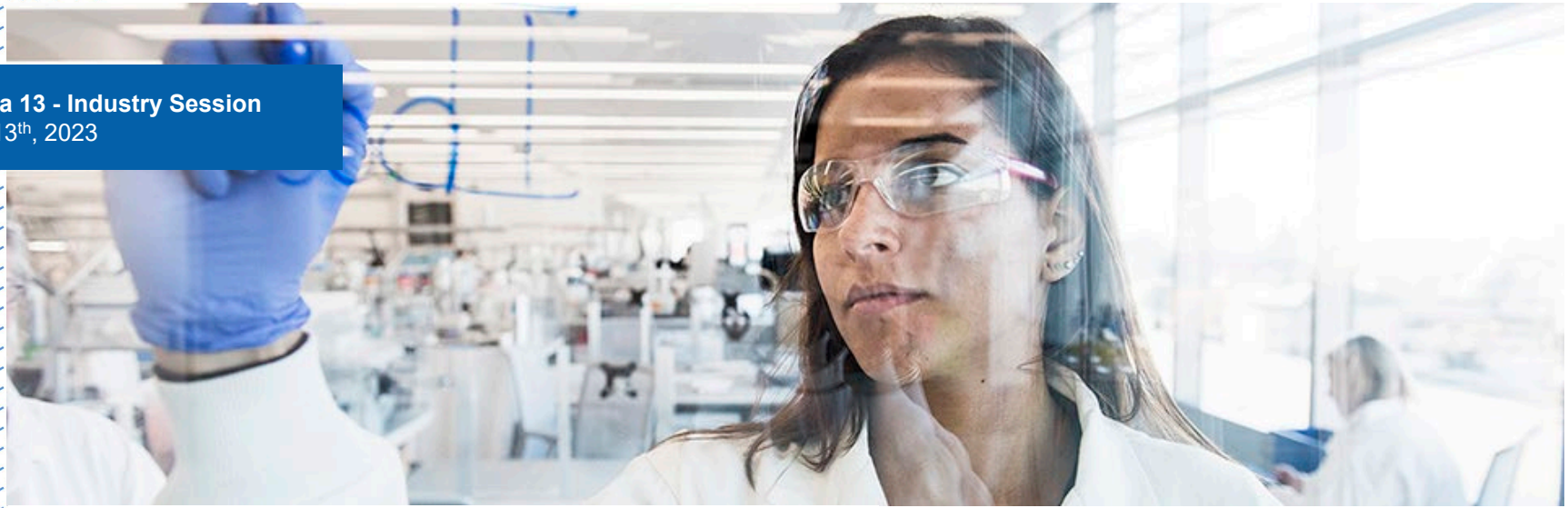
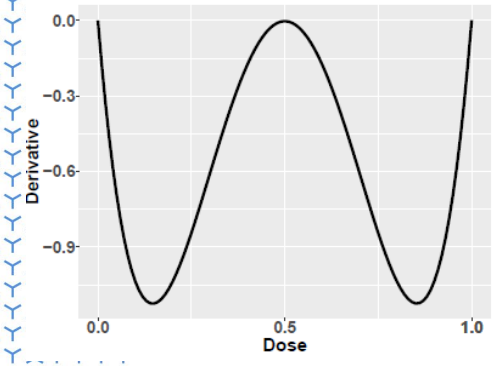
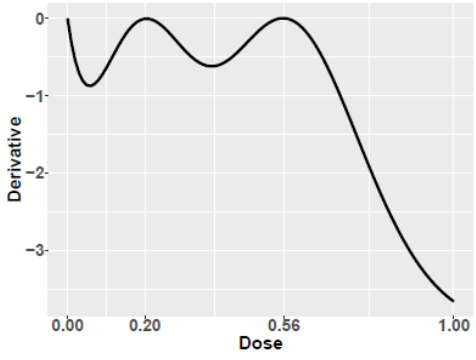
mODa 13 - Industry Session
July 13th, 2023







Optimal Design of Experiments in Drug Development

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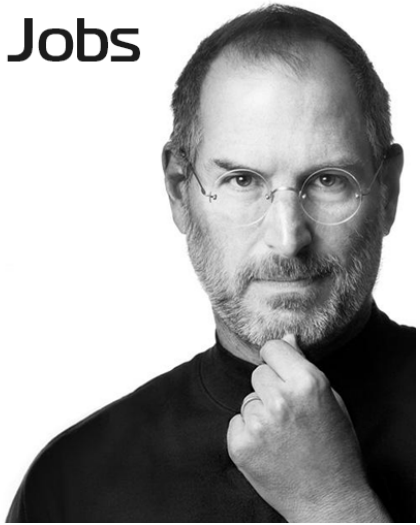
Design is not just what it looks like and feels like.
Design is how it works.

