Trial Designs for the Development of Treatment Parameters

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Disclosures

- None

Clinical Development

- Phase I- “Dose Finding”
  - Pharmacokinetics
  - Safety, feasibility
- Phase II – “Safety and Efficacy”
  - Safety, feasibility
  - Therapeutic activity
  - Informal comparisons
- Phase III-“Confirmatory”
  - Safety
  - Definitive evidence of efficacy
  - Formal comparisons designed to maintain acceptable statistical operating characteristics

Development

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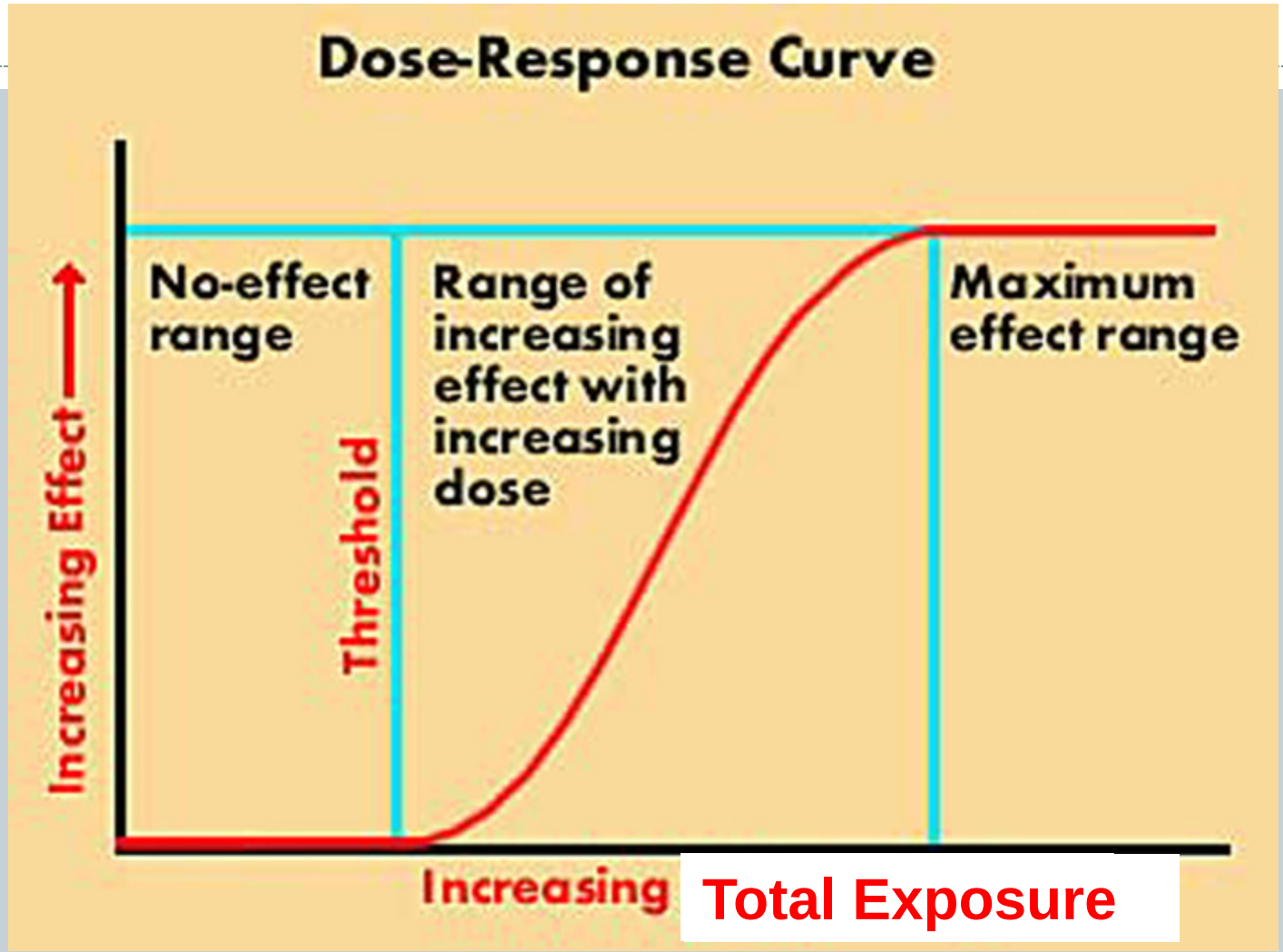
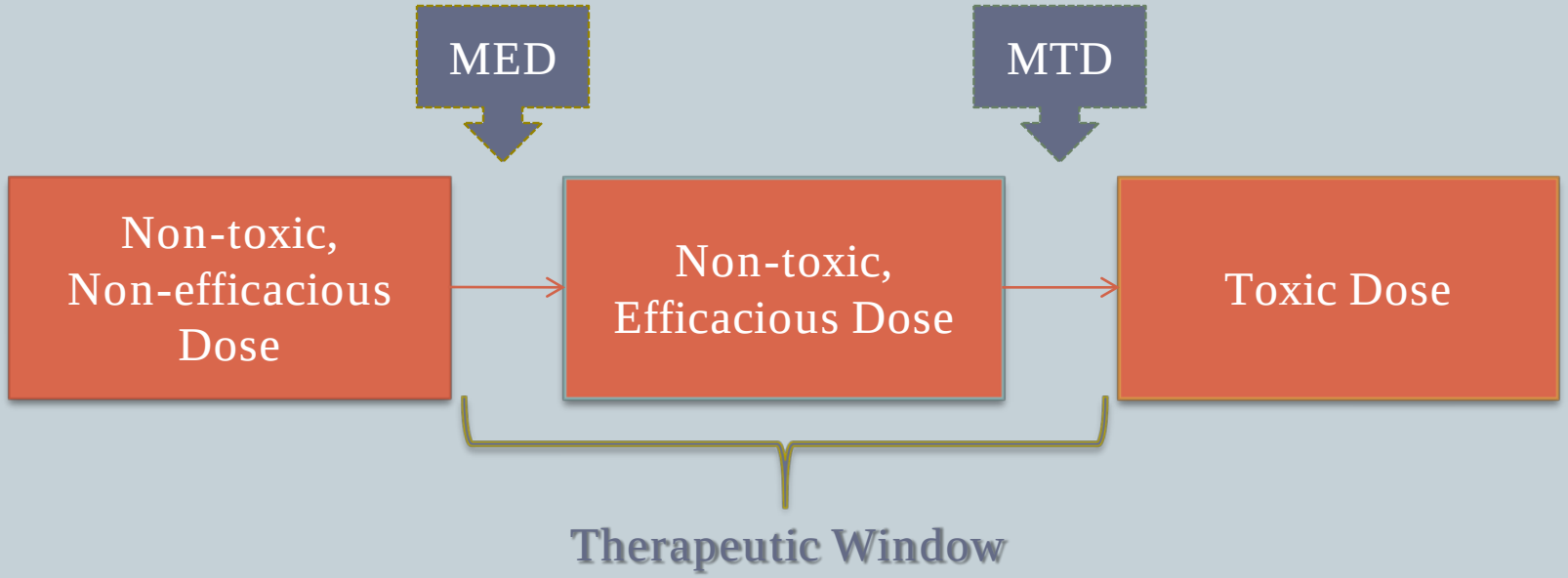
Dose-Finding Objectives

