2013

Dose-response and finding in phase II clinical studies — MCP-Mod Methodologies

Zhao Yang

Dose-response and finding in phase II clinical studies

— MCP-Mod Methodologies —

Zhao (Tony) Yang, Ph.D.
Senior Biostatistician

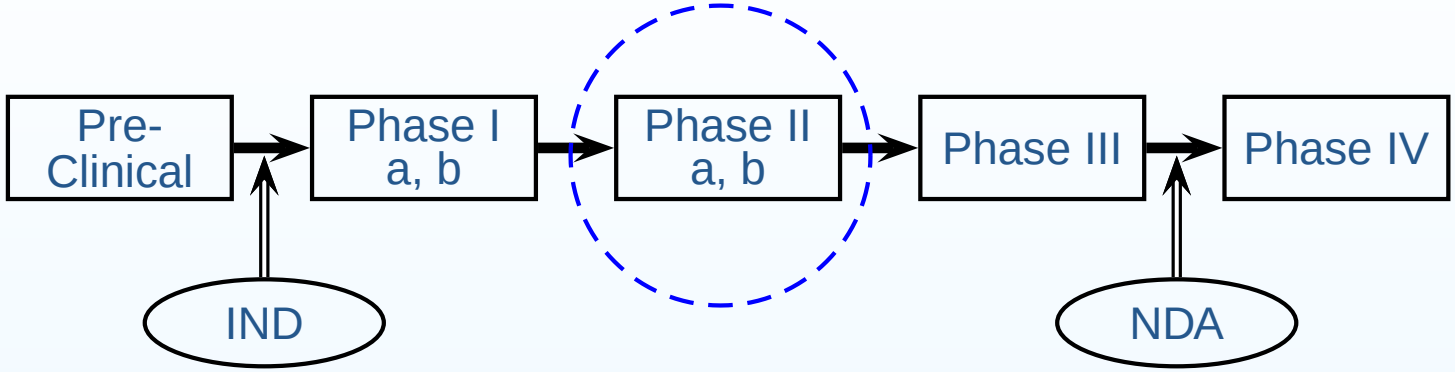
UCB BioSciences, Inc.

2013-05-13: Spring Global Statistics Day

Outline

Motivations and Rationales

Clinical Trials for Drug Development (1)



- The main goals in Phase II studies is to investigate the existence, nature, and extend of dose effect (Ruberg, 1995):

Notes

1. ***Proof-of-Concept (PoC)*** *- any evidence of dose response (i.e. treatment effect)?*
2. *Which doses exhibit a response different from the control response?*
3. *What is the nature of the dose-response relationship?*
4. ***Dose-selection*** *- which dose(s) to be took into Phase III study/marketing?*

"Evidence of a dose-response relationship is taken to be a more compelling finding than evidence of a positive effect that does not appear to be dose-related".

Clinical Trials for Drug Development (2)

In the Phase II studies,

- Generally, the purpose is not just to identify a “dose that works"(from the statistical significance of dose groups), but to identify the minimum effective dose (MED) or the entire dose-response profile. MED is the lowest dose for which a significant difference in the response is observed with the placebo. Too low dose $\Rightarrow$ no beneficial effect for the patient; too high dose $\Rightarrow$ considerable side effects;
- Phase IIa Studies (PoC) provide the best opportunity in early drug development to more accurately refine dose and dosing regimen focus for definitive dose–response Phase IIb investigations;
- Two major statistical strategies in dose finding trials. Multiple comparison procedure with very few assumptions, e.g. contrast tests, can be generally used to address the first two questions by taking the dose as qualitative factor, statistical modeling can answer the last two questions with some assumption.

Background (1)

- Poor understanding of dose-response for both efficacy and safety has been indicated by regulatory agencies and industry as a root cause of late phase attrition and post-marketing problems with approved drugs;

Notes

1. *Failure rate of Phase III trial reaches to 50%, part of the failure is attribute to improper target dose estimation and selection in Phase II, and incorrect/incomplete dose-response knowledge;*
2. *A number of high-profile withdrawals from market of approved drugs;*
3. *FDA repoted 20% of the approved drugs between 1980 and 1989 had the initial dose changed by more than 33%, in most cases lowering it.*

- A significant overall trend is rarely accompanied by significant treatment differences at all dose levels.

Background (2)

- Two key regulatory documents. ICH-E4 (1994) “Dose Response Information to Support Drug Registration":

Notes

1. *“Assessment of dose-response should be an integral component of drug development";*
2. *“Purpose of dose-response information is to find the Smallest dose with a discernible useful effect."*
3. *“Regulatory agencies and sponsors should be open to new approaches and receptive to reasoned exploratory data analysis in analyzing and describing dose-response data."*

“Guidance for Industry: Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications"by FDA CDER and CBER in 2003;

- Need to develop designs and methods for efficient learning about dose-response, enabling better and faster decision making on dose selection and improved labeling.

Common pitfalls and limitations in dose finding

Estimating dose-finding is considerably harder than testing for it, and dose-finding should be an integrated component of drug development, but:

- Model uncertainty is rarely acknowledged, but has severe consequences: model selection problems, biased estimates, overfitting, overconfident conclusions, etc.;
- Traditional modeling approaches are often not appropriate, if the class of considered working models is too narrow;
- Traditional hypotheses tests (e.g. Dunnett test) are not appropriate for dose estimation (only applicable for statistical significance of dose groups);
- Dose-finding studies have multiple objectives, neither of these approaches acknowledges that;
- Current sample sizes for dose-finding studies, based on power to detect statistical significance of dose groups, are inappropriate for dose selection and dose-response estimation.

Regression Modelling

Basic Idea

As one of the two major classical strategies in dose finding trials: multiple comparison procedures and model-based approaches.

- Assumes a functional relationship between the response and the dose (a quantitative factor) according to a pre-specified parametric model, e.g. logistic, an E_{max} or a linear log-dose model;
- The fitted model is then used to estimate an adequate dose to achieve a desired response.

Notes

1. ***Pros**: easy to implement; flexibility in investigating the effect of doses not used in the actual study; can accommodate clinical/regulatory requirements;*
2. ***Cons**: validity of trial conclusions highly depends on the correct choice of the dose-response model, which is an unknown **priori**.*

- Dilemma: unknown ***priori*** vs inclusion in the protocol.

Model Set-up

Parametric modeling the dose-response relationship for IID continuous response variable Y_{ij} by

$$Y_{ij} = f(d_i, \boldsymbol{\theta}) + \varepsilon_{ij}, \quad \varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2)$$

where $i = 1, \cdots, k$ and $j = 1, \cdots, n_i$. Y_{ij} is the response for subject j within dose group i. d_1 is the placebo group, and $\boldsymbol{\mu} = (\mu_1, \cdots, \mu_k)$ as the mean response vector.

To facilitate the MCP-Mod methods, a standardized model need to be defined for deriving the initial parameter estimation based on the prior dose-response assumption,

$$Y_{ij} = f(d_i, \boldsymbol{\theta}) = \theta_0 + \theta_1 f^0(d_i, \boldsymbol{\theta}^0)$$

θ_0 is the location parameter and θ_1 is the scale parameter, $\boldsymbol{\theta}^0$ define the shape.

Common models (1)

A selection of frequently used dose-response models

Model	$f(d_i, \boldsymbol{\theta})$	$f^0(d_i, \boldsymbol{\theta}^0)$
Linear	$\mathsf{E}_0 + \delta d$	d
Linear log-dose	$\mathsf{E}_0 + \delta \log(d + c)$	$\log(d + c)$
E_{max}	$\mathsf{E}_0 + \frac{\mathsf{E}_{max} d}{\mathsf{ED}_{50} + d}$	$\frac{d}{\mathsf{ED}_{50} + d}$
Exponential	$\mathsf{E}_0 + \mathsf{E}_1 \left[\exp\left(\frac{d}{\delta}\right) - 1\right]$	$\exp\left(\frac{d}{\delta}\right) - 1$
Logistic	$\mathsf{E}_0 + \frac{\mathsf{E}_{max}}{1 + \exp\left(\frac{\mathsf{ED}_{50} - d}{\delta}\right)}$	$\frac{1}{1 + \exp\left(\frac{\mathsf{ED}_{50} - d}{\delta}\right)}$
Sigmoid E_{max}	$\mathsf{E}_0 + \frac{\mathsf{E}_{max} d^h}{\mathsf{ED}_{50} + d^h}$	$\frac{d^h}{\mathsf{ED}_{50} + d^h}$
Quadratic	$\mathsf{E}_0 + \beta_1 d + \beta_2 d^2$	$d + \frac{\beta_2}{\lvert\beta_1\rvert} d^2$ for $\beta_2 < 0$
Beta	$\mathsf{E}_0 + \mathsf{E}_{max} B(\alpha, \beta) \left(\frac{d}{D}\right)^{\alpha} \left(1 - \frac{d}{D}\right)^{\beta}$	$B(\alpha, \beta) \left(\frac{d}{D}\right)^{\alpha} \left(1 - \frac{d}{D}\right)^{\beta}$

Note: D is the scale parameter and generally set as the 1.2*(maximum dose), $B(\alpha, \beta) = (\alpha + \beta)^{\alpha+\beta} / (\alpha^{\alpha} \beta^{\beta})$.

Common models (2)

Some notes about the commonly used models

- In linear log-dose model, c is a fixed offset value to avoid problems with dose$= 0$, generally set as 1;
- E_{max} is the maximum effect attributable to the drug (compared with the basal effect with dose at $d = 0$, the maximum increase of drug effect), hence, it is possible that E_{max} is different for different models;
- ED_{50} is the dose which produces 50% of E_{max};
- In the Sigmoid E_{max} model, the parameter h is the slope factor (Hill factor) which measures sensitivity of the response to the dose change of the drug, determining the steepness of the dose–response curve. As h increases, the dose range (ratio of ED_{90} to ED_{10}) tightens. Hence, the larger the value of h, the more sensitive the response is to changes in the dose of the drug.

Target Dose Estimation (1)

Once an adequate dose–response model has been chosen and successfully fitted to the data, one may proceed to estimate the target dose(s) of interest, e.g. MED. Let Δ denote the smallest clinically relevant difference by which we expect a dose to be better than placebo. Δ does not depend on the particular dose–response model under consideration, but only on the objectives of the drug development program.

- For the fitted model, the MED can be generally estimated as

$$\widehat{\text{MED}} = \text{argmin}\{d \in (d_1, d_k] : \widehat{f}(d) > \widehat{f}(d_1) + \Delta\}$$

  $\widehat{f}(\cdot)$ is the predicted mean response at a dose.

- From the MCP-Mod proposal, the MED can then be estimated as

$$\widehat{\text{MED}} = \text{argmin}\{d \in (d_1, d_k] : \widehat{f}(d) > \widehat{f}(d_1) + \Delta, L_d > \widehat{f}(d_1)\}$$

  L_d is the corresponding lower bound of the $1 - 2\gamma$ CI for the predicted mean response, γ is commonly set as 0.025 or 0.05.

Target Dose Estimation (2)

In practice, several models are fitted to the data, and using some information criteria (IC) to pick the model is not appropriate,

- Lack of error control: e.g. picking the model with the smallest AIC, then the Type I error will be significantly inflated due to the ignorance of model uncertainty;
- Lack of incorporation of potential parameter constraints.

Instead of picking single model, weighting across the models to circumvent the concerns:

- Based on IC: weighted estimate across the L selected models

$$\widehat{\text{MED}} = \sum_{l=1}^{L} w_l \widehat{\text{MED}}_l,$$

$$w_l = p_l \exp\left(-\frac{\text{IC}_l}{2}\right) \left[\sum_{j=1}^{L} p_j \exp\left(-\frac{\text{IC}_j}{2}\right)\right]^{-1}, l = 1, \cdots, L$$

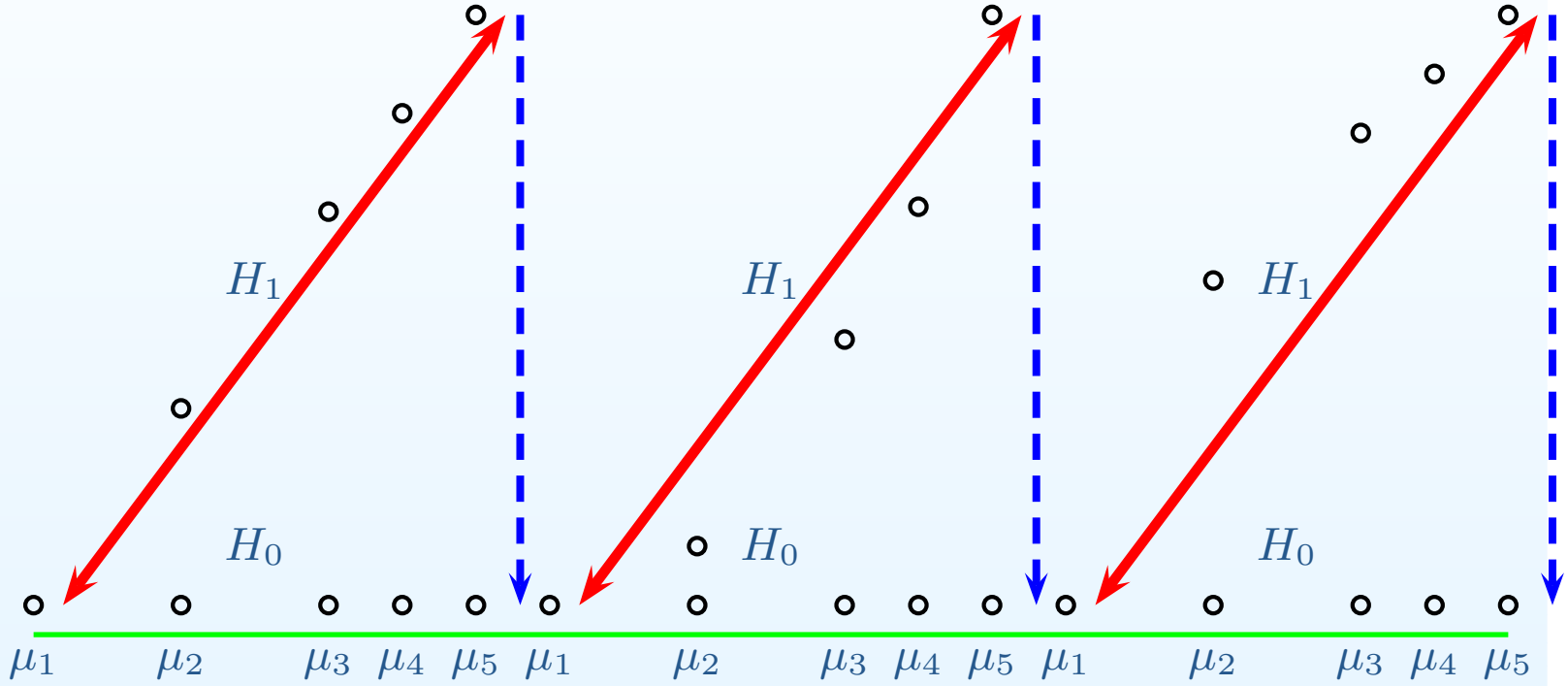
  p_l is the prior model weight, and IC (information criteria) can be AIC or BIC.

