Standard Operating Procedure (SOP)

MANAGEMENT OF DOSE ESCALATION IN RESEARCH STUDIES AT UHBW

SETTING Trust wide

AUDIENCE All research delivery staff at University Hospitals Bristol and Weston (UHBW), all Clinical Research Facility staff

ISSUE Dose escalation in research studies requires assessment of accurate data and careful decision making by appropriately trained and qualified research staff to ensure participant safety.

QUERIES Contact CRF Operations Manager

Document History

SOP number	SOP 029	**SOP Version**	1.0
Effective Date	04/MAR/2024	**Review Date**	04/MAR/2026

Review date	Version number	Version date	Effective date	Author/ Reviewer	Authorised by
N/A - Original	V1.0	02/FEB/2024	04/MAR/2024	Margie Pavey	Diana Benton on behalf of Trust Research Group

Version Number	Reason for change
V1.0	N/A Original

1. Introduction

Dose Escalation (DE) is a term used to describe sequential administration of a drug, increasing the dose at subsequent regular intervals following the review of available data from the previous dose level. DE is often conducted as part of a Phase I study and typically determines the Maximum Tolerated Dose (MTD) or recommended dose for Phase II trials.

These types of trials usually include a small number of patients and may include healthy volunteers. Deciding to place patients or healthy volunteers on a higher dose is a safety decision and therefore should be based on accurate information.

DE decisions made on an unvalidated dataset put participants and UHBW at high risk.

2. Purpose

The purpose of this procedure is to set out the Trust expectations for DE studies and to provide a standardised approach to demonstrating Principal Investigator oversight of the DE process. Adherence to the procedure will ensure safety of participants is protected by confirming:

- The Principal Investigator has been adequately informed about data used to make the DE decision.
- That a verified quality control process is in place to ensure accuracy of the data.
- That the PI is satisfied with the DE decision and formally documents their authorisation to escalate at site.

3 Scope

In Scope: This procedure applies to all research studies involving dose escalation conducted within UHBW.
Out of scope: This procedure does not apply to studies conducted within UHBW that do not involve dose escalation.

4. Responsibilities

4.1 The Principal Investigator (PI) is responsible for the following:

4.1.1 Prior to Research & Development (R&D) confirmation of capacity and capability, risk assessing the Sponsor's DE strategy outlined in the study protocol and other applicable supporting documents to ensure compliance with UHBW expectation for DE studies.

4.1.2 The medical oversight of the research participants under their care and ensuring they have sufficient information about data used for dose escalation to make appropriate decisions for these participants.

4.1.3 Demonstration within the Investigator Site File (ISF) of due diligence measures taken to ensure they have sufficient understanding of the data and are satisfied:

- that the DE strategy has been adhered to
- that data used to make the DE decision is accurate
- that appropriate quality control checks have been made on data used to inform the DE decision

4.1.4 Ensuring that their authorisation to dose escalate is formally documented in the ISF and circulated to the relevant parties (e.g. pharmacy).

4.2 UHBW Research and Development Office (R&D) is responsible for the following:

4.2.1 Research Management Facilitators (RMFs)will ensure that where appropriate the PI has completed and endorsed a local Dose Escalation Assessment and Mitigation Plan (TMPL_ 128) prior to issuing Confirmation of Capacity and Capability (C&C).

4.2.2 The RMF with support from R&D colleagues will support the PI, where required, to facilitate a side letter to the Clinical Trial Agreement (CTA) (see section 6.2 Risk assessment and mitigation planning).

4.2.3 All R&D staff are responsible for ensuring strict adherence to Data Integrity principles when performing any of the activities within the scope of this SOP.

5. Abbreviations and Definitions

Abbreviations and Definitions	
CRF	Clinical Research Facility
DE	Dose escalation
GCP	Good Clinical Practice
ISF	Investigator Site File
MTD	Maximum tolerated dose
PI	Principal Investigator - (PI)
R&D	Research and Development
RMF	Research Management Facilitator
SOP	Standard operating Procedure.
UHBW	University Hospitals Bristol and Weston NHS Foundation Trust

Definitions	
Early Phase	Early phase, or phase I and phase II, trials are the first step in testing new medicines that have been developed in the laboratory.
Dose Escalation study	In a Dose Escalation study the dose of the test drug is sequentially administered, increasing the dose at regular intervals following the review of available data from the previous dose level by a safety review committee (or equivalent). Dose Escalation is often conducted as part of a Phase I study and typically determines the Maximum Tolerated Dose (MTD) or recommended dose for phase II trials. See section 6.5 Dose Escalation Tree

6. Procedure

6.1 UHBW Dose Escalation (DE) Expectations

The sponsor must ensure a detailed DE process is outlined within the research study protocol, Data Monitoring Committee (DMC) charter or equivalent document and latest approved versions must be available to the participating sites at all times.

