'[1] (section 4.8.10) should be covered.

3.8 Consent forms should be signed by the participant, the researcher or a representative of the researcher delegated to obtain consent. An independent witness is not routinely required except in the case of consent by a participant who may be blind, illiterate etc.

3.9 Consent by a legal representative/consultee is required for:

- Children age 15 and under
- Participants deemed unable to consent for themselves because of mental incapacity or disability.
- Participants in an emergency or acute situation where obtaining their consent is not possible at the time.

Note: Management of the above situations must be addressed within the protocol and appropriate legal representative/consultee information sheets and consent forms must be provided.

3.10 The CI may delegate the practical aspects of risk assessment to a trial/data manager or researcher (delegated designee) as appropriate but should take responsibility for providing overall supervision and final sign-off of this task.

4. CROSS REFERENCES

4.1 CG-QMS SOP CG03 Risk Assessment

4.2 CG-QMS SOP CG05 Ethics Applications

4.3 CG-QMS SOP CG06 Regulatory Applications

4.4 CG-QMS SOP CG12 Amendments

4.5 CG-QMS SOP CGIB1 Investigator Brochure

[1] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf

4.6 RG-QMS RG03 Document Control – (Study documents)

5. PROCEDURE

Note: All documents must be version controlled and dated as per RG03 Document Control – (Study documents).

The Chief Investigator (or delegated nominee) shall:

4.7 Complete a trial related risk assessment in accordance with SOP CG03 Risk Assessment

5.1 Prepare a clinical research protocol using the appropriate protocol template located at https://lncn.ac/clinical_res

5.2 Liaise with any relevant clinical colleagues and study management staff for advice and inclusion of text as appropriate to the study.

- For CTIMPs this must include a pharmacist
- Seek advice particularly for those aspects of the study treatment where the CI is not the expert e.g. radiology, pathology.
- Ensure PPI involvement where necessary.

5.3 Liaise with a statistician (as appropriate) when choosing primary outcomes, formulating primary study hypotheses based on the chosen outcomes, determining clinically significant differences, proposing a study design with the appropriate sample size and power calculations, writing prespecified statistical analysis plans, carrying out statistical analyses, interpreting results, and safeguarding the integrity and validity of the study when there is any modification of the protocol.

5.4 Compile an investigator brochure (IB) if required (CTIMP/Device study) as per SOP CGIB1 Investigator Brochure, or, collate together summary information and a Summary of Product Characteristics (SmPC) for the IMPs to be used.

5.5 Submit documents for peer review as necessary depending on the study. Taking into consideration any feedback and/or recommendations.

5.6 Prepare participant information sheets and consent forms using appropriate templates available at https://lncn.ac/clinical_res giving specific attention to considerations of the consent requirements for:

- children (defined as age 15 and under)
- persons with any incapacity that may affect their ability to consent
- the taking and retention of biological samples
- the taking and retention of personal details and long-term follow-up
- the use of audio and audio-visual recording equipment and use of direct quotations or identifiable data

5.7 Where required, ensure that translation is available, where English may not be the first language of any potential participants.

5.8 Prepare any other study related documents (including but not limited to): adverts, questionnaires, interview/focus group topics/themes, recruitment materials (compliant with the University's Guidelines for the Production of Research Materials), GP letter, data collection forms (where the participant is required to complete).

Note: The Research Governance Team (RGT) may be contacted at any stage for advice related to the clinical research.

Research Governance Review

A member of the RGT shall:

5.9 Undertake a review of all study documentation for insurance and governance purposes, to ensure completeness, consistency and compliance with any relevant legislation(s)/framework(s) and UoL policies.

5.10 Advise the CI (or delegated nominee) of any revisions required and review any subsequent drafts.

5.11 Advise the CI (or delegated nominee) when documents are acceptable and sponsorship confirmed in line with SOP CG01 Sponsorship

Use of agreed documents

The CI shall:

5.12 Ensure that approved documents are uploaded to IRAS (or the University of Lincoln Ethics Approval system) and submitted for approval in accordance with SOP CG05 Ethics Application and CG06 Regulatory Approvals

5.13 Ensure that all applicable permissions are in place prior to use.

5.14 Ensure that any subsequent changes to protocol or supporting documents must follow SOP CG12 Amendments

6. FLOW CHART

None required.