- Bayesian model averaging: the posterior distributions under each of the investigated models are weighted according to their posterior model probabilities.

Single Contrast Tests

Definition (1)

A contrast can be thought as a RULER to measure (mimic) the shape of the response profile from different dose groups.



The test statistic based on contrast is a measure of distance: if the RULER can drag down H_1 to H_0, i.e. the distance between H_1 and H_0.

Definition (2)

The contrast test was initially proposed by Abelson and Tukey (1963). Let $\theta_1, \cdots, \theta_k$ denote the true values of the true response variable in k dose groups (including the placebo), any sequence of c's satisfying

$$\sum_{i=1}^{k} c_i = 0$$

define a contrast $\sum_j c_j \widehat{\theta}_j$, once a contrast has been selected, the corresponding t statistic can be calculated as

$$t = \left(\sum_{i=1}^{k} c_i \widehat{\theta}_i \right) \left[\text{SE} \left(\sum_{i=1}^{k} c_i \widehat{\theta}_i \right) \right]^{-1}$$

- the key to implementing this approach is a set of contrast coefficients that satisfy what Abelson and Tukey describe as the ***maximin*** criterion;

Common Contrasts

- Popular contrast tests for monotone data include linear, modified linear, and maximin, and all the contrast coefficients that will be, in general, highly correlated with the unknown response profile regardless of their specific values.
- maximin contrast coefficients was proposed by Abelson and Tukey, and the term "maximin" was used to describe their contrasts is because the c_j were developed in an attempt to maximize the minimum squared correlation between c_j and the unknown response profile considering all possibilities under the monotonicity assumption.
- The formula for computing the jth linear coefficient is $c_j = j - k/2$;
- The formula for computing the jth maximin coefficient is:

$$c_j = \sqrt{(j-1)\left(1 - \frac{j-1}{k}\right)} - \sqrt{j\left(1 - \frac{j}{k}\right)}$$

- Modified linear (also called linear-2 and linear-2–4 contrasts) are essentially simple approximations to the maximin contrast.

Comments

- A well-chosen contrast among the estimated effects of the studied doses can make a powerful test for detecting the existence of a dose response relationship;
- A contrast-based test attains its greatest power when the pattern of the coefficients has the same shape as the true dose response relationship. However, it loses power when the contrast shape and the true dose response shape are not similar;
- A primary test based on a single contrast is often risky; two (or more) appropriately chosen contrasts can assure sufficient power to justify the cost of a multiplicity adjustment. This will raise the need for multiple contrast tests (MCT).

Multiple Contrast Tests

Basics

The concept of multiple contrast tests (MCTs) was first described by Mukerjee et al. (1986, 1987). As the name implies, there are q sequence of c_{qi}'s satisfying

$$\sum_{i=1}^{k} c_{qi} = 0 \Rightarrow \boldsymbol{C}_{q\times k} = (\boldsymbol{c}_1, \cdots, \boldsymbol{c}_q) = \begin{pmatrix} c_{11} & c_{12} & \cdots & c_{1k} \\ c_{21} & c_{22} & \cdots & c_{2k} \\ \vdots & \vdots & \ddots & \vdots \\ c_{q1} & c_{q2} & \cdots & c_{qk} \end{pmatrix}$$

- MCTs tried to cover most parts of the alternative space, hence it overcomes, at least partially, the disadvantage from single contrast test: strong shape-dependence. The resulting test statistic builds just the maximum over q of such single contrasts $T^{\text{MC}} = \max\left\{T_1^{\text{SC}}, \cdots, T_q^{\text{SC}}\right\}$;
- the joint distribution of T_i^{SC}'s will by definition be a central $q-$variate $t-$distribution with ν degrees of freedom and correlation matrix $\boldsymbol{R} = \{\rho_{l,m}\}_{l,m}, l, m = 1, \cdots, q.$

Technical Notes (1)

Many well-known test can be formulated as a MCT,

- many-to-one test of Dunnett (1955), suppose there are k treatment groups are compared to a placebo which leads to the $k \times (k+1)$ contrast matrix

$$\boldsymbol{C} = (\boldsymbol{c}_1, \cdots, \boldsymbol{c}_k) = \begin{pmatrix} -1 & 1 & 0 & 0 & \cdots & 0 \\ -1 & 0 & 1 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ -1 & 0 & 0 & 0 & \cdots & 1 \end{pmatrix}$$

- The tests in the isotonic regression, like Williams' $\bar{t}$ - test, Marcus's $\bar{t}^{\text{mod}}$ −test;
- Other popular MCT includes: pairwise contrast; Helmert contrast; reverse Helmert contrast; linear contrast; and etc

Technical Notes (2)

The general framework to propose new MCT and define the contrast matrix C, taking $k = 3$ as an example.

- First decompose $H_A : \mu_0 \leq \mu_1 \leq \mu_2 \leq \mu_3$ in all possible scenarios as

$$H_A = \bigcup_{i=1}^{7} H_{A(i)} \Leftarrow \begin{cases} H_{A(1)} : \mu_0 = \mu_1 = \mu_2 < \mu_3 \\ H_{A(2)} : \mu_0 < \mu_1 = \mu_2 = \mu_3 \\ H_{A(3)} : \mu_0 = \mu_1 < \mu_2 = \mu_3 \\ H_{A(4)} : \mu_0 < \mu_1 = \mu_2 < \mu_3 \\ H_{A(5)} : \mu_0 < \mu_1 < \mu_2 < \mu_3 \\ H_{A(6)} : \mu_0 = \mu_1 < \mu_2 < \mu_3 \\ H_{A(7)} : \mu_0 < \mu_1 < \mu_2 = \mu_3 \end{cases}$$

- Choose the suitable contrast for each sub-alternative, the criteria can be based on certain optimization arguments (Abelson and Tukey, 1963), i.e. maximizes the minimum correlation between $\boldsymbol{\mu}$ and $\boldsymbol{c}$ under the corresponding constraint;
- Clearly, a linear contrast would be a good choice for $H_{A(5)}$, but a bad one for $H_{A(1)}$ or $H_{A(2)}$(convex and concave dose-response shapes, respectively).

Multiple Comparison Procedures with Modelling Techniques

Brief History

- Tukey et at (1985): first noticed acknowledgement of the model uncertainty in the dose-response research;
- Michael Branson, Jose Pinheiro, and Frank Bretz (2003): proposal of MCP-Mod methodology appeared as an Novartis internal technical report;
- Bretz, Pinheiro, and Branson (2005): technical report published on *Biometric*;
- 2006 to now, $\cdots$: papers or book chapter;
- Ongoing research topic from the pharmaceutical industry: ADDPLAN, extending the method from different purpose, refining the test procedure;
- Industry: > 30 Novartis studies from various therapeutic areas have used this approach.

Goal of MCP-Mod

- Finding the right dose is not that simple: true shape of dose-response model is typically unknown;
- Choice of a working model may have a substantial impact on dose selection, and model selection using observed data needs to account for statistical uncertainty and associated multiplicity issues.
- Useful to have a unified approach combining the advantages of MCP and modeling approaches: this is the goal of MCP-Mod.

Basic Ideas (1)

Assume a set $\mathcal{M} = \{M_m : m = 1, \cdots, M\}$ of M candidate models. Denote the unknown mean vector $\boldsymbol{\mu}_m = (\mu_{m1}, \cdots, \mu_{mk})$ from the mth model $f_m(d_i, \boldsymbol{\theta})$, and $\boldsymbol{\mu}_m^0 = (\mu_{m1}^0, \cdots, \mu_{mk}^0)$ from its standardized model $f_m^0(d_i, \boldsymbol{\theta}^0)$.

For the mth model, let $\overline{Y}_{mi} = \sum_{j=1}^{n_i} Y_{ij}/n_i$ be the average response for dose group i, and $\overline{\mathbf{Y}}_m = (\overline{Y}_{m1}, \cdots, \overline{Y}_{mk})$ be the sample mean vector.

For the mth model, we would like to find the optimal contrast $\mathbf{c}_m = (c_{m1}, \cdots, c_{mk})$ to maximize the power to detect the dose-response shape, i.e. testing the hypothesis

$$H_0^m : \mathbf{c}_m \boldsymbol{\mu}_m' = \mathbf{0}; \quad H_1^m : \mathbf{c}_m \boldsymbol{\mu}_m' > \mathbf{0}$$

Basic Ideas (2)

The contrast statistic T_m using the optimal contrast for the mth model,

$$T_m = \left(\sum_{i=1}^{k} c_{mi} \overline{Y}_{mi} \right) \left(\widehat{S}_m \sqrt{\sum_{i=1}^{k} \frac{c_{mi}^2}{n_i}} \right)^{-1}$$

Under H_0, T_m follows a t distribution with degree of freedom as N - # of parameters in the model. Under H_1, T_m follows a t distribution with non-centrality parameter as

$$\tau_m(\mathbf{c}_m, \boldsymbol{\mu}_m) = \left(\sum_{i=1}^{k} c_{mi} \mu_{mi} \right) \left(\sigma \sqrt{\sum_{i=1}^{k} \frac{c_{mi}^2}{n_i}} \right)^{-1}$$

The non-centrality parameter determine the power under the contrast $\mathbf{c}_m$.

Basic Ideas (3)

Finding the optimal contrast $\mathbf{c}_m = (c_{m1}, \cdots, c_{mk})$ for maximizing the power was then translated into maximizing the non-centrality parameter $\mathbf{c}_m$ which is independent of θ_0 and θ_1.

$$g(\mathbf{c}_m, \boldsymbol{\mu}_m) = \sigma^2 \tau_m^2(\mathbf{c}_m, \boldsymbol{\mu}_m) = \sigma^2 \left(\mathbf{c}_m \boldsymbol{\mu}_m'\right)^2 \left(\sigma^2 \sum_{i=1}^{k} \frac{c_{mi}^2}{n_i}\right)^{-1}$$

$$= \overbrace{\left[\mathbf{c}_m \left(\theta_0 \mathbf{1} + \theta_1 \boldsymbol{\mu}_m^0\right)'\right]^2}^{\mathbf{c}_m \mathbf{1} = \mathbf{0}} \left(\sum_{i=1}^{k} \frac{c_{mi}^2}{n_i}\right)^{-1}$$

$$= \theta_1^2 \left[\mathbf{c}_m \left(\boldsymbol{\mu}_m^0\right)'\right]^2 \left(\sum_{i=1}^{k} \frac{c_{mi}^2}{n_i}\right)^{-1} = \theta_1^2 g(\mathbf{c}_m, \boldsymbol{\mu}_m^0)$$

where $\boldsymbol{\mu}_m^0$ depends on the prior information $\boldsymbol{\theta}_m^0$ and determine the shape of the dose-response.

Basic Ideas (4)

Based on $g(\mathbf{c}_m, \boldsymbol{\mu}_m^0)$, using the Lagrange method and applying the constraint of unit Euclidean length $||\mathbf{c}|| = 1$ to get the optimal contrast $\mathbf{c}_m^{\text{opt}}$

$$g(\mathbf{c}_m, \boldsymbol{\mu}_m^0) = \left[\mathbf{c}_m \left(\boldsymbol{\mu}_m^0\right)'\right]^2 \left(\sum_{i=1}^{k} \frac{c_{mi}^2}{n_i}\right)^{-1}$$

$$\Rightarrow \mathbf{c}_m^{\text{opt}} = \frac{\boldsymbol{\mu}_m^0 - \overline{\mu}_m^0 \mathbf{1}}{||\boldsymbol{\mu}_m^0 - \overline{\mu}_m^0 \mathbf{1}||}$$

where $||\mathbf{a}||$ is the $L_2 -$ norm defined as $||\mathbf{a}|| = \sqrt{\sum_{i=1}^{k} a_i^2}$

Thus, each model in $\mathcal{M}$ can get the optimal contrast $\mathbf{c}_m$, $m = 1, \cdots, M$, and calculate the statistics T_m, $m = 1, \cdots, M$.

Basic Ideas (5)

Using M models, to control the FWER,

$$\text{FWER} = P\left(\exists m \in \{1, \cdots, M\} : T_m > q_{1-\alpha} | H_0^m\right) = \alpha$$

a common decision rule is to combine the individual contrast statistic using the maximum of the M test statistics $T_{\text{max}} = \max\{T_1, \cdots, T_m\}$, and $q_{1-\alpha}$ is the multiplicity-adjusted critical value.

