

## Glasgow Clinical Trials Unit Standard Operating Procedure

SOP number	<b>21.025</b>	Version	<b>2.0</b>
Title	<b>Management of Dose Escalation in Early Phase IMP/ATIMP Clinical Trials</b>		

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SOP category	NHS GG&C Pharmacy - Sponsor IMP Management			
Staff category				
Staff category	R	A	C	I
Lead Pharmacist, Clinical Trials		X		
Chief Investigator	X			
Study Statistician	X			
Research Governance Manager	X			
Pharmacovigilance Manager	X			
Clinical Trial Monitor(s)	X			
Data Management Centre	X			
Study Project Manager(s)	X			
R&I Pharmacist(s)	X			
R&I Coordinator				X
Research & Innovation Systems Manager				X
Lead Clinical Trial Monitor				X

### 1. Scope

This Standard Operating Procedure (SOP) applies to clinical trials with a dose escalation element that are Sponsored/Co-Sponsored by NHSGGC. Glasgow Oncology CTU maintain their own operational SOPs.

### 2. Purpose

The purpose of this SOP is to define the overarching requirements for those clinical trials of Investigational Medicinal Products (IMPs) or Advanced Therapy Investigational Medicinal Products (ATIMPs) that incorporate a dose escalation (DE) element within the trial design. An overview of the dose escalation process is provided in Figure 1.

### 3. Procedures

#### 3.1. Background

Dose escalation decisions are critical to the safety and integrity of a clinical trial and must be conducted in accordance with Good Clinical Practice (GCP) requirements. Sponsors have a duty to ensure that risks to participants are minimised and to that end, protocol design and management of the DE process is key. Those making DE decisions must be appropriately experienced (both in their role-related training and in the protocol) and have sufficient assurances that the data on which the decision is made is complete and accurate (reported and verified). Decisions once made must be communicated to all relevant staff. The Trial Master File must also allow for the full reconstruction of the decision.

Early phase trials and particularly First in Human (FIH) clinical trials are inherently high risk, but good trial design and conduct in line with currently available UK/EU guidance will minimise participant and organisational risks.<sup>1-4</sup>

#### 3.2. Sponsor Risk Assessment

A thorough evaluation of the potential risks and their proposed mitigations in relation to DE must be documented as part of the Sponsor Risk Assessment throughout the life-cycle of the trial in line with SOP 51.004 Risk Assessment. The content of the risk assessment will inform the development of the protocol, subsequent amendments and the study specific Dose Escalation Plan (DEP).

#### 3.3. Protocol Requirements

The dose escalation procedure in the clinical trial protocol must be transparent but sufficiently flexible to cover foreseeable events in order to minimise the need for multiple amendments.

#### 3.4. Cohort Management

Sites are required to track provision of Patient Information Sheets (PIS) and subsequent consent or refusal to participate in the proposed research. Participants should only be approached where there is a potential treatment 'slot' available. Form 21.025A is a template cohort management form and will be used in addition to any screening log requirements as per SOP 56.002 Project Management Trial Set-up. This form may be adapted to meet the trial requirements.

#### 3.5. Dose Escalation Operational Plan (DEOP)

The DEOP is a controlled, study specific document that is supplementary to the protocol and provides detailed information on dose escalation processes, particularly the associated logistics. It is a Sponsor document that details operational arrangements that are specific to the study. It is not intended for regulatory submission, but forms part of the Trial Master File (TMF). A template is provided in Form 21.025B and details the roles of teams who have operational activities to be undertaken for any dose escalation meeting. This form may be adapted to meet the specific trial requirements. The DEOP will be circulated by the PM at the early set-up TMGs for completion by the relevant team members. The DEOP is complementary to the Safety Review Committee Charter (see below) and provides operational information on management of the DE process.

The DEOP must be formally approved by Sponsor (Research Governance Manager or Lead Pharmacist Clinical Trials/R&I), University of Glasgow Governance team and the study statistician prior to issue of the Sponsor Regulatory Green Light (RGL).

