Phase I Oncology Designs:
Comparison of Select Designs

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Outline

- Phase I Oncology Studies
- Traditional 3+3 Study Design
- Alternative Designs
- Design Methodology
- Comparison using Simulation
- Remarks

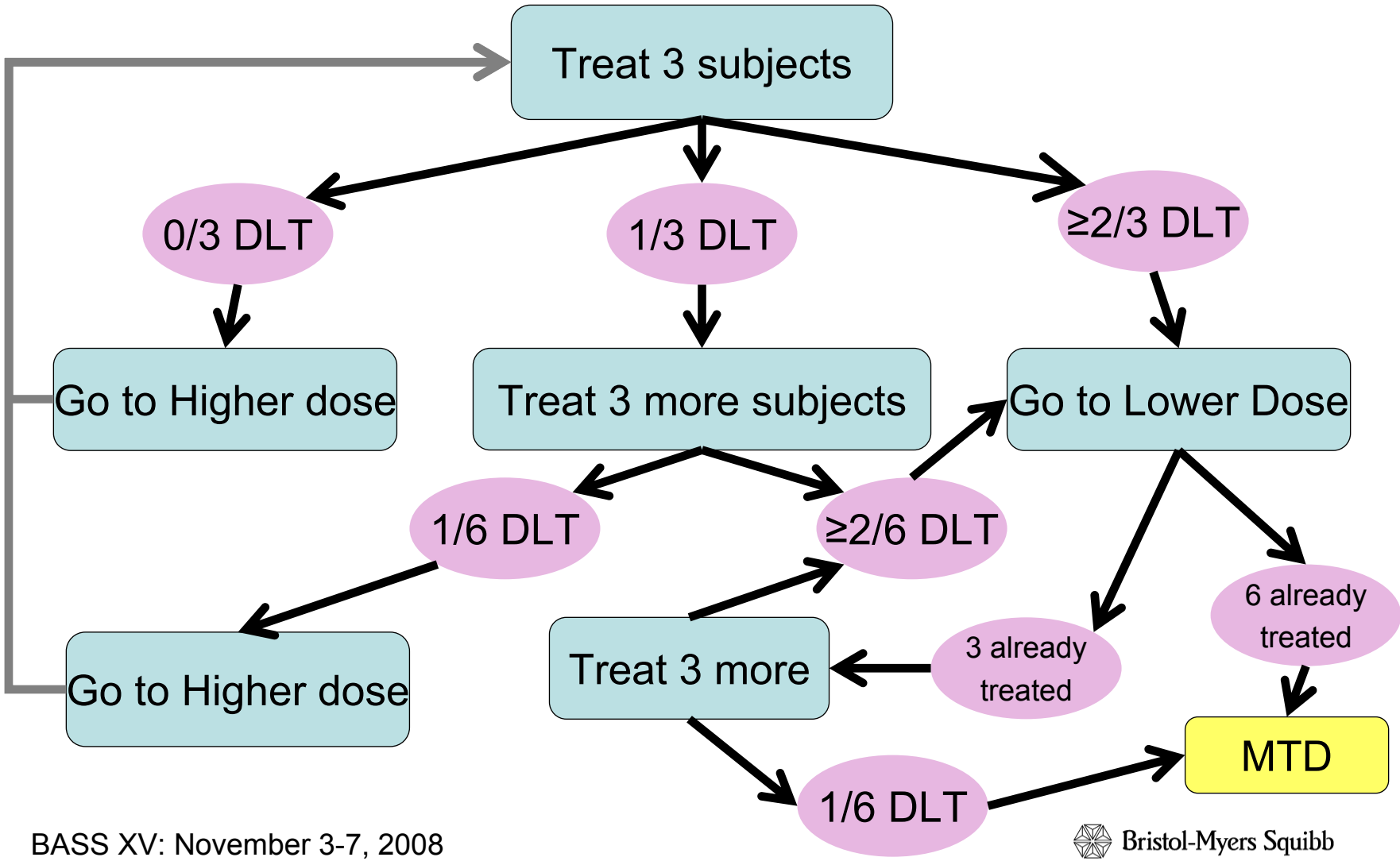
Phase I Oncology Studies

- Typically small, uncontrolled dose escalation studies
  - Multiple ascending dose (MAD)
  - Option to expand at maximum tolerated dose (MTD)
- Objectives
  - Identify the MTD
  - Determine recommended Phase II dose (RP2 dose)
  - Establish safety and tolerability
- Pre-specified dose levels
  - Choice of dose levels driven by pre-clinical data and perhaps drug supply
- Patients studies
  - Certain degree of side effects is acceptable
  - Ethical concern of treating subjects at sub-optimal dose levels

