Introduction to CRM and Dose Finding

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Disclosures

The presenter has no commercial or financial interests, relationships, activities, or other conflicts of interest to disclose.

Outline

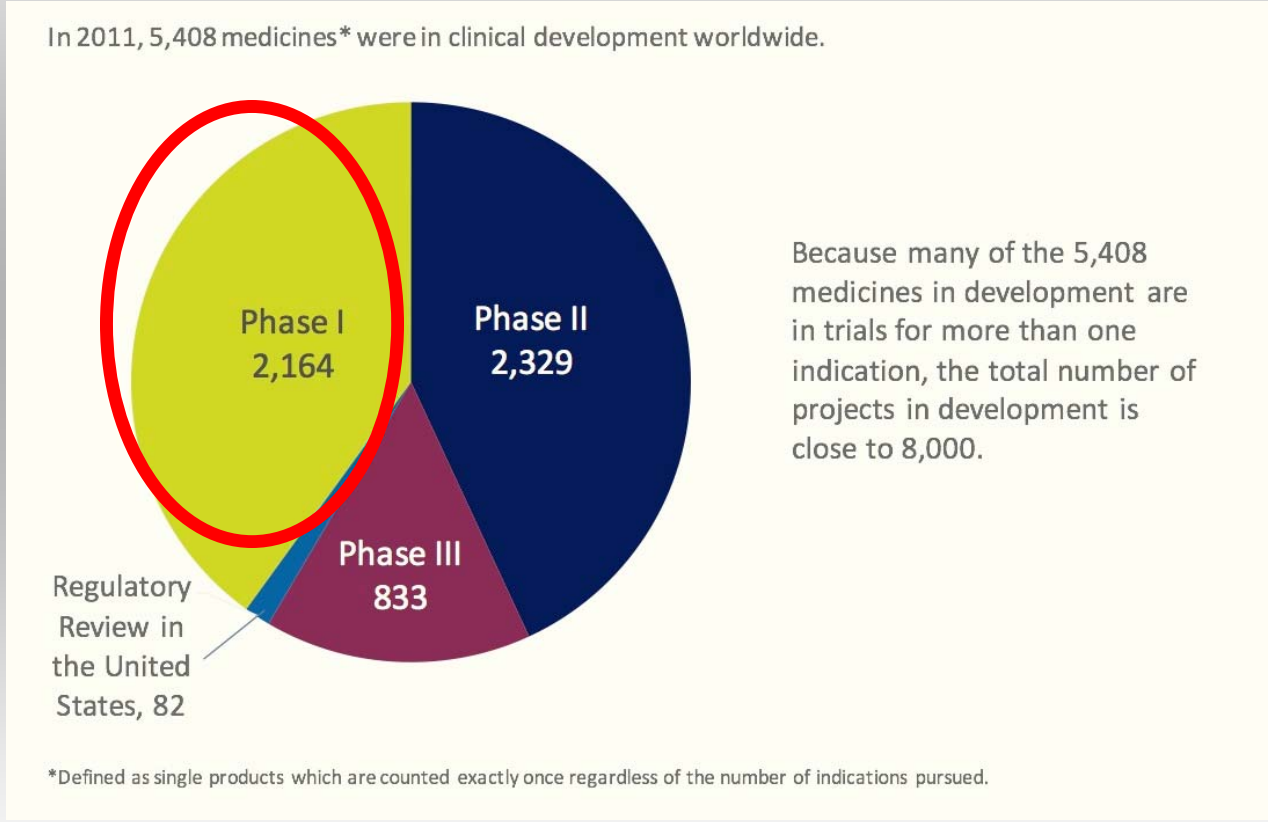
- Phase 1 Trials: Objectives and NeuSTART
- Continual Reassessment Method (CRM)
- Dose Finding with other endpoints

Phase 1 Trial

- **Objective: Evaluate safety and tolerability of a new drug**
  - A "first in humans" drug
  - An approved drug for new population/indication
  - When used in combination with other drugs

- **Objective: Finding the maximum tolerated dose (MTD)**
  - Determine a high & potentially efficacious dose with acceptable toxicity (RP2D); Nitrogen mustard (1940s)
  - Define an upper limit of dose for future investigation

Translational Research



Pharmaceutical Research Manufacturers of America. 2013 Biopharmaceutical Research Industry Profile

Phase 1 Trial

- **Endpoints:** Adverse event, Dose-limiting toxicity (DLT), Tolerability or feasibility, PK
- A DLT should include the specific type of adverse event over a specified observation schedule
- An example of "Hypothesis" statement: To determine the maximum dose of drug *X* that causes a *DLT* with probability *p* in patients with disease D

NeuSTART

- Neuroprotection with Statin Therapy for Acute Recovery Trial (Elkind et al., 2008, Int J Stroke)
- A phase 1 dose escalation study of high-dose lovastatin in acute ischemic stroke: Determine the highest dose of lovastatin that can be administered in AIS patients with <10% probability of myotoxicity or hepatotoxicity
- **DLT:**
  - ALT/AST/CK exceeding predefined thresholds on days 1, 2, 3, 5, 7, and 30
  - Clinical liver and muscle toxicity during 30d

NeuSTART

- **Maximum tolerated dose:** Allow 10% of DLT
- **Feasibility:** Completers (got at least 9 doses out of 12)
- **Dose escalation Method:** Two-stage Continual Reassessment Method (CRM)
- **Sample size:** Total N = 33

NeuSTART

Table 2. Dose escalation plan in case of no dose-limiting toxicity (DLT)

Phase 1B Cohort #	Cohort size (N)	Lovastatin Dose q6h for 72h	Dose days 3-30
1	3	1mg/kg/day	20 mg/day
2	3	3mg/kg/day	20 mg/day
3	3	6mg/kg/day	20 mg/day
4	3	6mg/kg/day	20 mg/day
5	3	8mg/kg/day	20 mg/day
6	3	8mg/kg/day	20 mg/day
7	3	8mg/kg/day	20 mg/day
8	3	10mg/kg/day	20 mg/day
9	3	10mg/kg/day	20 mg/day
10	3	10mg/kg/day	20 mg/day
11	3	10mg/kg/day	20 mg/day
Total	**33**		

The DSMC will meet and discuss continuation to the next cohort after every cohort of three patients. These dose levels apply before any dose-limiting toxicity (DLT) is observed. Dose (de-)escalation will be conducted according to the time-to-event CRM once a DLT is observed.