In the event an amendment is required to the protocol during the DE phase, a record must be maintained in the study specific risk assessment and TMG minutes to demonstrate that the DEOP was reviewed by the TMG and the implications for any changes considered.

### 3.6. SDV Data Checks for Dose Escalation Decisions

In order to ensure compliance with Good Clinical Practice (GCP) it is imperative that clinical data that informs dose escalation decisions is complete, accurate, and verified, particularly for data that is linked to major safety and stopping criteria. SDV of the key data as defined in the dose escalation section of the protocol is an essential quality requirement of the DE decision making process and will be completed by the study Monitor(s), supported by the responsible data centre, Sponsor stakeholders and CI as appropriate. To ensure visibility across all key parties, the Source Data Verification (SDV) and QC (Quality Control) requirements for DE data will be documented within the DEP.

The DEP will include anticipated timelines for completion of SDV and where appropriate QC checks and an agreed escalation and resolution process. It will also include how participant data that is utilised in the DE process but has not been subject to SDV/QC will be highlighted for example in the event of late breaking data.

Other activities performed by the Monitor(s) that are not related to DE will be conducted in accordance with the relevant SOPs and contained within the Monitoring Plan.

### 3.7. Pharmacovigilance (PV) Requirements for Dose Escalation Decisions

Accurate and verifiable collation of all reported adverse events for each dosing cohort is a fundamental element of the DE process. The detailed process for resolution of outstanding AEs/SAEs and verification of PV data prior to the SRC taking place will be detailed within the DEP. All other usual PV activities will be conducted in accordance with the relevant SOPs and in line with the study specific PV plan.

### 3.8. Preparation of DE Data Report(s)

The study statistician will be overall responsible for preparation of report(s) for the SRC using the data held by the trial data management centre. The agreed format for the presentation of data will be drafted by the data management centre and confirmed by the SRC. Review of cumulative data from previous cohorts must also be taken into account thus allowing oversight of late emerging safety issues that may have occurred after the cut-off time for the previous dose escalation decision. The monitors will provide a report of the data that has been subject to source data verification.

### 3.9. Dose Escalation Decision Meeting Planning

The DE meeting should be scheduled and planned once either the dose level is completed or the pre-specified minimum data cut-off has been achieved. The study specific DEP will detail the timeline between the end of cohort and when the DE meeting may be scheduled. This should take into account the necessary time for completion of SDV and QC checks plus report preparation for the SRC. The site PI(s) must be provided with the opportunity to review and respond to the collated data for their site before the SRC review.

Unless an ad hoc meeting of the SRC is required, members of the SRC must be provided with all necessary reports in advance of the meeting, the timeline of which will be stipulated in the DEP.

DE meetings may need to be scheduled on an ad hoc basis in the event of emerging data that requires more urgent review by the SRC, in which case all reasonable efforts must be made to provide the minimum data as guided by the CI and study statistician required by the SRC to consider necessary actions. Meetings may be held in person, via teleconference or videoconferencing (preferable). Once the minutes are agreed, any recordings of the DE meeting will be deleted.

### 3.10. Composition of Safety Review Committee (SRC)

The role of the SRC is to assess the safety and tolerability of a specific cohort level and to provide a final decision either to progress to the next planned dose cohort or to implement an alternate action. The decisions of the SRC must be in accordance with the current approved study protocol. The Sponsor/Co-Sponsor will be responsible for setting up the SRC with input from the Chief Investigator. A draft SRC Charter will be circulated to SRC members by Sponsor prior to the Inaugural Meeting. A Chair will be appointed with the agreement of the Sponsor and CI. The SRC may co-opt other members as necessary during the life of the study. **Table 1** provides guidance on roles with 'voting rights' and quorate requirements for the SRC. The actual requirements for each trial will be documented within the SRC Charter. A template charter is provided in Form 21.025C. This form may be adapted to meet the trial requirements.