Steve Jobs



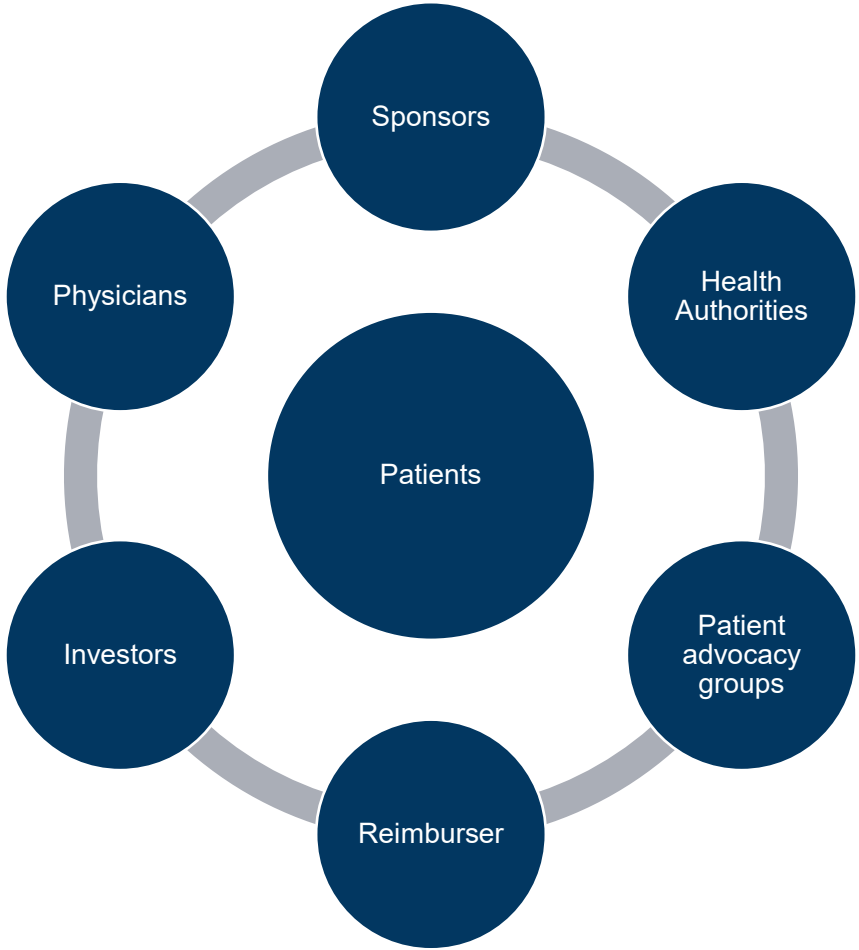
Outline

1. Background on drug development
2. Phase I dose–toxicity studies
3. Phase I/II efficacy–toxicity studies
4. Phase II dose-ranging studies
5. Phase III randomized controlled trials
6. Population PK/PD experiments
7. Future perspectives and some open problems

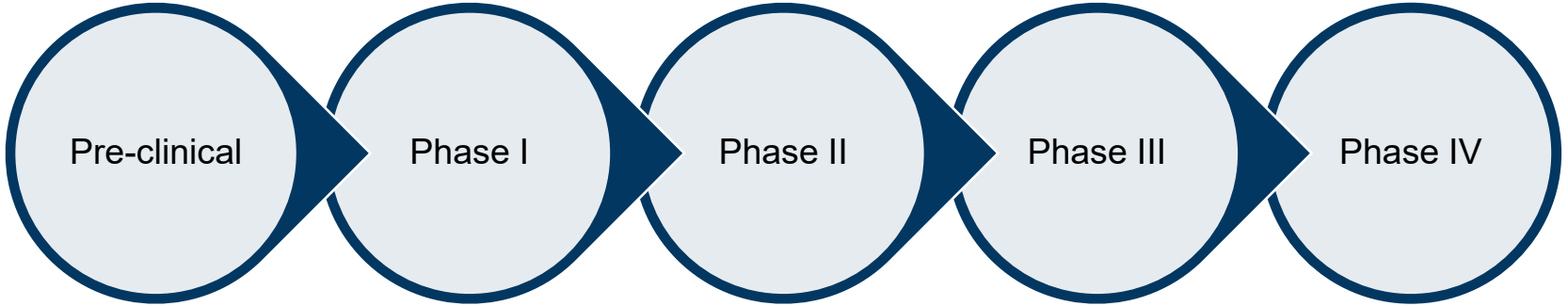
Drug Development

Goal: develop new safe and effective medicines for unmet medical needs

- Long (10+ years from discovery to market)
- Complex (scientifically, operationally, must comply with regulatory requirements)
- Expensive (~2.6B USD of R&D costs*)
- Risky (many compounds fail; only ~9.6% of drug development programs make it to approval)



Drug development programs include multiple studies of increasing complexity



- Animal studies to calibrate dose range for phase I studies in humans
- Utilize safety, PK, and PD data to project dose and regimen for phase II
- Update PK/PD models to optimize dose and regimen in phase III
- Assess probability of success
- Test clinical hypotheses in RCTs
- Refine dose and regimen for special populations
- Optimization of drug use
- Population PK/PD models