Experimental regimen: Acute high-dose lovastatin in acute ischemic stroke

Elkind et al. (2008) Int J Stroke

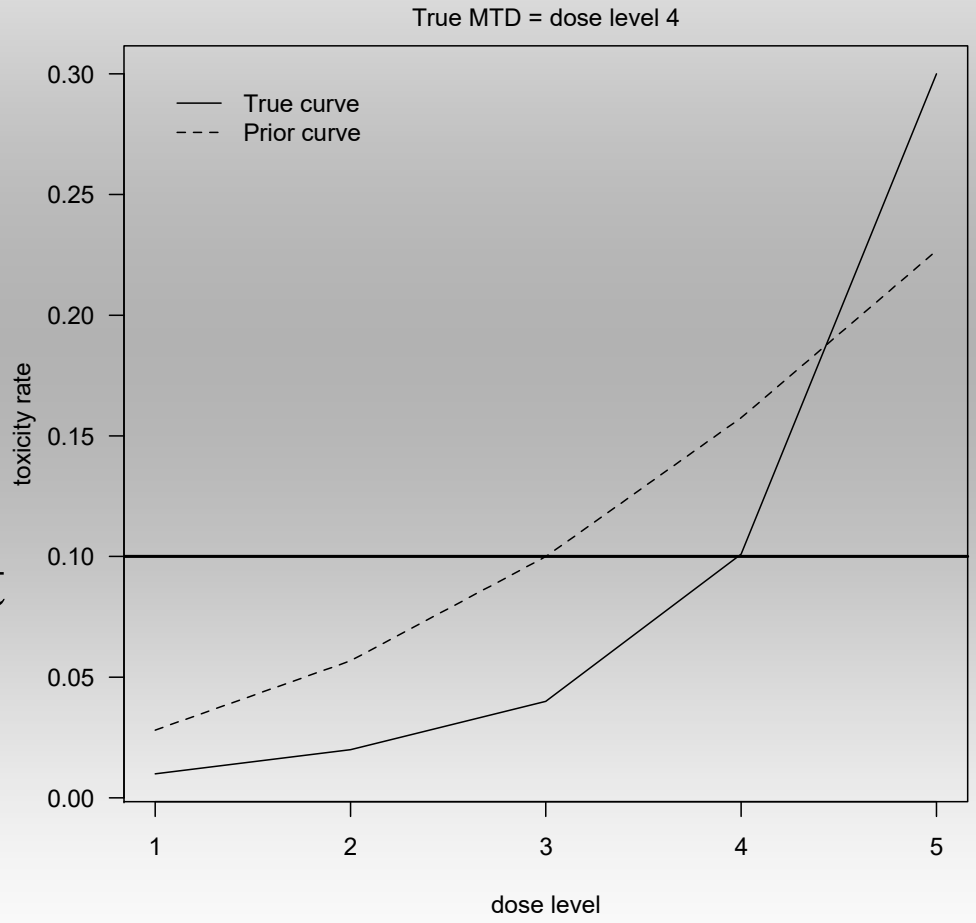
NeuSTART

CRM:

- Stage 1: Follow dose escalation plan in Table
- Once, a DLT is observed ➔ Stage 2:
  - Reassess the dose-toxicity model based on interim data
  - Treat the next patient at the model-based MTD; reassess the dose-toxicity model with new data

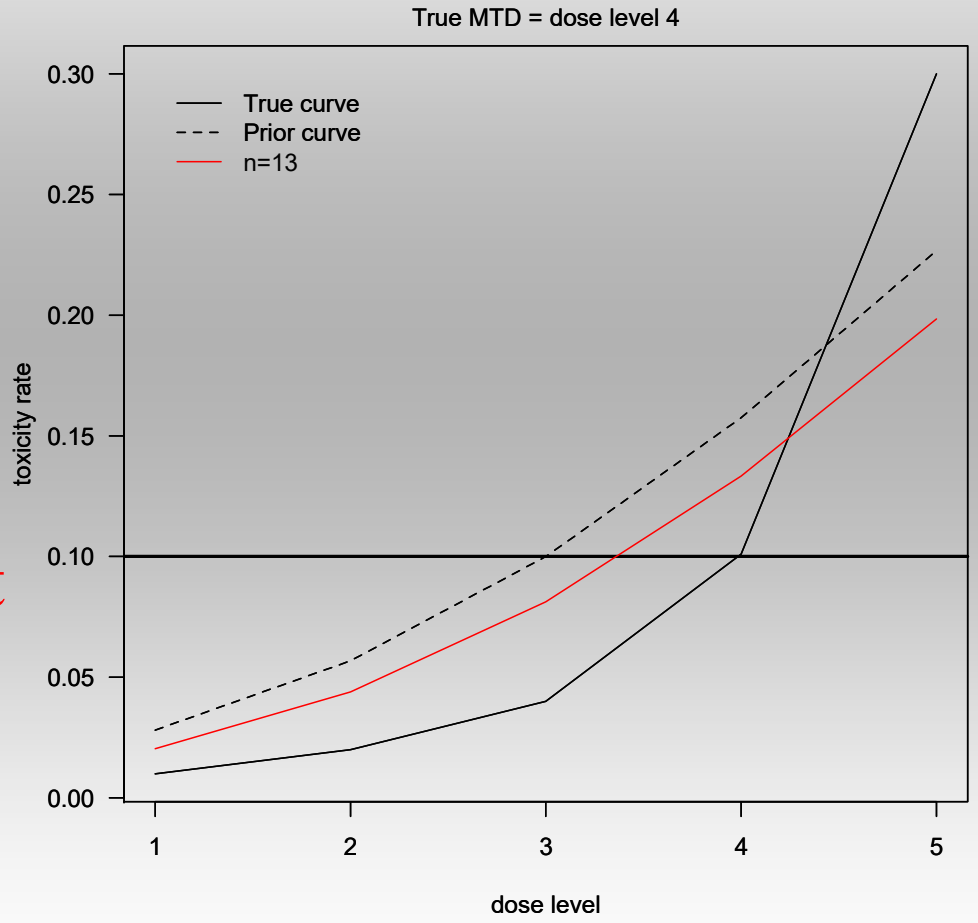
CRM: How it operates

- Model-based
- Require prior guesses
- Estimate dose-toxicity curve continually using accrued data
- Treat next patient(s) at *estimated* MTD



