
Practical Considerations on Simulations for Adaptive Dose- Escalation and Dose-Ranging Trials

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Based on work of

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Overview of dose-escalation and dose-ranging trials

General framework of the simulation report

Dose escalation

Dose ranging

Summary and discussion

Dose-escalation and dose-ranging studies



Overview

- Typically done in exploratory development phase (i.e. Phase 1, Phase 2)
- Primary objective: to study multiple doses and find “optimal” dose
 - Specific meaning of “optimal” depends on study objectives:
 - with respect to safety: maximum tolerated dose (MTD)
 - with respect to efficacy:
 - dose delivering maximum or close to max. effect (e.g. ED75, ED90)
 - minimally effective dose (MED)
 - with respect to both: “safe” and “effective” dose
 - Specific requirements for “safe” and “effective” can be quantified based on clinical /commercial objectives
- Additional objectives may include characterizing entire dose-response, dose-toxicity, exposure-response curves

Dose-escalation (D-E) and dose-ranging (D-R) studies



Similarities and Difference

Similarity

- Multiple doses studied within one trial
- “Learn” phase of development
- Attempt to characterize relationship between endpoint of interest and dose

Difference:

- D-E studies :
 - focused on tolerability or PK/PD endpoints
 - First-in-Humans (FIH) trials
 - Typically sequential, movement within dose range restricted
- D-R studies:
 - focused on efficacy
 - done in patients, FIH info usually available to guide design
 - multiple doses can be studied in-parallel
 - movement within dose-range not restricted

Both DE and DR study designs rely on modeling and simulation heavily, but methodology is different
=> simulation reports differ as well

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Key elements of simulation report for an adaptive study

General template (abbreviated)

- **Introduction**
- **Simulation Inputs:**
 - *benchmark (standard) design*
 - *proposed adaptive design(s) and their variants (if any)*
 - *clinical response scenarios*
 - *performance metrics to include in operating characteristics*
- **Simulation Results**
- **Summary and recommendations**
- **References**
- **Appendix**

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Content of simulation report for dose-escalation trial



Introduction: focused on trial objectives and rationale for selected design candidates

- These studies are typically First-in-Human (FIH) studies of the new treatment
- Because of FIH nature, the core objectives of dose escalation studies are centered around safety and tolerability
 - If early signal of efficacy is assessed, it usually plays a secondary role
- Learning about dose-toxicity relationship inevitably leads to some toxicity being observed
- Core objective of a dose-escalation trial is to protect safety of the subjects while accomplishing this learning in most efficient way possible
- The balance between learning and protection is implemented via restrictions on how aggressive the dose-escalation scheme can be:
- This depends on:
 - Patient population (patients vs. healthy volunteers)
 - Severity of disease (oncology vs. other diseases)
 - How much we want to learn: MTD only or entire curve (e.g. dose exposure)

Objectives of the trial are not varied through simulation, but its important to discuss it in simulation report with sufficient detail so that the rationale for methodology approach and selected design is clear

Simulation Input for DE studies



Description of “standard” and adaptive designs

- All D-E are adaptive, by definition
- “Standard” design, to be used as benchmark for performance
 - 3+3 design (oncology)
 - Similar “algorithmic” or cross-over or balanced incomplete block designs (in other TA)
- Proposed adaptive design(s) and their variants (if any)
 - Rule-based methods
 - **mTPI** (*Ji and Wang , 2013*)
 - **Up-n-Down** design (*Gezmu and Flournoy, 2006*)
 - Model-fitting methods
 - **mCRM** (*Braun et al 2002*)
 - **BNLRM** *Neuenschwander et al. (2008)*
 - Non-oncology: Bayesian design for PK/PD models (*Whitehead et al. 2001*)

Simulation Input for DE studies :