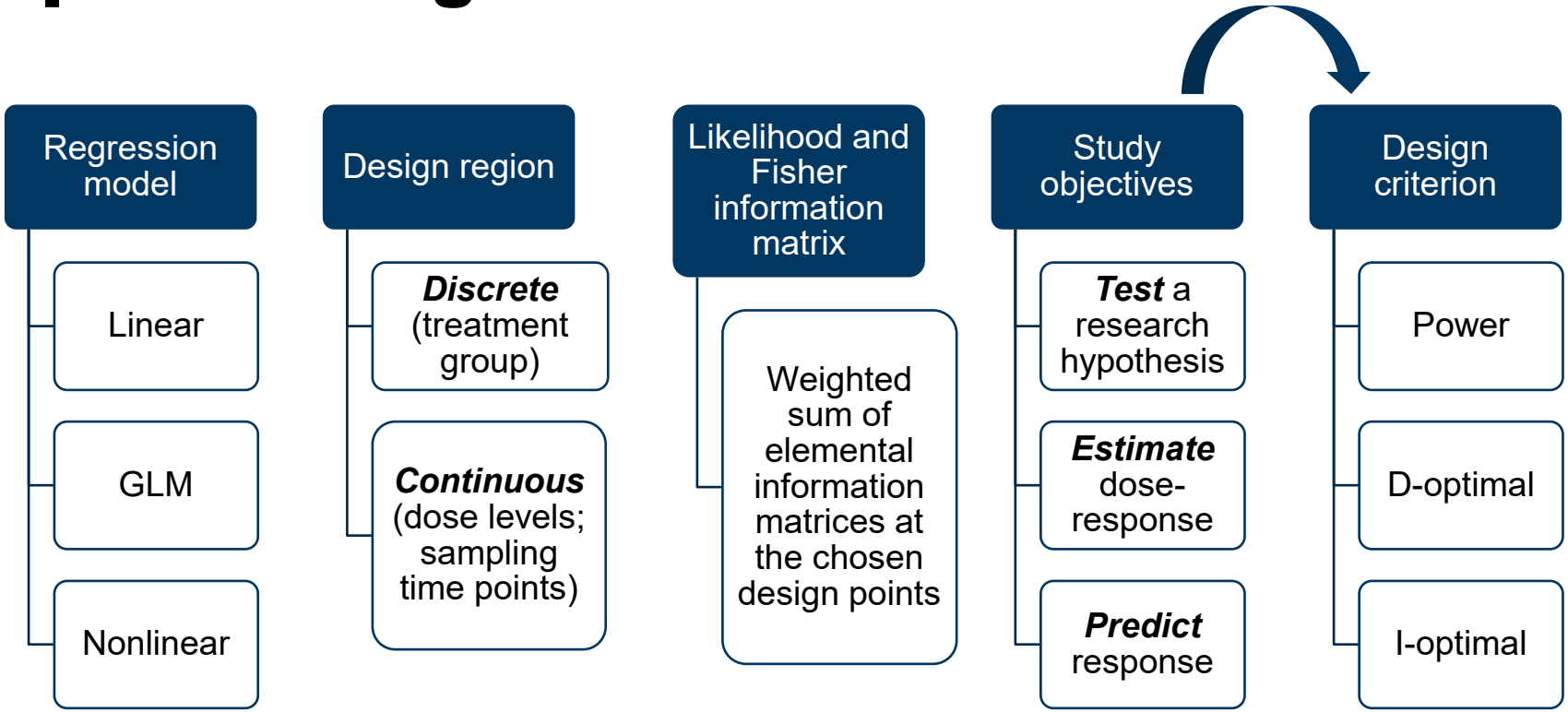
Why optimal design?

To achieve higher quality results (higher power, more accurate estimates of treatment effects) for the given resource constraints

To have lower sample size and/or decreased study cost (and potentially faster study completion) for the given data quality objectives

Study participant benefit: maximize information from the trial while minimizing exposure of study subjects to suboptimal treatments

Optimal design considerations

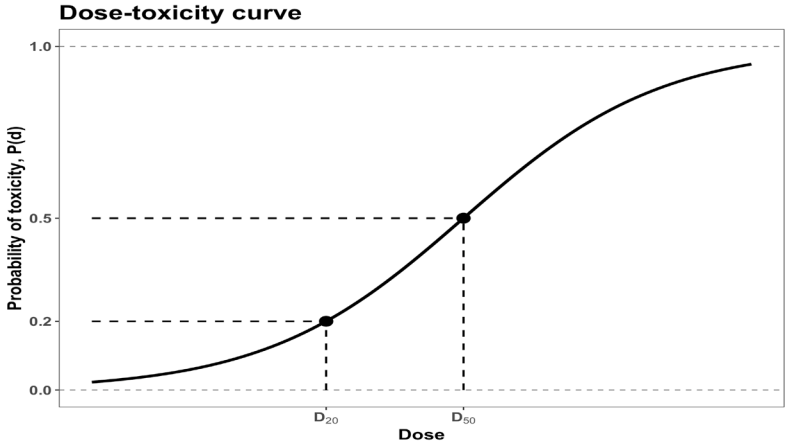


Phase I dose-finding study

- $0 \leq d_1 < d_2 < \cdots < d_K$ - study doses
- Outcome: Toxicity (Yes/No)
- Probability of toxicity is modeled using a 2-parameter logistic curve:

$$P(d) = \Pr(Y = 1|d) = \frac{1}{1 + e^{-(\alpha+\beta d)}}$$

- α and $\beta > 0$ are unknown parameters; monotone increasing dose-toxicity relationship



- Estimands of interest:
  - $P(d)$ for a given $d > 0$
  - Maximum Tolerated Dose - say, 20th percentile of the dose-tox curve: $D_{20} = (\log\left(\frac{0.2}{1-0.2}\right) - \alpha)/\beta$

Phase I dose-finding study
How can the design be optimized?

- Design: $\boldsymbol{\xi} = \{(d_i, \rho_i), i = 1, \ldots, K\}$
  - d_i's – dose levels
  - $\rho_i = n_i/n$ – allocation proportion for d_i; n = sample size
- Fisher Information Matrix (FIM) for design $\boldsymbol{\xi}$:

$$\boldsymbol{M}(\boldsymbol{\xi}, \alpha, \beta) = n \sum_{i=1}^{K} \rho_i \boldsymbol{M}_i(\alpha, \beta)$$, where $\boldsymbol{M}_i(\alpha, \beta)$ = information at dose d_i

- Optimal design problem:

$$\text{minimize } \Phi\left(\boldsymbol{M}^{-1}(\boldsymbol{\xi}, \alpha, \beta)\right) \text{ w.r.t. } \boldsymbol{\xi}$$

$\Phi = \det \Rightarrow$ D-optimality $\Rightarrow$ min(volume of the confidence ellipsoid for α, β)

- Convex optimization theory, algorithms and numerical techniques, all beyond the scope of presentation; see Fedorov and Leonov (2014) and references therein

