# DOSE PROGRESSION AND STOPPING RULES

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| **DOCUMENT NO.:** | **CR016 v1.0** |
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| **ISSUE DATE:** | **07-Feb-2020** |
| **EFFECTIVE DATE:** | **21-Feb-2020** |

## 1 INTRODUCTION

1.1 The Academic & Clinical Central Office for Research & Development (ACCORD) is a joint office comprising clinical research management staff from NHS Lothian (NHSL) and the University of Edinburgh (UoE).

1.2 To ensure the safety of all trial subjects, it is vital that 'dose progression', meaning the escalation to the next consecutive dose in line with the dose progression rules are described in formalised procedures and the approved protocol. By detailing how the dose progressions process will be undertaken, a clear documented dose progression decision can be made by the Sponsor, Chief Investigator (CI) and the Principal Investigator(s) (PI).

## 2 PURPOSE

2.1 To describe the procedure for reviewing data and documenting the dose progression decision in accordance with applicable legislation and the relevant early phase guidance.

## 3 SCOPE

3.1 This SOP applies to study investigator teams involved in dose progression studies Sponsored by NHSL and / or the UoE, and to ACCORD personnel involved in review/approval of dose progression decisions.

## 4 RESPONSIBILITIES

4.1 It is the responsibility of the CI to;

- Document the dose progression plan in the protocol and / or Data Monitoring Committee (DMC) charter,
- Collate and quality control (QC) check the dose progression data and produce a dose progression DMC report for the DMC,
- Verify the accuracy of the data used to make the dose progression decision
- Make a documented decision regarding dose progression,
- Ensure dose progression decision forms from the Sponsor and site PI(s) are completed and filed in the Trial Master File (TMF), where applicable,
- Communicate the outcome of dose progression decision to all relevant parties.

4.2 The Sponsor Representative, or designee, is responsible for making a documented decision regarding dose progression following review of the required documentation, communicating the outcome to the CI and filing evidence of dose progression decision making in the TMF and / or Sponsor File.

4.3 The PI has the medical responsibility for the trial subjects under their care and as such are responsible for ensuring that they have the information about the data used (e.g. for starting dose and for the dose progression decision), so they can make the decision for the subjects under their care.

4.4 The PI is responsible for satisfying themselves that the data used to make the dose progression decision has been QC checked prior to making a documented decision regarding dose progression at their site, and filing evidence of their dose progression decision making in the Investigator Site File (ISF).

4.5 The ACCORD Clinical Trials Monitor is responsible for monitoring of data required for dose progression decision making, prior to circulation to the statistician and/or DMC (where documented in the study specific monitoring plan).

4.6 The Trial Statistician is responsible for analysing data where applicable for inclusion in the DMC data review report;

## 5 PROCEDURE

### 5.1 Dose Progression Plan

5.1.1 The CI, or designee, will document the dose progression plan and stopping rules in the protocol and / or DMC charter. This will include details on the collection of subject data at all required timepoints (including if any time-sensitive safety concerns arise for example when a stopping rule has been met), the verification of data for accuracy (including QC checking) , the study progression and decision making process (including the circulation of data to relevant parties) and communication plan.

5.1.2 The proposed dose progression plan will be appraised at the Combined Risk Assessment (ACCORD SOP GS002) and a mitigation plan documented where required.

### 5.2 Dose Progression Process

5.2.1 The CI, or designee (e.g. Trial Manager), will collect all relevant dose progression data (e.g. safety and tolerability data) on subjects as defined in the protocol and / or DMC Charter, and verify the data by performing QC checks. If applicable, source data verification / QC may be conducted by the ACCORD Clinical Trials Monitor as per the study specific monitoring plan. Once the QC process is complete and all associated actions closed, the Clinical Trials

Monitor will release the data to the CI, or designee (e.g. statistician) for analysis and inclusion in the DMC data review report.

5.2.2 The CI, or designee, will compile the DMC data review report including evidence of the QC checks performed and where applicable, seek input from the Trial Statistician. This report must be controlled with a version number and date on the title page and all subsequent pages as per ACCORD Document Version Control SOP (QA008). This DMC data review report will be authorised and signed by the CI.

5.2.3 The CI, or designee, will provide the DMC data review report to members of the DMC and the Sponsor Representative(s) ahead of the scheduled DMC meeting according to the DMC charter (ACCORD SOP CR015).