- To establish an optimal biological dose to move to Phase II studies
- May involve
  - Estimation of pharmacokinetic parameters
  - Assessment of tolerability and feasibility
  - Quantification of the toxicity profile



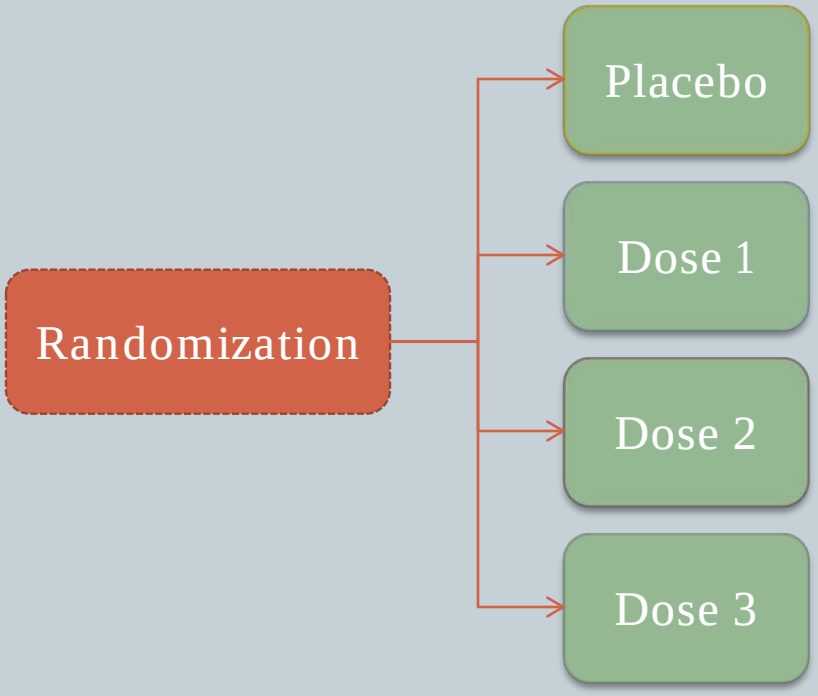
Defining the Optimal Dose



- Maximum Tolerated Dose (MTD): the highest dose without unacceptable toxicity
- Minimum Effective Dose (MED): the lowest dose with clinically significant efficacy

Idealized Phase I Design:

- Treat dose-finding like a Phase III clinical trial with randomization, etc.