Under $H_0 = \bigcap H_0^m$, T_{max} follows a multivariate t distribution MVT$(\nu; \mathbf{0}, \mathbf{R})$, where $\nu = N - k$, k is the total number of dose groups, and $\mathbf{R} = (\rho_{ij})$

$$\rho_{ij} = \left(\sum_{l=1}^{k} \frac{c_{il} c_{jl}}{n_l}\right) \left(\sqrt{\sum_{l=1}^{k} \frac{c_{il}^2}{n_l} \sum_{l=1}^{k} \frac{c_{jl}^2}{n_l}}\right)^{-1}, 1 \leq i, j \leq M$$

Basic Ideas (6)

Under $H_1 = \bigcup H_1^m$, i.e. under alternative hypothesis that the $m-$th model is true, the maximum contrast test statistic $T_{\max}$ follows multivariate non-central t distribution MVT$(\nu; \boldsymbol{\delta}_m, \mathbf{R})$, where $\nu = N - k$, k is the total number of dose groups.

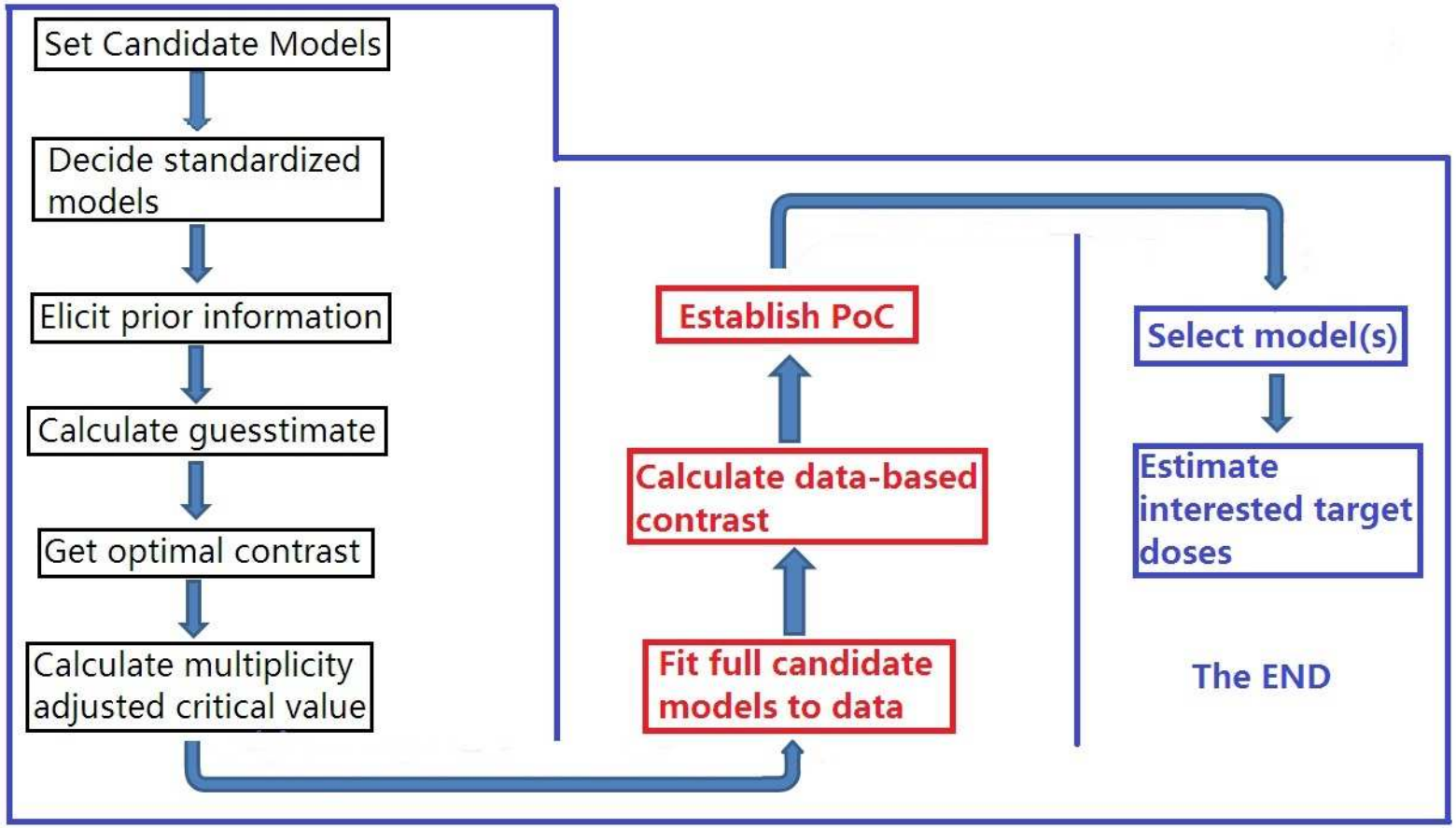
The $\boldsymbol{\delta}_m = (\delta_{m1}, \cdots, \delta_{mM})$ is the non-centrality parameter vector

$$\delta_{ml} = \left(\sum_{i=1}^{k} c_{li}\mu_{mi}\right)\left(\sigma\sqrt{\sum_{i=1}^{k}\frac{c_{li}^2}{n_i}}\right)^{-1}, l = 1, \cdots, M$$

H_0 and H_1 are used to determine the significance of models in $\mathcal{M}$ and study design, respectively. Upon H_0 was rejected, the appropriate models can be used to decide the interested doses.

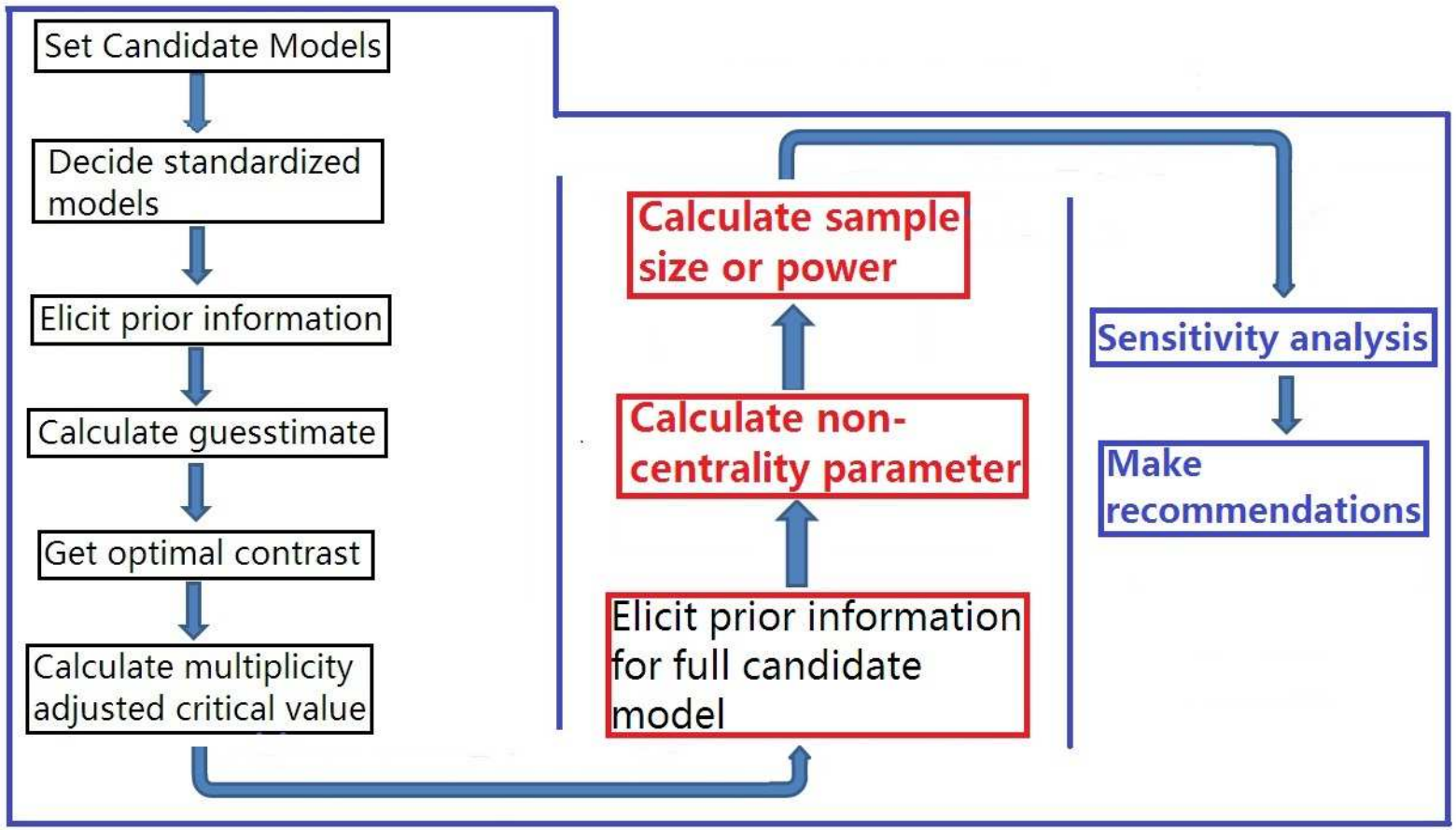
Basic Ideas (7)

Schematic process for the data analysis using MCP-Mod.



Basic Ideas (8)

Schematic process for the study design using MCP-Mod.



Prior Information (1)

A selection of frequently used dose-response models

Model	$f(d_i, \boldsymbol{\theta})$	$f^0(d_i, \boldsymbol{\theta}^0)$
Linear	$\mathsf{E}_0 + \delta d$	d
Linear log-dose	$\mathsf{E}_0 + \delta \log(d+1)$	$\log(d+1)$
E_{max}	$\mathsf{E}_0 + \frac{\mathsf{E}_{max} d}{\mathsf{ED}_{50} + d}$	$\frac{d}{\mathsf{ED}_{50} + d}$
Exponential	$\mathsf{E}_0 + \mathsf{E}_1 \left[\exp\left(\frac{d}{\delta}\right) - 1\right]$	$\exp\left(\frac{d}{\delta}\right) - 1$
Logistic	$\mathsf{E}_0 + \frac{\mathsf{E}_{max}}{1 + \exp\left(\frac{\mathsf{ED}_{50} - d}{\delta}\right)}$	$\frac{1}{1 + \exp\left(\frac{\mathsf{ED}_{50} - d}{\delta}\right)}$
Sigmoid E_{max}	$\mathsf{E}_0 + \frac{\mathsf{E}_{max} d^h}{\mathsf{ED}_{50} + d^h}$	$\frac{d^h}{\mathsf{ED}_{50} + d^h}$
Quadratic	$\mathsf{E}_0 + \beta_1 d + \beta_2 d^2$	$d + \frac{\beta_2}{\lvert\beta_1\rvert} d^2$ for $\beta_2 < 0$
Beta	$\mathsf{E}_0 + \mathsf{E}_{max} B(\alpha, \beta) \left(\frac{d}{D}\right)^{\alpha} \left(1 - \frac{d}{D}\right)^{\beta}$	$B(\alpha, \beta) \left(\frac{d}{D}\right)^{\alpha} \left(1 - \frac{d}{D}\right)^{\beta}$

Note: D is the scale parameter and generally set as the 1.2*(maximum dose), $B(\alpha, \beta) = (\alpha + \beta)^{\alpha+\beta} / (\alpha^{\alpha} \beta^{\beta})$.

How to elicit the guesstimate for the parameter(s) in the standardized model, $f^0(d_i, \boldsymbol{\theta}^0)$?

Prior Information (2)

For E_{max} model, ask the question: Given a dose d^*, what's the prior expected percentage of the maximum effect E_{max}, denoted as p^*?

The initial guesstimate for ED_{50} can be calculated as

$$p^* = f^0(d, ED_{50}) = \frac{d^*}{ED_{50} + d^*} \Rightarrow \widehat{ED}_{50} = \frac{d^*(1-p^*)}{p^*}$$

If different pair (d^*, p^*) are available, the average of the corresponding $\widehat{ED}_{50}$ can be used as an initial guesstimate, or use different estimates $\widehat{ED}_{50}$ to determine different sets of model contrasts for the E_{max} model.

The initial guesstimate for ED_{50} in Sigmoid E_{max} model can be similarly determined given the Hill parameter h which control the steepness of the model at the ED_{50}.

Prior Information (3)

For Exponential model, ask the question: Given a dose d^*, what's the prior expected percentage increase over the placebo effect, denoted as p^*?

Assuming percentage increase at the maximum dose d_{max} is 1, the initial guesstimate for δ can be calculated numerically as

$$p^* = \frac{\mathsf{E}_0 + \mathsf{E}_1\left[\exp\left(\frac{d^*}{\delta}\right) - 1\right] - \mathsf{E}_0}{\mathsf{E}_0} = \frac{\mathsf{E}_1\left[\exp\left(\frac{d^*}{\delta}\right) - 1\right]}{\mathsf{E}_0}$$

$$1 = \frac{\mathsf{E}_1\left[\exp\left(\frac{d_{\text{max}}}{\delta}\right) - 1\right]}{\mathsf{E}_0}$$

$$\Rightarrow \exp\left(\frac{d^*}{\delta}\right) - p^* \exp\left(\frac{d_{\text{max}}}{\delta}\right) = 1 - p^*$$

If different pair (d^*, p^*) are available, the average of the corresponding $\widehat{\delta}$ can be used as an initial guesstimate, or use different estimates $\widehat{\delta}$ to determine different sets of model contrasts for the Exponential model.

Prior Information (4)

For Logistic model, ask the question: Given doses d_1^* and d_2^*, what are the prior expected percentage of the maximum effect E_{max}, denoted as p_1^* and p_2^*?

The initial guesstimate for ED_{50} and δ can be calculated as

$$\widehat{ED}_{50} = \frac{d_1^* \text{logit}(p_2^*) - d_2^* \text{logit}(p_1^*)}{\text{logit}(p_2^*) - \text{logit}(p_1^*)}; \quad \widehat{\delta} = \frac{d_2^* - d_1^*}{\text{logit}(p_2^*) - \text{logit}(p_1^*)}$$

$$\text{where} \quad \text{logit}(p) = \log\left(\frac{p}{1-p}\right)$$

If more than two pairs (d^*, p^*) are available, ED_{50} and δ can be obtained by regression $\text{logit}(p^*)$ on d^*: letting b_0 and b_1 be the intercept and slope, $\widehat{ED}_{50} = -b_0/b_1$ and $\widehat{\delta} = 1/b_1$. Alternatively, use different sets of model contrasts.