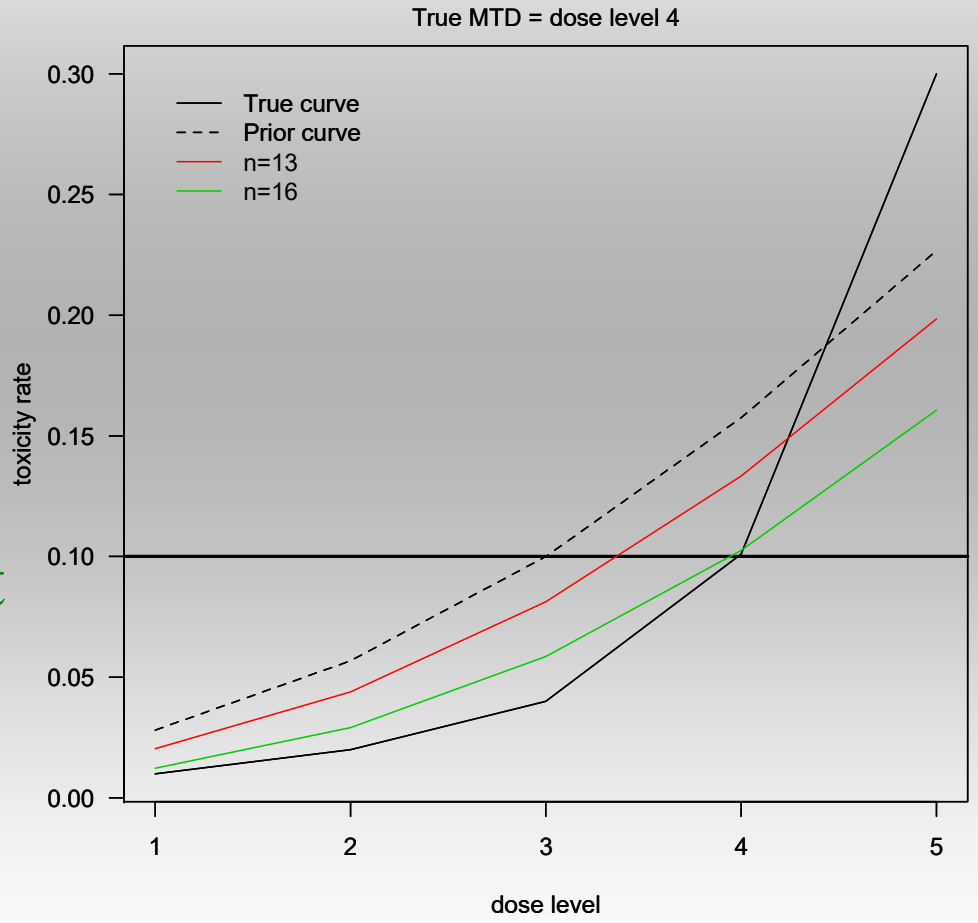
CRM: How it operates

- Model-based
- Require prior guesses
- Estimate dose-toxicity curve continually using accrued data
- Treat next patient(s) at *estimated* MTD: dose level 3



CRM: How it operates

- Model-based
- Require prior guesses
- Estimate dose-toxicity curve continually using accrued data
- Treat next patient(s) at *estimated* MTD: dose level 4



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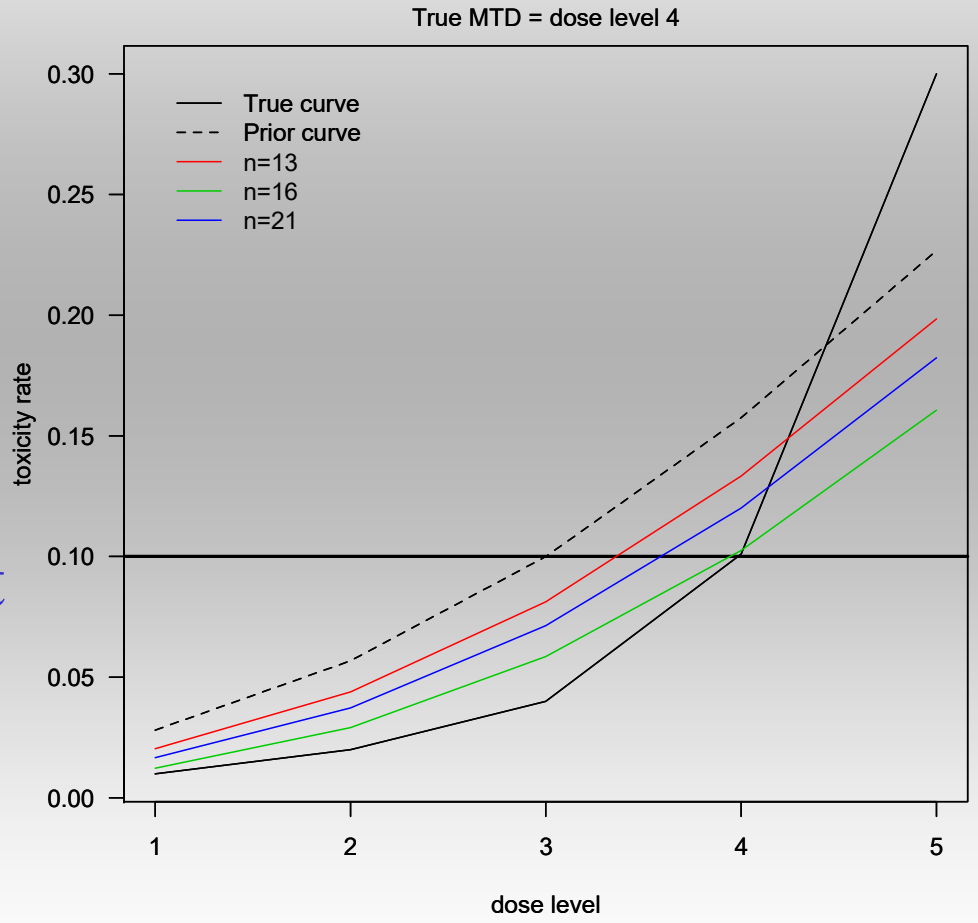

