Early Phase Trial Designs in Rare Diseases

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Disclaimer

The primary purpose of this presentation is educational – it is intended to provide information on the presenter's thinking on early phase clinical trial designs in rare diseases.

This presentation reflects the views of the presenter and should not be construed to represent the views or policies of Novartis.

Outline

1. Background on development of novel therapies for rare diseases
2. Phase 1 dose–toxicity studies
3. Phase 1/2 efficacy–toxicity studies
4. Some other important topics

1. Background on development of novel therapies for rare diseases

Rare diseases

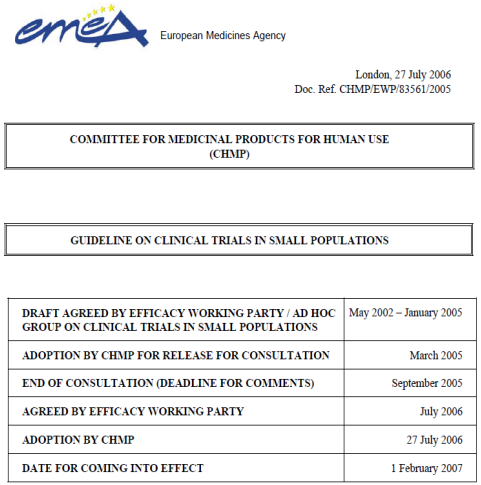
- Rare disease (RD) – a disease or condition affecting less than 200,000 people in the US (US Orphan Drug Act, 1983)
- In EU, a similar framework exists for orphan medicines that address diseases affecting fewer than 5 in 10,000 in the European Economic Area
- Incentives for development of therapeutics for RDs include prolonged patent protection and market exclusivity, tax credits, and exemption of user fees

Rare disease drug development: Challenges

- Small and heterogeneous patient populations => great concern on how to design and conduct clinical trials for obtaining substantial evidence on safety and effectiveness for approval
- RD clinical trials must meet the same standards as those for more prevalent diseases (EMA, 2006)*
- Many RDs have poorly understood natural history, lack fit-for-purpose biomarkers or endpoints measuring benefits or risks
- Many RDs have genetic basis, present in childhood and last into adulthood => optimal time of intervention is a challenge

* EMA Guideline on Clinical Trials in Small populations (London, 27 July 2006)

Rare disease drug development: Some relevant regulatory guidelines



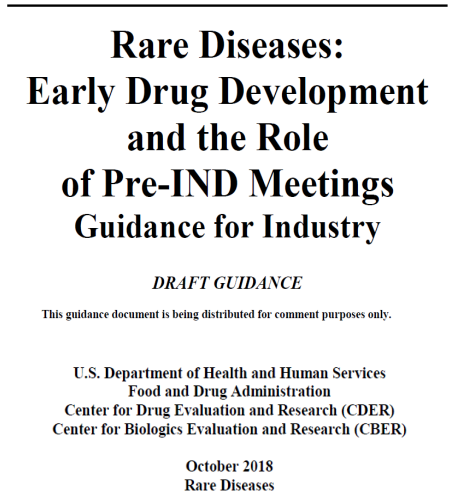
European Medicines Agency

London, 27 July 2006
Doc. Ref. CHMP/EWP/83561/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

GUIDELINE ON CLINICAL TRIALS IN SMALL POPULATIONS

DRAFT AGREED BY EFFICACY WORKING PARTY / AD HOC GROUP ON CLINICAL TRIALS IN SMALL POPULATIONS	May 2002 – January 2005
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	March 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	September 2005
AGREED BY EFFICACY WORKING PARTY	July 2006
ADOPTION BY CHMP	27 July 2006
DATE FOR COMING INTO EFFECT	1 February 2007



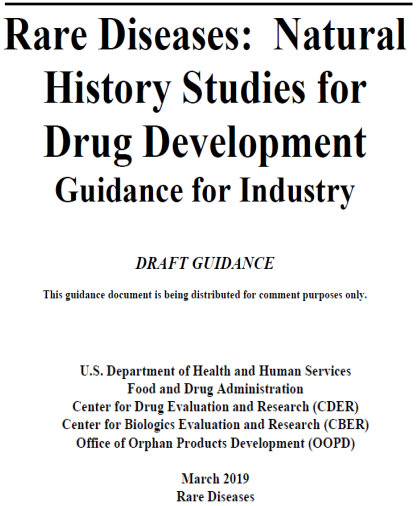
**Rare Diseases:
Early Drug Development
and the Role
of Pre-IND Meetings**
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2018
Rare Diseases



**Rare Diseases: Natural
History Studies for
Drug Development**
Guidance for Industry

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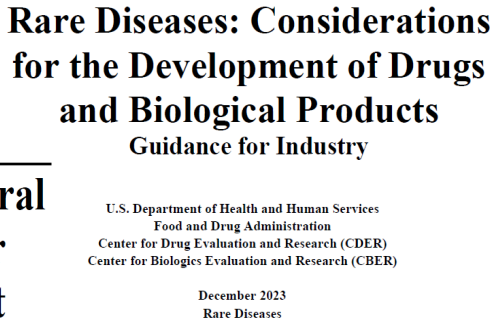
Office of Orphan Products Development (OOPD)