The following information about the DE must be clearly defined:

a. The number of participants required per cohort.
b. The minimum data time points (i.e., the minimum number of visits which a participant must have completed)
c. The minimum critical dataset required to inform the DE decision.
d. The approach to replacement of withdrawn participants
e. Sentinel dosing approach. Please note, if sentinel dosing is not required, **the PI should risk assess and determine any local mitigations if deemed appropriate.**
f. Where sentinel dosing is required, the mechanism/s for preventing dosing prior to completion of the required sentinel participants.
g. Individual participant stopping criteria.
h. Cohort stopping criteria.

i. Trial stopping criteria.

6.1.1 Risk assessment and mitigation planning

As outlined in 4.1 the PI is responsible for ensuring a robust risk assessment is conducted on the DE process to ensure it complies with the expectations outlined in this SOP. For early phase trials, the risk assessment must be documented using the Dose Escalation Assessment and Mitigation Plan (TMPL_128).

The Dose Escalation Assessment and Mitigation Plan (TMPL_128) must be reviewed and endorsed by the CRF Senior Management and Prioritisation Group if the trial is to be conducted in the CRF or by the R&D Senior Management Team if elsewhere in the trust, prior to confirmation of capacity and capability.

Where the risk assessment has required further information or clarifications from the Sponsor, correspondence must be retained and referenced in the Dose Escalation Assessment and Mitigation Plan (TMPL_128).

Where there are identified non-compliance/s to UHBW expectation, and mitigations are required, consideration must be given to the implementation of a side letter to the Clinical Trial Agreement (CTA) to detail the responsibilities for the mitigations. PI's must liaise with the RMF in R&D relation to this. An example of when a side letter may be recommended would be where responsibility for aspects of data quality control (QC) are to be delegated to site.

6.1.2 Source Data Verification/Quality Control Data

It is very important that the data used to make the dose escalation decision are accurate and robust. Therefore, all data to be used for the dose escalation decision should undergo a documented quality control (QC) process.

The Sponsor is responsible for performing Quality Control (QC) checks on 100% of the critical dataset prior to the dose escalation meeting (unless a reduced QC target is planned, in which case, this must be clearly described in the protocol so the regulators can see the rationale and are aware of any reduced QC in advance).

For multi-site studies, the Principal Investigator must be provided with documented assurance of the level of QC performed at all other participating sites.

The percentage of QC must be formally documented by the Sponsor and communicated in writing to the PI.

6.1.3 Data

The PI must be provided with information relating to the data on which the dose decision has been made. This can be achieved in several ways, for example:

- PI (or delegated representative) being present at the dose escalation meeting where data are presented and reviewed
- PI is provided with a data package / dose escalation interim report
- PI is provided with minutes from the dose escalation meeting (minutes must contain sufficient information regarding the critical data reviewed)

• PI is provided with a dose escalation summary document which contains a breakdown of the critical data reviewed.

6.1.3 Dose Escalation meeting (e.g., Data Monitoring Committee - DMC) or equivalent

a. The following must be clearly defined:
- when the dose escalation meetings will take place
- who is required to attend the DE meetings
- minimum quorum required to make a DE decision

b. The PI must have documented evidence of when the meeting took place and who was present, in order to verify compliance with the planned meeting quorum.

6.1.4 Escalation Decision

a. The Principal Investigator (PI) has the medical responsibility for the trial subjects under their care and is responsible for ensuring they have sufficient information about data used for dose escalation decisions so they can make the decision for participants under their care.

b. The outcome of the DE meeting must be clearly documented. An appropriate individual should circulate the written outcome of the DE meeting to all DE meeting attendees.

c. The PI must give written authorisation for the DE to proceed.