Phase 1 Design Concerns

- Simplicity
- Correct identification/estimation of MTD
- Treat few subjects at sub-optimal levels and overly toxic levels
- Sample Size
- Gain knowledge of toxicity rate

Traditional 3+3 Design Algorithm



Traditional 3+3 Design

- Pros
  - Widely accepted
  - Simple and flexible
  - Protects against excessive toxicity
- Cons
  - No statistical basis
  - No target toxicity
  - Too slow dose escalation
  - Many patients may be treated in sub-therapeutic dose range

Motivation to Examine Alternative Designs

- Pursue statistical rigor in determining MTD
  - 3+3 has no statistical justification
  - MTD can be estimated by modeling
- Gain experience with methodologies
  - Understand trade offs
  - Identify ideal situations for implementation
  - Wider acceptance

Alternative Phase 1 Study Designs

- Standard 3+3 Design – MTD is identified
- Bayesian approaches – MTD can be estimated
  - Continual reassessment method (CRM)
    - Original CRM
    - Modified CRM (mCRM)
  - Escalation with overdose control (EWOC)
  - Toxicity probability intervals (TPI)
  - Decision-theoretic approaches
  - Bayesian sequential optimal design
- Accelerated titration design (ATD) – two stage design
- Random walk rules (RWR) - nonparametric approach
- Pharmacokinetic (PK) guided dose escalation

Problem Setup

- Notations

  At each cohort *i*:

  d_i: Dose tested

  n_i: Sample size

  x_i: Number of DLTs

  τ : Toxicity tolerance prob.

  γ : Unknown MTD

- Problem

$$\text{Given}: \quad d_1,\ldots,d_j \quad x_1,\ldots,x_j \quad n_1,\ldots,n_j$$

$$\text{To Find}: d_{j+1}, \text{or}, \gamma, \text{such that } \Pr\{\text{DLT at } \gamma\} \le \tau ?$$

The Generic Bayesian Approach

- Model $x \sim \text{Binomial}(n, p)$

  $p = \Pr\{DLT; d, \theta\}$

- Prior on θ $g(\theta)$

- Posterior $p(\theta \mid x_1, \ldots, x_j; n_1, \ldots, n_j, d_1, \ldots, d_j)$

$$= \frac{\prod_{i=1}^{j} p^{x_i} (1-p)^{n_i - x_i} \cdot g(\theta)}{\int \prod_{i=1}^{j} p^{x_i} (1-p)^{n_i - x_i} \cdot g(\theta) d\theta}$$

$$\propto \prod_{i=1}^{j} p^{x_i} (1-p)^{n_i - x_i} \cdot g(\theta)$$

Continual Reassessment Method

[O'Quigley, et al 1990]

- Model $p = f(d)^{\alpha}$

  f : monotone increasing function of dose d

- Prior $\exp(-\alpha)$

- Dose Escalation

  Find the dose level d_{j+1} such that

  $E\left[p|data;d_{j+1}\right]$ is close to τ

Modified CRM

[Goodman, et al 1995; Thall & Lee, 2003]

- Model

$$p = \frac{\exp(\alpha + \beta\tilde{d})}{1 + \exp(\alpha + \beta\tilde{d})}$$

$\tilde{d}$: dose in log scale and centered.