March 2019
Rare Diseases



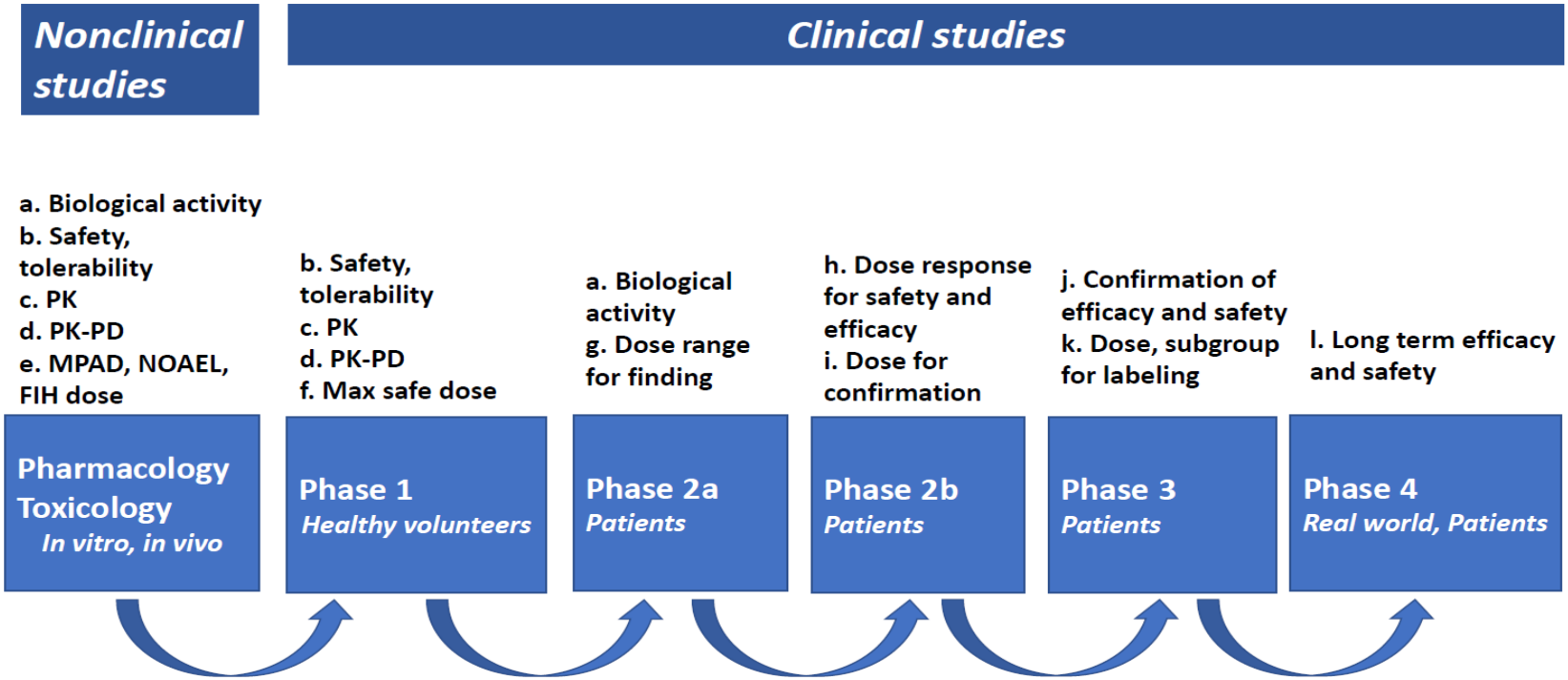
**Rare Diseases: Considerations
for the Development of Drugs
and Biological Products**
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

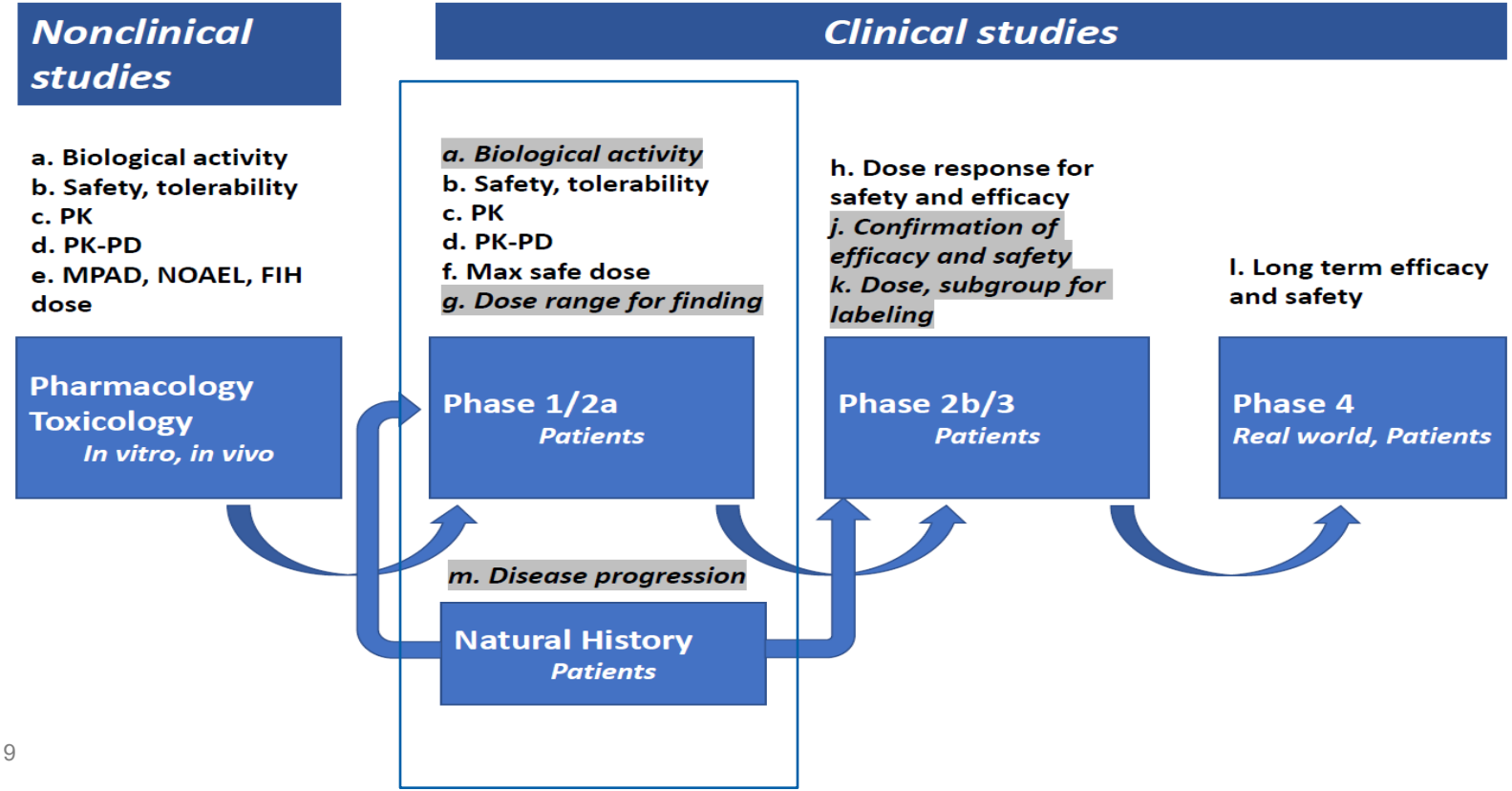
December 2023
Rare Diseases

For more information, please visit
Guidance Documents for Rare Disease Drug Development | FDA
Orphan designation: Overview | European Medicines Agency (europa.eu)