CRM: How it operates

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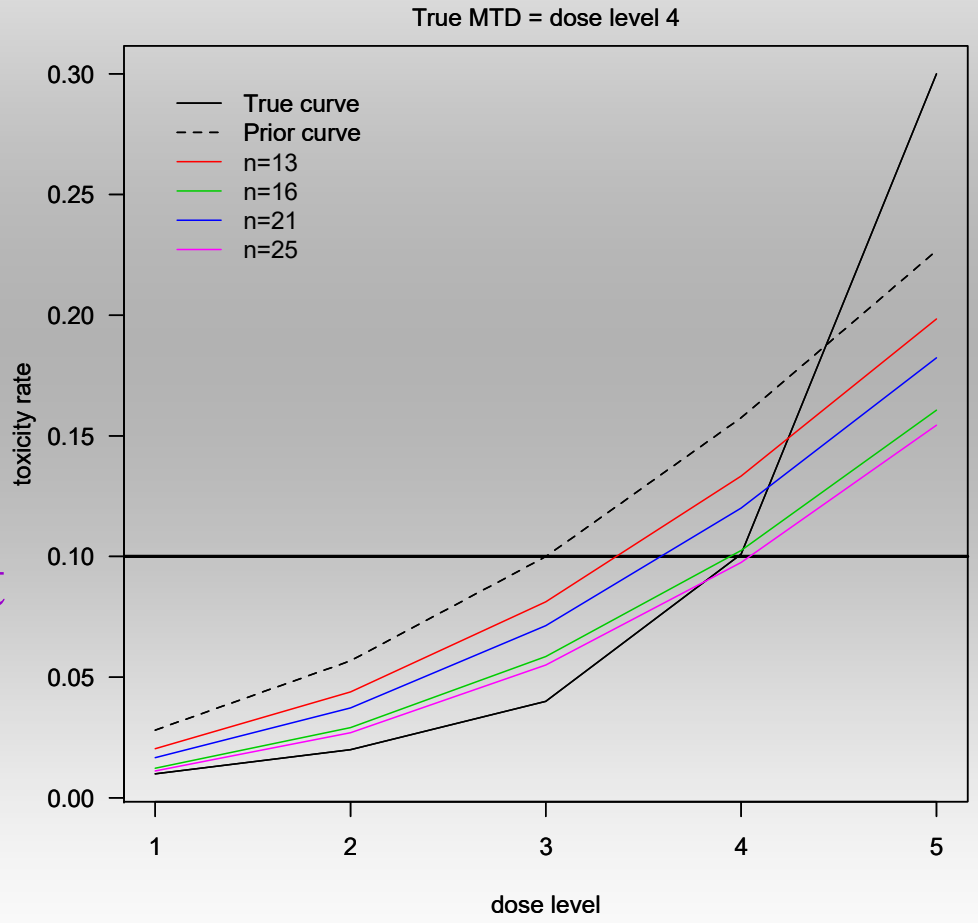
- Estimate dose-toxicity curve continually using accrued data
- Treat next patient(s) at *estimated* MTD: dose level 4



https://dosepath.shinyapps.io/dtp-crm_test/

CRM: Clinical inputs

1. DLT: AE definition and observation period
2. Maximum DLT rate tolerated; e.g., 10%
3. Number of dose levels to be tested
4. Starting dose and/or starting dose escalation plan
5. Sample size: N

How to choose DLT rate

- Some useful questions to ask:
  - What is the convention? E.g., p = 0.20 to 0.25 for cancer chemotherapy
  - What is the safety endpoint? E.g., hypotension; elevated liver enzymes; etc.
  - "Is it acceptable if one in 10 patients experience hypotension?", "How about one in 5?", etc.

How to choose number of dose levels

- Doses should be sufficiently distinct
- Some useful questions to ask:
  - What is the largest dose? And the smallest dose?
  - Use PK to determine increment
  - Use convention to determine increment
    - Fixed dose increment (pills)
    - Exponential increment (vaccine; antibody)
    - Fibonacci – not particularly right or wrong

How to choose starting dose

- A “safe” choice: start with the lowest experimental dose (level 1)
  - Also ask about “fall back dose”, level 0
- CRM allows starting in the middle of the dose panel – if the dose is considered safe

How to choose N

- Preliminary sample size can be determined for an approximate accuracy (“power”) at an effect size (“odds ratio”)
  - For initial budgeting purposes
  - Odds ratio of toxicity rate of two adjacent doses
  - Accuracy = probability of correctly choosing the MTD
- Final planning: Use simulation to fine tune CRM model and sample size

Sample size calculation

```
> library(dfcrm)
> theta = 0.1     # Target toxicity rate
> K = 4           # Number of dose levels to be tested
> psi = 2         # Effect size (slope of logistic dose-toxicity curve)
> acc = 0.6       # An accuracy index; to be explained later
> nobj = getn(acc, theta, K, psi)
> nobj
 Target rate:                        0.1
 Number of dose levels:              4
 Effect size (odds ratio):           2
 Required accuracy:                  0.6
 Calculated sample size:   40


>
```

Fine-tuning using simulation

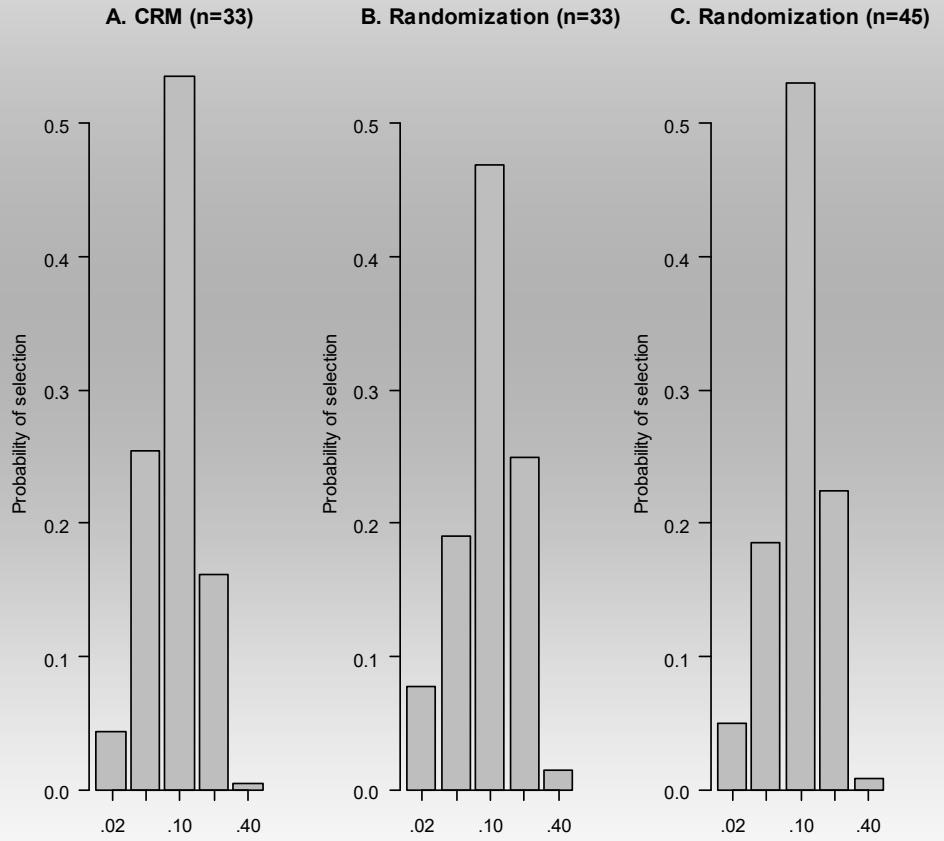
N = 40	Probability selecting MTD when the true MTD is dose**				*Ave*
	1	2	3	4	
Four dose-toxicity scenarios	.81	.43	.45	.69	.60

Average accuracy

**Under an odds ratio of 2.0

CRM: Why

- *Higher efficiency*
- Target rate: 10%
- Toxicity odds increases 2.5 times per dose level
- Logistic regression was used to estimate the MTD at trial's end



Cheung and Kaufmann (2011, *Stroke*)