Phase I dose-finding study
D-optimal design

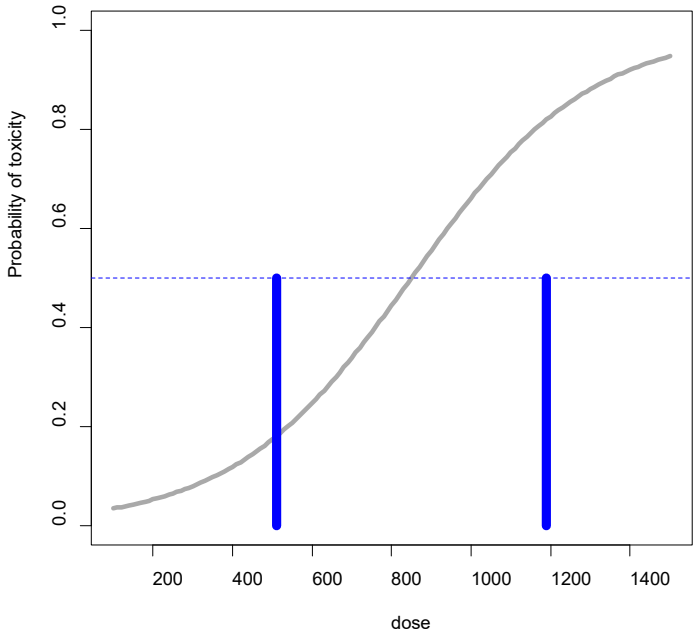
- The D-optimal design minimizing $|\boldsymbol{M}^{-1}(\alpha, \beta)|$ is 2-point, symmetric around D_{50}, equally supported at the 17.6th and 82.4th percentiles of the curve (Wetherill, JRSSB 1963)

$$\xi^*_{D-opt} = \left\{(D_{17.6}, \frac{1}{2}), (D_{82.4}, \frac{1}{2})\right\}$$

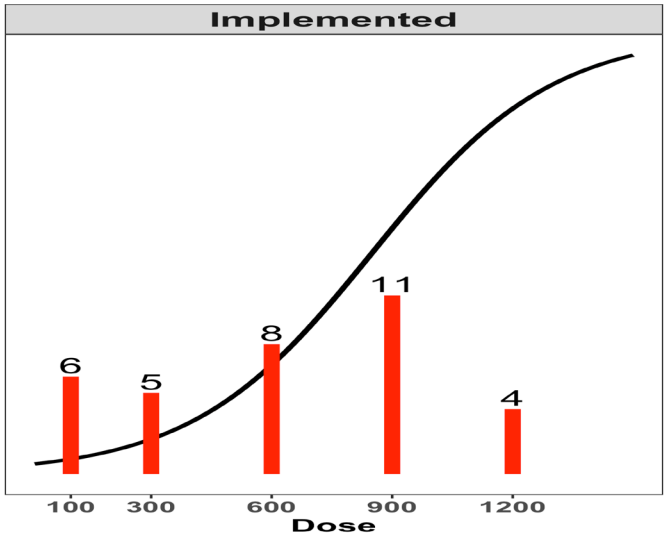
$$D_{18} = \frac{\log(0.176/0.824) - \alpha}{\beta}, \text{ and}$$

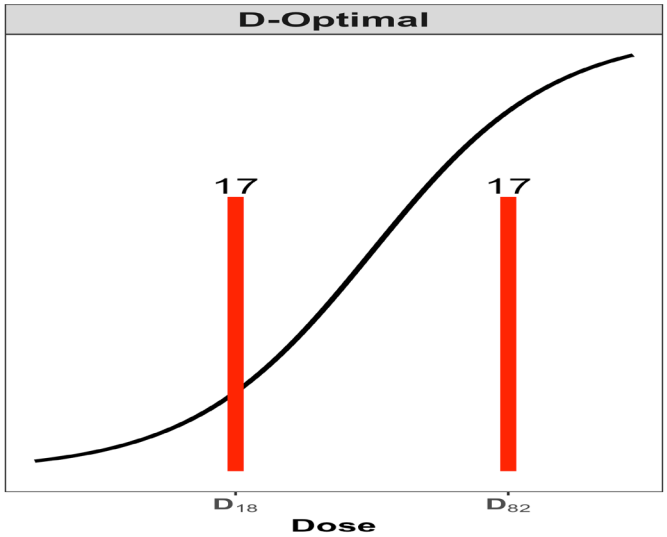
$$D_{82} = \frac{\log(0.824/0.176) - \alpha}{\beta}$$

- Yang and Stufken (2009) gave a general solution for nonlinear models with two parameters



Phase I dose-finding study
Example: How to facilitate a comparison among designs?





- Efficiency of the implemented design $\boldsymbol{\xi}$ (Karp et al., 2001) relative to the D-optimal design $\boldsymbol{\xi}^*$(for the same sample size) is $D_{eff} = \frac{|\boldsymbol{M}^{-1}(\boldsymbol{\xi}^*,\boldsymbol{\theta})|}{|\boldsymbol{M}^{-1}(\boldsymbol{\xi},\boldsymbol{\theta})|} = \left\{\frac{3.45\cdot10^{-7}}{5.16\cdot10^{-7}}\right\}^{1/2} = 0.82$

Phase I dose-finding study
What are merits and limitations of optimal designs?

Merits

- ODs provide important theoretical benchmarks to compare various designs w.r.t. selected optimality criteria
- If properly implemented, ODs can help achieve study goals with a reduced sample size/study cost
- D-optimal design maximizes information for estimating the entire dose-toxicity curve

Limitations

- ODs depend on the choice of statistical model
- ODs frequently depend on the true parameter values (local optimality)
- D-optimal design allocates 50% of subjects to the doses with toxicity probabilities 18% and 82% - may not be ‘clinically optimal’
- Frequently require advanced numerical optimization

Phase I dose-finding study
Can a design combine 'treatment' and 'learning' goals?