Drug Development: 'Traditional' Approach

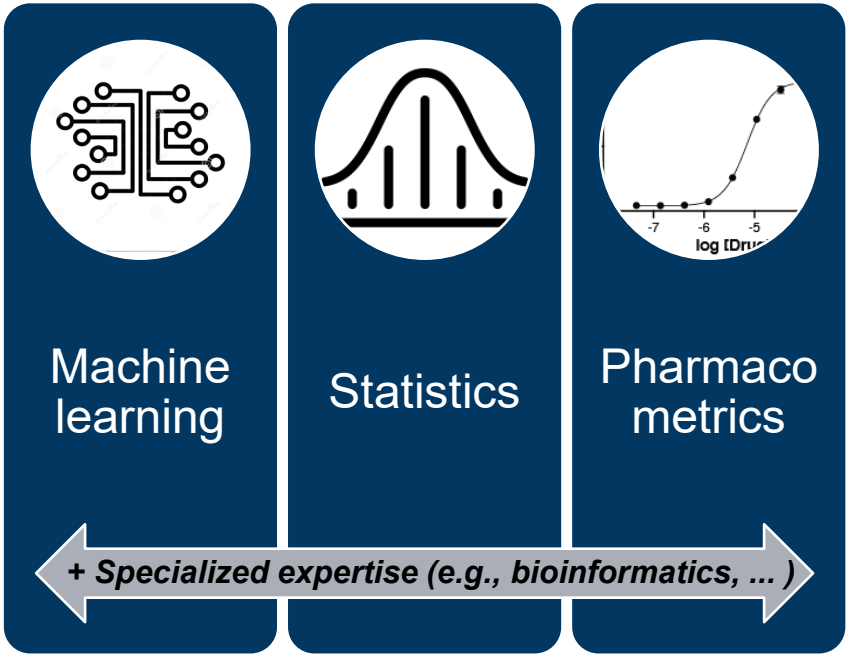


Drug Development: 'Non-Standard' Approach



Statistical input for a rare disease clinical development program

- RWE and Natural History Data
- Phase 1/2 trials
- Phase 2/3 trials
- Phase 4 trials



Phase 1 and Phase 1/2 studies

Why?

- To evaluate product safety and tolerability
- To assess pharmacological (and) clinical activity

How?

- Staggered cohort dose escalation
- Endpoints: safety/ tolerability; molecular biomarkers (if available); response
- Sample size: depends on the disease (3 per dose level?)
- Patient population/control group/blinding?

Outcomes

- Characterization of short-term safety/tolerability/early efficacy
- Dose–exposure–response model (keeping in mind small sample size and other limitations)
- Recommended phase 2/3 dose

Treatment vs Experimentation Dilemma

- To treat or to learn?
  - A tradeoff between individual ethics (maximizing clinical benefit for each trial participant) vs. collective ethics (maximizing clinical benefit of future patients)
  - Adaptive designs (e.g., response-adaptive randomization)?
- Multiple experimental treatments from different sponsors – can we engage in a collaborative effort to identify “optimal” treatments?
  - Master protocols?

2. Phase 1 dose–toxicity studies

Phase 1 clinical trials (in oncology)

- Typically small, uncontrolled (no placebo control group), sequential study of patients with the disease
- Goal: determine the maximum tolerated dose (MTD) of the experimental drug
  - MTD is thought to provide clinical efficacy with “acceptable” level of side effects
  - Accurate determination of MTD is critical, since it will be taken forward for testing in Phase 2 clinical trials
- Toxicity (side effects) are severe ⇒ design considerations are very important
  - Balance between individual and collective ethics: maximum information from the minimum number of study patients

Statistical methods for phase 1 trials

- A monotone relationship between the dose level and the risk of toxicity is assumed
- Two different philosophies in the MTD definition*:
  i. Risk of toxicity is a sample statistic
  ii. Risk of toxicity is a probability, and the MTD is a quantile of a monotonic dose–toxicity curve, to be estimated based on experimental data
- Approach ii) can use nonparametric or parametric statistical models

Phase 1 designs to determine MTD

Algorithm-based and nonparametric designs

- Require no parametric assumption on dose-toxicity relationship
- Algorithm-based => dose escalation decisions can be tabulated before the trial starts

Examples:

- 3+3 and A+B designs
- Accelerated titration designs
- Up-and-down designs

Model-assisted (MA) designs

- Use a simple statistical model (e.g., binomial) for efficient decision-making
- Unlike MB designs, all decision rules can be pre-tabulated

Examples:

- Modified toxicity probability interval (mTPI) design
- Bayesian optimal interval (BOIN) design
- Many others

Model-based (MB) designs

- Assume some parametric statistical model for the dose-toxicity curve
- Dose assignments are made (group) sequentially based on the updated dose-toxicity curve

Examples:

- Continual reassessment method (CRM)
- Bayesian logistic regression method (BLRM)
- Many others

Sverdlov et al. Adaptive clinical trial designs for phase I cancer studies. Statistics Surveys 2014. doi: 10.1214/14-SS106
Yuan et al. Model-assisted designs for early-phase clinical trials: Simplicity meets superiority. JCO Precis Oncol. 2019. doi: 10.120/PO.19.00032

Phase 1 design: Building blocks

- A set of doses to be studied: $d_1 < d_2 < \cdots < d_K$
- Maximum sample size
- Starting dose level
- Cohort size (number of patients to be assigned per dose)
- Statistical model for dose–toxicity curve
- Method for sequentially assigning doses to cohorts (adaptive dose escalation)
- Stopping rule
- Criterion for choosing an MTD at the end of the study
  - Select MTD empirically from the set of studied doses or estimate MTD by extrapolating beyond these doses?