- Prior

$$\alpha \sim \mathrm{N}(\mu_\alpha, \sigma_\alpha^2)$$

$$\beta \sim \mathrm{N}(\mu_\beta, \sigma_\beta^2)$$

- Dose Escalation

$$\text{Find the } \tilde{\mathrm{d}}_{\mathrm{j+1}} \text{ such that } \mathrm{E}\left(\mathrm{p} \mid \text{data}; \tilde{\mathrm{d}}_{\mathrm{j+1}}\right) = \tau$$

Modified Trial Conduct

- Start at the lowest dose and proceed
- Dose escalation permitted only to the next higher dose

Estimation with Overdose Control (EWOC)

[Babb, Rogatko, and Zacks(1998)]

- Model $$p = \frac{\exp(\alpha + \beta d)}{1 + \exp(\alpha + \beta d)}$$

- Transformation

$$\left.\begin{aligned} \rho_0 &= \frac{\exp(\alpha + \beta d_0)}{1 + \exp(\alpha + \beta d_0)} \\ \tau &= \frac{\exp(\alpha + \beta \gamma)}{1 + \exp(\alpha + \beta \gamma)} \end{aligned}\right\} \Rightarrow p = \pi(\rho_0, \gamma, d)$$

- Prior

$$\rho_0 \sim U(0, 0.2) \quad \gamma \sim U(d_{\min}, d_{\max})$$

EWOC Dose Selection

- Dose Estimation

  Based on marginal posterior distribution of

$$F_{\gamma}(x) = \Pr(\gamma \leq x \mid data)$$

$$\text{dose for next cohort} :\Rightarrow F_{\gamma}^{-1}(\phi)$$

$$e.g., \phi = 0.25$$

- Dose Selection

  Compare with the predefined dose levels, select the one which is the largest below the estimated dose

Toxicity Posterior Probability Intervals (TPI)

[Ji, Li, Bekele (2007)]

- Model
  - Nonparametric for toxicity and dose levels
  - Higher dose higher toxicity
- Prior

  p_i ~ non-informative *Beta*

  suggested $p_i \sim Beta(0.005, 0.005)$
- Posterior

  $p_j \sim Beta(x_j + 0.005, n_j - x_j + 0.005)$

TPI Dose Selection

- Dose Escalation

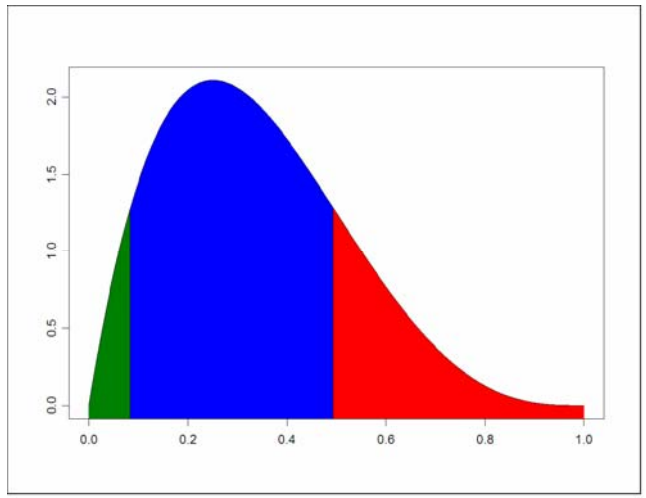
Pick constants K_1 and K_2, and let $\sigma_j = SD(p_j)$

$$\Pr_{up} = \Pr\left\{ 0 < p_j \le \tau - K_2\sigma_j \mid \text{data} \right\}$$

$$\Pr_{same} = \Pr\left\{ \tau - K_2\sigma_j < p_j \le \tau + K_1\sigma_j \mid \text{data} \right\}$$

$$\Pr_{down} = \Pr\left\{ \tau + K_1\sigma_j < p_j \le 1 \mid \text{data} \right\}$$

$$\Pr_{stop} = \Pr\left\{ p_j > \tau \mid \text{data} \right\}$$



- $\Pr_{stop}$ > threshold value, → stop
- $\Pr_{up}$ is largest, → dose increased
- $\Pr_{same}$ is largest, → dose unchanged
- $\Pr_{down}$ is largest, → dose reduced