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**Table 1:** Guidance on SRC members, capacity and quorate requirements

Role	Voting Capacity	Attendance required to be quorate?	Comments
Chief Investigator	Voting	Yes	May act as Chair
Principal Investigator(s)	Voting	At a minimum, at least 50% of site PIs must be in attendance or represented at the SRC	Where delegated and agreed by Sponsor, appropriately trained and experienced sub-investigator(s) may perform this role in the absence of the PI)
Statistician	Non-voting	Yes	
Independent Clinician*	Voting	If no IDMC then it is strongly recommended that at least one must attend	It is strongly recommended that a minimum of two independent clinicians are included on the SRC if an IDMC is not to be convened.
Expert Clinician**	SRC Decision	SRC Decision	
Expert(s)**	Advisory non-voting	SRC Decision	
Sponsor Pharmacist	Advisory non-voting	Yes	
Sponsor Representative(s) (SR) for each Sponsor	Advisory non-voting	Yes	The designated Sponsor representative may fulfil a dual role on the SRC e.g. have the role of Sponsor Pharmacist and Designated Sponsor Representative.
Pharmacovigilance Manager	Advisory non-voting	No	
Trial monitor(s)	Advisory non-voting	No	
Project Manager	Advisory non-voting	No	
Other	SRC Decision	No	

\* Independent Clinician(s) and Statistician may be required at Sponsor's/CI request particularly where a separate IDMC will not be established

\*\* Expert clinician or other expert may be co-opted on to the SRC as necessary

As per SOP 51.023, an Independent Data Monitoring Committee (IDMC) may also be convened. However, where the study protocol is strictly limited to dose escalation, with no subsequent expansion to assess efficacy of a final treatment dose, an IDMC may not be required. In this situation it is recommended that the SRC includes at least two independent clinicians. Any deviation from this recommendation must be robustly justified as part of the Sponsor Risk Assessment. Consideration should also be given to the inclusion of an independent statistician, particularly where statistical interpretation of data will inform the trial outcomes. Those serving in capacity as an Independent Clinician or Statistician must fully declare any potential conflicts of interest.

Observers will generally also be permitted to attend SRC meetings in a training capacity but are expected not to make any formal contribution to the meeting.

### 3.11. Inaugural SRC Meeting

The inaugural SRC meeting **must** occur prior to the Sponsor Regulatory Green Light (RGL). The following must be agreed:

- Agreement of final composition of the SRC
- Discussion and agreement of the SRC Charter
- Data requirements of the SRC for subsequent DE meetings

All voting members of the SRC (including any designees) will be required to agree to the SRC Charter prior to participating in SRC meetings. Minutes of the meeting must be made and retained in the TMF.

All necessary SRC voting members must have agreed and signed the SRC Charter in order to meet Regulatory Green Light requirements.

### 3.12. Subsequent SRC Meetings

All members of the SRC will be required to review the DE Data Report and documented Adverse Events (AEs) for that dose cohort. Prior to the start of the formal discussion, the SRC Chair will be responsible for deciding if the meeting is quorate and can therefore proceed as defined by the SRC Charter. As part of its deliberations, the SRC must decide, based on the data provided and the protocol, whether participants are evaluable. In the event the SRC finds that insufficient participants are evaluable, a dose escalation decision cannot be made. In accordance with the protocol, the SRC may decide to continue with the existing cohort or if necessary to implement other actions as permitted by the protocol. The SRC members are expected to come to a consensus on DE decisions.

The SRC must also consider whether adaptation of the protocol in other areas such as the required safety monitoring, or length of the follow-up period, need to be amended in order to safeguard study participants. The SRC will also be required to consider emerging data that may breach the pre-defined cohort or trial termination criteria. A template for the SRC Agenda is provided in Form 21.025C Template SRC Agenda. This form may be adapted to meet the trial requirements.