Phase 1 design example: 3+3

- Patients are treated in cohorts of size 3 starting with the lowest dose; never skip a dose when escalating; maximum of 6 patients are treated at any dose
- Suppose 3 patients are treated at dose d_j
  - 0/3 toxicities => escalate to d_{j+1}; 1/3 toxicities => stay at d_j; ≥2/3 toxicities => MTD has been exceeded
- Suppose 6 patients are treated at dose d_j
  - 1/6 toxicities => escalate to d_{j+1}; **1/6 toxicities => declare d_j as MTD**; ≥2/6 toxicities => MTD has been exceeded

- 3+3 design is simple and very popular in practice
- However, it has poor statistical properties – identifies MTD imprecisely and unreliably, and many patients are treated at suboptimal dose levels

Phase 1 design example: Random Walk Rule (RWR)

- Specify the target toxicity level (say, Γ=0.20) and let $b = \frac{\Gamma}{1-\Gamma}$ = bias coin probability. Dose assignments are made sequentially
- At a given dose d_j
  - If toxicity is observed => next patient is treated at the lower dose (d_{j-1})
  - If no toxicity is observed => next patient is randomized to stay at d_j (with prob. $1-b$) or to the next highest dose d_{j+1} (with prob. b)
- Suitable modifications are made at the lowest and highest doses
- RWR requires no assumption on the dose–toxicity curve other than monotonicity
- It clusters dose assignments around the target MTD. Empirical mode of dose assignments is an unbiased estimate of MTD
- A disadvantage: RWR cannot be tabulated before the trial starts

*Durham et al. A random walk rule for phase I clinical trials. Biometrics 1997. PMID: 9192462.

Phase 1 design example: modified toxicity probability interval (mTPI)

- Specify the target toxicity level (say, Γ=0.20)
- Three dosing intervals are defined for dose escalation decisions:
  - Underdosing (0, 0.17); Proper dosing (0.17, 0.23); Overdosing (0.23, 1)
- Assume a Bayesian beta-binomial model for toxicity probability at a given dose
- The interval with highest posterior probability triggers the decision for the next cohort of patients

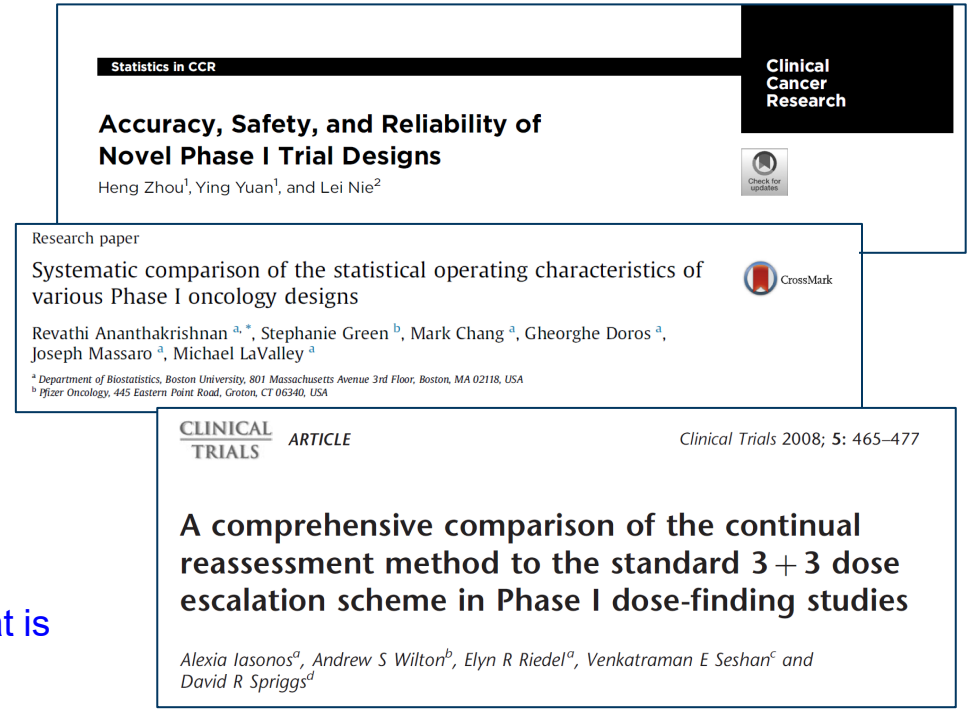
- mTPI rule is simple to implement - can be tabulated before the trial starts
- It generally outperforms 3+3 design in terms of MTD identification
- A disadvantage: mTPI decision rule lacks clear interpretation and may lead to increased risk of overdosing

Ji et al. A modified toxicity probability interval method for dose-finding trials. Clinical Trials 2010. doi:10.1177/1740774510382799