Bayesian Computing

- Previously perceived to be difficult to implement and a black box
- Methodology:
  - Numerical
  - MCMC
  - Weighted Resampling

General Comments

- Pros
  - Model based approach
  - Ability to incorporate pre-clinical information
  - Estimate MTD using all available safety data
- Cons
  - Perception by clinicians as black box method
  - Implementation requires validated software and additional resources

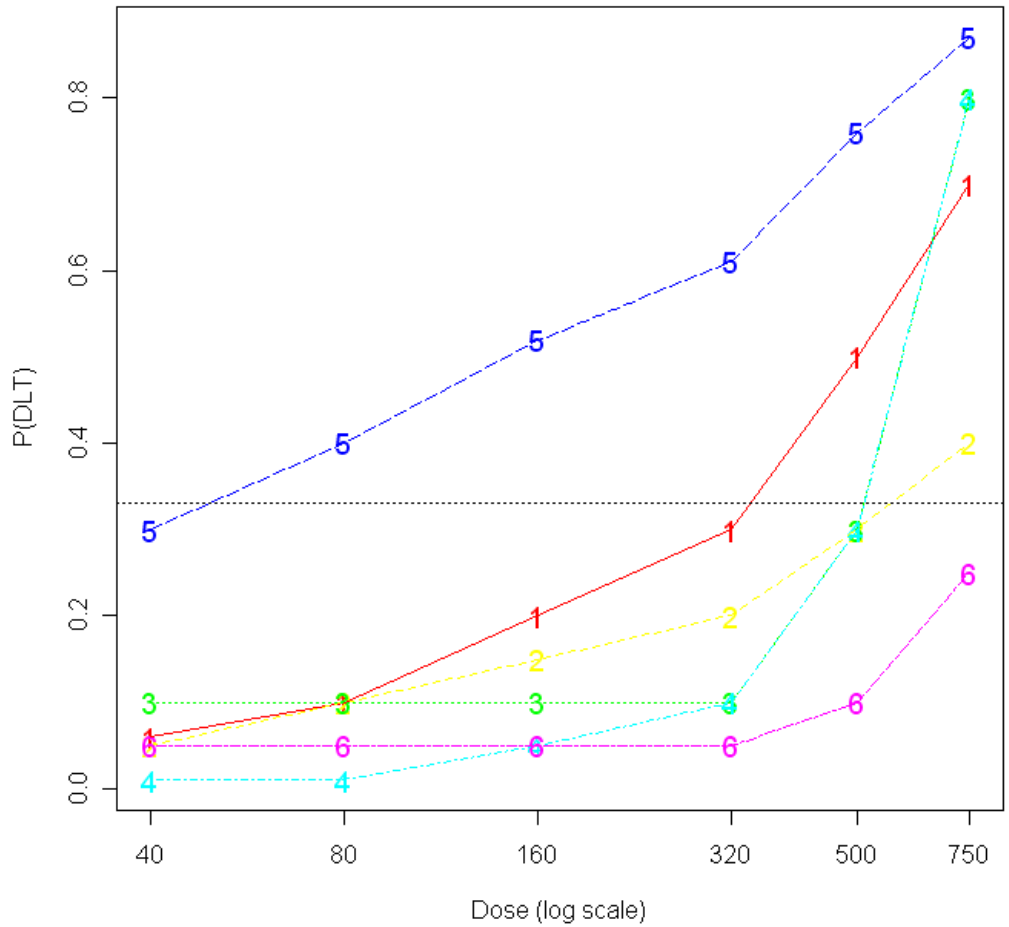
3+3, mCRM, TPI, and EWOC Simulation

- Compare design performance across 6 toxicity scenarios
  - MTD Selection
  - MTD Variability
  - Under/Over dosing
  - Sample size