CRM: Why

Design characteristics	**CRM**	**Randomization**
(a) Probability of correctly selecting the MTD[a]	0.54	0.47
(b) Probability of selecting an overdose[a]	0.17	0.26
(c) Average number of subjects treated at	**13**	**7**
(d) Average number of subjects treated at an overdose	**6**	**13**
(e) Median of toxicity odds ratio estimate[a]	5.2	2.6

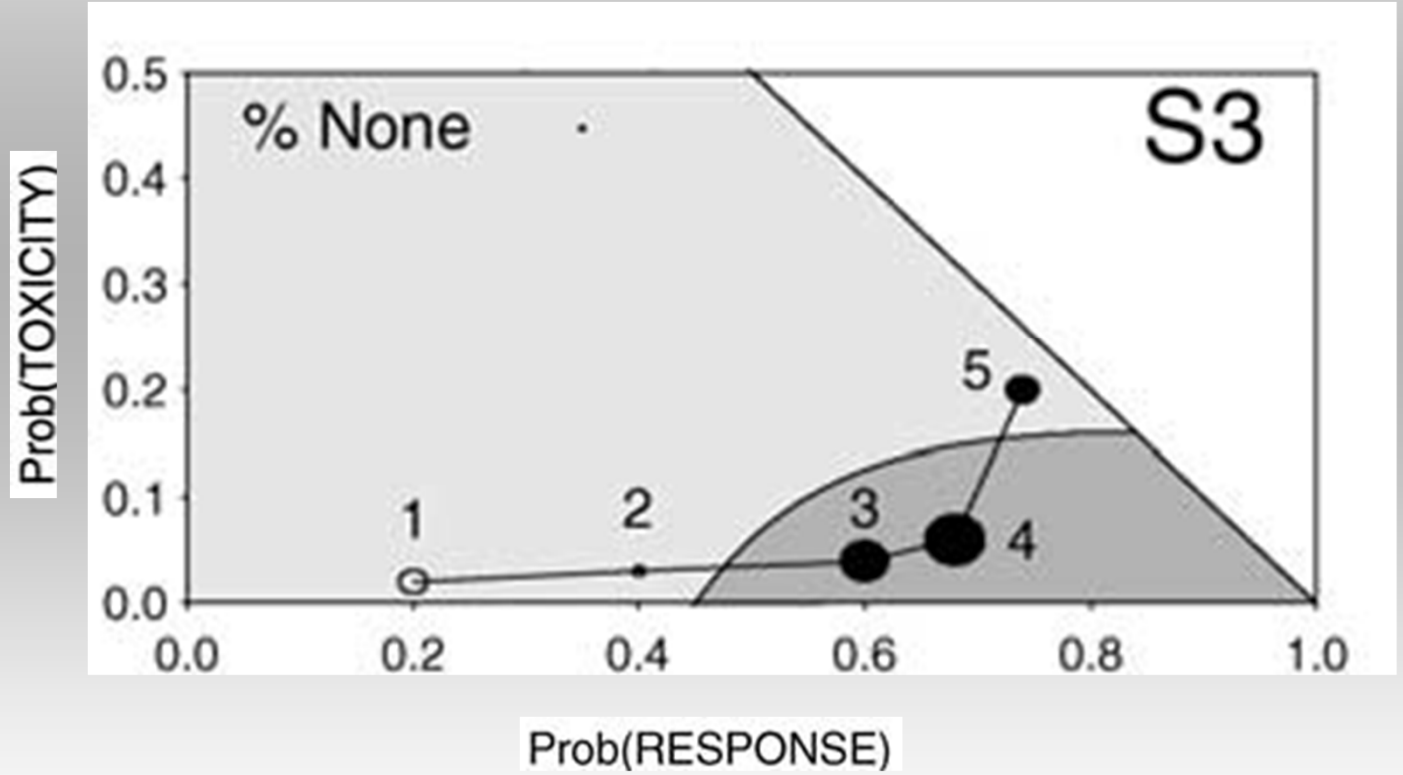
Other considerations

- Hybrid decision: model recommendation and DSMC
- Secondary outcomes are important, and are sometimes more important than DLT for next clinical phase: Feasibility, PK, pilot efficacy
- Use these other endpoints for dose escalation

Example: Phase 1/2 Trial

- Thrombolytic agent for acute stroke
- Trinary outcome (efficacy-toxicity)
  - Intracranial hemorrhage (Toxicity; $Y=2$)
  - Reperfusion without hemorrhage (Response; $Y=1$)
  - Neither ($Y=0$)
- Objective: Find dose with highest *desirability*, which increases with response rate and decreases with toxicity rate

Example: Phase 1/2 Trial



Thall and Cook (2004, Biometrics)

5 dose levels
Size of dot indicates desirability

Example: Phase 1/2 Trial

- CRM-like design
- Model-based:

  (A) Dose-toxicity relationship

  (B) Dose-response relationship

  (C) Correlation between toxicity and response

  – Estimate (A), (B), (C) continually using accrued data

  – Treat next patient(s) at dose with highest desirability based on most recent update
- Modeling is complicated, relies on simulation, and requires more upfront work

Example: CMD

- Congenital muscular dystrophies (CMD) are genetically heterogeneous neuromuscular disorders
- No pharmacological treatments available
- Phase 1 dose finding trial of omigapil in LAMA2 and COL6-related CMD
- Previously evaluated in adults pts with Parkinson's disease and ALS; volunteers for PK
- Objective of CALLISTO:
  - Find a dose with PK activity and safety in pediatrics and adolescents

Example: CMD

Specific PK target:

- AUC (0 – 24h), averaged at first 2 post-baseline visits
- **PK activity:** Find a dose with AUC > 3 ng h/ml
- Safety (Maximum tolerated dose, **MTD**): A dose that exceeds 33 ng h/ml with 10% probability or less