Many phase 1 designs are available

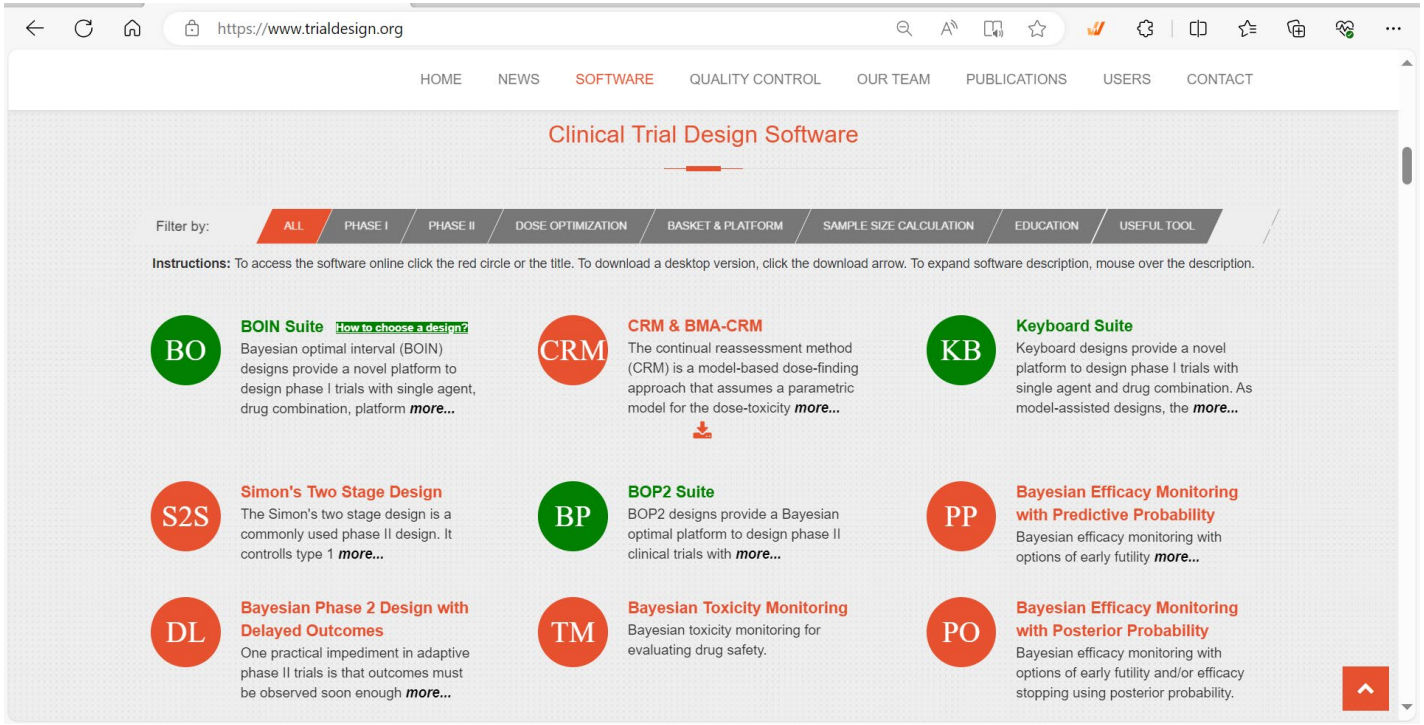
- Books:

- Simulation studies comparing various phase 1 designs:



Work with the statistician to select the design that is most fit for purpose for your trial!

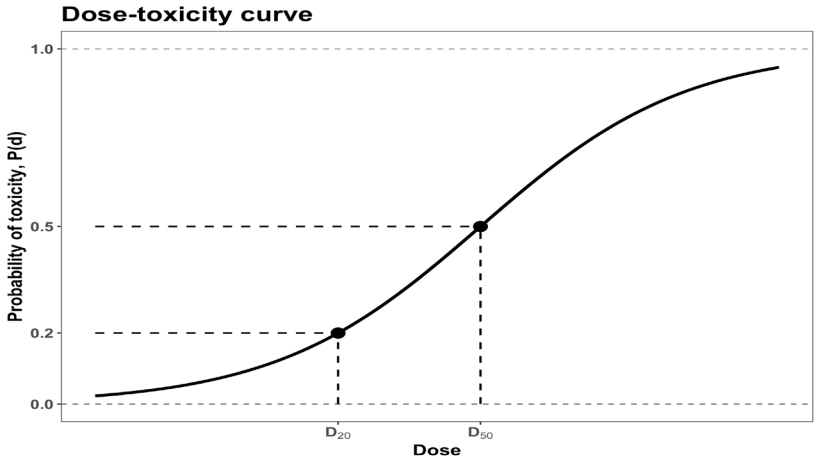
Software for phase 1 trial designs



And many more non-commercial software packages are available!

How to analyze data following phase 1 trial?

- $d_1 < d_2 < \cdots < d_K$ - study doses
- Outcome: Toxicity (Yes/No)
- Probability of toxicity can be modeled using a 2-parameter logistic curve:
- $\Pr(Toxicity|d) = \frac{1}{1+e^{-(\alpha+\beta d)}}$
- α and $\beta > 0$ are unknown parameters; monotone increasing dose-toxicity relationship



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

Data analysis following phase 1 trial

- Data structure: $\{(d_i, n_i, x_i), i = 1, \ldots, K\}$ – doses, number of patients at the doses, and number of toxicities
- Number of toxicities $x_i \sim Binomial(n_i, P_i)$, where $P_i = \frac{1}{1+e^{-(\alpha+\beta d_i)}}$
- Maximum likelihood estimates (MLEs) of (α, β) can be obtained => estimating the dose–toxicity curve
  - Other parameters can be readily estimated as they are functions of (α, β)
  - Associated uncertainties can be also quantified (e.g., using 95% confidence intervals)
- Modeling assumptions must be checked/verified => work with the statistician!

Example of phase 1 dose-toxicity study

- Phase I study of the ChemoTx agent R115777 conducted at the University of Maryland School of Medicine (Karp et al., 2001)
- n=34 patients with acute leukemia, treated at 5 different doses

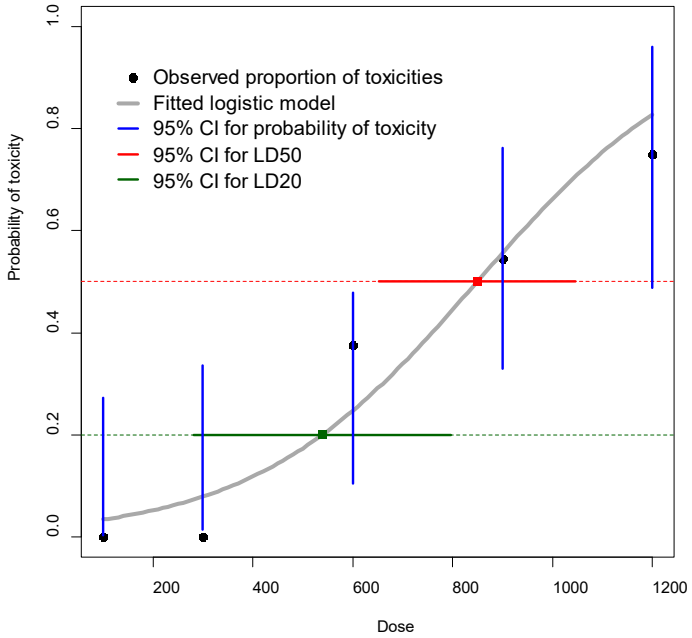
Dose	100mg	300mg	600mg	900mg	1200mg
Assigned	6	5	8	11	4
Number of toxicities	0	0	3	6	3
Proportion of toxicities	0	0	0.375	0.545	0.750

- 2-parameter logistic model was fitted:

	Estimate	95% CI
α	-3.7958	(-7.1276, -1.59015)
β	0.004468	(0.0016986, 0.0084355)

Karp et al. Blood, 97(11), 3361-9, 2001. https://doi.org/10.1182/blood.v97.11.3361

Example of phase 1 dose-toxicity study (Cont.)