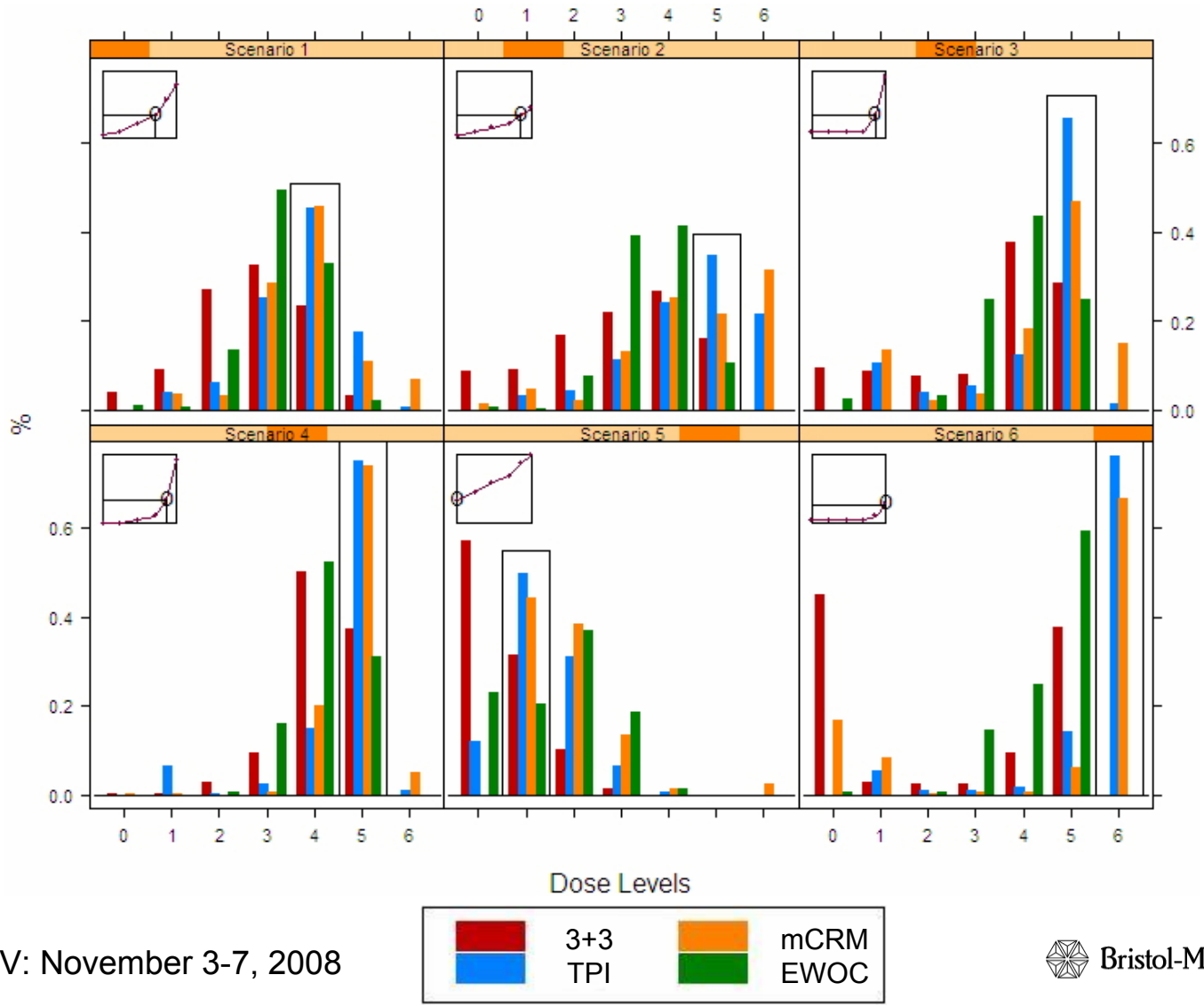
Simulation

- Implementation
  - 10,000 trials
  - Target toxicity of 0.33
  - Cohort Size of 3
  - Start at lowest dose
  - Maximum number of patients = 30 for Bayesian methods