Example: CMD

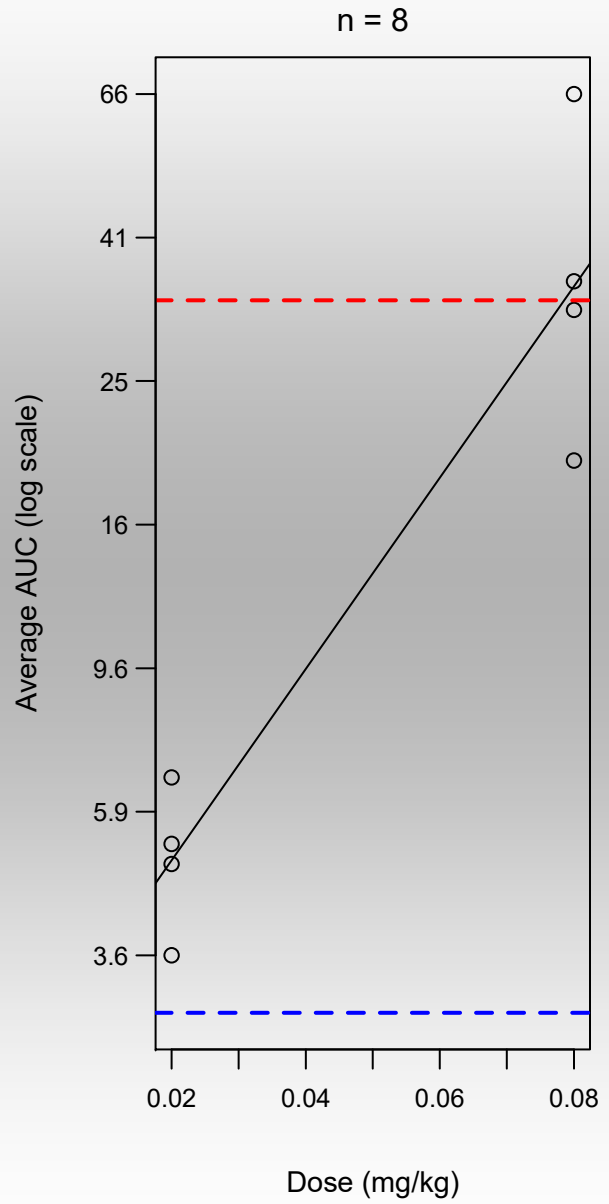
Specific PK target:

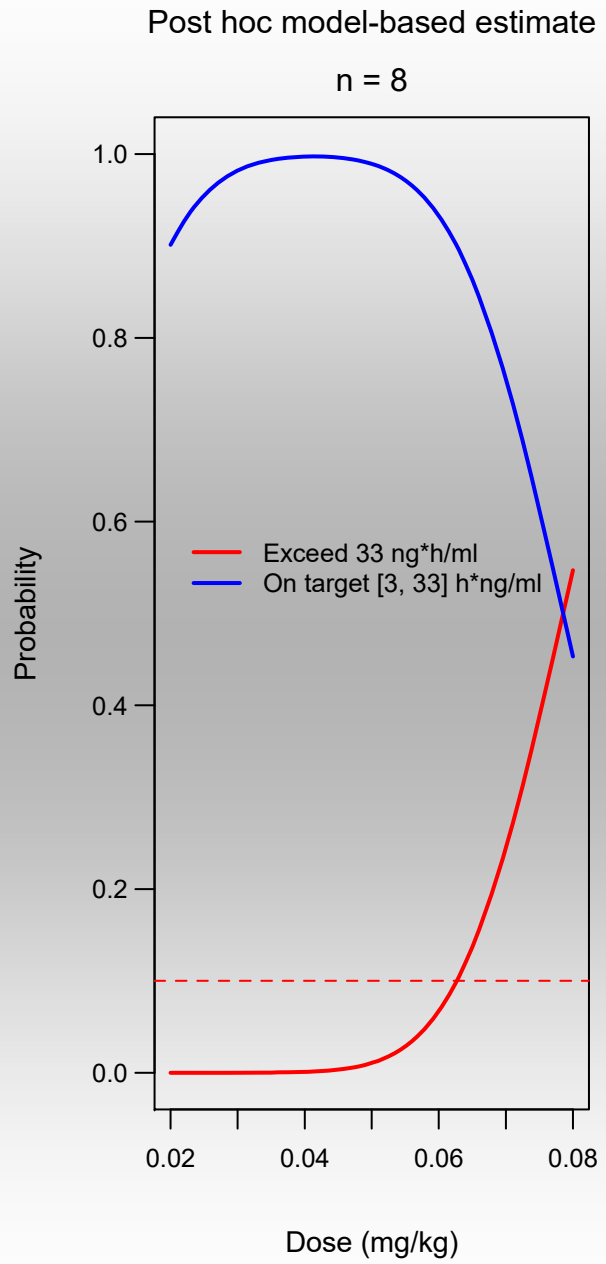
- AUC (0 – 24h), averaged at first 2 post-baseline visits
- **PK activity:** Find a dose with AUC > 3 ng h/ml
- **Safety** (Maximum tolerated dose, **MTD**): A dose that exceeds 33 ng h/ml with 10% probability or less

Example: CMD

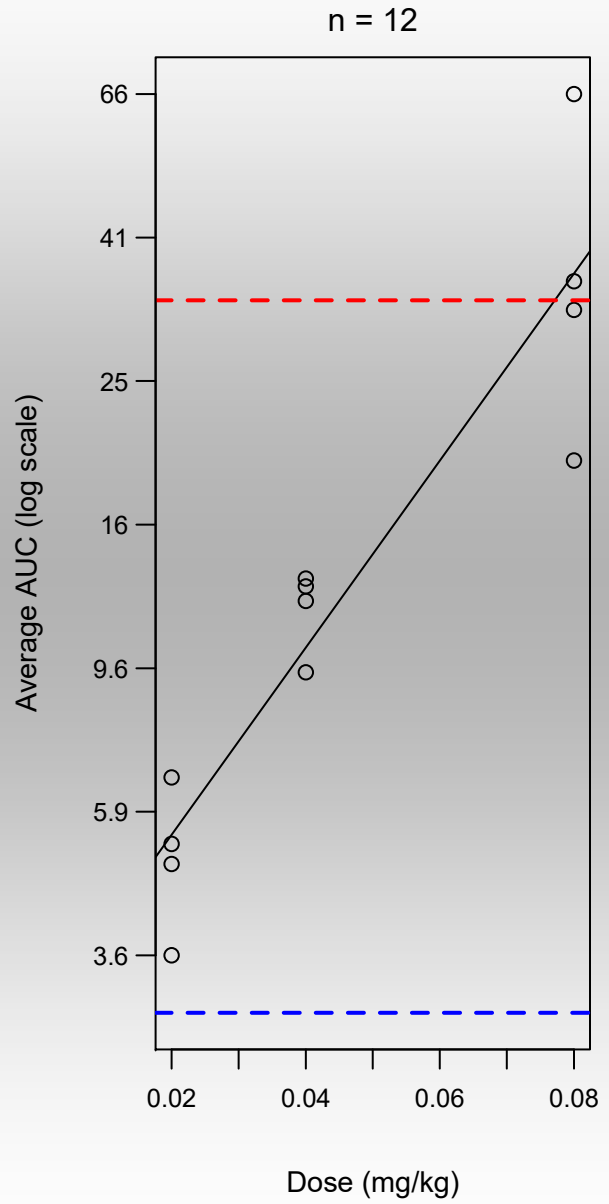
- Leach et al. (2017) Neuromuscular disorders
- N = 16-20 enrolled in cohorts of 4 in a dose escalation manner
- Pre-selected doses: 0.02, 0.08 and 0.2 mg/kg
- Start at 0.02 mg/kg. Use Continual Reassessment Method (CRM) for subsequent dose assignment
- Hybrid decision process: Investigators convened to discuss dosing and DSMB convened to approve
- Switch from CRM to SAVOR, a new class of dose escalation method that allows *dose interpolation*