Prior Information (5)

For Quadratic model for umbrella-shape form of the model, ask the question: Given doses d^*, what are the prior expected percentage of the maximum effect, denoted as p^*?

The initial guesstimate for $\delta = \beta_2/|\beta_1|$ with $\beta_2 < 0$ can be calculated as

$$p^* = \frac{\beta_1 d^* + \beta_2 (d^*)^2}{-\frac{\beta_1^2}{4\beta_2}} = \frac{d^* + \frac{\beta_2}{\beta_1}(d^*)^2}{-\frac{\beta_1}{4\beta_2}} = \frac{d^* + \delta (d^*)^2}{-\frac{1}{4\delta}}$$

$$\Rightarrow \widehat{\delta} = \frac{-1 \pm \sqrt{1 - p^*}}{2d^*}$$

The dose corresponding to the maximum effect is $d_{\text{opt}} = -\beta_1/2\beta_2 = -1/2\delta$, the solution becomes unique when conditioning on d_{opt} being greater or smaller than d^*

$$\widehat{\delta}^* = \frac{-(1 - \sqrt{1 - p^*})}{2d^*} \text{ for } d^* < d_{\text{opt}};\ \widehat{\delta}^* = \frac{-(1 + \sqrt{1 - p^*})}{2d^*} \text{ for } d^* \geq d_{\text{opt}}$$

Prior Information (6)

For Beta model, ask the question: Given doses d, what are the prior expected percentage of the maximum effect E_{max}, denoted as p^*, and what's the dose d_{max} corresponding to the maximum effect?

The initial guesstimate for α and β can be calculated numerically by solving the equation

$$\begin{cases} B(\alpha,\beta)\left(\frac{d^*}{D}\right)^{\alpha}\left(1-\frac{d^*}{D}\right)^{\beta} = p^* \\ B(\alpha,\beta)\left(\frac{d_{max}}{D}\right)^{\alpha}\left(1-\frac{d_{max}}{D}\right)^{\beta} = 1 \end{cases}$$

$$\text{where } B(\alpha,\beta) = \frac{(\alpha+\beta)^{\alpha+\beta}}{\alpha^{\alpha}\beta^{\beta}}$$

D is the scale parameter and generally set as the 1.2*(maximum dose).

Prior Information (7)

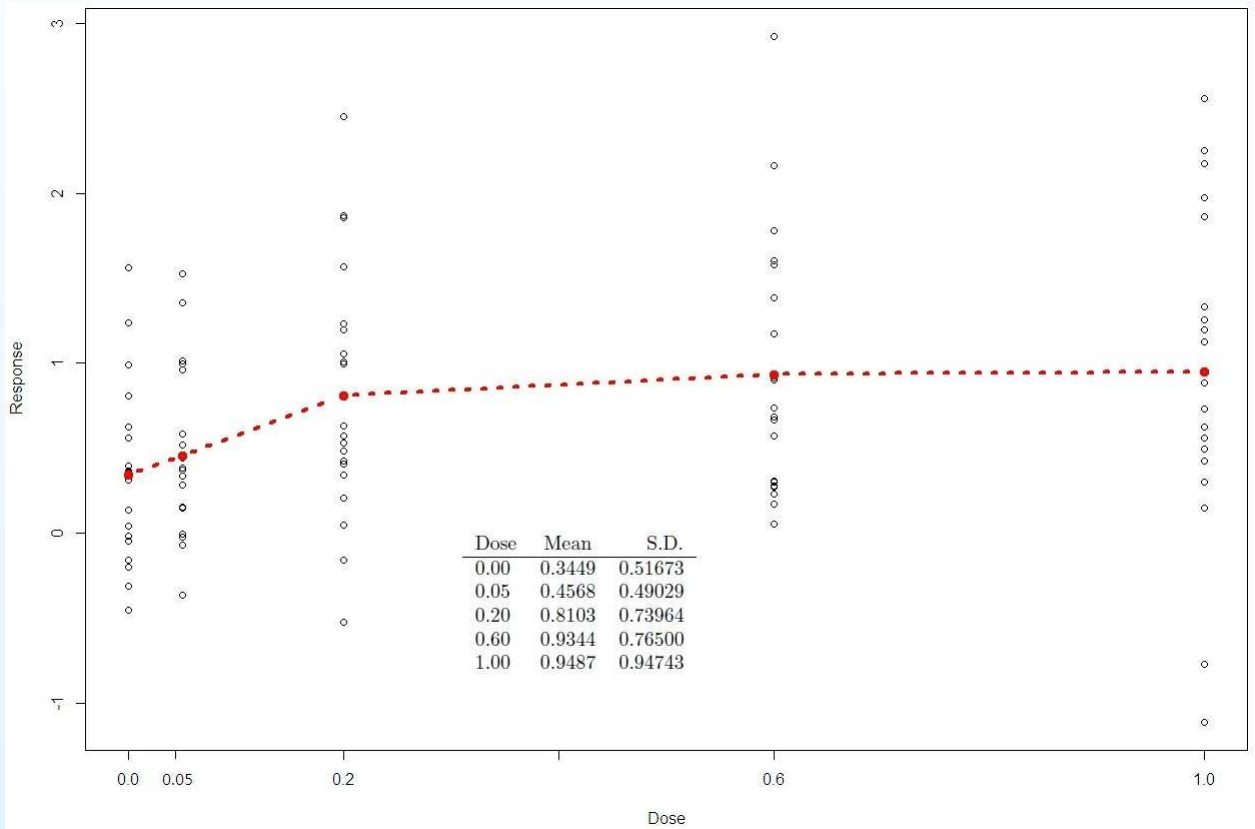
Though most of the models, the question to elicit the prior information is about the "expected percentage of the maximum effect E_{max}", the response may differ under different models, hence, it is suggested for statistician

Notes

1. *Discuss the potential candidate models with the clinical team to cover the possible dose-response shape space;*
2. *Based on the candidate models, statistician present the concrete figures to the clinical team;*
3. *Relying on the figures, statistician asks the questions to elicit the prior information under each individual model, e.g. under the E_{max} and logistic models, the same question "what's the dose associated with expected 50% percentage of the maximum effect E_{max}?"may have different response.*

Data Analysis (1)

A randomized double-blind parallel group trial with a total of 100 subjects (Bretz et al, 2005). 5 treatment groups with equal sample size $n = 20$: placebo, 0.05, 0.2, 0.6, and 1. The response variable was assumed to be normally distributed and larger value indicate better outcome.



Dose	Mean	S.D.
0.00	0.3449	0.51673
0.05	0.4568	0.49029
0.20	0.8103	0.73964
0.60	0.9344	0.76500
1.00	0.9487	0.94743

Data Analysis (2)

Taking the data example to illustrate the analysis process step-by-step:

Step 1: Collect the candidate models: E_{max}, linear, linear log-dose, exponential, and quadratic (umbrella-shape).

Step 2: Elicit the prior information to calculate the guesstimates for the standardized model from its candidate model.

Notes

1. *For E_{max} model: the dose 0.2 provide 50% of the maximum effect E_{max} $\Rightarrow \widehat{ED}_{50} = 0.2$;*
2. *For Exponential model: the dose 0.6 provide 50% of the improvement over the placebo effect* $\Rightarrow \widehat{\delta} = 1.216302$
3. *For quadratic model: the dose 0.2 provide 50% of the maximum effect* $\Rightarrow \widehat{\delta} = -0.732233$

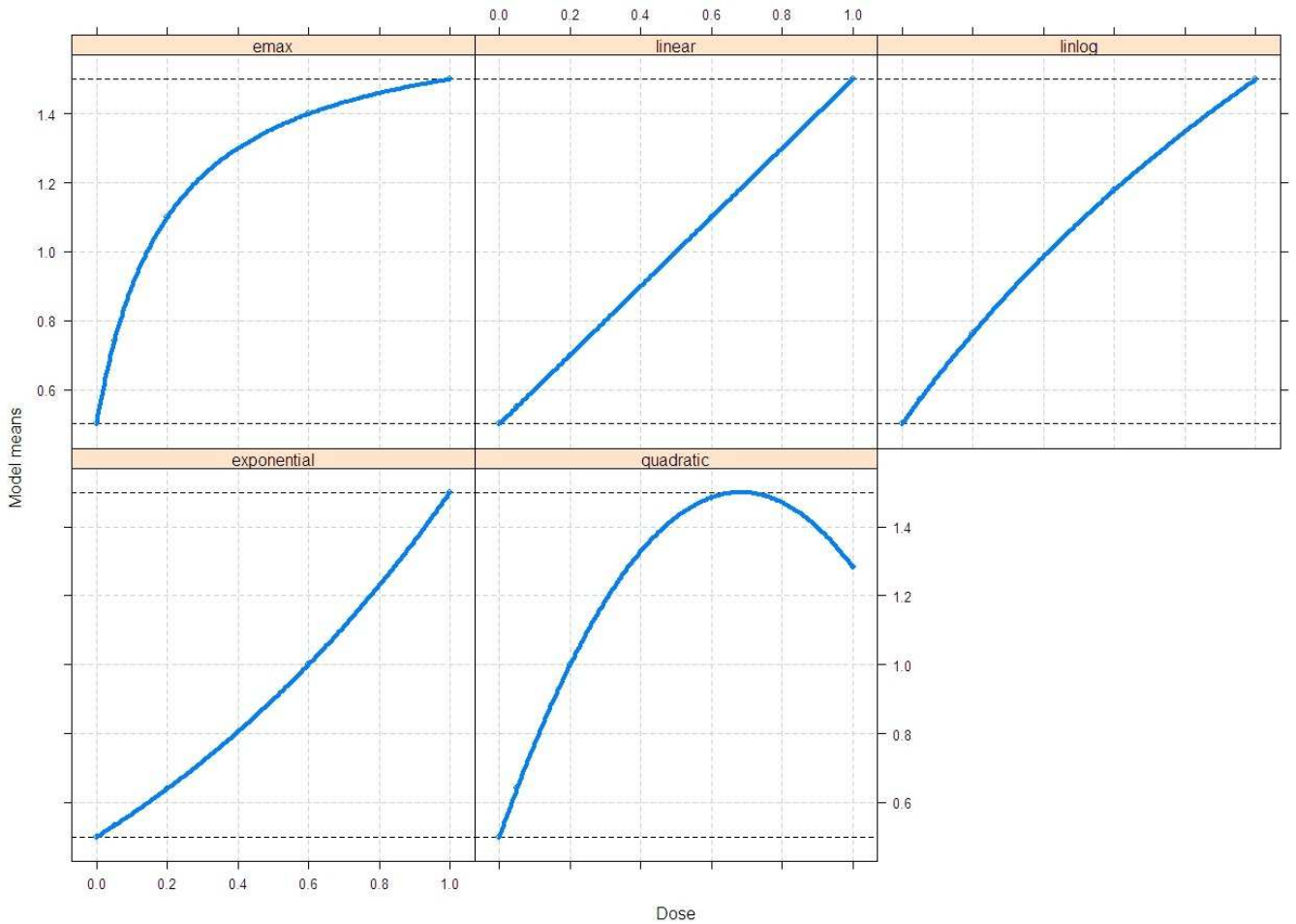
Data Analysis (3)

Step 3: Calculate $\boldsymbol{\mu}_m^0 = (\mu_{m1}^0, \cdots, \mu_{mk}^0)$ from its standardized model $f_m^0(d_i, \boldsymbol{\theta}^0)$ based on the guesstimate, and the overall average $\overline{\mu}_m^0 = N^{-1} \sum_{i=1}^k n_i \mu_{m1}^0$.

Model	$\boldsymbol{\mu}_m^0$	$\overline{\mu}_m^0$
E_{max}	(0, 0.2, 0.5, 0.75, 0.83)	0.45667
Linear	(0, 0.05, 0.2, 0.6, 1)	0.37
Linear log-dose	(0, 0.04879, 0.18232, 0.47000, 0.69315)	0.27885
Exponential	(0, 0.04196, 0.17872, 0.63771, 1.27542)	0.42676
Quadratic	(0, 0.04817, 0.17071, 0.33640, 0.26777)	0.16461

Data Analysis (4)

A graphical display of the standardized models which is based on the $\boldsymbol{\mu}_m^0 = (\mu_{m1}^0, \cdots, \mu_{mk}^0)$



Data Analysis (5)

Step 4: Calculate the optimal contrast coefficient for each candidate model based on