The minutes of each SRC meeting must be documented using the agreed study specific **Safety Review Committee Minute and Dose Escalation Decision** document. A template is provided in Form 21.025D. This form may be adapted to meet the trial requirements. The draft Safety Review Committee Minute and Dose Escalation Decision document must be formally reviewed and acknowledged by the Chair and Chief Investigator after all voting Members have been given the opportunity to comment. The study Project Manager (PM) will be responsible for collating the responses of voting members and informing the Chair as and when agreement of the draft minutes has been obtained. Any exceptions to this that are required in the event of planned leave or sickness must be discussed and agreed by a member of the senior management team and a record of the exemption retained in the TMF.

The SRC may, on occasion, make decisions other than DE decisions, via e-mail without convening a full DE meeting. For example, in the event that a participant fails to meet protocol requirements for evaluability it would be appropriate for the SRC to decide via e-mail, to expand a cohort by one participant with a view to obtaining sufficient evaluable patients to meet protocol DE data requirements. It is expected that those members with an advisory remit would be included in relevant communications. In the event of significant and serious safety concerns, a subset of the SRC may meet and provide urgent recommendations to the Sponsor.

### 3.13. DE Decision Approval, Agreement of Post DE Meeting Actions and Interim Communication

*DE decision approval:* After the DE meeting has taken place and the SRC members have agreed the draft minutes, the study PM will be required to formally finalise the Safety Review Committee Minute and Dose Escalation Decision. The CI and Chair must review and approve the **Safety Review Committee Minute and Dose Escalation Decision**. They must also prepare and agree an action plan to be implemented as an outcome of the DE meeting. Completion of the action plan will be managed by the study PM. The plan will usually include liaison and discussion with the following key groups as part of the 'Green to Dose' checklist:

- **Data Management Centre:** Formal communication to the Data Management Centre will be via a study specific form. A template Cohort Decision Form is provided for guidance. (Form 21.025F. This form may be adapted to meet the trial requirements).
- **Sponsor Pharmacy:** changes required to IMP management processes and dose preparation requirements as a consequence of the DE decision. Also time to complete any additional training with site investigator and pharmacy team.
- **Study Monitors:** any changes to monitoring requirements for next planned DE decision

Once the plan is agreed, and where dose escalation is to continue as per protocol, the study PM will be responsible for ensuring that all checks required for the issue of the 'Green to Dose' e-mail (A template Green to Dose Checklist is provided in Form 21.025G. This form may be adapted to meet the trial requirements).

*Interim communication:* The study PM will prepare an update e-mail communication that includes the anticipated plan and likely timelines for implementation for circulation to site staff as necessary. The communication must include clear warnings to the effect that no further dosing can take place until the Sponsor provides a 'Green to Dose' e-mail communication.

### 3.14. 'Green to Dose': Process for Communication of Dose Escalation Meeting Decision and Re-opening of eCRF/IWRS

The DE Plan will detail those staff who must be informed of the 'Green to Dose' communication. The communication package will include the following:

- The approved Safety Review Committee Minute and Dose Escalation Decision
- Copy of completed 'Green to Dose' Checklist

Once acknowledgement is received the study PM will usually issue a 'Green to Dose' e-mail to the following:

- **Site:** The local PI, lead site pharmacist and main site contact must all acknowledge receipt although in exceptional circumstances only the local PI and a designee of the lead site pharmacist is required to acknowledge receipt (e.g. in the event of sickness).
- **Other site contact:** It is anticipated that key contacts for local site teams will be retained by the study PM and the 'Green to Dose' e-mail should be circulated to the wider site team.
- **Data Management Centre:** This will be the trigger to deploy the agreed eCRF and IWRS changes and to re-open the eCRF to participant enrolment and randomisation (as applicable). The Data Management Centre will confirm back to the study PM once the necessary updates are deployed.

It is acknowledged that there may be a short time delay between the 'Green to Dose' e-mail being issued and the eCRF/IWRS changes being deployed, but this is expected to have minimal impact as participant enrolment in the DE phase of a study will often be pre-planned to some extent.