Constrained Bayesian optimal designs (Haines, Perevozskaya, and Rosenberger, 2003):

- 2-parameter logistic dose–toxicity model, with a prior distribution for $\boldsymbol{\theta} = (\alpha, \beta)$
- Constrained optimization problem:

$$E(\log|\boldsymbol{M}^{-1}(\boldsymbol{\xi}, \boldsymbol{\theta})|) \rightarrow \min \text{ (w.r.t. } \boldsymbol{\xi})$$

subject to to an "overdose" constraint: $\sum_{i=1}^{K} \rho_i \Pr(\mu_R \leq d_i) \leq \varepsilon$

(μ_R=maximum dose that cannot be exceeded; $\varepsilon > 0$ small, investigator-specified constant)

- Implementation in practice:
  - 2-stage: n_0 subjects are assigned to doses using some pilot design + n_1 subjects are assigned to doses according to updated optimal design
  - Sequential: Small pilot design + subsequent sequential assignments to maximize incremental gain in information while protecting patient safety

Phase I/II efficacy-toxicity study

- Development of a targeted therapy in oncology is different from that of a cytotoxic drug
  - Lower risk of toxicity
  - Efficacy may plateau at doses below MTD
- Seamless phase I/II designs incorporate toxicity and efficacy (response) in dose-finding objectives
  - Joint modeling of a dose–toxicity–efficacy relationship
  - Phase I/II trial is typically larger that a single phase I trial
  - Avoids administrative wait between phase I and II protocol activation

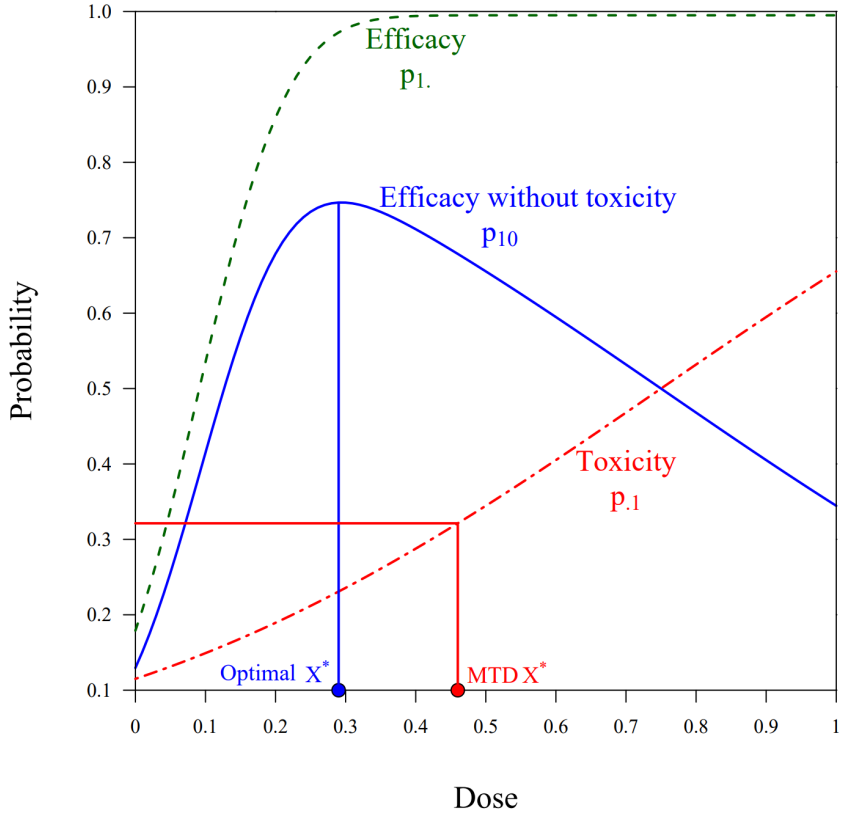
Phase I/II efficacy-toxicity study
Bivariate binary outcomes

- $\Omega = \{d_1 < \cdots < d_K\}$ - study doses
- Dose-toxicity and dose-efficacy probability curves

$$p_{\cdot 1}(d) = \Pr(Y_T = 1|d) \text{ (Tox)}$$

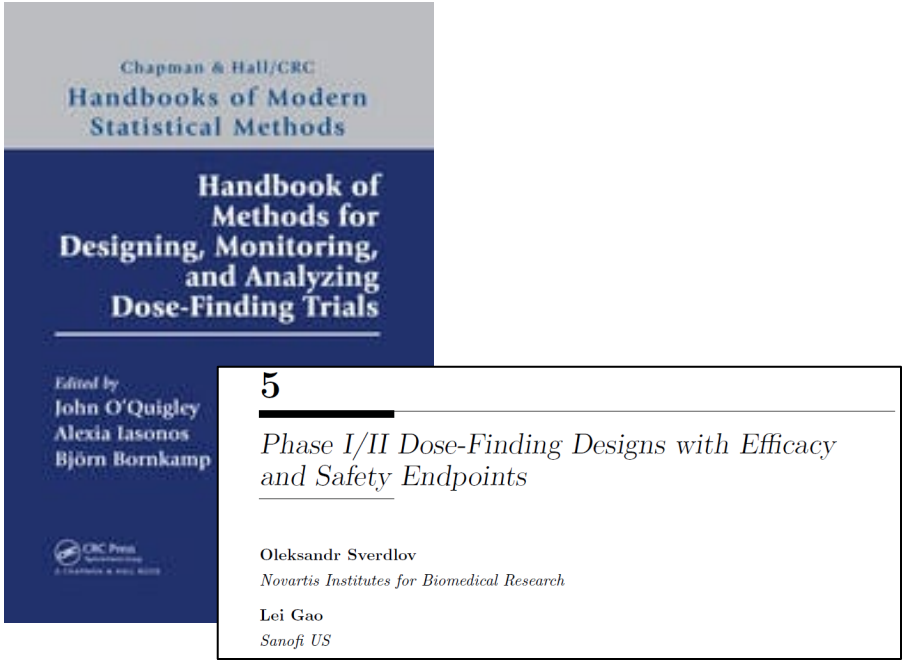
$$p_{1\cdot}(d) = \Pr(Y_E = 1|d) \text{ (Eff)}$$