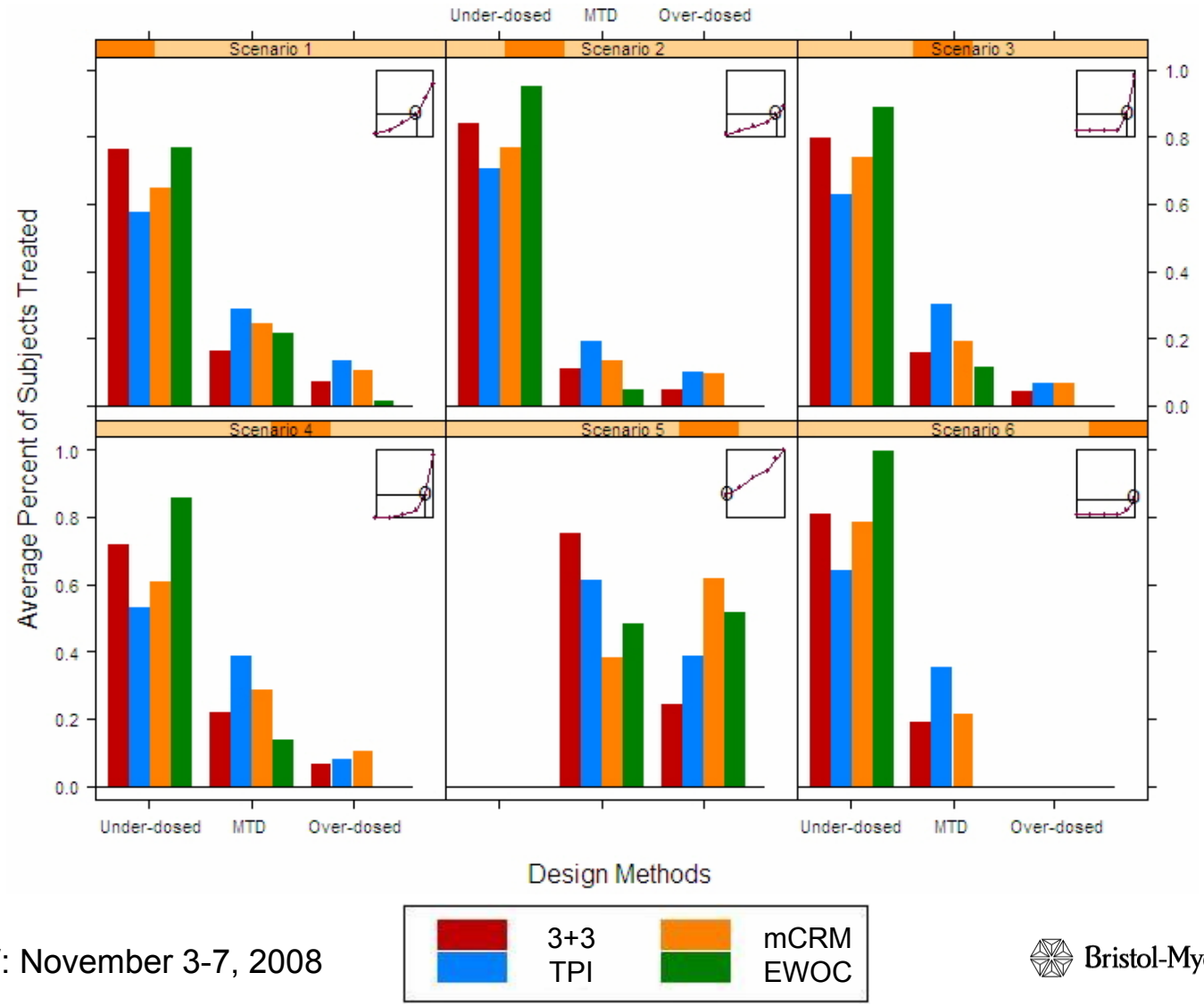
Toxicity Scenarios for Simulation



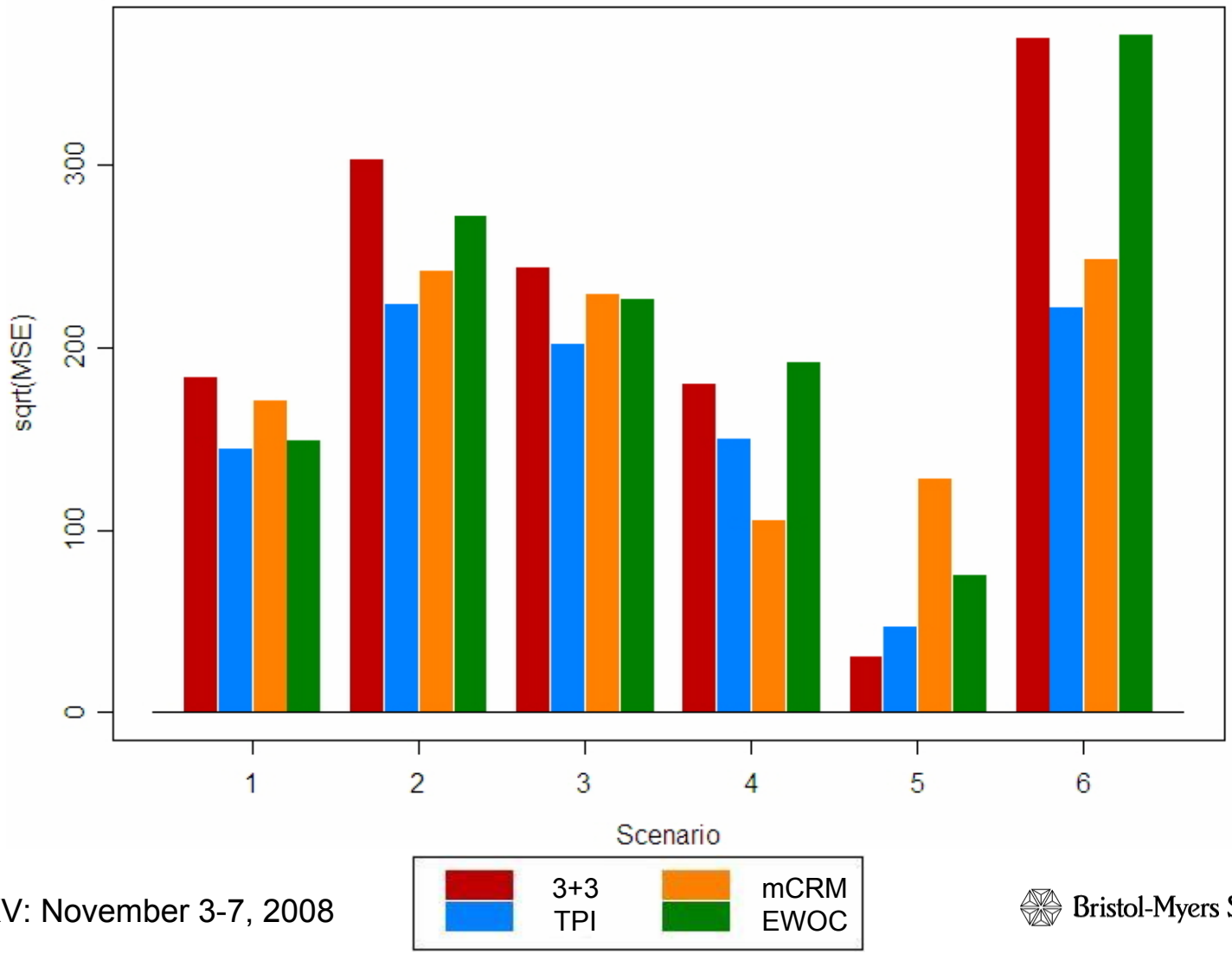
Distribution of MTD



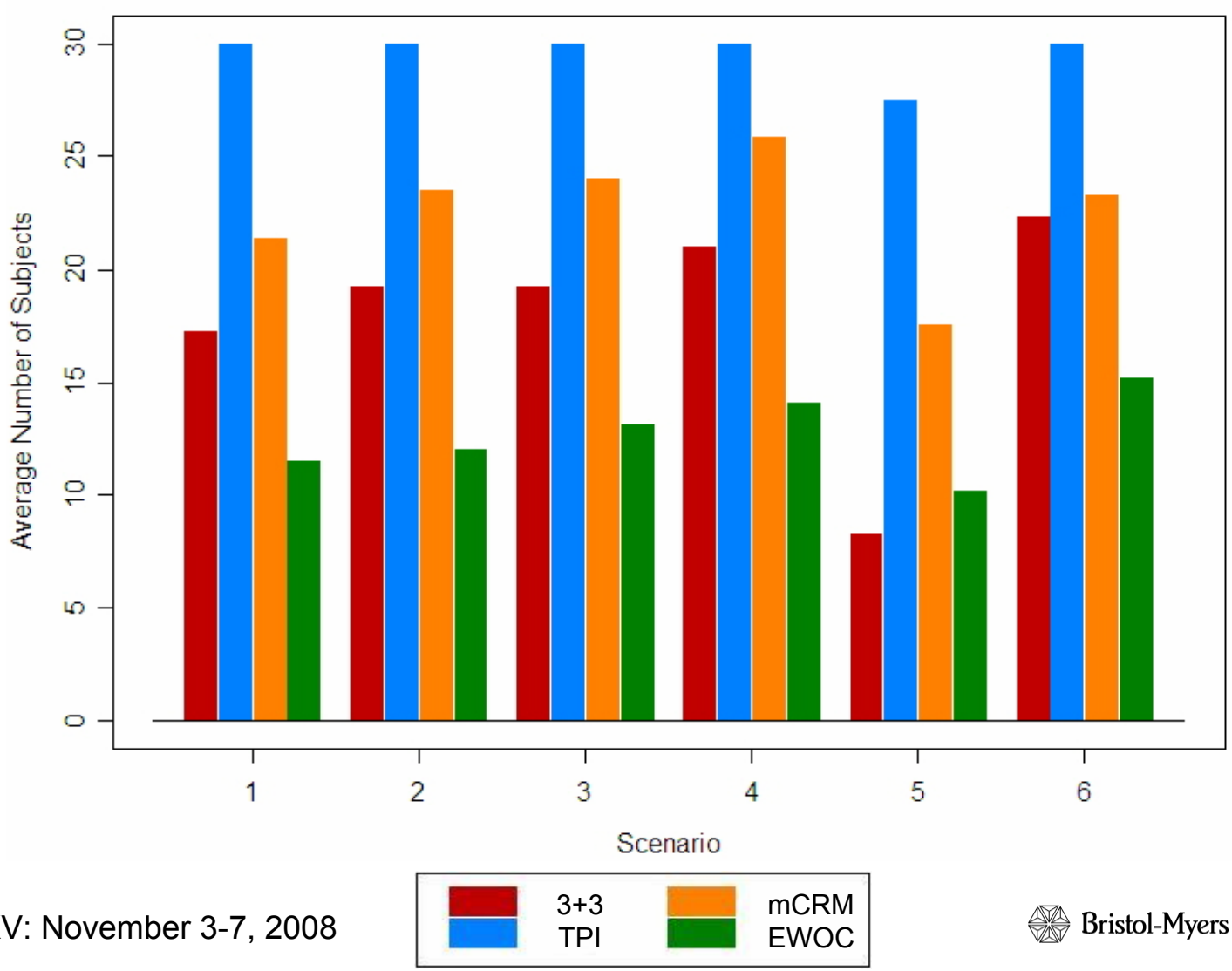
Proportion of Subjects Under/Over Dosed



Root Mean Squared Error of Selected MTD



Sample Size


Average Number of Subjects
0
5
10
15
20
25
30
1
2
3
4
5
6
Scenario
3+3
TPI
mCRM
EWOC

Overall Experience

	3+3	TPI	mCRM	EWOC
Simplicity of Implementation	☺	☺		
Few subjects treated at sub-optimal levels		☺	☺	
Few subjects treated at toxic levels		X	X	☺
Small sample size		X		☺
Identification/ Selection of MTD	X	☺	☺	

Remarks

- Use simulations to examine operating characteristics of 3+3 designs (and others) prior to study start-up
- Even with the traditional design, we can do model based estimation of MTD post-hoc
- Continue to evaluate the operating characteristics of alternative designs
- Proactively engage clinicians and senior management

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