Dose-Finding Designs

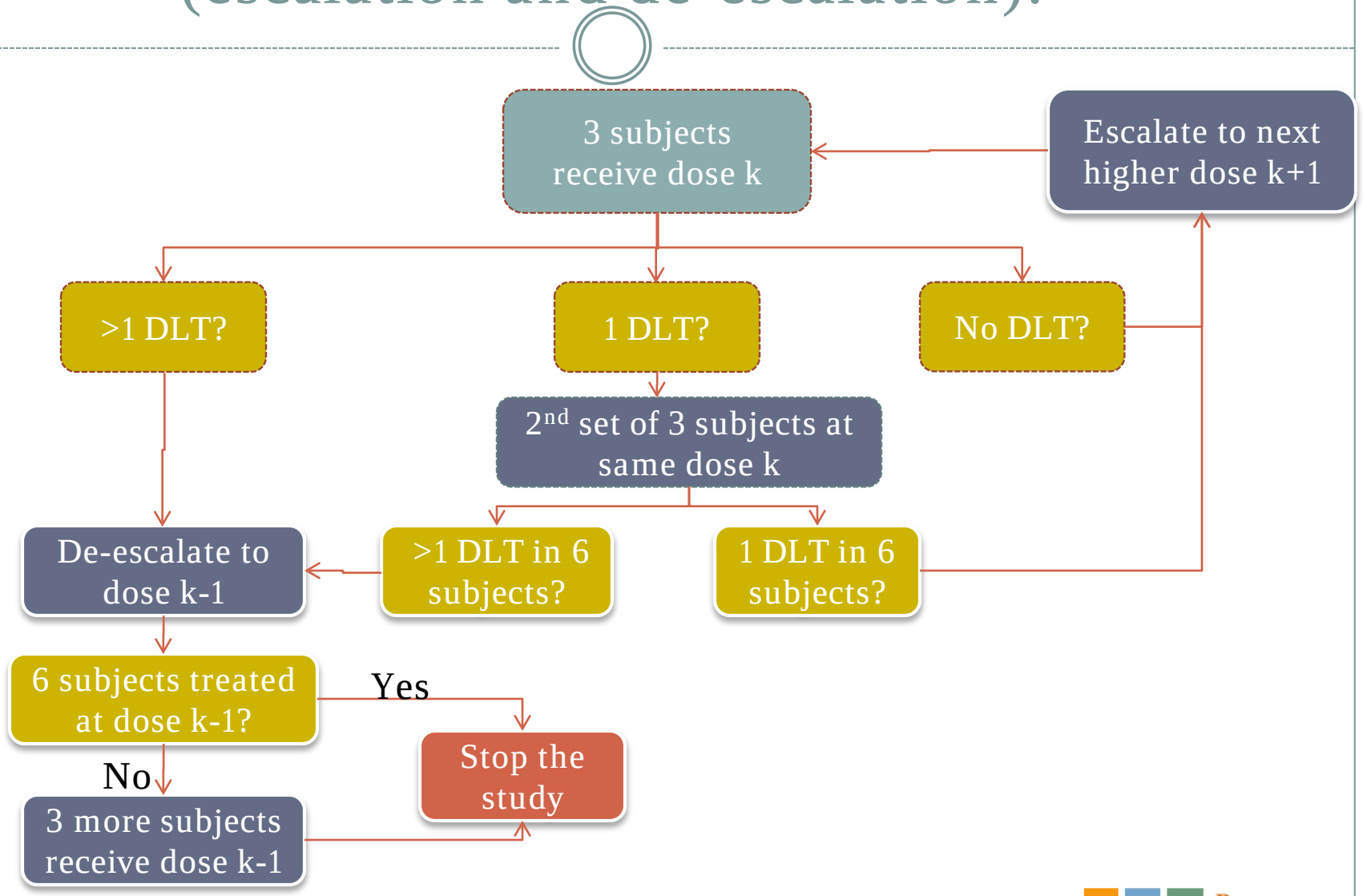
Rule-based

- Outcome: occurrence of target event (DLT)
- Dose levels pre-specified
- Stopping rule pre-specified
- (De-)escalation rules pre-specified
- Targets a 33% DLT probability