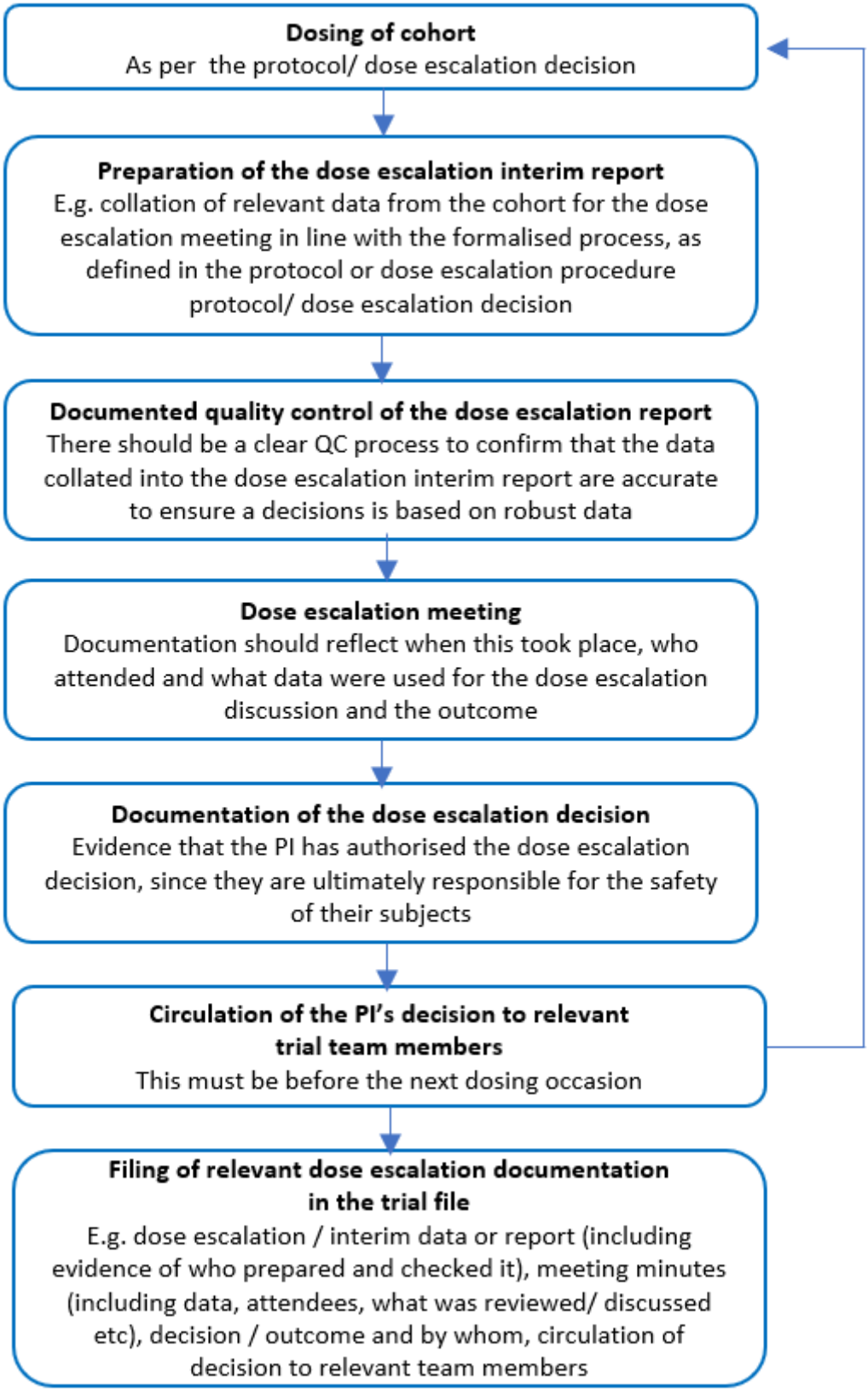
d. The PI must complete a Dose Escalation Authorisation Checklist (TMPL_129) and ensure it is circulated to all relevant parties e.g. (this list is not exhaustive):
- Pharmacy
- Delivery team
- Sponsor Representative

e. The outcome and PI authorisation to escalate at site, must be documented and filed in the Investigator Site File

6.4 Filing of Dose Escalation Documentation

6.4.1 There must be documentation in the ISF relating to the following (this list is not exhaustive):
- The local DE assessment and mitigation plan
- The dose escalation data (e.g., interim data report or equivalent)
- The DE meeting (including date, attendees, what was discussed)
- The DE decision/outcome
- The PI authorisation to dose escalate at site

6.5 Dose escalation decision tree



7 Dissemination and training in the SOP

This SOP will be disseminated to applicable research staff (including R&D) and will be available on the R&D website.

Plan Elements	Plan Details
The Dissemination Lead is:	Research Operations Manager
Is this document: A – replacing the same titled, expired SOP, B – replacing an alternative SOP, C – a new SOP:	C- This is a new SOP
If answer above is B: Alternative documentation this SOP will replace (if applicable):	
This document is to be disseminated to:	All applicable research staff (including R&D)
Method of dissemination:	For major updates to the SOP dissemination will be: 1. To Chief Investigators of UHBW Sponsored CTIMPs 2. Research Unit leads across UHBW 3. Head of Research Governance at UoB (where SOP is applicable) All updates (major and minor to the SOP) will be: 1. Updated on the trust Document Management System 2. Updated on the R&D website 3. Cascaded in the R&D e-bulletin
Is Training required:	All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP. The personal training log of the individual (and the Investigator Site File/Trial Master File if required) should be completed to document that the content of this SOP has been read and understood as described in *SOP_007 Research Training UHBW*

REFERENCES	MHRA Good Clinical Practice Guide MHRA Inspectorate blog – Dose Escalation – is it GCP compliant? https://mhrainspectorate.blog.gov.uk/2018/11/26/dose-escalation-is-it-gcp-compliant ABPI Guidelines for Phase I clinical trials 2018 edition MHRA Phase I Accreditation Scheme Guidance V4.1_ 12 Aug 2022 Strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products' Revision 1 20-Jul-2017 0.1.6 The Medicines for Human Use (Clinical Trials) Regulations

RELATED DOCUMENTS AND PAGES	TMPL_128 Dose Escalation Assessment and Mitigation Plan TMPL_129 Dose Escalation Authorisation Checklist
AUTHORISING BODY	Trust Research Group
SAFETY	Procedures must be in place to safely manage dose escalation in research studies to ensure participant safety.
QUERIES AND CONTACT	Contact the Research & Development department Ext.20233 or email research@uhbw.nhs.uk
AUDIT REQUIREMENTS	R&D departmental Quality Management System audits are undertaken annually.