



Division of Research and Innovation

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	Name	Position
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1. Scope

This SOP is applicable to

 All Great Ormond Street Hospital for Children (GOSH) or Institute of Child Health (ICH) staff who will be involved in the set-up and/or conduct of research studies that involve dose escalation.

Further to the requirements listed in this SOP, personnel must also comply with:

• Any additional study-specific requirements mandated by the PI, Sponsor or R&D.

2. Purpose

The purpose of this SOP is to outline the minimum requirements for performing studies that involve dose escalation.

3. Definitions/Abbreviations

Clinical Research – As per UK Framework for Health and Social Care Research and HRA/MRC 'Is my study research?' tool.

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Dose escalation – The progressive increase in dose following the review of available data from the previous dose level(s).

4. Responsibilities

Duties may be delegated but the responsibility always remains with those listed.

- 4.1 The study Principal Investigator (PI) is responsible for:
 - Ensuring that their study complies with the requirements detailed in this SOP.
 - Ensuring that the dose escalation procedure is detailed in the protocol and/or Risk Assessment.
 - Authorising the dose escalation decision (unless this is formally delegated to another suitably qualified investigator).
 - Ensuring the dose escalation procedure is followed and appropriately documented in the Investigator Site File (ISF) and medical notes.
- 4.2 All staff are responsible for:
 - Ensuring their practice meets the requirements of this SOP, the study protocol, GCP and any applicable legislation, policies, procedures or guidelines.

5. Procedure

For dose escalation studies, there must be a robust, clearly defined dose escalation procedure. This procedure must be followed and each step formally documented and filed in the Investigator Site File (ISF) and medical notes to demonstrate compliance and to allow for the reconstruction of the study.

5.1 Written Dose Escalation Procedure

The flowchart in Appendix 1 details the dose escalation stages and the minimum information that is required to be included within the written procedure at each stage. The procedure should be included in the protocol.

5.2 Dose Escalation

Dose escalation must follow the agreed procedure, unless this would be a risk to study participants (in this case contact the Joint R&D office IMMEDIATELY).

The dose escalation must not proceed if dose escalation limits are violated, unless an appropriate amendment receives the necessary approvals.

An amendment to the dose escalation procedure must have written approval from the Sponsor and appropriate authorities before it can be implemented.

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5.3 Dose Escalation in the Absence of the PI (Delegation)

The PI may delegate this task to another suitably qualified investigator involved in the clinical study, but this delegation must be formally authorised and documented in the study delegation log before this individual performs the activity.

5.4 The Quality of Data Used to Make Dose Escalation Decisions

It is imperative that the data used to make the decision are accurate. Therefore, all data used for the dose escalation decision must be subject to quality control (QC) procedures and this QC must be documented. The PI must request clarification from the Sponsor that any data received from an external source (e.g. from the Sponsor or another NHS Trust) has also been quality controlled. If data is in a draft format, this must be clearly documented and justified and consideration given to the influence of this data on study decisions.

5.5 Dose Escalation Documentation and Compliance

The site file must contain and clearly reflect the data reviewed and the decisions taken. All dose escalation steps must be clearly documented and retained in the ISF in order to demonstrate compliance with the dose escalation procedure and this SOP. Dose escalation documentation will be subject to audit to ensure compliance with this SOP.

6. Related Documents

NA

7. References

- MHRA Good Clinical Practice Guide (Grey Guide)
- MHRA Phase I Accreditation Scheme Requirements
- MHRA Phase I Accreditation Scheme Guidance Document
- ABPI (2012) Guidelines for Phase I Clinical Studies
- ABPI (2011) First in Human Studies

8. Appendices

• Appendix 1: Minimum Information Required For Dose Escalation Process

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Appendix 1: Minimum Information Required For Dose Escalation Process

Cohort Dosing

Define:

- The number of subjects per cohort.
- How the dose escalation data will be captured.
- The precautions (between doses, and cohorts) and stopping rules (for a subject, cohort, and study).
- If dose leaders are used, the process to ensure that dose leaders are not all are assigned placebo.



Preparation of the dose escalation interim report

Define:

- The number of subjects required to complete each cohort.
- The minimum set of data required (it is otherwise assumed a complete set will be reviewed).
- For multi-centre studies, consideration for amalgamtation and circulation of data from each site.



Documented quality control of the dose escation interim report

Define:

- How the data will be quatlity controlled to ensure they are accurate and robust.
- Who will prepare the report and who will perform the QC



Documented dose escalation decsion meeting

Minutes must include the date, attendees, what was reviewed/discussed, and the decision/outcome. Define:

- The minumum quorum of study and Sponsor personnel required to make the decision.
- The conditions under which dose escalation must not occur.



Documentation of the dose escalation decision

The decision to escalate must be formally approved (and documented) by the Sponsor and the PI (or delegate; delegations must be agreed and documented in advance). Define:

- How the decision is to be documented, communicated and retained (including data retention).
- The system for preventing dose escalation if the required parameters are not met.



Circulation of the PI's decision to relevant study team members

The PI (or delegate) must authorise the dose escalation decision. The decision surrounding dose escalation must be clearly documented before any further subjects are dosed.

The PI (or delegate) must inform Pharmacy and the study team in a timely manner to ensure they are provided with the outcome of dose decision meetings to facilitate IMP dispensing in line with the decision as supported by the study protocol.

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