- **Sponsor:** The following Sponsor staff must be informed:
  - Research Governance Manager
  - Lead Clinical Trial Monitor and Trial Monitor
  - Research & Innovation Systems Manager
  - Lead Pharmacist, Clinical Trials /R&I
  - Senior R&I Pharmacist and Technician
  - Pharmacovigilance/Trial Safety Manager

The study specific requirements will be detailed in the DE Plan. No further acknowledgement is required from any parties.

### 3.15. Retention of Key Documents Relating to Dose Escalation

The following must be retained as part of the TMF:

- Signed SRC Charter for each voting member
- Completed Cohort Tracking Forms
- Evidence of completion of SDV by trial monitors and acknowledgement by Data Management Centre prior to generation of DE Data Report
- Evidence of completion of PV review by PV manager and acknowledgement by Data Management Centre prior to generation of DE Data Report
- DE Data Report to SRC
- Safety Review Committee Minute and Dose Escalation Decision document
- Acknowledgement of Safety Review Committee Minute and Dose Escalation Decision by each SRC member
- SRC(s) and CI approval of Safety Review Committee Minute and Dose Escalation Decision
- SRC(s) and CI agreement of post-DE meeting action plan
- Communications relating to the implementation and completion of the agreed DE meeting action plan including minutes or summaries of any meetings/decisions made.
- Local PI, main site contact and lead site pharmacist acknowledgement of the approved **Safety Review Committee Minute and Dose Escalation Decision** provided with the Green to Dose e-mail.
- 'Green to Dose' Checklist
- Confirmation by Data Management Centre for deployment of eCRF and IWRS and re-opening to participant enrolment and randomisation (where applicable).
- Any other relevant communications



### 3.16. Deviations from Protocol Defined Dose Escalation and Dose Escalation Plan

Deviations from the protocol defined dose escalation plan or SRC decision, will warrant an immediate stop to further enrolment and dosing to allow the Sponsor time to review the situation and if necessary inform the SRC and implement appropriate remedial actions.

It is difficult to be proscriptive regarding deviations from the study specific dose DE Plan as these could range from minor to major deviations but they should be dealt with as per any deviation to an agreed process i.e. study PM may be able to manage through discussion at TMG or escalation to Senior Management Team depending on urgency and risk.

### 4. Referenced documents

- Form 21.025A - Cohort Management
- Form 21.025B - Dose Escalation Operational Plan
- Form 21.025C - Template SRC Charter
- Form 21.025D - Template SRC Agenda
- Form 21.025E - Safety Review Committee Minute and Dose Escalation Decision
- Form 21.025F - RCB Cohort Decision Form
- Form 21.025G - Green to Dose checklist
- SOP 51.004 - Risk Assessment
- SOP 51.023 - Sponsor process for an IDMC
- SOP 56.002 - Project Management Trial Set-up

### 5. Related documents

1. Association of the British Pharmaceutical Industry. Guidelines for Phase I clinical trials (2018 edition). <https://www.abpi.org.uk/publications/guidelines-for-phase-i-clinical-trials-2018-edition/> (accessed 07.07.2023)
2. European Medicines Agency. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf) (accessed 07.07.2023)
3. MHRA Phase I accreditation scheme guidance document (August 2022) [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/1102630/2.\\_MHRA\\_Phase\\_I\\_Accreditation\\_Scheme\\_Guidance\\_v4.1\\_12\\_August\\_2022.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1102630/2._MHRA_Phase_I_Accreditation_Scheme_Guidance_v4.1_12_August_2022.pdf) (accessed 07.07.2023)
4. MHRA. Dose escalation – is it GCP compliant? <https://mhrainspectorate.blog.gov.uk/2018/11/26/dose-escalation-is-it-gcp-compliant/> (accessed 07.07.2023)

### 6. Document history

Version	Date	Description
1.0	02/05/2025	First Release
2.0	26/05/2025	Change to require SRC Chair to approve SRC minutes and action plan and removal of Sponsor Representative approval. Title change to Form 21.025B

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**Figure 1:** Flow chart of Dose Escalation process