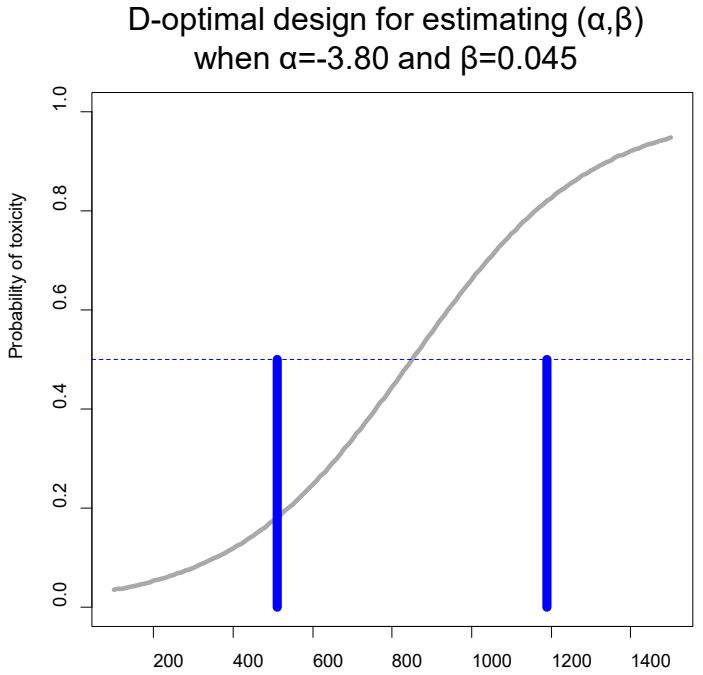
- Estimates of toxicity probabilities (with 95%CI) at study doses were obtained (blue)
- Estimate of D_{20} (dark green):

Dose D_{20}	95% CI
539	(282, 797)

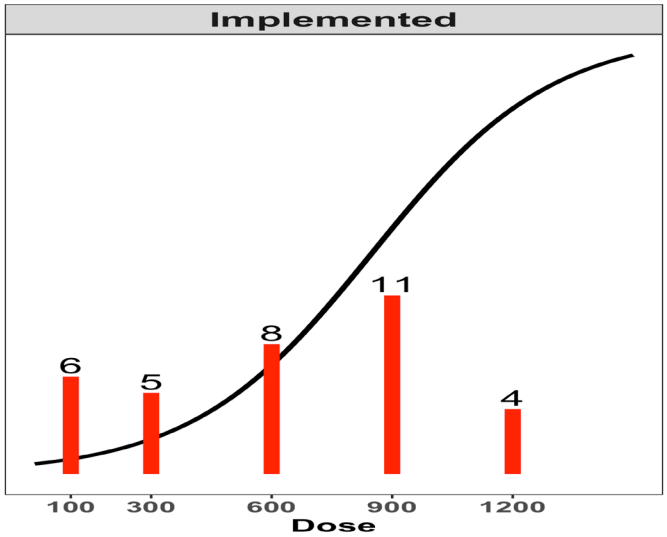
- The dataset is small (n=34) ⇒ estimation uncertainty is high

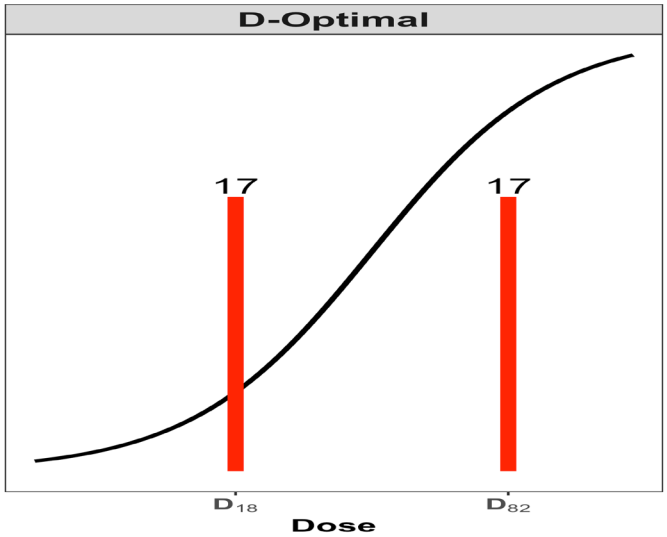
Can we optimize the design of the next phase 1 study (for a similar compound)?

- D-optimal design maximizes the information on the dose-toxicity curve
  - It is a 2-point design, equally supported at the 18th and 82nd percentiles of the curve
  - It depends on the true model parameters (unknown upfront, but estimates may be available)
  - It may not be “clinically optimal”
  - It can be used as a “benchmark” to facilitate a comparison among different designs



How to facilitate a comparison among designs?





- Efficiency of the implemented design (Karp et al., 2001) relative to the D-optimal design (for the same sample size, n=34) is 82%
- The sample size of the implemented design would have to be increased by 18% (n=6 extra patients) to match the efficiency of the D-optimal design

Summary of Phase 1 designs: Strategic Considerations

- Q1: How to quantify the study objectives?
- Q2: How to construct a design that facilitates learning about dose–toxicity relationship while protecting subjects from exposure to too toxic doses?
- Q3: How to analyze data following the implemented design and make decisions about the MTD?

Please work with the statistician!