- Efficacy without toxicity: $p_{10}(d) = \Pr(Y_E = 1|Y_T = 0, d) \times \Pr(Y_T = 0|d)$
- Study goals:
  - Estimate Optimal dose
  - Cluster dose assignments at and around Optimal dose



Phase I/II efficacy-toxicity study
Various designs have been proposed

- Nonparametric up-and-down design (Ivanova, 2003)
- Bayesian ‘best intention’ designs
  - Bivariate CRM (Braun, 2002)
  - Eff-tox method (Thall and Cook, 2004)
- Adaptive penalized optimal designs (Dragalin and Fedorov, 2006)
- It is difficult to recommend any particular design as “best”



Phase I/II efficacy-toxicity study
Adaptive penalized ODs (Dragalin and Fedorov, 2006)

- Statistical model for dose–response: $\pi_{T,E}(d, \boldsymbol{\theta})$, $d \in \Omega$
- Fisher information matrix: $\mathbf{M}(\boldsymbol{\xi}, \boldsymbol{\theta}) = \sum_{k=1}^{K} \rho_k \pi_{T,E}(d_k, \boldsymbol{\theta})$
- Cost function penalizing doses with low success and high toxicity: $\phi(d, \boldsymbol{\theta}, C_E, C_T) > 0$ (where $C_E, C_T \geq 0$ are user-specified constants)
- Penalized OD problem:

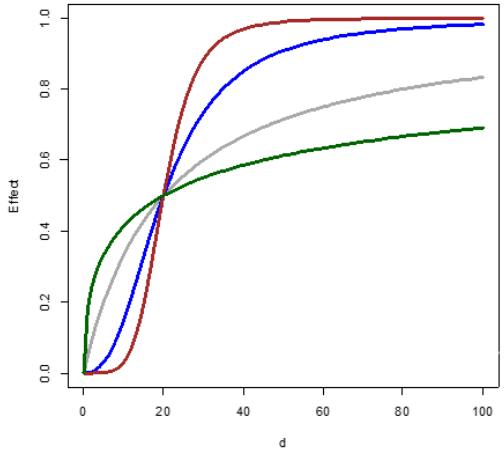
$$\log \frac{|\mathbf{M}^{-1}(\boldsymbol{\xi}, \boldsymbol{\theta})|}{\sum_{k=1}^{K} \rho_k \phi(d_k, \boldsymbol{\theta}, C_E, C_T)} \rightarrow \min \text{ (w.r.t. } \boldsymbol{\xi})$$

- Implementation: some ‘start-up’ dose-escalation design to ascertain initial data for estimating $\boldsymbol{\theta}$, then sequential dose assignments to maximize incremental increase of information per cost unit

Phase I/II efficacy-toxicity study
Potential value of adaptive penalized optimal designs

- Substantial improvement in accuracy of dose–response estimation compared to ‘best intention’ designs (Dragalin and Fedorov, 2006; Dragalin, Fedorov, and Wu, 2008)
- Good balance between ‘treatment’ and ‘learning’ goals in small-to-moderate experiments; known asymptotic properties (Pronzato, 2010)
- Bayesian adaptive penalized D-optimal design has competitive performance to Thall and Cook’s Eff-Tox method (Gao and Rosenberger, 2013)
- While in practice it may be difficult to gain IRB clinical approval for these designs, they may be more readily applicable in animal studies where ethical issues are not as high as in human experiments

Phase II dose-ranging study



- Randomized, placebo- and/or active-controlled trial with several doses of an investigational drug, with sample sizes up to several hundred patients
- Research questions in phase II:
  - Is there any evidence of a drug effect (proof-of-concept)?
  - Which dose(s) exhibit a response different from the control?
  - What is the dose–response relationship?
  - What is the “optimal” dose for taking into phase III?
- Design considerations:
  - Sample size
  - Dose levels
  - Allocation proportions for the chosen doses

Phase I/II dose-ranging study
Optimal designs

Various optimal designs are available for addressing different study goals under different dose-response models:

- Biedermann, Dette, and Zhu (2007, JSPI)
- Dette, Bretz, Pepelyshev, and Pinheiro (2008, JASA)
- Dette, Kiss, and Bevanda (2010, Biometrika)
- Padmanabhan and Dragalin (2010, Biom J)
- Miller, Guilbaud, and Dette (2007, J Biopharm Stat)
- And many more...