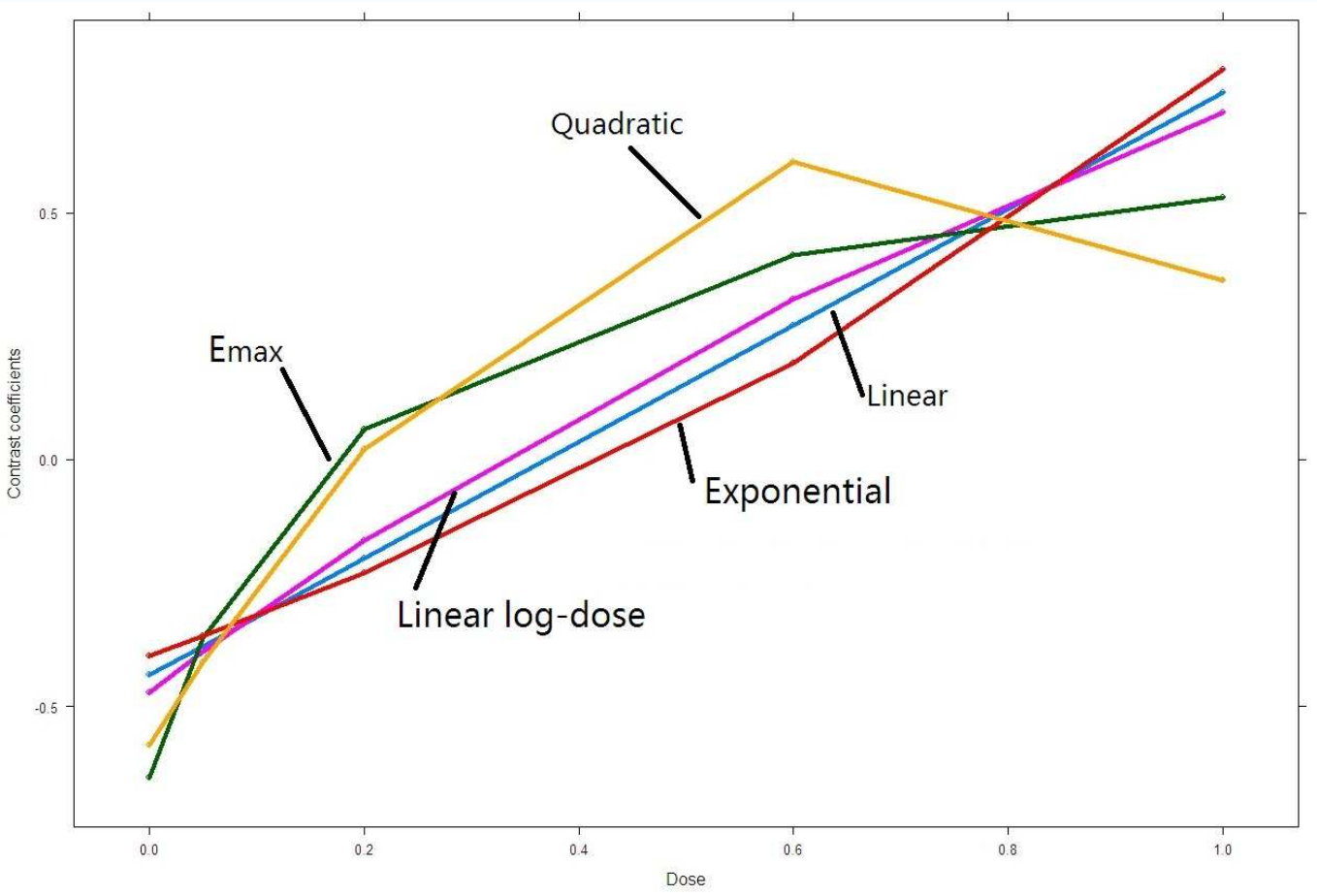
$$\mathbf{c}_m^{\text{opt}} = \frac{\boldsymbol{\mu}_m^0 - \overline{\mu}_m^0 \mathbf{1}}{||\boldsymbol{\mu}_m^0 - \overline{\mu}_m^0 \mathbf{1}||}$$

where $||\mathbf{a}||$ is the $L_2 -$ norm defined as $||\mathbf{a}|| = \sqrt{\sum_{i=1}^{k} a_i^2}$

Model	$\mathbf{c}_m^{\text{opt}}$
E_{max}	(-0.64311453, -0.36145853, 0.06102547, 0.41309546, 0.53045213)
Linear	(-0.4366561, -0.3776485, -0.2006258, 0.2714349, 0.7434955)
Linear log-dose	(-0.4725740, -0.3898889, -0.1635919, 0.3239457, 0.7021092)
Exponential	(-0.3968503, -0.3578269, -0.2306533, 0.1961600, 0.7891705)
Quadratic	(-0.5789339, -0.4095205, 0.0214611, 0.6041821, 0.3628112)

Data Analysis (6)

The optimal contrast coefficients are plotted as follows, and the shapes for linear, linear log-dose, and the exponential are quite similar which may lead to high correlation.



Data Analysis (7)

Step 5: Calculate the correlation matrix $\mathbf{R} = (\rho_{ij})$ for the optimal contrasts based on

$$\rho_{ij} = \frac{\sum_{l=1}^{k} \frac{c_{il} c_{jl}}{n_l}}{\sqrt{\sum_{l=1}^{k} \frac{c_{il}^2}{n_l} \sum_{l=1}^{k} \frac{c_{jl}^2}{n_l}}}, 1 \leq i, j \leq M$$

Model	E_{max}	Linear	Linear log-dose	Exponential	Quadratic
E_{max}	1	0.9115981	0.9411204	0.8701340	0.9636940
Linear	0.9115981	1	0.9963592	0.9946842	0.8368887
Linear log-dose	0.9411204	0.9963592	1	0.9824159	0.8802010
Exponential	0.8701340	0.9946842	0.9824159	1	0.7761737
Quadratic	0.9636940	0.8368887	0.8802010	0.7761737	1

Data Analysis (8)

Step 6: Calculate the multiplicity-adjusted critical value $q_{1-\alpha}$ based on the multivariate t distribution, i.e. MVT$(\nu; \mathbf{0}, \mathbf{R})$, where $\nu = N - k$, k is the total number of dose groups.

This distribution will be used to calculate the adjusted $p-$value and $q_{1-\alpha}$ can also be used to determine the significance for each candidate model.

Notes

1. *The underlying rationale: under null hypothesis, the joint distribution for contrasts based on $\overline{\boldsymbol{Y}}_m$ is equivalent to the one based on $\boldsymbol{\mu}_m^0$;*
2. *It seems advisable to set a fixed seed for the calculation, though the difference for each $q_{1-\alpha}$ is appreciably small .*

For the example, $q_{1-\alpha} = 1.905294$ for one-sided $\alpha = 0.05$.

Data Analysis (9)

Step 7: Fit the full candidate models to data, and get the parameter estimation.

Model	Parameter estimation	$\widehat{S}_m$
E_{max}	$\widehat{E}_0 = 0.3216, \widehat{E}_{max} = 0.7463, \widehat{ED}_{50} = 0.1422$	0.7061
Linear	$\widehat{E}_0 = 0.4923, \widehat{\delta} = 0.5586$	0.7144
Linear log-dose	$\widehat{E}_0 = 0.4650, \widehat{\delta} = 0.8392$	0.7114
Exponential	$\widehat{E}_0 = 0.5109, \widehat{E}_1 = 0.8331, \widehat{\delta} = 2$	0.7203
Quadratic	$\widehat{E}_0 = 0.3902, \widehat{\beta}_1 = 1.7684, \widehat{\beta}_2 = -1.2318$	0.7081

$$\text{where } \widehat{S}_m^2 = \sum_{i=1}^{k}\sum_{j=1}^{n_i} \frac{\left(Y_{ij} - \overline{Y}_i\right)^2}{N-k}$$

Step 8: Calculate the contrast statistic T_m using the optimal contrast coefficient for each candidate model,

$$T_m = \left(\sum_{i=1}^{k} c_{mi}\overline{Y}_i\right)\left(\widehat{S}_m\sqrt{\sum_{i=1}^{k}\frac{c_{mi}^2}{n_i}}\right)^{-1}, m = 1, \cdots, M$$

T_m follows t distribution with degree of freedom as $N - \#$of parameters in the candidate model.

Data Analysis (10)

Step 9: Calculate raw $p-$value and multiplicity adjusted $p-$value for candidate models. To control FWER,

$$\text{FWER} = P\left(\exists m \in \{1, \cdots, M\} : T_m > q_{1-\alpha} | H_0^m\right) = \alpha$$

The maximum contrast test statistic $T_{\max} = \max\{T_1, \cdots, T_m\}$ follows multivariate t distribution $\text{MVT}(\nu; \mathbf{0}, \mathbf{R})$, where $\nu = N - k$, k is the total number of dose groups.

$$\begin{aligned} & T_{\max} = \max\{T_1, \cdots, T_m\} \\ \Rightarrow & P\left(T_{\max} \leq q_{1-\alpha}\right) = P\left(T_1 \leq q_{1-\alpha}, \cdots, T_m \leq q_{1-\alpha}\right) \end{aligned}$$

Data Analysis (11)

The results from Step 8 and Step 9 are summarized as follows, and the multiplicity adjusted critical value $q_{1-\alpha} = 1.905294$ for one-sided $\alpha = 0.05$.

Model	$t-$statistic	# of parameter	Raw $p-$value	Adjusted $p-$value	AIC
E_{max}	3.4641	3	0.000397	0.000871	219.1383
Linear	2.9715	2	0.001864	0.003694	220.4986
Linear log-dose	3.1086	2	0.001230	0.002270	219.6494
Exponential	2.7923	3	0.003152	0.005654	223.1305
Quadratic	3.3865	3	0.000512	0.000953	219.7193

All the candidate models are statistically significant which establishing the PoC, and this process account for model uncertainty.

Notes

1. *Every single contrast test translates into a decision procedure to determine whether the given dose-response shape is statistically significant, based on the observed data;*
2. *Those models that are associated with a significant contrast test result form a set of good models, reference set $\mathcal{M}^*$;*
3. *In contrast to a direct model based approach, this process take case of possible model mis-specification.*

Data Analysis (12)

Step 10: Choose the appropriate model(s) for MED estimation given the absolute clinically relevant difference Δ with respect to placebo (from guidelines/clinicians),

Notes

1. *Choose one model from $\mathcal{M}^*$: based on the maximum contrast statistic or the minimum AIC value. Then proceed to estimate the MED;*
2. *Keep all the models in $\mathcal{M}^*$, and apply model averaging techniques to produce weighted estimates across all models in $\mathcal{M}^*$.*

Data Analysis (13)

For each model in $\mathcal{M}^*$

$$\widehat{\text{MED}}_{m^*} = \min\{d \in (d_1, d_k] : \widehat{f}(d) > \widehat{f}(d_1) + \Delta, L_d > \widehat{f}(d_1)\}$$

$\widehat{f}(\cdot)$ is the predicted mean response at a dose, L_d is its corresponding lower bound of the $1 - 2\gamma$ CI, γ is commonly set as 0.025 or 0.05.

The model averaging techniques produce weighted estimate across L model in $\mathcal{M}^*$

$$\widehat{\text{MED}} = \sum_{l=1}^{L} w_l \widehat{\text{MED}}_l,$$

$$w_l = p_l \exp\left(-\frac{\text{IC}_l}{2}\right)\left[\sum_{j=1}^{L} p_j \exp\left(-\frac{\text{IC}_j}{2}\right)\right]^{-1}, l = 1, \cdots, L$$

p_l is the prior model weight, and IC (information criteria) can be AIC or BIC.

Data Analysis (14)

Setting $\Delta = 0.4$ and $\gamma = 0.05$, the estimated MEDs for each model in $\mathcal{M}^*$ are

Model	MED	AIC	w_l
E_{max}	0.1642	219.1383	0.3160
Linear	0.7161	220.4986	0.1601
Linear log-dose	0.6107	219.6494	0.2447
Exponential	0.7843	223.1305	0.0429
Quadratic	0.2813	219.7193	0.2363
Overall MED	0.4161012		

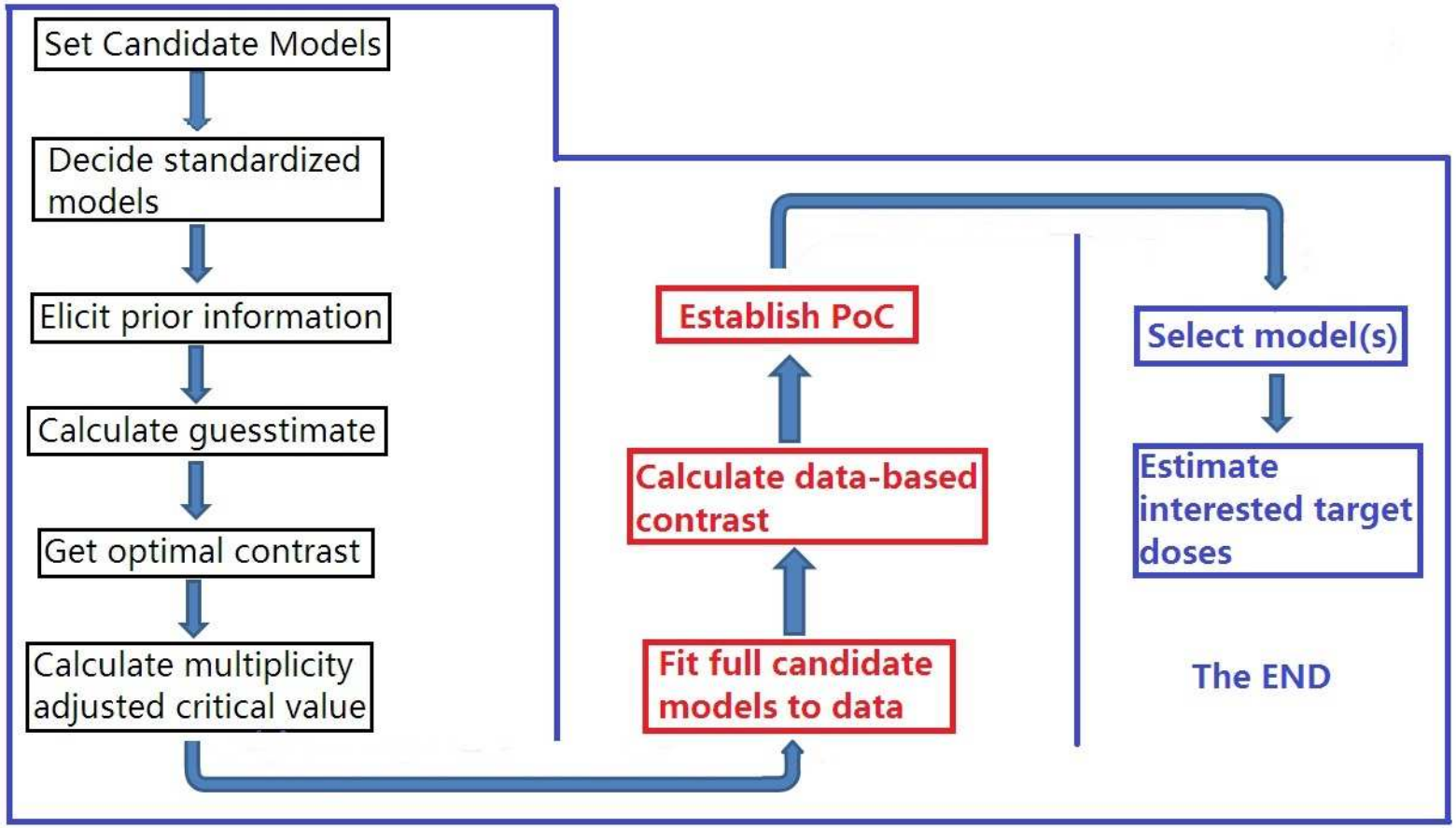
Data Analysis (15)

Step 11: Make conclusion and recommendation to the dose used for Phase III study.