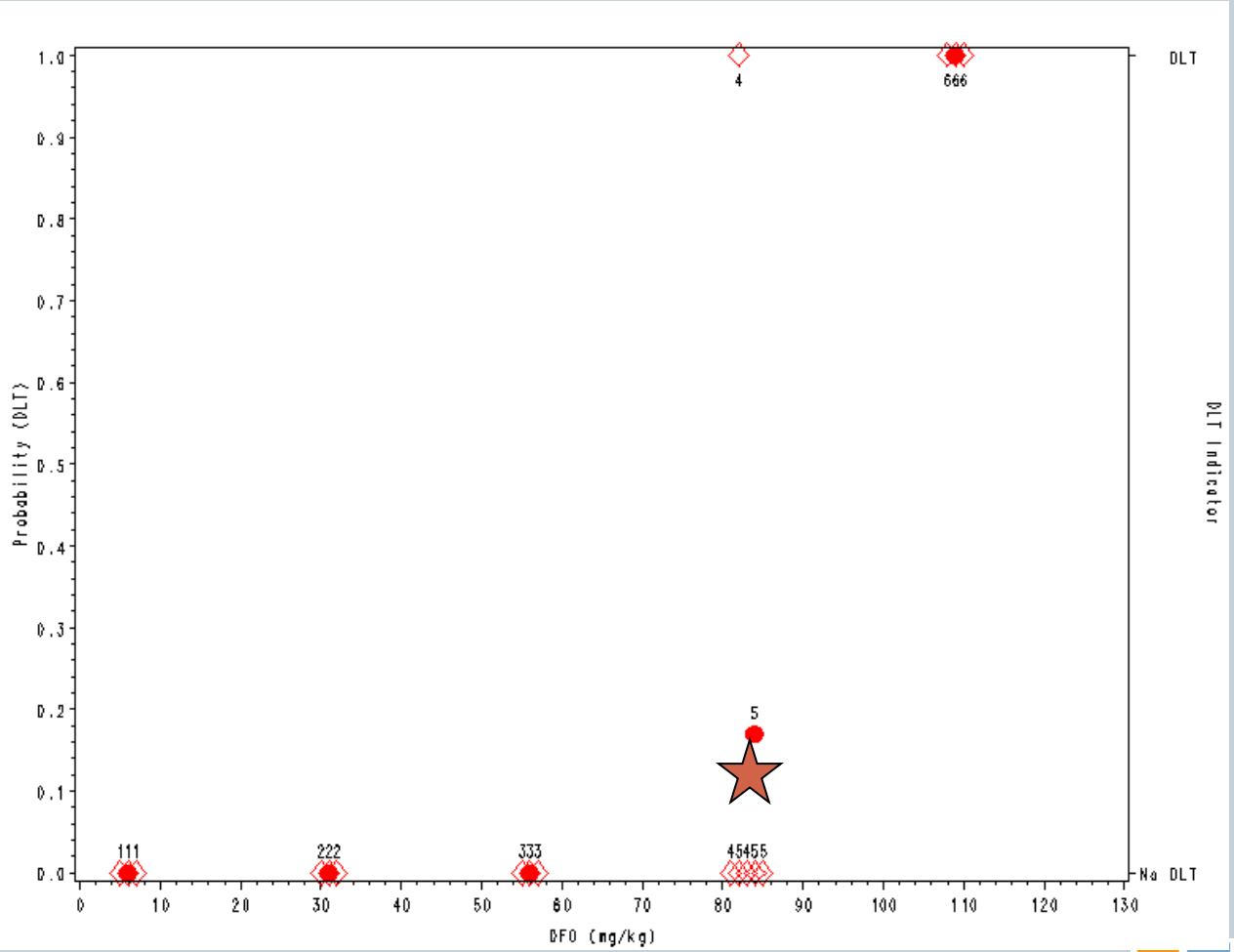
Model-based

- Outcome: occurrence of target event (DLT)
- Pre-specifying dose levels not necessary
- Stopping rule pre-specified
- (De-)escalation determined by estimation of the dose-toxicity curve
- Can target a pre-specified DLT probability in its search for the MTD

Traditional 3 + 3 (escalation and de-escalation):



Clinical Perspective:



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Rule-based Designs

Advantages

- Simple to implement
- Small sample size
- Familiar
- Do not require special software

Disadvantages

- Pre-specified dose levels
- Patients treated well below therapeutic range
  - MTD too conservative
  - Takes a long time for the MTD to be reached
- Decision rules do not use all available data
- Estimate of the optimal dose is biased and variable

Operating Characteristics

Clinical Perspective

- Concentrate dosing around the MTD
- Minimize the number of patients treated at subtherapeutic levels
- Obtain information re: inter-patient variability and cumulative toxicity

Statistical Perspective

- High probability of terminating at/near the true MTD
- Low probability of stopping before the true MTD
- Small probability of escalating beyond the MTD