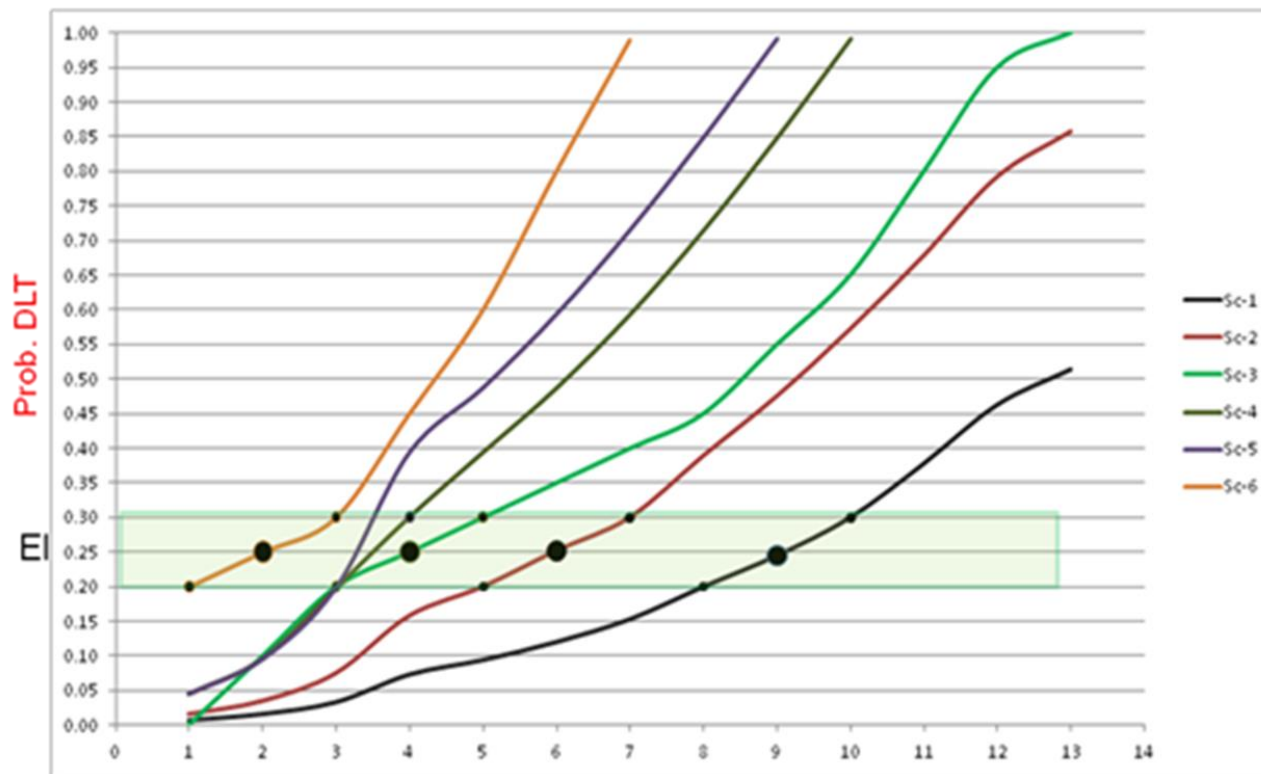


Developing a comprehensive set of toxicity scenarios to be used in simulation

- The degree to which safety of subjects in trial is protected cannot be adequately assessed without creating a wide-enough set of clinical scenarios of *dose-toxicity relationship for simulation*
- Needs to span all plausible dose-toxicity scenarios
- Include some extremes and sufficient variation:
 - *very safe drug*
 - *very toxic drug*
 - *something "in-between"*
 - *most influential: location of MTD (from starting dose) and steepness of curve*