- Doses $0.2, 0.6$, or 1 are significantly better than placebo;
- all doses well tolerated;
- Suppose the doses are the only options to manufacture IP, the next highest dose neighboring the selected dose level is 0.6;
- In principle, any dose lying above 0.42 may be defined as an acceptable dose, provided that the gain in efficacy does not result in an unacceptable increase in the risk of safety profile: the risk-benefit ratio. Hence, with the feasibility of manufacturing, the dose level ≥ 0.42 can be determined as the dose used for further drug development.

Data Analysis (16)

Schematic process for the data analysis using MCP-Mod.



Study Design (1)

Following the example presented by Pinheiro et al (2006, JBS), suppose we will develop a Phase II study of a drug for the indication of generalized anxiety disorder(GAD). Placebo and 5 active doses are to be used: 10, 25, 50, 100, and 150mg.

- The clinical team has limited prior information about the shape of the dose-response profile;
- From literature and pre-clinical data, the maximum treatment effect (δ_{max}) is expected to be 0.4σ larger than the placebo effect (δ_0), i.e. $\delta_{\text{max}} - \delta_0 = 0.4\sigma$;
- For simplicity, suppose $\delta_0 = 0$ and $\sigma = 1$.

We would like to investigate the sample size and power profile and make recommendation to the team to establish the PoC of the drug.

Study Design (2)

Illustrate the study design process step-by-step:

Step 1: Collect the candidate models: E_{max}, linear, logistic, exponential, beta with $d_{\text{opt}} = 25$mg, and beta with $d_{\text{opt}} = 100$mg, where d_{opt} is the dose corresponding to the maximum effect.

Step 2: Elicit the prior information to calculate the guesstimates for the standardized model from its candidate model. The information from clinical team is

Notes

1. *Dose 25mg provide 50% of the maximum effect under E_{max} model;*
2. *Dose 50mg provide 50% of the maximum effect and 99% of maximum effect at 100mg under logistic model;*
3. *For Exponential model: the dose 100 provide 46.342% of the improvement over the placebo effect;*
4. *For Beta model with $d_{opt} = 25$mg, dose 100mg provide 43.3775% of the maximum effect;*
5. *For Beta model with $d_{opt} = 100$mg, dose 50mg provide 67.0405% of the maximum effect.*

Study Design (3)

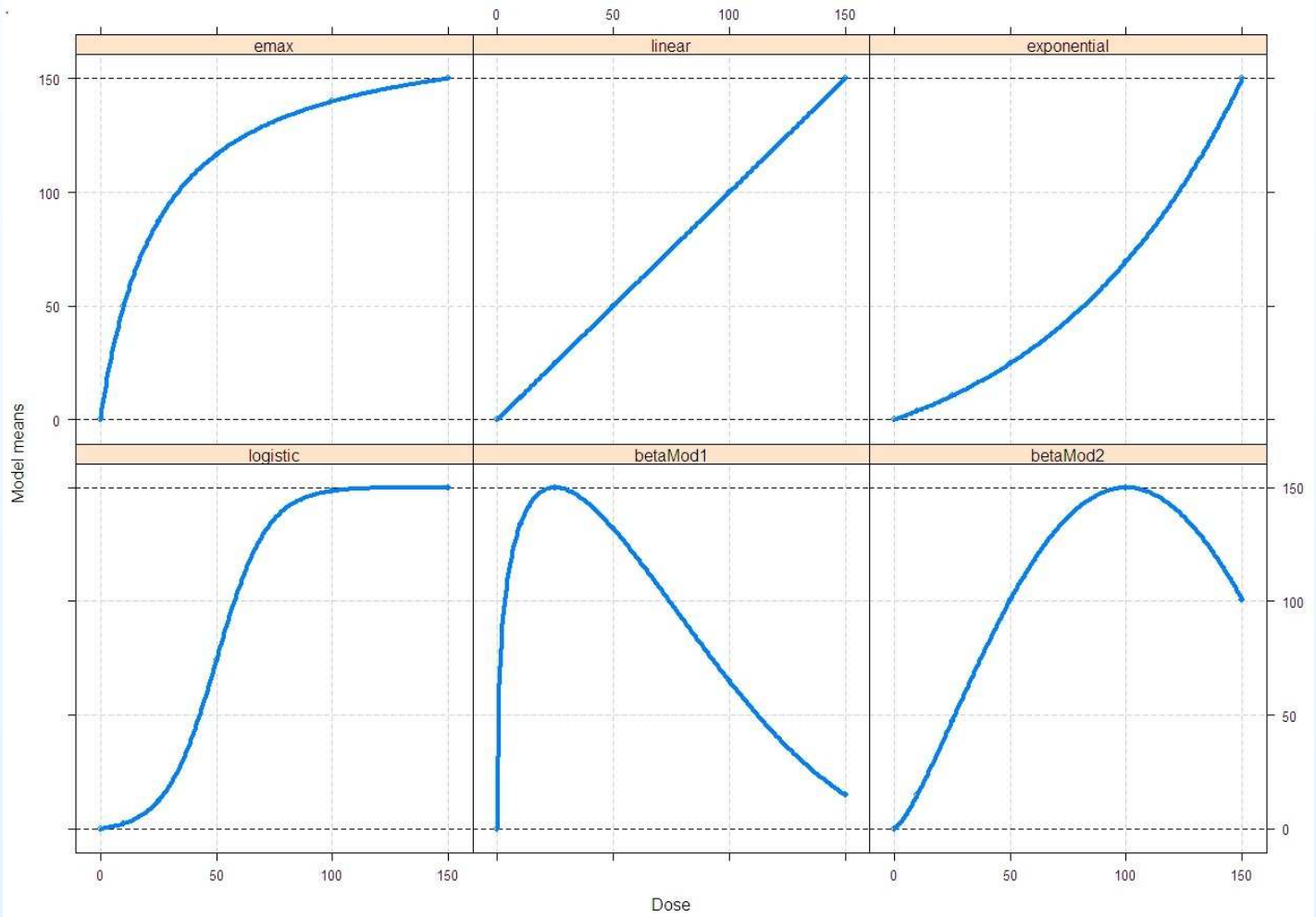
The prior information leads to the standardized model as

Model	Standardized model
E_{max}	$\frac{d}{25+d}$
Linear	d
Exponential	$\exp\left(\frac{d}{85}\right)$
Logistic	$\left[1+\exp\left(\frac{50-d}{10.88111}\right)\right]$
$Beta_1$, $d_{opt}=25$mg	$B(0.33,2.31)\left(\frac{d}{200}\right)^{0.33}\left(1-\frac{d}{200}\right)^{2.31}$
$Beta_2$, $d_{opt}=100$mg	$B(1.39,1.39)\left(\frac{d}{200}\right)^{1.39}\left(1-\frac{d}{200}\right)^{1.39}$

The scale parameter in $Beta_1$ and $Beta_2$ models was set to 200 which is to ensure that the value under the standardized model is 1 at the d_{opt}.

Study Design (4)

Step 3: Calculate $\boldsymbol{\mu}_m^0 = (\mu_{m1}^0, \cdots, \mu_{mk}^0)$



Study Design (5)

Step 4: Calculate the optimal contrast coefficient for each candidate model

Model	$\mathbf{c}_m^{\text{opt}}$
E_{max}	(-0.705746, -0.316667, -0.024858, 0.202105, 0.383675, 0.461491)
Linear	(-0.427960, -0.351310, -0.236336, -0.044712, 0.338536, 0.721783)
Exponential	(-0.331672, -0.301919, -0.250181, -0.140826, 0.202851, 0.821747)
Logistic	(-0.406451, -0.392428, -0.328855, 0.061078, 0.528606, 0.538050)
Beta_1, $d_{\text{opt}} = 25$mg	(-0.566143, 0.351578, 0.460756, 0.337966, -0.120702, -0.463454)
Beta_2, $d_{\text{opt}} = 100$mg	(-0.533386, -0.417987, -0.165518, 0.244772, 0.627347, 0.244772)

Step 5: Calculate the correlation matrix $\mathbf{R} = (\rho_{ij})$ for the optimal contrasts

Model	E_{max}	Linear	Exponential	Logistic	Beta_1 $d_{\text{opt}} = 25$	Beta_2 $d_{\text{opt}} = 100$
E_{max}	1	0.873	0.765	0.883	0.085	0.916
Linear	0.873	1	0.975	0.954	-0.381	0.792
Exponential	0.764	0.975	1	0.876	-0.487	0.638
Logistic	0.883	0.954	0.876	1	-0.352	0.914
Beta_1	0.085	-0.381	-0.487	-0.352	1	-0.028
Beta_2	0.916	0.792	0.638	0.914	-0.028	1

Study Design (6)

Step 6: Elicit parameter estimation in the full candidate model to calculate $\boldsymbol{\mu}_m = (\mu_{m1}, \cdots, \mu_{mk})$, i.e. determining the location (θ_0) and scale (θ_1) parameters in the model $Y = \theta_0 + \theta_1 f^0(d_i, \boldsymbol{\theta}^0)$. Given the values for $\boldsymbol{\theta}^0$,

- The first is about the placebo effect;

$$\delta_0 = \theta_0 + \theta_1 f^0(0, \boldsymbol{\theta}^0)$$

- The second is about the dose corresponding to the maximum response δ_{max} within the dose range of the study;

$$\delta_{\text{max}} = \theta_0 + \theta_1 f^0(d_{\text{max}}, \boldsymbol{\theta}^0)$$

These guesstimates are needed to determine $\boldsymbol{\mu}_m$, the non-centrality vector $\boldsymbol{\delta}_m$, and the power calculation.

Study Design (7)

In the example, $\delta_{\text{max}} = 0.4$ and $\delta_0 = 0$

- For E_{max}, Logistic, and exponential models, $\delta_{\text{max}} = 0.4$ expected to occur at dose 150mg, which leading the parameter;

Model	Parameters
E_{max}	$\text{E}_0 = 0, \text{E}_{\text{max}} = 7/15$
Exponential	$\text{E}_0 = 0, \text{E}_{\text{max}} = 0.08264711$
Logistic	$\text{E}_0 = -0.004041, \text{E}_{\text{max}} = 0.404082$

- For Beta_1 and Beta_2 models, δ_{max} occurs at $d_{\text{opt}} = 25, 100$ respectively, due to the scale parameter set up, $\text{E}_{\text{max}} = 0.4$.

Study Design (8)

Step 7: Based on $\boldsymbol{\mu}_m$, the contrast statistic T_m for each candidate model can be denoted as,

$$T_m = \left(\sum_{i=1}^{k} c_{mi}\mu_i\right)\left(\sigma\sqrt{\sum_{i=1}^{k}\frac{c_{mi}^2}{n_i}}\right)^{-1}, m = 1, \cdots, M$$

Under alternative hypothesis that the $m-$th model is true, the maximum contrast test statistic $T_{\max} = \max\{T_1, \cdots, T_m\}$ follows multivariate non-central t distribution MVT$(\nu; \boldsymbol{\delta}_m, \mathbf{R})$, where $\nu = N - k$, k is the total number of dose groups. The $\boldsymbol{\delta}_m = (\delta_{m1}, \cdots, \delta_{mM})$ is the non-centrality parameter vector

$$\delta_{ml} = \left(\sum_{i=1}^{k} c_{li}\mu_{mi}\right)\left(\sigma\sqrt{\sum_{i=1}^{k}\frac{c_{li}^2}{n_i}}\right)^{-1}, l = 1, \cdots, M$$

Study Design (9)

The non-centrality parameter vectors are calculated as

Model	E_{max}	Linear	Exponential	Logistic	$Beta_1$ $d_{opt} = 25$	$Beta_2$ $d_{opt} = 100$
E_{max}	0.3427	0.2992	0.2620	0.3025	0.0291	0.3139
Linear	0.3038	0.3479	0.3393	0.3319	-0.1324	0.2757
Exponential	0.2651	0.3382	0.3468	0.3039	-0.1687	0.2214
Logistic	0.3739	0.4041	0.3711	0.4235	-0.1490	0.3869
$Beta_1$	0.0331	-0.1483	-0.1895	-0.1371	0.3895	-0.0108
$Beta_2$	0.3157	0.2730	0.2200	0.3148	-0.0095	0.3446

The non-centrality parameter under Logistic model $0.4235\sqrt{n}$ is the largest one among all 6 candidate models

Notes

1. *Comply with the assumptions from the study design;*
2. *It is expected that Logistic model will provide maximum power.*

Study Design (10)

Under the sample size $\boldsymbol{n} = (n_1, \cdots, n_k)$, the power for model m to detect the PoC can be calculated as