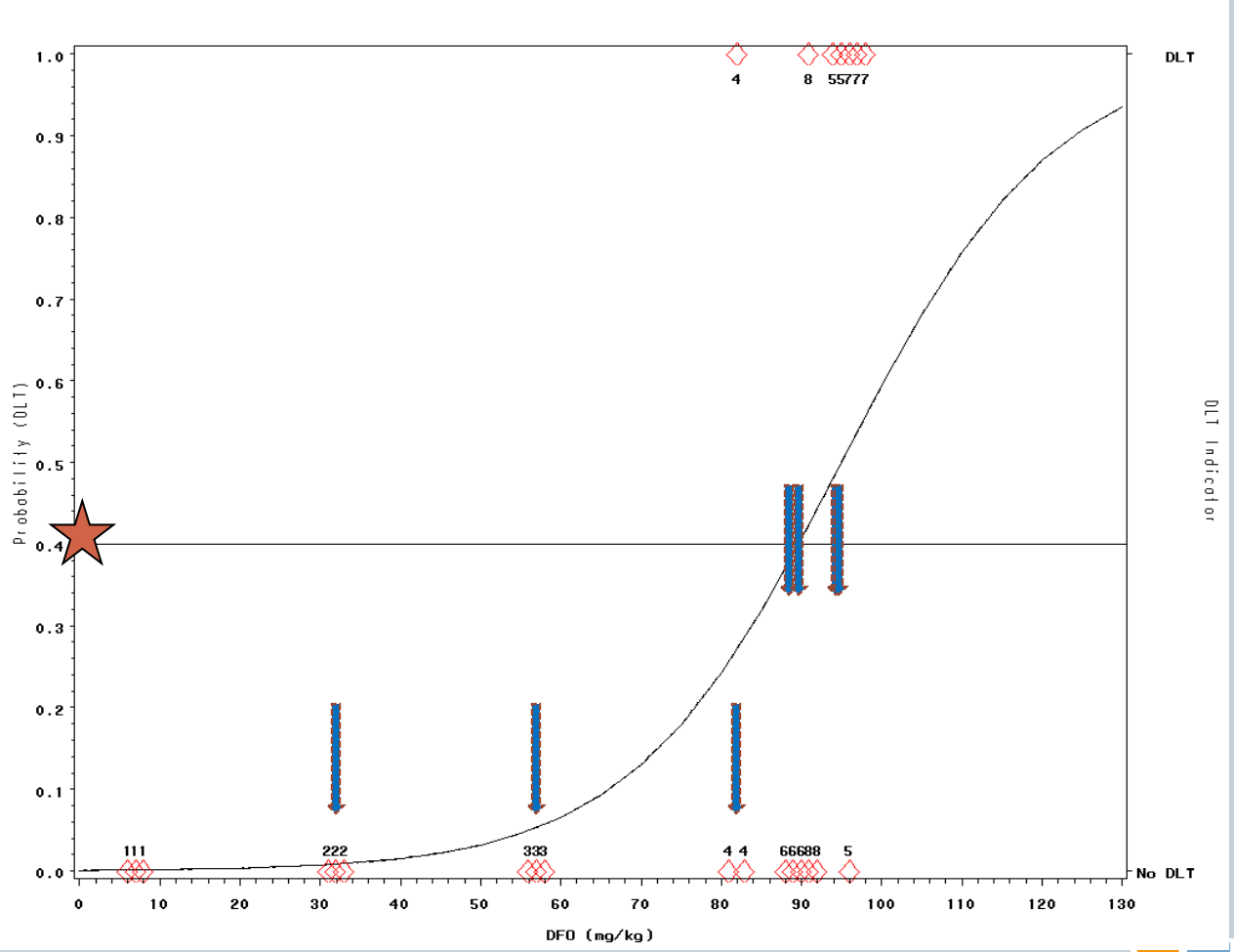
Continual Reassessment Method (CRM)

- First cohort is treated at the MTD identified based on a hypothesized dose-toxicity curve.
- After each outcome (absence/presence of a DLT) is known: the curve is re-estimated, and the MTD identified, using all of the available data
- The next cohort is treated at the current estimate of the MTD.
  - Process repeated until stopping rule reached.
    - Target sample size treated at MTD
    - Convergence/precision achieved
    - Maximum sample size reached
  - After the planned N subjects have been treated, the MTD is considered to be the dose of the N+1st subject.

Variations

- Modifications to the CRM
  - Treat a small cohort of subjects at each dose
  - Restrict escalation process so that doses do not increase too quickly
    - Choose low starting dose selected using conventional criteria
    - Incremental increases in dose until a DLT has been observed
    - Do not allow skipping over untried doses
- CRM with Expansion Cohort: enroll additional (6-15) subjects to be treated at the final MTD

CRM Simulated Trial



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Continual Reassessment Method

Advantages

- Clinical judgment and statistical rigor
- Statistical model uses cumulative information from *all* patients
- Estimates MTD from a continuous spectrum of doses
- Unbiased estimation
- Reaches MTD sooner
- Requires only a starting dose
- Does not depend strongly on the starting dose