5.2.4 Depending on the study design (e.g. blinded or unblinded) the DMC will produce open and / or closed minutes. The decision of the DMC on whether to recommend proceeding with dose progression will be documented in the open minutes. The open minutes of the DMC meeting will be received by the CI, and Sponsor Representative as per the DMC Charter (ACCORD SOP CR015).

5.2.5 The Sponsor Representative and CI will review the open DMC minutes and DMC data review report and make a documented decision regarding dose progression. The dose progression decision form (CR016-F01) will be used to document the Sponsor(s) and CI decision regarding dose progression, unless otherwise agreed with the Sponsor Representative, or designee.

5.2.6 The Sponsor Representative, or designee, may call a meeting with the wider ACCORD Sponsorship group to assist with decision making.

### 5.3 Dose Progression Decision

5.3.1 Once a decision has been reached, the Sponsor Representative, or designee, will communicate the outcome of their dose progression decision to the CI (and if applicable Trial Manager).

5.3.2 If the Sponsor and CI make a decision to proceed with dose progression (CR016-F01), the CI, or designee (e.g. Trial Manager), will cascade all information required (e.g. DMC data review report , open DMC minutes and CR016-F01) to all PI(s) to make a dose progression decision at their site.

5.3.3 The CI, or designee, will issue the dose progression decision to relevant parties as detailed in the dose progression plan (for example clinical and pharmacy teams, Trial Steering Committee) in advanced of the next dosing occasion. Dose progression will not proceed without documented authorisation from the DMC, CI, and Sponsor(s). Site specific dose progression will not proceed without the additional authorisation of the site PI.

5.3.4 If a PI decides not to proceed with dose progression (whether patient or site specific), justification will be provided in form CR016-F01 and communicated to relevant parties.

5.3.5 All evidence surrounding the dose progression decision making process will be filed in the TMF and / or Sponsor File by the Sponsor Representative (or designee) or CI/Trial Manager, if applicable.

5.3.6 The PI, or designee, will be responsible for filing evidence of the dose progression decision making process in the ISF held at their site.

## 6 REFERENCES AND RELATED DOCUMENTS

- MHRA Inspectorate Blog: Dose Escalation – is it GCP compliant (26-Nov-18)
- ABPI Guidelines for Phase I Clinical Trials 2018 Edition
- CR016-F01 Dose Progression Decision Form
- GS002 Combined Risk Assessment
- QA008 Document Version Control
- CR015 Data Monitoring Committee and Trial Steering Committee Charters

## 7 DOCUMENT HISTORY

| Version Number | Effective Date | Reason for Change |
|---|---|---|
| 1.0 | 21-Feb-2020 | New SOP |
| / | / | Periodic Review 12-Jan-22: No changes were deemed necessary to the SOP/CR016-F01 following review by the author. New review date of 21-Feb-24 has been assigned. |
| / | / | Periodic Review 19-Feb-24: No changes were deemed necessary to the SOP/CR016-F01 following review by the author. New review date of 21-Feb-26 has been assigned. |

## 8 APPROVALS

| Sign | Date |
|---|---|
| L. Mackenzie<br>AUTHOR: Lorn Mackenzie, QA Manager, NHS Lothian | Feb 20, 2024 |
| Elizabeth Craig<br>Elizabeth Craig (Feb 20, 2024 11:26 GMT)<br>APPROVED: Elizabeth Craig, Senior Clinical Trials Monitor, NHS Lothian | Feb 20, 2024 |

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| Heather Charles<br>Heather Charles (Feb 20, 2024 11:25 GMT)<br><br>AUTHORISED: Heather Charles, Head of Research Governance, NHS Lothian | Feb 20, 2024 |

# CR016 Dose Progression and Stopping Rules v1.0 (no changes necessary following 2024 author review)

Final Audit Report 2024-02-20

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|---|---|
| Created: | 2024-02-20 (Greenwich Mean Time) |
| By: | Gavin Robertson (v1grobe9@exseed.ed.ac.uk) |
| Status: | Signed |
| Transaction ID: | CBJCHBCAABAAmy694EPIBAbpx4v6oxtCmgAE6w-QI72u |

## "CR016 Dose Progression and Stopping Rules v1.0 (no changes necessary following 2024 author review)" History

Document created by Gavin Robertson (v1grobe9@exseed.ed.ac.uk)
2024-02-20 - 09:27:50 GMT- IP address: 62.253.82.233

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2024-02-20 - 09:30:20 GMT

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2024-02-20 - 09:32:46 GMT- IP address: 104.47.1.254

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2024-02-20 - 11:26:08 GMT- IP address: 62.253.82.233

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