Appendix A

Justification for the Study and Study Design

Potential Hazard or Harm	**Points to consider**
Insufficient non-clinical or prior studies	Toxicology and/or experimental data to support use of the treatment in humans. Knowledge of the effects in humans
Plausibility of the treatment regime proposed	Capacity for delivering the treatment; cost; time, inconvenience to the participants; supplies logistics
Unclear objectives / hypothesis or unclear endpoints	Appropriateness of conducting the study; usefulness of the data; would the question be answered; ability to publish
Lack of independent peer review	Expert review of the study design to support the justification
Lack of expert input	Appropriateness of the study design; ability to meet objectives; capacity to deliver the treatment; permissions required e.g. ARSAC license
Randomisation procedure	Robustness: blinding and emergency un-blinding, supplies logistics; withholding effective treatment

Participant Safety, Wellbeing and Rights

Potential Hazard or Harm	**Points to consider**
Incurring adverse events (AEs)	Likelihood of AEs; expected AEs, including number, and distinguishing between known and unknown adverse events; level of seriousness and severity

Serious adverse event management	Information given to the participant and instructions for notification; system for expedited review, assessment and reporting of SAEs; clinical management of SAEs
Incurring extra treatments or withholding of treatment	Exposure to radiation and chemicals; extra treatments such as surgery or prolonged treatment; treatment may not be as effective as standard
Non-compliance or non-completion of the treatment regimen	Effect on endpoints; safety and efficacy implications; ongoing or follow-on treatment for the patient; possible withdrawal symptoms (CTIMP)
Failure to protect privacy or confidentiality including disclosure of confidential or personal information	Data storage facilities, access and security; participant identification on databases and study notes; disclosure of sensitive or incriminating information.
Failure to exclude pregnancy (if applicable) or failure to follow-up pregnancy outcomes	Effect on the unborn and health of the mother; systems to ensure that eligibility criteria are met; information given to the participant.

Participant Informed Consent

Potential Hazard or Harm	**Points to consider**
Insufficient or incorrect information given	Legal implications; eligibility criteria should be reflected; possible enrolment of ineligible participants; ethical and moral aspects.
Coercion into participation or exclusions	Incentives used; type and style of information given; language interpretation; eligibility criteria; logistics of the study from the participants' perspective
Entering participants without consent or assent	Legal implications; contravention of human rights; possible misconduct.
Withdrawal	Participant retention strategy; participants ongoing treatment after withdrawal, response to withdrawal requests (such as removal of data and samples); the information given to participants
Withholding new information	Continuing consent and right to withdraw; possible safety implications

Data Integrity

Potential Hazard or Harm	**Points to consider**
Lack of study power	Data could be unusable, objectives not answered;
Incorrect eligibility criteria	Validity of results; study objectives met; potential safety issues

Non-adherence to the protocol	Effect on results; safety issues; compliance to treatment regime and systems to record this; recovery of unused products (CTIMPs)
Incomplete data or incorrect data	Data could be unusable; effect on outcomes and results; implication for future practice
Database back-up and archiving	Loss of the data; inability to reconstruct the study; audit trail to confirm data changes

Study Management

Potential Hazard or Harm	**Points to consider**
Failure to recruit to targets or complete the study	Effect on statistical power and overall results; should the study continue; moral implications if study not completed; needless exposure to risks and adverse events for participants
Non-robust systems for data collection	Accrual of incorrect data and effect on results; safety monitoring (due to late data collection); effect on interim analyses
Study committees fail to meet or failure to act on recommendations of the Trial Steering Committee (TSC) or Data Monitoring Committee (DMC)	Stopping rules breached; safety monitoring; recruitment targets; effect on interim analyses
Insufficient/lack of monitoring	Stopping rules breached; safety monitoring; incorrect data accrued, effect on results; contravention of legal obligations
Loss of participants to follow-up	Effect on results; effect on safety/efficacy assessment
Fraud	Robustness of computer systems; contracts in place; training