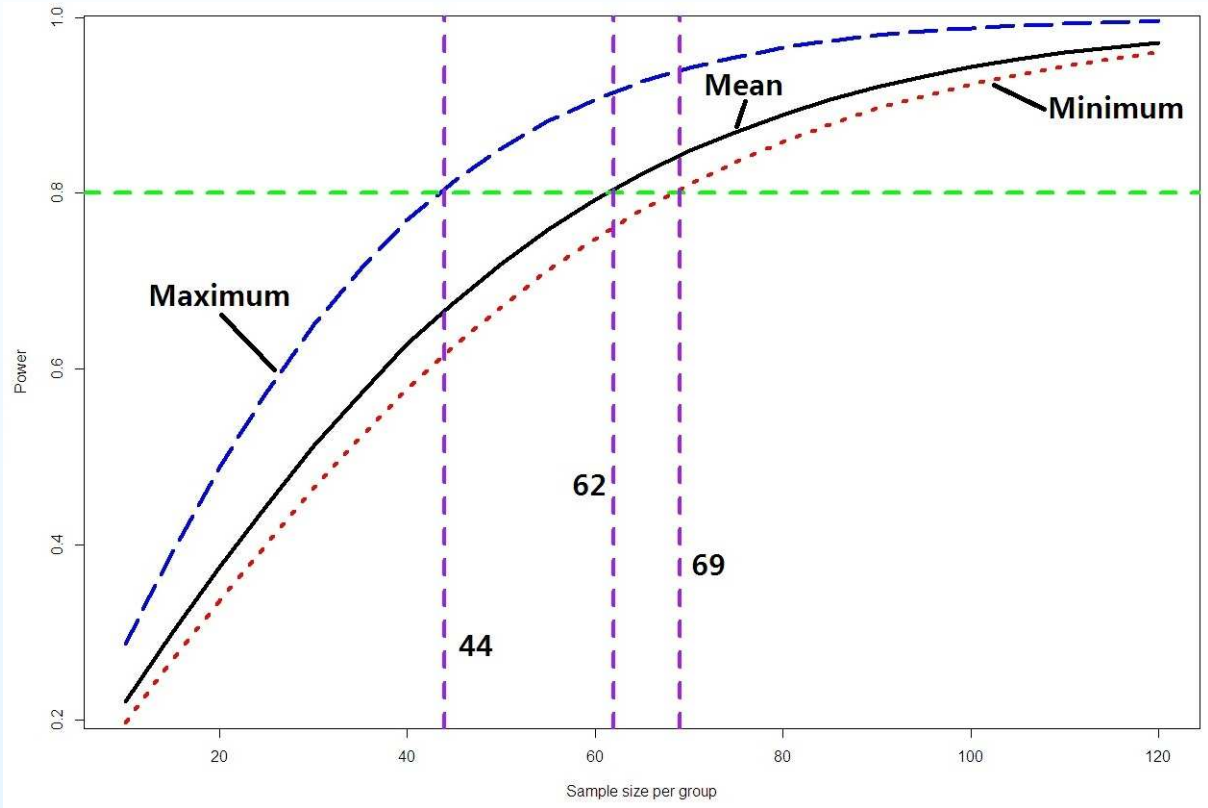
$$P\left(\max_l T_l \geq q_{1-\alpha} | \boldsymbol{\mu} = \boldsymbol{\mu}_m\right)$$
$$= 1 - P\left(T_1 < q_{1-\alpha}, \cdots, T_M < q_{1-\alpha} | \boldsymbol{\mu} = \boldsymbol{\mu}_m\right)$$

Assuming equal sample size in the example,

- The power for each candidate model can be calculated at a given sample size $n = n_1 = \cdots = n_k$;
- Among all the power from candidate models, a plot of minimum, average, and maximum power to the sample size can be used to select the smallest sample size ensuring the expected power π^*;
- It is noted that the power, sample size, and the critical value $q_{1-\alpha}$ under H_0 are intervened together, hence, the sample size need to be calculated iteratively.

Study Design (11)

Power curve with varying sample size



To achieve the desired power level of 0.8, the sample size range from 44 to 69, and based on the mean power curve, it is expected to have 62 subjects per arm.

Study Design (12)

A list of the power for individual candidate model with $n = 40$ to 70

n	E_{max}	Linear	Exponential	Logistic	$Beta_1$ $d_{opt} = 25$	$Beta_2$ $d_{opt} = 100$
40	0.594	0.609	0.576	0.769	0.632	0.585
45	0.641	0.657	0.626	0.814	0.686	0.633
50	0.684	0.701	0.671	0.851	0.733	0.677
55	0.724	0.741	0.712	0.882	0.776	0.717
60	0.758	0.776	0.748	0.907	0.812	0.753
65	0.790	0.806	0.781	0.928	0.843	0.785
70	0.818	0.834	0.810	0.943	0.870	0.814

Logistic model provides the maximum power which verify the study design assumption and higher non-centrality parameter.

Given the expected sample size $n = 62$/per arm, the critical value $q_{1-\alpha} = 2.151$ for one-sided $\alpha = 0.05$.

Study Design (13)

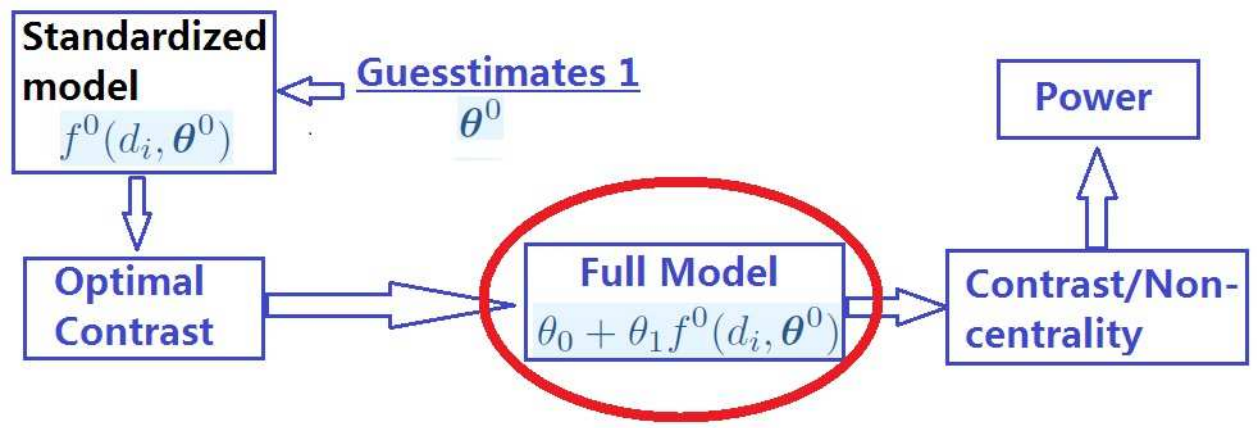
Step 8: Sensitivity analysis. The specification of guesstimates for the parameters in the **standardized** version of the models in $\mathcal{M}$ is the crucial step in the MCP-Mod. The sensitivity analysis to the mis-specification of the parameters in the **standardized** models need to be investigated at the design stage which is also critical for the future data analysis.

Three different power values are used: **nominal** power; **actual** power; and **potential** power.

Two measure of power loss are defined for the investigation:

- $LP_1 =$ nominal power $-$ actual power : measures the difference between planned and actually get;
- $LP_2 =$ potential power $-$ actual power : measure the power loss due to incorrect guesstimates.

Study Design (14)



- Nominal power: The power calculated under the guesstimates, i.e. the planned power;
- Potential power: The power calculated under the true parameter values, i.e. taking the true values as guesstimate;
- Actual power: Using the guesstimates to calculate the optimal contrast, but using the true parameter values to calculate the mean vector under full model, i.e. what one actually get.

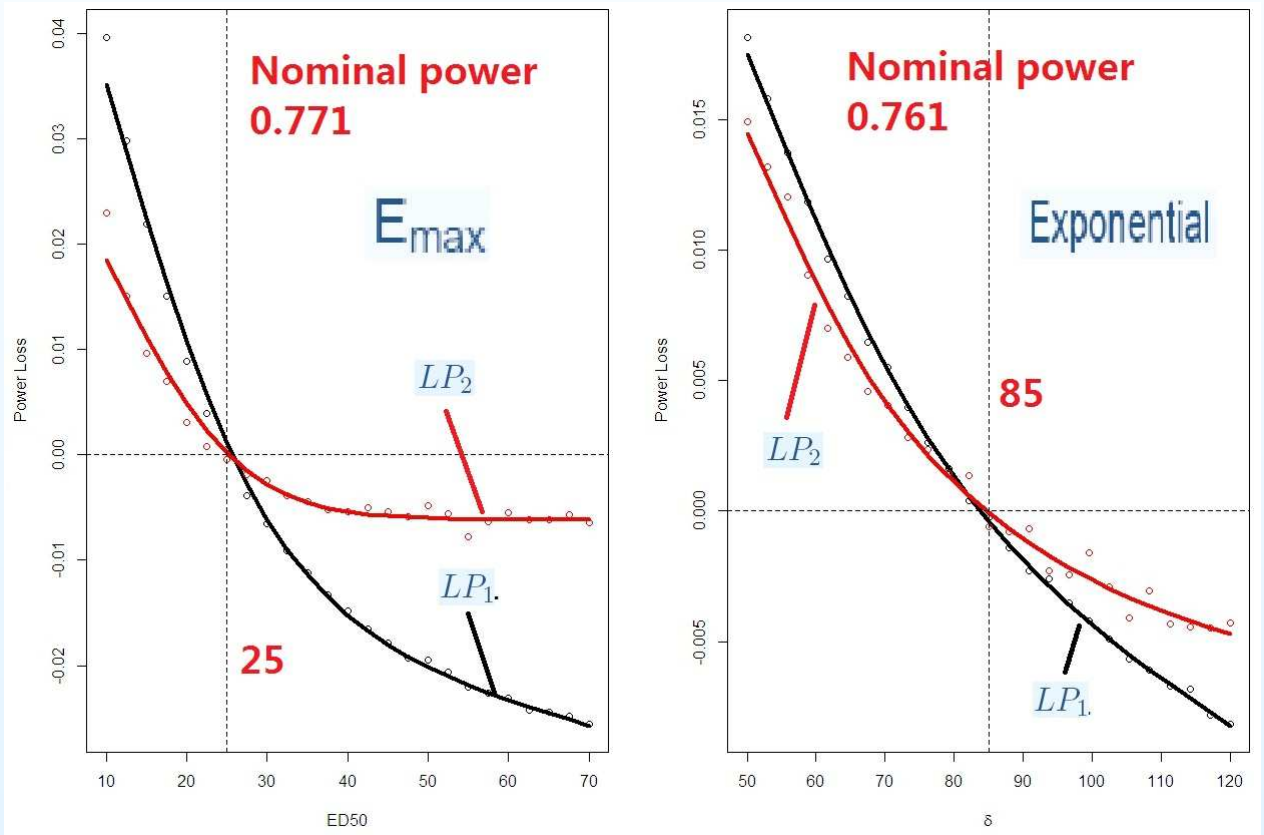
Study Design (15)

Taking logistic model as an example:

- The guesstimates are $\widehat{\text{ED}}_{50} = 50$ and $\widehat{\delta} = 10.88111$;
- Suppose we know the true values $\text{ED}_{50} = 40$ and $\delta = 5$;
- Suppose we have $n = 60/$per arm;
- The nominal power only uses the guesstimates: power = 0.906;
- The potential power only use the true values: power = 0.945;
- The actual power uses the guesstimates to calculate the optimal contrast, but use the true parameters to plug in the full model in the power calculation: power = 0.933.

Study Design (16)

Under the sample size $n = 62$/per arm, for the E_{max} model, assume the ED_{50} varying from 10 to 70, and for the Exponential model, δ varies from 50 to 120.



Study Design (17)

For LP_1 curve in the E_{max} model, gain in the actual power for parameter values larger than the guesstimates 25.

ED_{50}	E_{max}	Linear	Exponential	Logistic	$Beta_1$ $d_{opt} = 25$	$Beta_2$ $d_{opt} = 100$
10	2.5996	2.0248	1.7059	2.0317	0.8141	2.2729
25	2.6983	2.3559	2.0629	2.3820	0.2290	2.4718
30	2.7045	2.4140	2.1302	2.4400	0.1115	2.4937
40	2.7040	2.4960	2.2293	2.5186	-0.0671	2.5137
50	2.6956	2.5505	2.2989	2.5678	-0.1969	2.5170
60	2.6842	2.5889	2.3503	2.6002	-0.2959	2.5125
70	2.6720	2.6170	2.3900	2.6222	-0.3741	2.5042

- The non-centrality value under E_{max} model for different ED_{50}, but the contrast calculated under $ED_{50} = 25$;
- For $ED_{50} > 25$, with $ED_{50} \uparrow$, the non-centrality value $\downarrow$ for E_{max} model, but the non-centrality value $\uparrow$ for all other candidate models;
- Hence, the actual power increase with $ED_{50} \uparrow$, "picking-up" other models to cover the loss of power from E_{max} model.
- For $ED_{50} = 10$, non-centrality value $\downarrow$ for all candidate model except $Beta_1$, leading to the power loss.

Study Design (18)

For LP_2 curve in the E_{max} model, smaller gain in the actual power for parameter values larger than the guesstimates 25.

	Non-centrality		Critical Value	
ED_{50}	Actual	Potential	Actual	Potential
10	2.5996	2.6719	2.148	2.172
25	2.6983	2.6983	2.149	2.151
30	2.7045	2.7071	2.147	2.146
40	2.7040	2.7204	2.151	2.141
50	2.6956	2.7295	2.149	2.138
60	2.6842	2.7358	2.149	2.135
70	2.6720	2.7402	2.150	2.134

- For $ED_{50} > 25$, the non-centrality parameter using the optimal contrast is larger than the corresponding value using the actual power optimal contrast;
- The critical values used with the potential power are smaller than the fixed actual power critical value 2.149;
- It seems that the potential power should be larger than the actual power. Counter-intuitive?