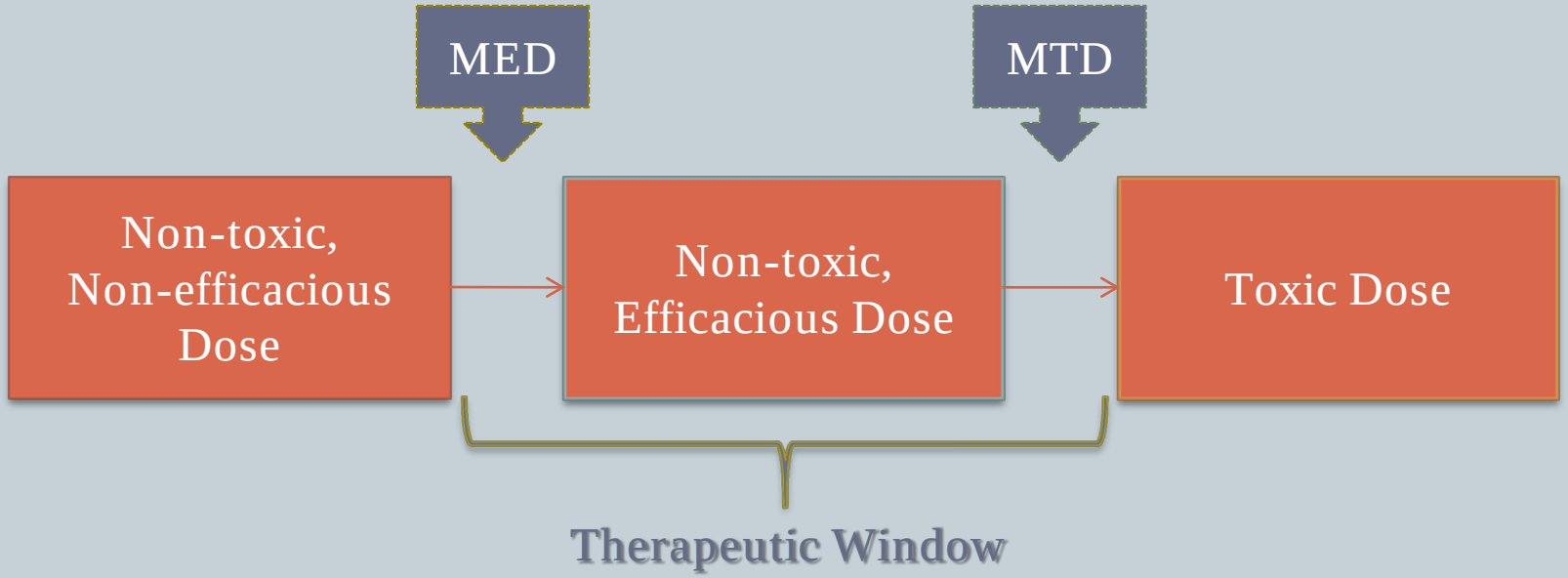
Disadvantages

- Comparatively complex – statistical software and statistical input required
- Potential to expose patients to high (and thus toxic) doses.

Variations

- Escalation with Overdose Control (EWOC): constrains the predicted proportion of patients who receive an overdose
- Time-to-Event CRM (TITE-CRM): extends the CRM for late-onset effects
- Ordinal CRM: extends the CRM to allow for ordinal toxicity ratings

Defining the Optimal Dose



Finding Effective Doses

- Use CRM to target Minimum Effective Dose, rather than Maximum Tolerated Dose
- Trichotomous outcome (Tri-CRM)
  - No toxicity, no efficacy
  - No toxicity, efficacy
  - Toxicity
- Joint modeling of bivariate outcome (bivariate CRM)

Phase II Objectives

- Safety
  - Estimate the frequency of side effects (tolerability)
- Efficacy
  - Identify drugs/doses with potential efficacy
  - Quickly discard drugs/doses without promise
- Feasibility
  - Compliance
  - Route of administration
  - Delivery
  - Cost
  - Recruitment

Selection Designs

- Goal: Select the "best" among *K* interventions (or *K* interventions and a control) to move forward
- Sample size determined to ensure that, if the "best" treatment is superior by at least *D*, then it will be selected with high probability
  - the probability of correct selection may be less than desired if the difference is less than *D*
  - Estimation of the difference between two treatments?
  - Evidence that the "best" treatment is worth moving forward?
- Sequential Selection Designs
  - Selection + Superiority
  - Selection + Futility

A two-stage design for a phase II clinical trial of coenzyme Q10 in ALS (Levy et al, 2006)

