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Bayesian Model Comparison for Dose Response Studies

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Disclaimer

- Expository work on recent developments on BMCPMod by Frank Fleischer, Sebastian Bossert, Qiqi Deng, Christina Loley, Jana Gierse (2022) *Pharmaceutical Statistics*.
- MCPMod is well established statistical method. BMCPMod is a Bayesian extension to MCPMod where we assume prior distribution on the mean response.
- No GSK clinical trail data were used. Simulated data has been used for this project.

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Drug Development

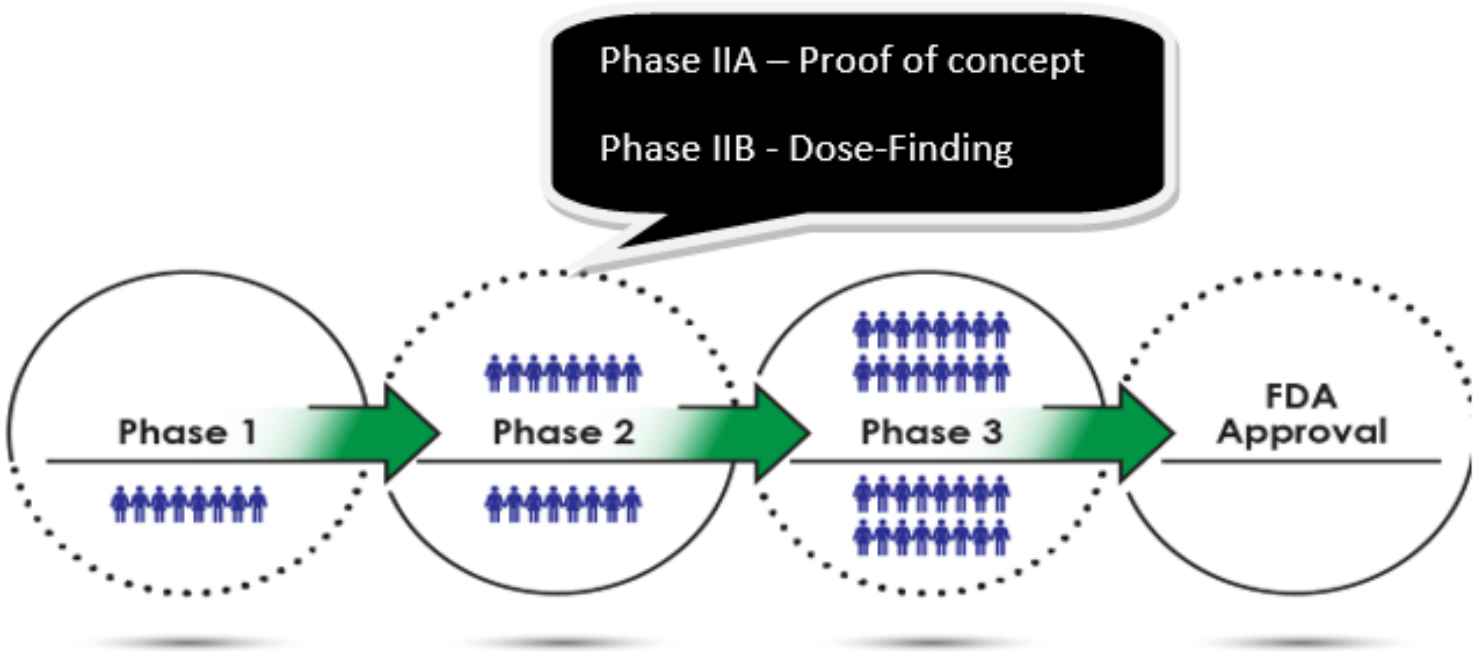

Figure: Drug Development

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Drug Development

Why Phase II trials are important?

- Historically initially marketed drugs have later been recognized as excessive doses.
- It is believed by many that high attrition rate in Phase III is largely driven by inadequate dose selection.
- Selection of dose(s) to advance into the Phase III is one of the most challenging decisions during drug development.
- Dose response studies have a huge impact on dose selection process for the success of Phase III trial.
- It reduces the resources/cost/time.

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Key Definitions

- **Dose** is the amount of drug administered to achieve a desired benefit (e.g., 500mg paracetamol).
- **Response** is an observation or effect shown by body to the drug.
- **MED** (Minimum Effective Dose) is the smallest dose above which a desired efficacy outcome is obtained.
- **MTD** (Maximum Tolerated Dose) is the dose beyond which the drug cannot be tolerated (due to high safety signals). Doses below the MTD are safe.
- **Therapeutic window:** If MED$<$MTD then the interval (MED, MTD) is called the Therapeutic window. Doses can be prescribed in this window and optimal dose(s), if any, should lie in this window.

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Objectives

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1. To understand the underlying dose response relationship
2. To identify MED, intermediate dose(s) and MTD.
3. To find an optimal dose for Phase III that will be
   - high enough to be effective yet
   - low enough to have acceptable safety

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ANOVA

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ANOVA Test

1. Step1: Testing the difference between means of different dose groups.
   - Hypotheses:
     - $H_0 : \mu_1 = \mu_2 = ... = \mu_4$
     - $H_a : \mu_l \neq \mu_m$, where μ_l and μ_m are two sample means out of all samples.
2. Step2: Post hoc Tests
   - If H_0 is rejected then proceed with pairwise comparison of mean response and compare it with adjusted critical value.