3. Phase 1/2 efficacy–toxicity studies

Phase 1/2 dose-finding designs

- Conventional approach: Phase 1 to identify MTD => Phase 2 to study activity (response) at MTD
- Targeted therapy development:
  - Lower potential for toxicity
  - Dose-response curve may peak/plateau at doses below MTD
- Phase 1/2 designs incorporate toxicity and efficacy (response) in dose-finding objectives

Potential advantages of phase 1/2:

- Doses with desirable risk-benefit can be identified more efficiently than in a sequence of phase 1 and 2 trials
- Joint modeling of dose-efficacy-toxicity relationship can be useful
- Phase 1/2 trial avoids an administrative wait between phase 1 and 2 protocol activation

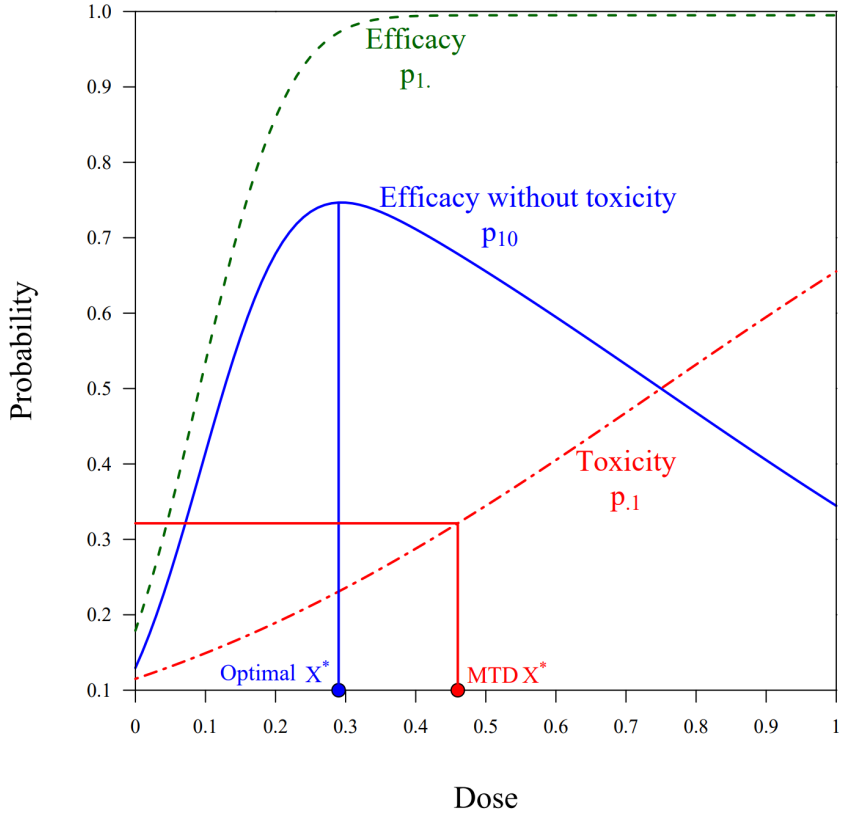
Phase 1/2 – Bivariate binary outcomes

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

  $\Pr(Y_T = 1|d)$ (Toxicity)

  $\Pr(Y_E = 1|d)$ (Efficacy)

  Efficacy without toxicity
- Study goals:
  - Estimate Optimal dose
  - Cluster dose assignments at and around Optimal dose



Phase 1/2 adaptive designs

Nonparametric designs

- No specific parametric assumption is made on dose-toxicity-efficacy relationship
- In adaptations, data only from the most recent cohort of patients is utilized

Example:

- Up-and-down design (Ivanova, 2003)

Bayesian utility-based designs

- Use parsimonious models with Bayesian priors for the dose-toxicity-efficacy curve
- Perform dose assignments adaptively, to target doses with “desirable” efficacy and toxicity rates

Examples:

- Bivariate CRM (Braun, 2002)
- Eff-Tox (Thall & Cook, 2004)

Adaptive penalized optimal designs

- Use parsimonious models for the dose-toxicity-efficacy curve
- Perform dose assignments adaptively, to minimize some criterion providing a tradeoff between statistical efficiency and ethics

Examples:

- Adaptive penalized optimal designs (Dragalin & Fedorov, 2006)

Up-and-down design*

- A 3-category outcome model is used:

$$Z = \begin{cases} 0, & (no\ efficacy, no\ toxicity); \\ 1, & (efficacy\ without\ toxicity); \\ 2, & (toxicity) \end{cases}$$

- For the jth patient, suppose the dose is d_m, and the outcome is Z_j.
- The next patient's dose is one of $\{d_{m-1}, d_m, d_{m+1}\}$:
  - d_{m+1}, if $Z_j = 0$
  - d_m, if $Z_j = 1$
  - d_{m-1}, if $Z_j = 2$
- Appropriate modifications are made at the lowest and highest doses

Design highlights:

- Very simple to implement
- Has established theoretical properties (induces a Markov chain on the lattice of doses)
- Has high probability of correct identification of Optimal dose

*Ivanova A. (2003) A new dose-finding design for bivariate outcomes. *Biometrics* **59**, 1001-1007.

Bivariate CRM*

- 1-parameter logistic models for marginal efficacy and toxicity probabilities $\pi_T(x, \beta_1)$, $\pi_E(x, \beta_2)$ with non-informative priors for components of $\boldsymbol{\theta} = (\beta_1, \beta_2, \rho)$
- Pre-specified "desirable" eff. and tox. rates: (π_E^*, π_T^*)
- Dose assignment algorithm:
  - Given data from j patients, update $\widehat{\boldsymbol{\theta}}_j$, $\pi_T(x, \hat{\beta}_1)$, $\pi_T(x, \hat{\beta}_2)$
  - The dose for the next cohort is chosen to minimize the "distance" to (π_E^*, π_T^*)
- Early stopping for excess toxicity and/or lack of efficacy

Design highlights:

- Has high chance to correctly identify the target dose when dose-response curves are steep around that dose
- Has high chance to stop the trial early when no target dose exists
- Statistical software is available

Braun TM (2002) The bivariate continual reassessment method: extending the CRM to phase I trials of two competing outcomes. Controlled Clinical Trials 23, 240-256