Study Design (19)

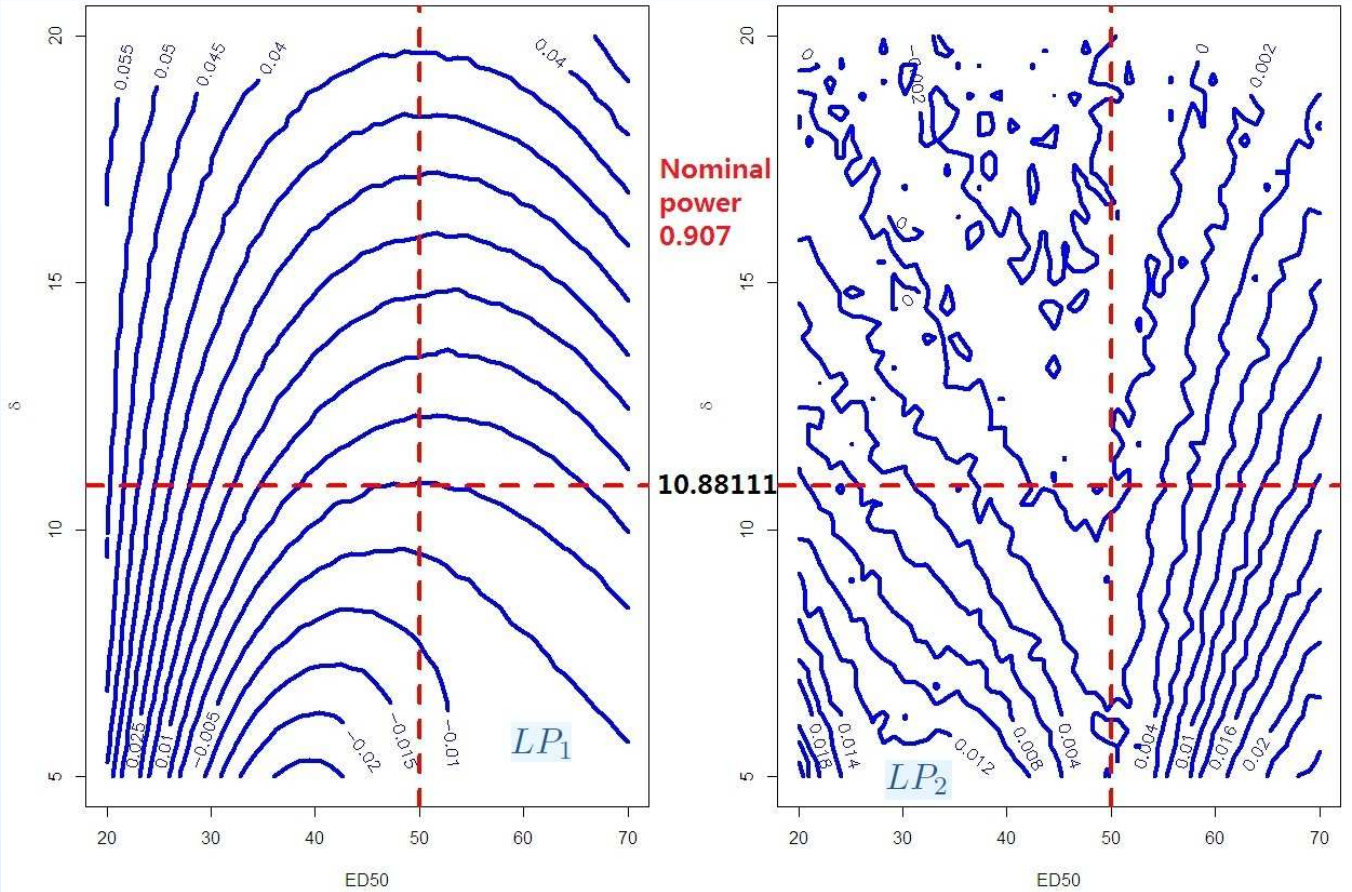
The smaller power gain in the actual power for parameter values larger than the guesstimates 25 is due to the increased correlations between the E_{max} model contrast and the remaining model contrasts in the potential power calculation which leads to reduced coverage of the shape space.

ED_{50}	Linear	Exponential	Logistic	$Beta_1$ $d_{opt} = 25$	$Beta_2$ $d_{opt} = 100$
10	0.758	0.638	0.760	0.305	0.851
25	0.873	0.764	0.883	0.085	0.916
30	0.892	0.787	0.901	0.041	0.921
40	0.917	0.819	0.926	-0.025	0.924
50	0.934	0.842	0.941	-0.072	0.922
60	0.946	0.859	0.950	-0.108	0.918
70	0.955	0.872	0.957	-0.137	0.914

It is complex and challenging to describe and interpret the results due to the interaction between the parameter values and candidate models, the LP_1 and LP_2 provides some useful tools.

Study Design (20)

Under the sample size $n = 62/$per arm, for logistic model, assume the ED_{50} varying from 20 to 70, and δ varies from 5 to 20.



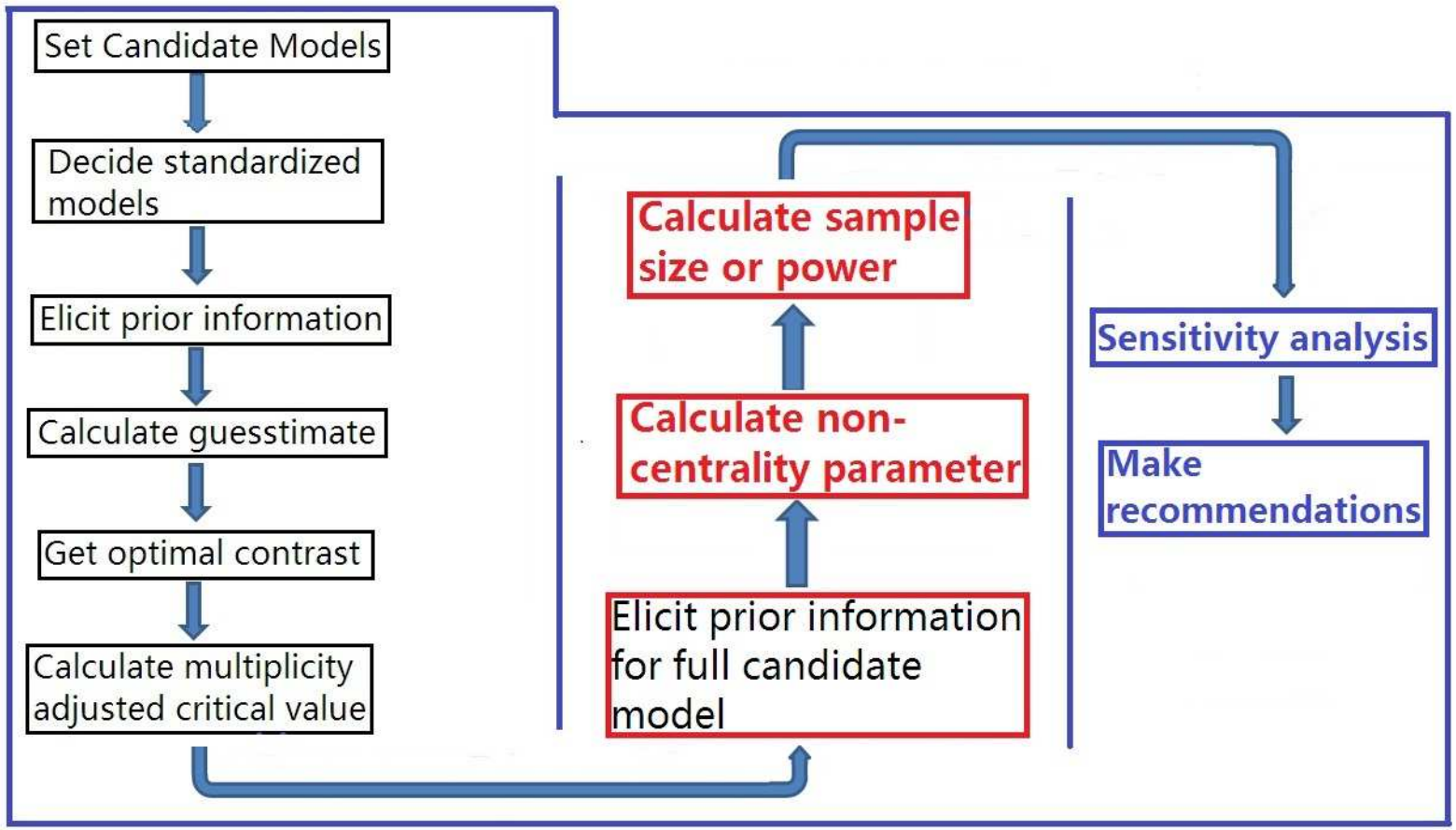
Study Design (21)

To design a dose-finding Phase II study using the MCP-Mod

- It is desirable to include candidate set $\mathcal{M}$ providing broad coverage of the dose-response shape space, but to avoid choosing the highly correlated model contrasts;
- The power loss associated with mis-specification of the parameters in the standardized model is often negligible for reasonable candidate set $\mathcal{M}$, because the deviation of one model parameter can be covered by some other model in $\mathcal{M}$;
- In case the power loss is not acceptable, inclusion of additional model in $\mathcal{M}$ can be considered.
- Therefore, model-based dose-finding designs should be used routinely in drug development and low number of models is recommended (typically $4-5$ models);
- Linear and E_{max} models are often included in candidate set; other models (e.g., quadratic, logistic, exponential, $\cdots$) are included as needed.

Study Design (22)

Schematic process for the study design using MCP-Mod.



Design Considerations

Type of Design

There are four most common dose finding study designs to find the optimal doses for phase III trials

- Parallel Dose Comparison: It is the most popular design in Phase II development when larger studies are done to explore safety and effectiveness of a new drug;
- Dose Titration: Dose go up/down for the same subject. Each subject starts at a low dose and receive an incrementally higher dose until the MTD is reached. Generally, for treatment of chronic conditions where a drug will be used for a long period of time, and likely to see a significant difference in the way each subject reacts, e.g. hypertension medication;
- Dose Escalation: Limited information about the safety profile and start with lower doses first. Start with one group of subjects (cohort) $\rightarrow$ give them a low dose $\rightarrow$ observe some period of time $\rightarrow$ if no safety issues noted $\rightarrow$ enroll a new group of subjects and give a higher dose $\rightarrow \cdots \rightarrow$ reach the MTD or planned highest dose. Commonly used in the oncology study;
- Cross-over: Subjects are randomized to a sequence of IP and placebo, for drug quickly eliminated from the body and stability of the disease state.

Statistical Methods

Statistical methods for parallel or cross-over are readily available. For flexible-dose titration or dose escalation, the statistical analysis method is challenging and often problematic due to the selection bias caused by 'titration-to-response'. DLME or MSM can be used to evaluate dose-response. Xu et al (2012, *Pharm Stat*), Lipkovich et al (2012, *Pharm Stat*),

- Dynamic linear mixed effect (DLME) model: The current response is assumed to be a function of covariates and the previous responses. The first-order dynamic model may be of most importance in biomedical research, i.e. the primary driving force for dose titration is the previous response levels;
- Marginal structural model (MSM): A weighted regression analysis for repeated measures with time-dependent confounders (i.e., due to response-to-treatment feedback) by treating exposure history as a time-varying covariate. A two-stage procedure: calculating weight and fit the model. The validity of MSM approaches depends on some assumptions, and final results from the available weight leads to some underestimation.

Summary and Notes

Alternative Methods

- Including baseline covariates in MCP-Mod;

$$Y_{ij} = \mathbf{x}_j \boldsymbol{\beta} + \theta_1 f^0(d_i, \boldsymbol{\theta}^0)$$

- MCP-Mod-like procedure for the binary data;
- Taking dose group as qualitative factor, and apply the Dunnett's procedure or partitioning principle;
- Adaptive dose-finding techniques from frequentist or Bayesian perspective.
- Comfortable with the MCP-Mod? A new development based on the LRT without relying on the prior information.

Go/Not Go Decision

- Assurance (probability of success, PoS): an acceptable probability level of success (the pivotal phase III trials demonstrate a statistically significant drug effect) to plan a confirmatory trial when the Phase II results are available. O'Hagan et al (2005, *Pharm Stat*);
- Discounting phase II results to plan phase III: phase II studies are often run in more homogenous populations than the subsequent population in phase III, over-estimating the true treatment effect and the positive finding may be due to chance. Wang et al (2006, *Pharm Stat*) and Kirby et al (2012, *Pharm Stat*);
- Evaluate PoS in dose selection for Phase III: incorporating the efficacy and safety profile to evaluate the PoS and select the most promising dose for Phase III. Lisovskaja and Burman (2012, *SIM*);
- Program-level optimization: Complex consideration to investigate the net present value (NPV) by integrating patient population, trial costs, relationship of efficacy and the tolerability profile of the IP (at the recommended dose), related products already on the market place, and profits of these marketed products. Patel et al (2012, *DIJ*).

Key References

1. N Ting (2005). *Design and Analysis of Dose Response Clinical Trials*, New York: Springer-Verlag.
2. J Pinheiro, B Bornkamp, and F Bretz (2006). Design and Analysis of Dose-finding Studies Combining Multiple Comparisons and Modeling Procedures. *Journal of Biopharmaceutical Statistics*, 16: 639–656.
3. F Bretz, J Pinheiro, and M Branson (2005). Combining multiple comparisons and modeling techniques in dose-response studies. *Biometrics*, 61: 738–748.
4. F Bretz, J Hsu, J Pinheiro, and Y Liu (2008). Dose finding - A challenge in statistics. *Biometrical Journal*, 4: 480–504.
5. A Dmitrienko, AC Tamhane, and F Bretz (2010). *Multiple testing problems in pharmaceutical statistics*. New York: CRC Press.
6. A Dmitrienko, C Chuang-Stein, and R D'Agostino (2007). *Pharmaceutical Statistics Using SAS: A Practical Guide*. Cary, NC: SAS Institute Inc.
7. B Klingenberg (2009). Proof of concept and dose estimation with binary responses under model uncertainty. *Statistics in Medicine*, 28: 274–292.
8. B Bornkamp, J Pinheiro, and F Bretz (2009). MCPMod: An R Package for the Design and Analysis of Dose-Finding Studies. *Journal of Statistical Software*, 29(7): 1–23.

Questions?

The final slide will be posted on my personal workpage `http://works.bepress.com/zyang/`

“Begin at the beginning” the King said, gravely, “and go on till you come to the end; then stop."