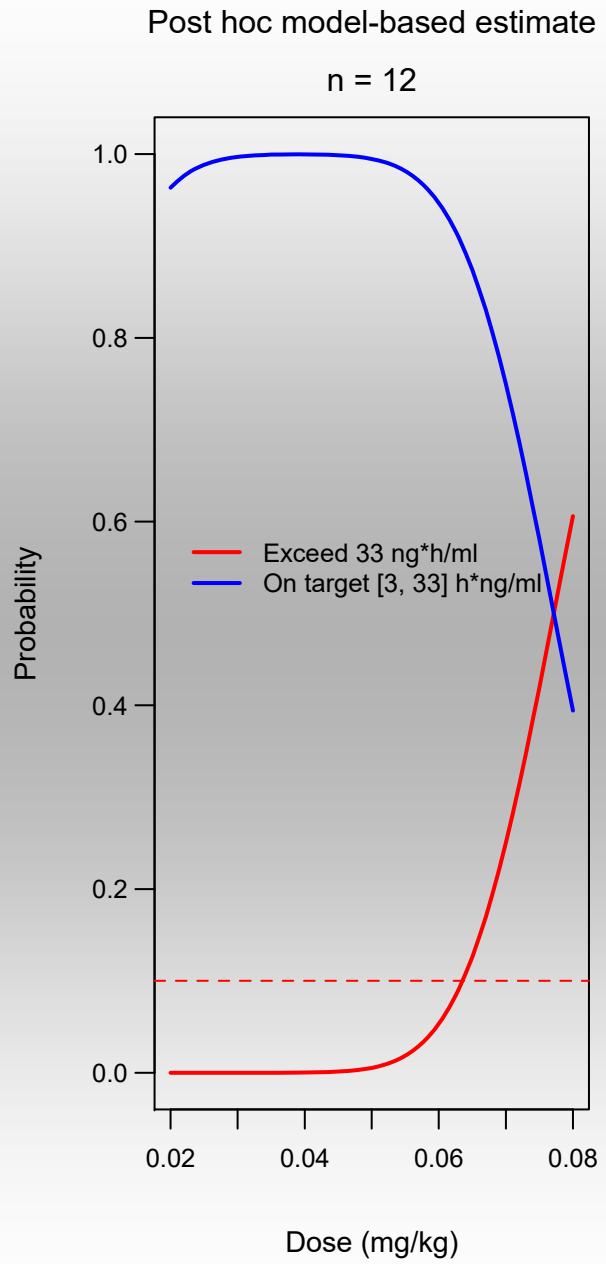
SAVOR: 0.04 or 0.05 mg/kg
Hybrid decision: 0.04 mg/kg