Phase II dose-ranging study
Example: D-optimal design for time-to-event outcomes

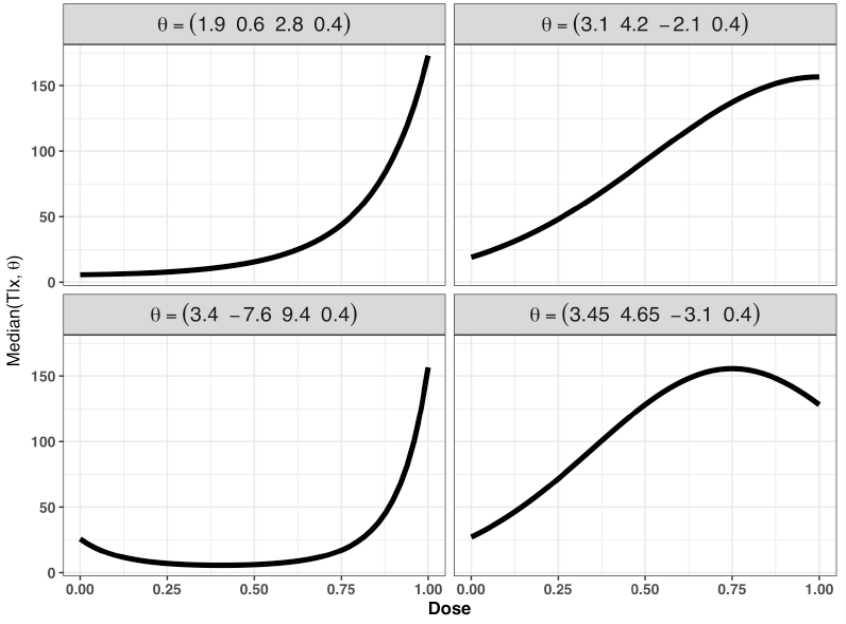
- Quadratic dose-response model for event times: $T \sim Weibull$ with

$$Median(T) = \exp(\beta_0 + \beta_1 d + \beta_2 d^2)\,(\ln 2)^b$$

Doses: $d \in [0,1]$; 0 =placebo; 1=MTD
Parameters: $\boldsymbol{\theta} = (\beta_0, \beta_1, \beta_2, b)$, $b > 0$

- Observations may be right-censored
- Objective: estimate dose–response as accurately as possible by allocating n subjects to 'most informative' dose levels

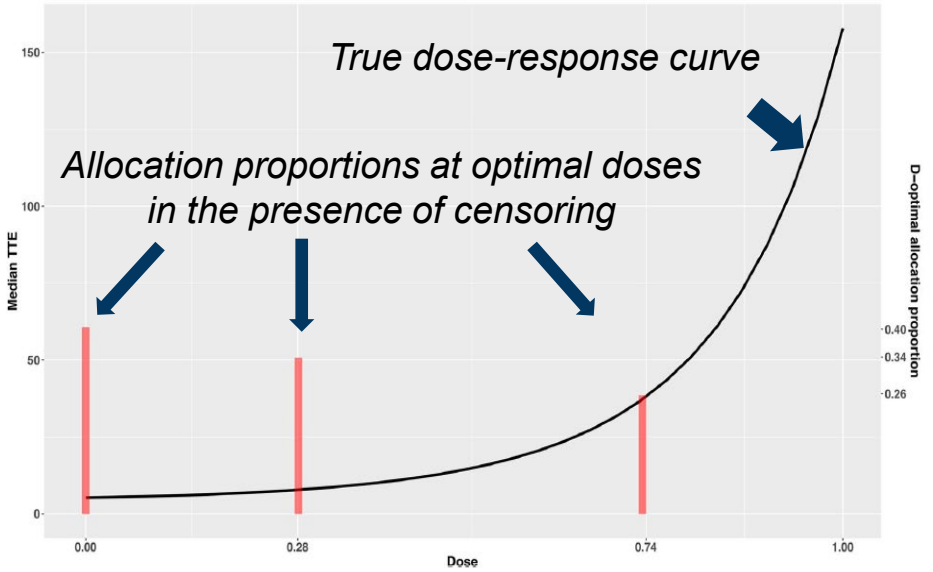
Plausible median time-to-event dose-response



Phase II dose-ranging study
Potential value of optimal design for time-to-event outcomes (Ryeznik et al., 2018a, b)

- D-optimal design depends on the underlying model and the amount of censored data
- Equal allocation (uniform) design may be inefficient
- Adaptive D-optimal design with early stopping facilitates learning about the model and can reduce study size with better estimation accuracy than the uniform design

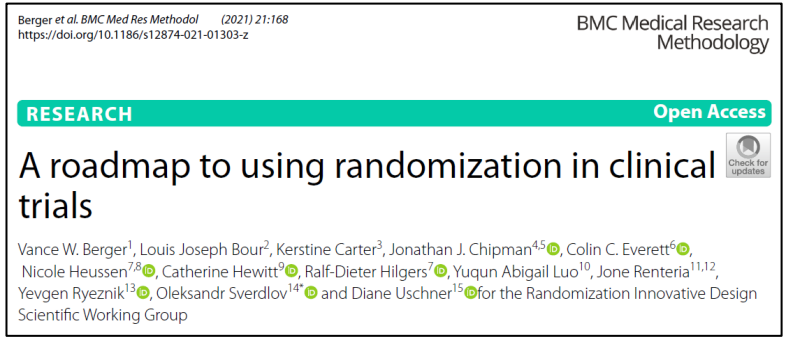
Weibull model with $\beta_0 = 1.9$, $\beta_1 = 0.6$, $\beta_2 = 2.8$, $b = 0.65$, and average probability of event = 50%



Phase III randomized controlled trial (RCT)
Design considerations

- Primary outcome
- Number of treatment arms
- Choice of control group
- Number of study sites
- Sample size
- Allocation ratio
- Randomization procedure

- Allocation ratio
  - Equal (1:1) allocation is frequently (but not always) optimal
- Randomization procedure
  - Tradeoff between treatment balance and allocation randomness



Berger *et al. BMC Med Res Methodol* (2021) 21:168
https://doi.org/10.1186/s12874-021-01303-z

BMC Medical Research Methodology

RESEARCH Open Access

A roadmap to using randomization in clinical trials

Vance W. Berger[1], Louis Joseph Bour[2], Kerstine Carter[3], Jonathan J. Chipman[4,5], Colin C. Everett[6], Nicole Heussen[7,8], Catherine Hewitt[9], Ralf-Dieter Hilgers[7], Yuqun Abigail Luo[10], Jone Renteria[11,12], Yevgen Ryeznik[13], Oleksandr Sverdlov[14*] and Diane Uschner[15] for the Randomization Innovative Design Scientific Working Group