Example 1 : set of clinical scenarios for dose-toxicity

Non-parametric (explicit) curves specification



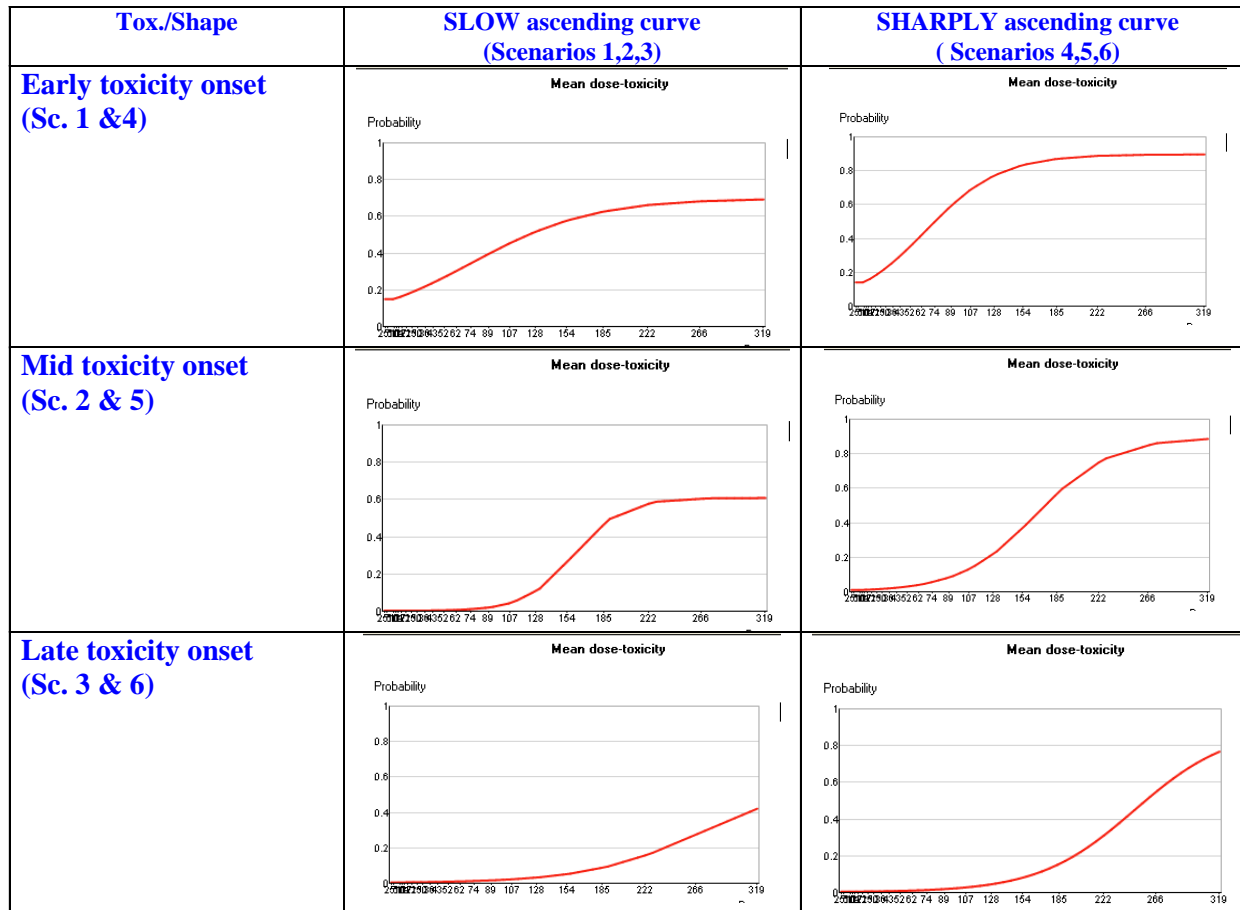
= MTD (Prob[DLT]=25%)

= Lower and Upper limit for EI (Prob[DLT] in the range 20%-30%)

Example 2: set of clinical scenarios for dose-toxicity



Parametric (model-based) specification; check against design working model



Simulation Output for DE studies



Operating characteristics to report

- Competing designs tested across multiple clinical scenarios
- Two types of metrics are commonly reported:
 - dose-based characteristics
 - scalar characteristics (arrange in a "matrix": design*scenario)

Metric	Comment:
Probability of each dose being picked as MTD	dose-based, best reported as histogram
Interval Probability of choosing MTD: <ul style="list-style-type: none">• Correctly• Underestimating• Overestimating• Not able (all doses too toxic)	Characterizes whether the trial meets its primary objective of determining MTD accurately to be further tested in Ph2 trials. The target range of DLT is typically 18-33% but this can vary
Mean (SD) of toxicity response at each dose	Assess the accuracy of the dose-toxicity estimation (and model fit, if model is used).
Sample Size	Scalar
Duration of the study	Scalar
Overall toxicities (number/proportion)	Scalar
Number of overdosed patients	Scalar; to track number of overdoses even if no DLT has occurred