SAVOR: 0.05 or 0.06 mg/kg
Hybrid decision: 0.06 mg/kg





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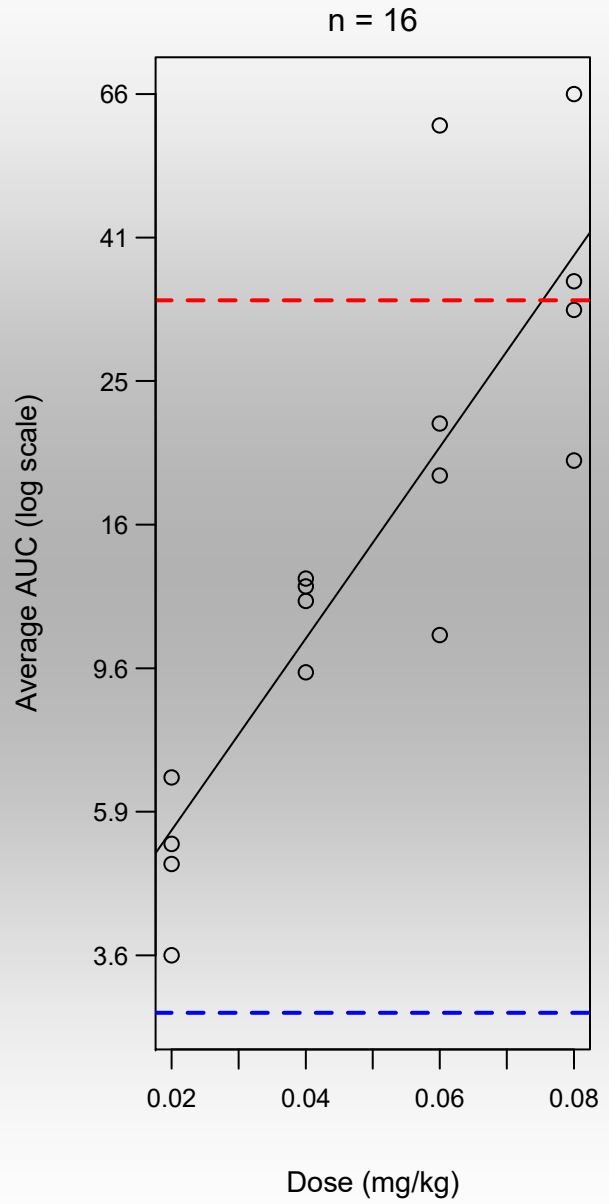
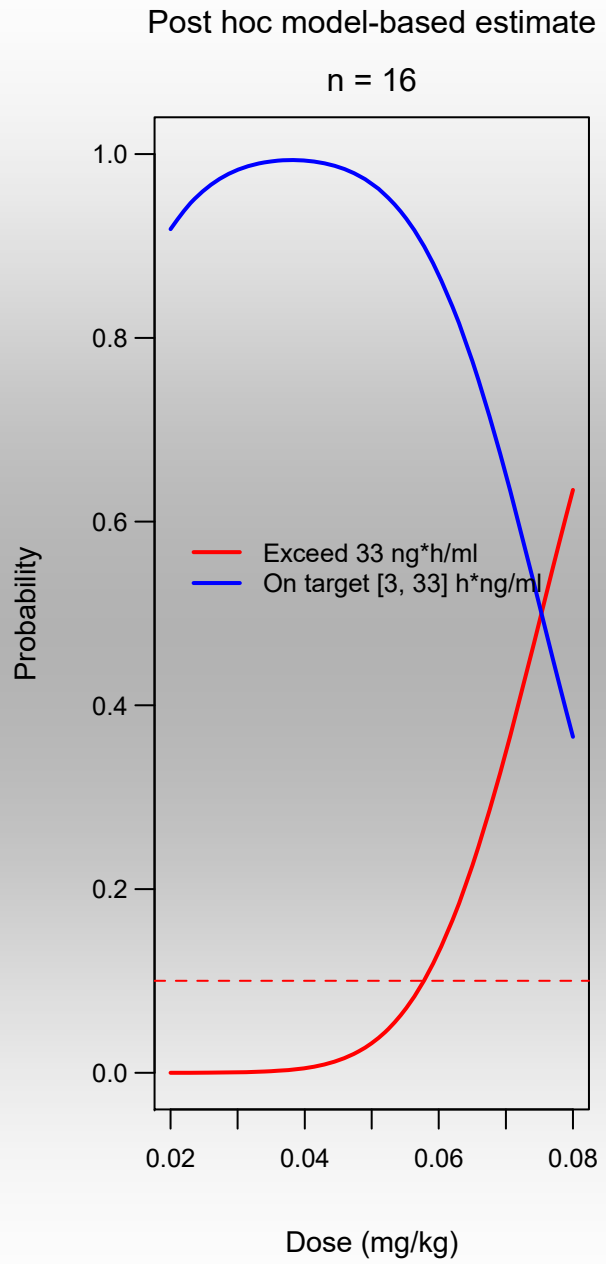
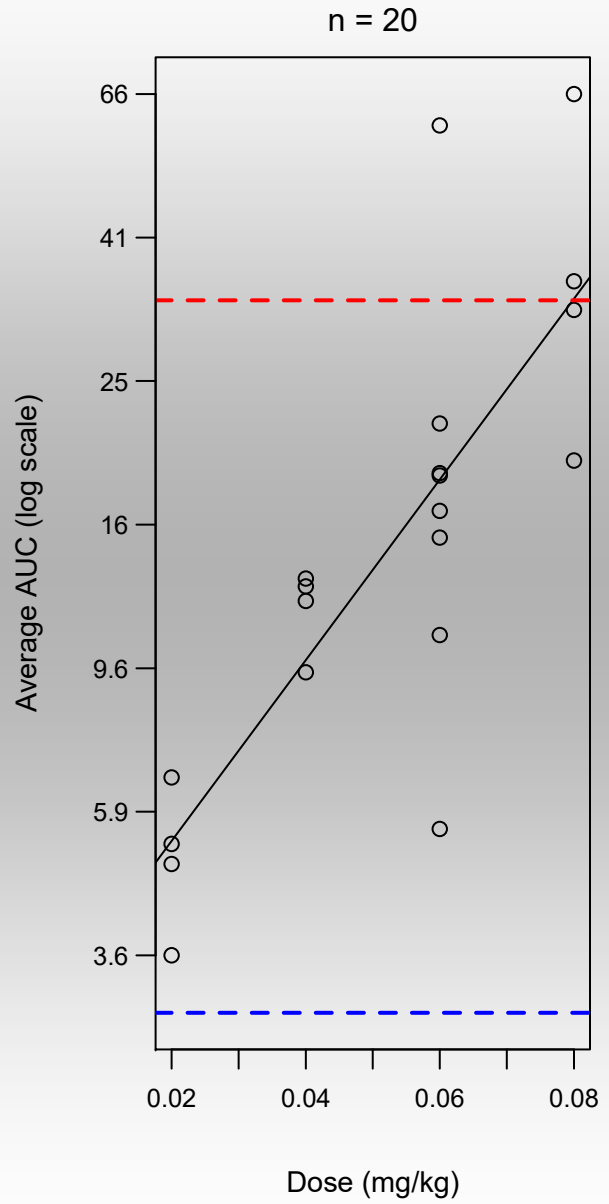
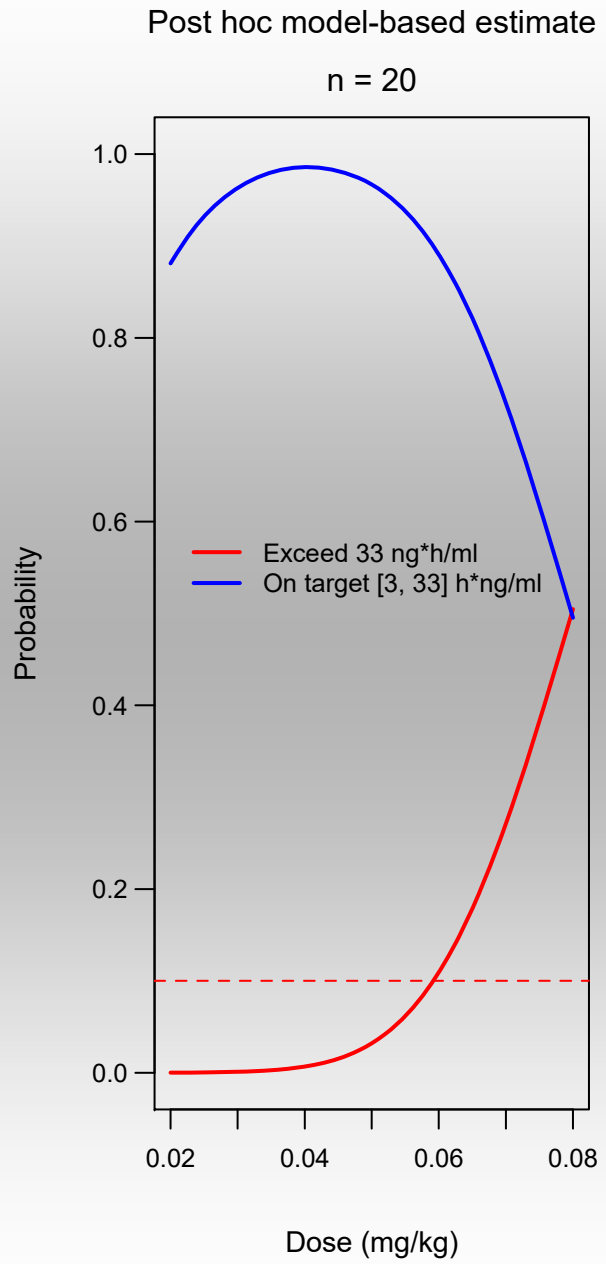




SAVOR: 0.06 or 0.07 mg/kg
Final MTD: 0.06 mg/kg





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Stochastic approximation with virtual observations for dose-finding on discrete levels

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- **S**tochastic **A**pproximation with **V**irtual **O**bservation **R**ecursion
- Second-generation adaptive dose finding that allows dose addition/deletion, and improves efficiency by using continuous (e.g., PK) data instead of dichotomized data (in CRM)

Discussion

- Early phase dose finding trials are critical to the eventual success of drug development. Worst case scenario: wrong dose of the right drug treated at phase 3
- Adaptive designs such as the CRM and SAVOR can improve the accuracy of dose finding, and enhance how patients are dosed during a trial
- Require *prospective* planning
- With new class of targeted therapies, interests in orphan drugs, and rare diseases, dose finding with non-DLT endpoint may be used