Phase III randomized controlled trial (RCT)
Design considerations

Unequal allocation may sometimes be preferred:

- Heteroscedastic outcomes
- Unequal treatment cost
- Ethical considerations
- Vaccine RCTs
- Platform trials

Response-adaptive randomization (RAR) to target optimal allocation in a K-arm RCT:

- Well-developed theory (Hu and Rosenberger, 2003), conceptually different from “Thompson sampling”
- Estimators and statistical tests have known asymptotic properties under widely satisfied conditions

Response-adaptive randomization (RAR)
Further challenges and opportunities

Robertson et al. (2023) provides a fresh outlook at methodological and practical aspects of RAR in clinical trials

Some important research questions:

- How to define ‘optimal allocation’ given that the number of experimental treatment arms is not known upfront? (Bofill Roig et al., 2023)
- How to modify allocation to the shared control over time given that experimental arms may be added/dropped during the study? (Kaizer et al., 2018)
- Incorporating stratification factors (genetic signatures and other predictive biomarkers) (Atkinson, 2015 Biometrika)
- Strong control of the type I error rate

Population PK/PD studies

- PK: description of the plasma concentration of a drug as a function of time (what the body does to the drug)
- PD: description of the drug effects (what the drug does to the body)
- PK/PD model links the effect of dose on trug concentration and drug response over time
  - Mechanistic modeling of individual subject profiles with an assessment of corresponding uncertainty

Nonlinear mixed effects model (NLMEM) (Fedorov and Leonov, 2014 Chapter 7)

$$\boldsymbol{Y}_i = \boldsymbol{f}(\boldsymbol{t}_i, \boldsymbol{d}_i, \boldsymbol{\theta}, \boldsymbol{\eta}_i) + \varepsilon_i,\ i = 1, \ldots, n$$

- $\boldsymbol{Y}_i$ = vector of responses
- $\boldsymbol{f}$ = nonlinear (vector) function
- $\boldsymbol{d}_i$ = vector of administered doses
- $\boldsymbol{t}_i$ = vector of sampling time points
- $\boldsymbol{\theta}$ = vector of typical parameter values
- $\boldsymbol{\eta}_i \sim MVN(\mathbf{0}, \boldsymbol{\Omega})$ = inter-individual variabilities
- $\boldsymbol{\varepsilon}_i \sim MVN(\mathbf{0}, \boldsymbol{\Sigma})$ = measurement errors

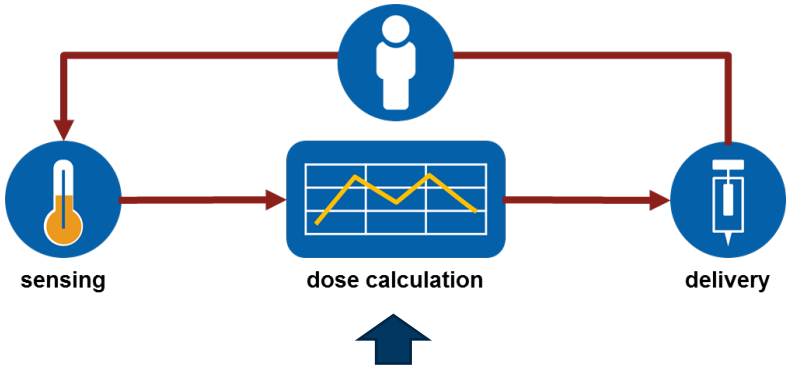
Population PK/PD studies
Optimal Designs

- OD in this context involves maximization of some criterion of the population FIM which is not a closed-form expression (Mentre et al., 1997)
- Elements to be optimized: dose; sampling times; sampling frequency, etc.
- Value:
  - ODs can help characterize a typical pattern of PK over time and uncertainty in the observations (very important in small studies)
  - Number of sampling times may be reduced ⇒ savings in the study cost
  - Population ODs may help improve existing therapies or diagnostics
  - Population ODs may help bridge different populations (e.g., adult to children)
- Software: a head-to-head comparison of 5 different tools (Nyberg et al., 2015)

Population PK/PD studies
Model-based adaptive optimal designs (MBAOD)

- MBAOD attempts to overcome potential non-robustness to changes in the parameter values of locally optimal designs
- Examples:
  - PK bridging study from adults to children (Strömberg, 2016) – MBAOD requires fewer children to fulfill the FDA precision criteria compared to traditional estimation methodologies
  - Robust optimality criterion in MBAOD (Strömberg and Hooker, 2017) – reduced sensitivity to model misspecification and improved practicality of experimental design
- Software: R package MBAOD (https://github.com/andrewhooker/MBAOD)

Future Perspective
Optimal designs for biosensor data



Pharmacometric modeling & simulation to optimize:
- Time of sensing
- Dose level
- Timing of dose delivery

- Precision dosing in different chronic diseases/conditions, such as diabetes, HIV, Parkinson's disease
- Development, engineering, testing, and validation of closed-loop systems for disease management
- Complex research problems combining pharmacometrics, optimal control theory, machine learning, big data analytics, etc.

More details in two JSTP papers:

Journal of Statistical Theory and Practice, 7:753–773, 2013
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On Recent Advances in Optimal Allocation Designs in Clinical Trials

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Journal of Statistical Theory and Practice (2020) 14:10
https://doi.org/10.1007/s42519-019-0073-4

ORIGINAL ARTICLE

Check for updates

On Optimal Designs for Clinical Trials: An Updated Review

Oleksandr Sverdlov[1] · Yevgen Ryeznik[2,3] · Weng Kee Wong[4]

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