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Content of simulation report for dose-ranging trials



Introduction: trial objectives

- Generally, these studies follow after FIH in exploratory development
- any dose below MTD (from FIH) can be studied
- Consequently, focus shifts from tolerability to evaluation of effect of dose on efficacy
- Sometimes safety is also added as a formal objective driving the design, but more commonly, it's just monitored
- Key objectives of D-R study can be*:
 1. Detecting DR (Proof-of-Concept)
 2. Identifying clinical relevance of effect
 3. Selecting a target dose for Ph3
 4. Estimating the dose response

Content of simulation report for dose-ranging trials



Description of “standard” and adaptive designs

- Traditionally, fixed allocation design is used in this space
 - Patients allocated to a few selected doses and control in fixed proportions
 - decisions about the best doses are made at the end of the study
 - pair-wise comparisons to a control (usually placebo)
 - model-based decisions can be added to fixed design
- Adaptive designs (key elements) :
 - type of adaptation decisions (drop/add doses; change allocation; early stopping)
 - what “drives” decisions: model (e.g. Emax) or pairwise-comparisons or both (e.g. MCPMod)
 - For Bayesian designs, specify prior and provide rationale:
 - Informative prior to incorporate external data, e.g. historical control
 - Non-informative prior: to provide a starting point for continuous learning framework
 - Longitudinal model (if used) to impute long-term endpoints for interim analysis

Content of simulation report for dose-ranging trials



Developing a comprehensive set of toxicity scenarios to be used in simulation

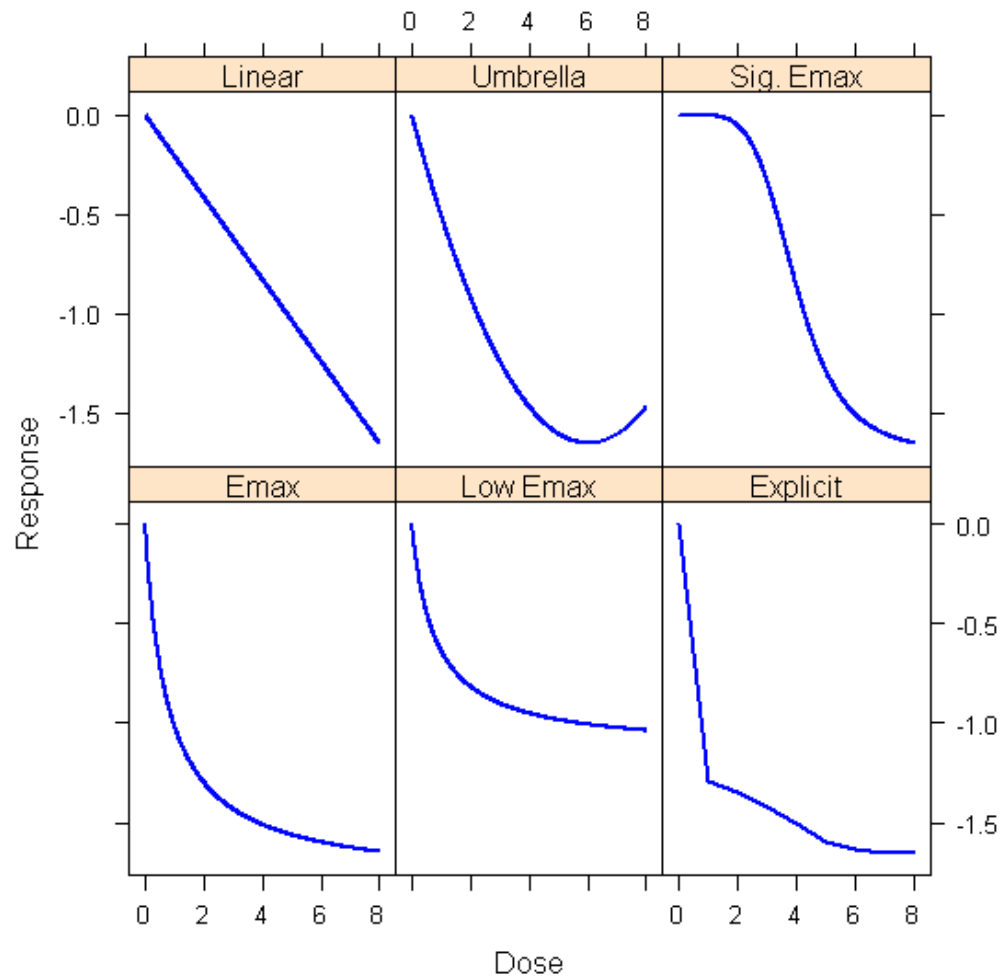
- Similar to dose-escalation studies, a good variety needs to be explored
- At the same time keeping the set clinically meaningful and reasonably small
- Effective drug
 - various shapes
- Non-effective drug*
- Moderately effective drug