Eff-Tox method*

- 6-parameter bivariate model for (efficacy, toxicity) with independent normal priors for components of $\boldsymbol{\theta}$
- Investigator-elicited efficacy-toxicity contour to quantify "desirability" of doses and direct dose assignments
- Dose assignment algorithm:
  - At each step determine a set $\mathcal{A}$ of "acceptable" doses satisfying the requirements for toxicity and efficacy probabilities
  - If $\mathcal{A} = \emptyset$, stop the trial; otherwise select $X_{j+1} \in \mathcal{A}$ that has maximum "desirability"

Design highlights:

- Has very good operating characteristics (probability of correct dose selection/early stopping); high proportion of optimum dose assignments)
- Statistical software is available from MD Anderson website

Thall PF, Cook JD (2004) Dose-finding based on efficacy-toxicity trade-offs. Biometrics 60, 684-693.

Adaptive Penalized Optimal Designs*

- Start with some parametric probability model for (efficacy, toxicity):

$$\pi_{a,b}(d, \boldsymbol{\theta}) \ \ (a, b \in \{0,1\})$$

- Consider the Fisher information matrix for $\boldsymbol{\theta}$ (a measure of estimation precision of the design)
- Design a study adaptively, to minimize some statistical criterion while penalizing the doses that are too toxic and/or inefficacious

Design highlights:

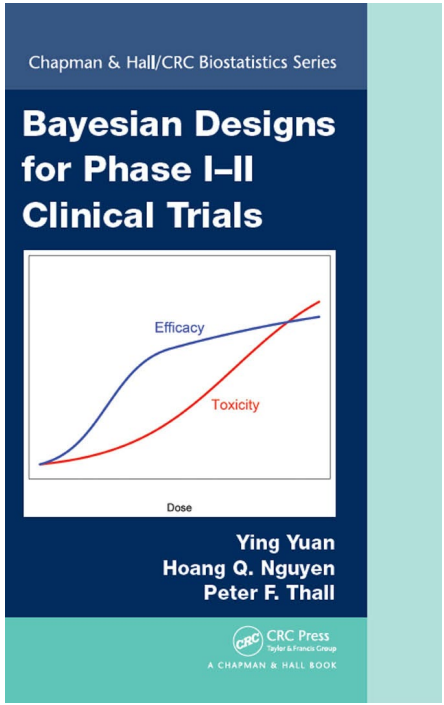
- Provides substantial improvement in terms of accuracy of estimation of the dose-efficacy-toxicity relationship/ target dose
- Have established asymptotic properties (consistency/asymptotic normality) of the estimators

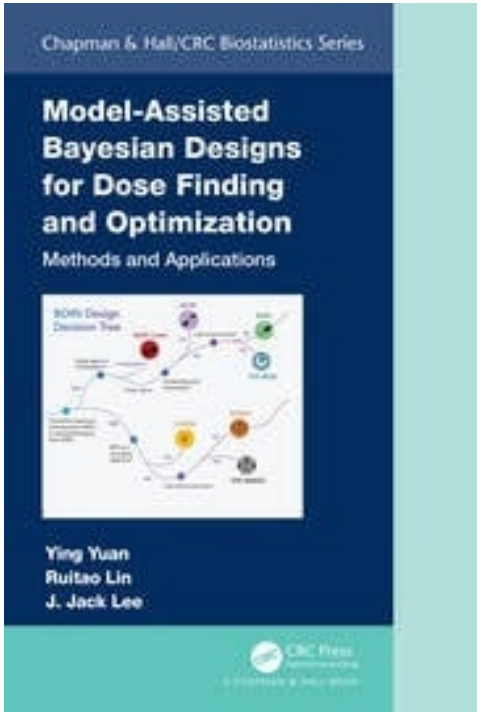
Dragalin V, Fedorov V (2006) Adaptive designs for dose-finding based on efficacy-toxicity response. Journal of Statistical Planning and Inference 136, 1800-1823.

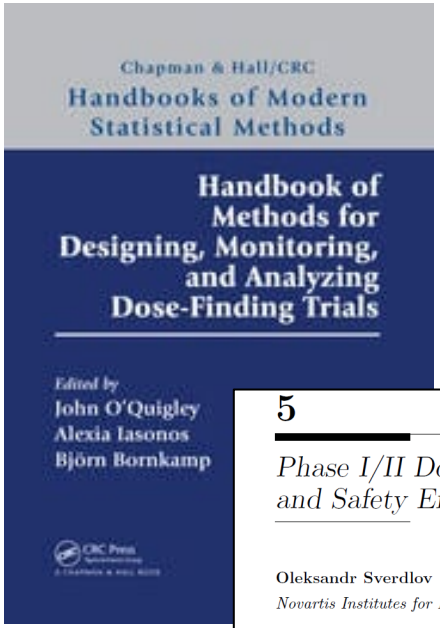
Phase 1/2: which design to use?

- Difficult to recommend any particular design as “best”; design performance depends on the trial goals and underlying dose-efficacy-toxicity relationship
- A tradeoff between design simplicity and efficiency:
  - Up-and-Down Design is very simple to implement
  - Bivariate CRM and EffTox require more calibration
  - Adaptive penalized optimal designs result in improved accuracy of estimation but may be challenged to be endorsed by IRBs
- Overall, phase 1/2 designs outperform the conventional 3+3 ⇒ have higher chance of selecting a dose that is both safe and efficacious
- Simulations under standard to worst-case scenarios should be routinely used to calibrate the design before it is implemented in practice

Phase 1/2 designs: Useful references








5

Phase I/II Dose-Finding Designs with Efficacy and Safety Endpoints

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Novartis Institutes for Biomedical Research

Lei Gao
Sanofi US

Please work with the statistician!

4. Some other important topics

Additional topics on clinical trial designs for rare diseases

- Adaptive designs (single-arm and multi-arm trials) with Bayesian borrowing from historical data
- N-of-1 trials
- Master protocols (basket, umbrella, platform trials)
- Ranking and selection designs; response-adaptive randomization
- Many more...

This may be a topic for a separate presentation.

Thank you!