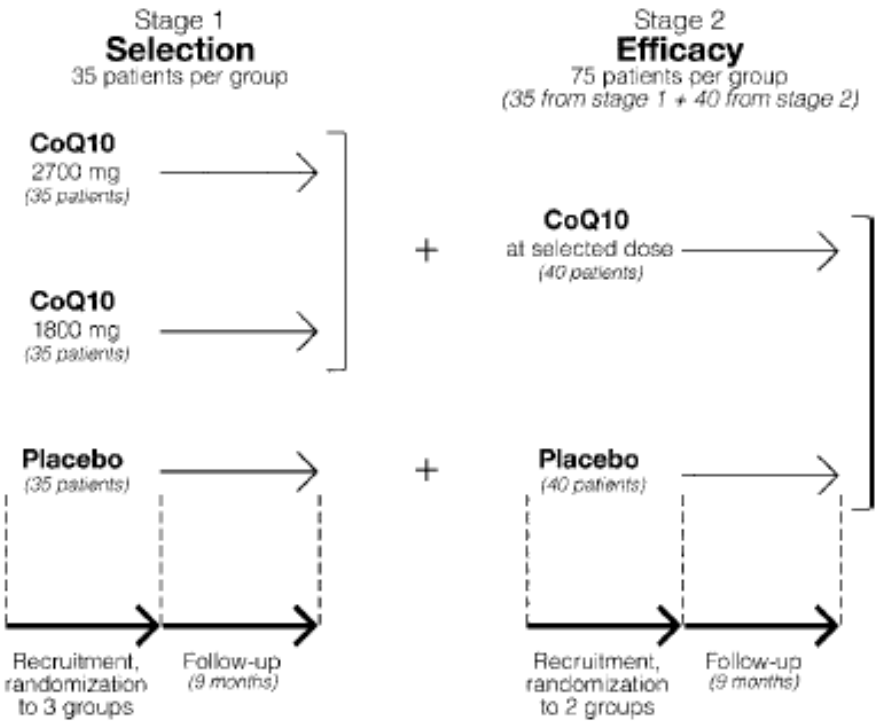


Figure. Two-stage phase II design of the Clinical Trial of High Dose Coenzyme Q10 in ALS (QALS study; total: 185 patients, 105 in stage 1 and 80 in stage 2).

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Early Two-Stage Design with Adaptive Randomization

- There may **not** be strong rationale to assume that the MTD is the optimal one
  - Interventions with low toxicity
  - Dose-toxicity and dose-efficacy relationships are not monotonically increasing
- More relevant to use efficacy-driven dose finding designs with safety boundaries
  - Binary toxicity information (yes/no DLT)
  - Continuous efficacy outcomes
  - Modeled independently

Two-Stage Design with Adaptive Randomization

- Goals:
  - Identify the optimal dose to maximize efficacy while maintaining safety
  - Higher allocation to more therapeutic doses and lower percentage of untreated patients
  - Easy to understand and implement (frequentist approach, standard software)
  - Flexible to accommodate a variety of continuous efficacy outcomes (fold-change, absolute count, etc.)
- Two-stage design:
  - **Stage 1**: establish safety profile of prespecified doses and collect efficacy outcomes
  - **Stage 2**: adaptively randomize subjects to safe doses with emphasis towards those with higher efficacy

Two-Stage Design with Adaptive Randomization Application to an Immunotherapy Cancer Trial

- Adoptive T-cell transfer for patients with metastatic melanoma
- Immunologic (efficacy) outcome: T-cell percent persistence at 15/30 days compared to baseline
  - Percent persistence is a prognostic factor of clinical outcome (complete & partial response in solid tumors)
- Findings
  - More patients treated at doses with higher efficacy
  - Improvement in efficacy estimation
  - Design can accommodate any cohort size

Exploratory phases take time…

- Adaptive designs may take even more
  - Statistical effort in the planning phase
- … but the time spent can provide valuable information
  - Optimal dosing
  - Safety assessment
  - Preliminary evidence of efficacy
  - Logistics (blinding, randomization, outcomes assessment)