*Discussed in more detail in context of type 1 error control

Example 3: set of dose-response clinical scenarios



Ref: Dragalin et al (2010)



Simulation Output for DR studies



Key metrics to report

- Two different groups of charts/graphs are useful:
 1. Particular metric across design × scenario combinations:
 - allows different design's performance to be compared across scenarios
 - helps in design elimination process
 2. Several metrics combined for a particular design × scenario combination:
 - allows in-depth look into design performance
 - more useful at the final design selection stage to verify desired properties
- Trial-level and subject-level charts:
 - very useful during design discussion phases or to answer questions
 - rarely used in simulation reports due to high level of detail

Simulation Output for DR studies



Examples of core metrics to include in operating characteristics

Key Metrics	Purpose
Mean (standard deviation) of the total number of subjects in the trial	Quantify benefits of stopping for futility or early success
Proportion of outcomes: <ul style="list-style-type: none">▪ Early success▪ Late success▪ Late futility▪ Early futility	High level characterization of the expected outcome for the dose-response scenario. For example, early futility is desirable under flat dose-response. Success can be defined based on predictive probability or posterior probability etc.
Proportion of time each dose is selected as a target (e.g. target is ED _x , MED)	For a given dose-response scenario, these proportions may be assessed against the “correct” selection (e.g., which dose is the true MED)
Mean (standard deviation of) number of subjects per dose	Assess how the adaptive allocation assigns subjects to address the research question (e.g., to find MED)
Mean (standard deviation of) response at each dose	Assess the accuracy of the dose-response estimation
Bias and Root Mean Squared Error of response at each dose	Assess the accuracy of the dose-response estimation
Mean probability of clinically significant difference for each dose	Quantifies the predictive probabilities of achieving a pre-specified treatment effect over control
Adjusted and/or unadjusted p-values/CI for pair-wise comparisons with control for each dose	Quantifies the frequentist p-values/CI for comparison of the response at each dose versus control

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Summary



- Adaptive Design (AD) simulation plays increasingly important role in modern drug development
 - As a result, [simulation report](#) becomes [a key design justification document](#) and as such, a regulatory document
- The work presented today is based on joint effort of several industry experts attempting to come up with [best practices in planning an AD simulation](#) and documenting it via simulation report
- We have focused on 2 types of AD:
 - AD for [dose-escalation](#) studies
 - AD for [dose-ranging](#) studies
- Both have multiple doses and frequently include modeling
- The key objectives of [DE](#) and [DR](#) designs are focused on [tolerability](#) and [efficacy](#), respectively
- Consequently, the key metrics reported in sim. report for these 2 designs are different:
 - [Percentage of studies identifying MTD correctly](#) is the focus of dose-escalation
 - [Percentage of studies making “correct” efficacy decision](#) (POC, dose-selection, DR estimation) is the focus of the dose-ranging studies
- In addition to key metrics, both types of design require examination of allocation pattern, overall sample size and protecting trial subject’s safety
 - In dose-escalation studies, the latter is quantified more formally by summarizing [percentages of overdosed subjects/toxicities](#) occurring in process of learning about MTD

References



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