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ANOVA

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Limitations of ANOVA approach

- Doses are considered as qualitative factor in traditional ANOVA approach.
- This leads us selecting dose more or less than the actual dose required.
- It has a very vague idea about the shape of the dose response relationship.
- In Anova the means are joined by straight line. We can observe an un-smooth fit.
- For a better understanding of dose response relationship modelling approach is required in Dose Finding.

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Model-Based comparison

- The modelling approach to dose finding is based on an assumed functional relationship between the response and the dose, treated as a quantitative variable.
- The model fitted is used to test for the presence of dose response and to estimate an adequate dose(s) to achieve a desired response

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Dose Response Models

- Model: $f(d, \theta) = \theta_0 + \theta_1 f^0(d, \theta^0)$
- Emax Model: $E_0 + E_{\max} \frac{d}{(ED_{50}+d)}$
- Linear Model: $E_0 + \delta d$
- Exponential Model: $E_0 + E_1 \exp(\frac{d}{\delta})$
- Logistic Model: $E_0 + E_{max} \frac{1}{(1+exp[\frac{ED_{50}-d}{\delta}])}$

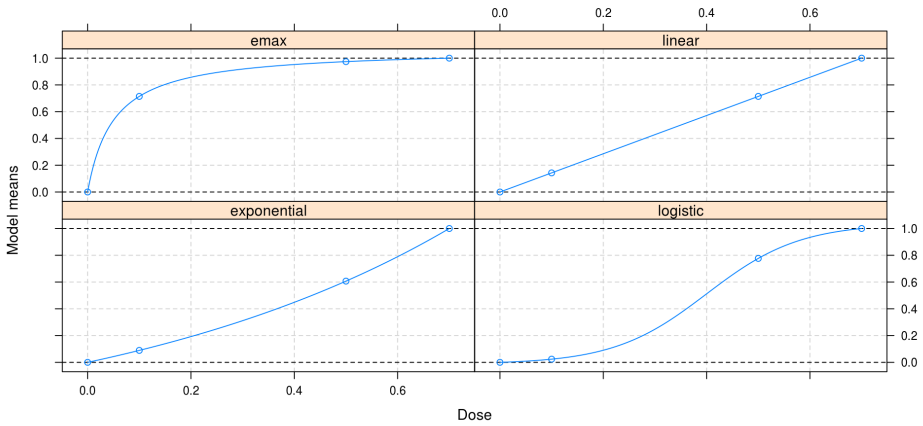

Figure: Dose Response Models

MCP-Mod method

- Multiple Comparison Procedure - Modelling (MCP-Mod) Technique approach was proposed by Bretz, Pinheiro, and Branson (2005) and was approved by FDA.
- **MCP-Mod** combines both into single method
  1. MCP Stage: Select best model(s) with appropriate contrasts controlling FWER from a class of candidate models.
  2. Mod Stage: Model using best model and find target dose(s) of interest.

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MCP-Mod method

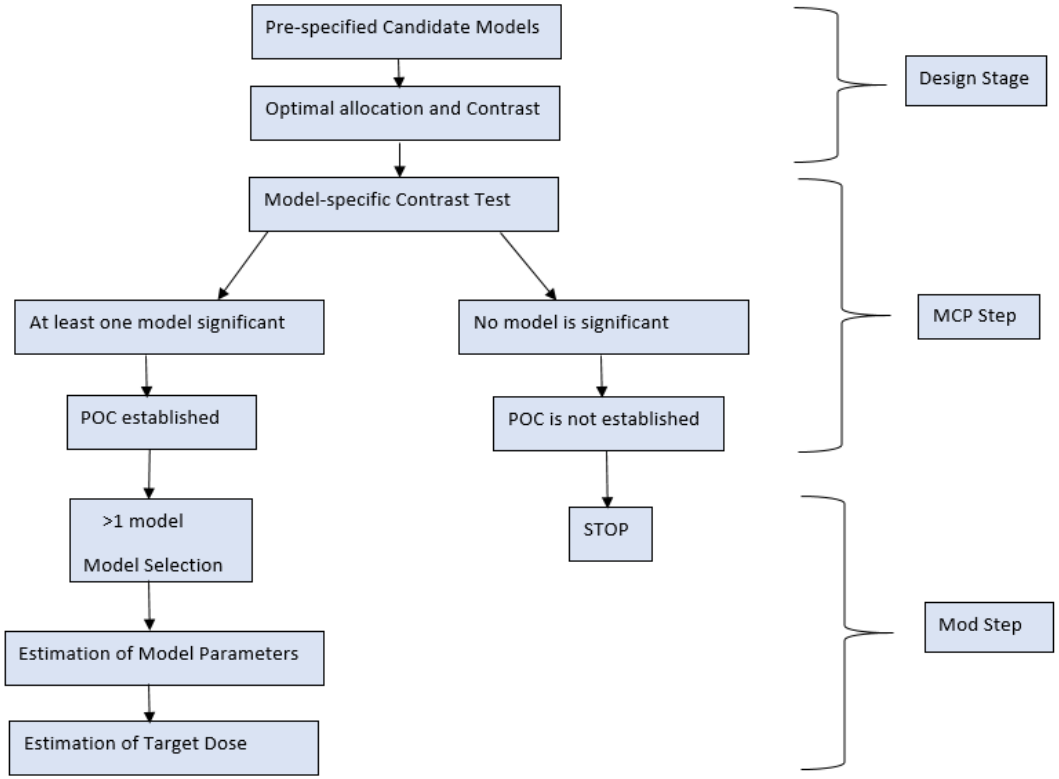

Figure: MCPMod - Overview

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MCP-Mod method

- Response Y_{ij} is observed for a set of parallel groups of patients.
- k active doses groups: $d_1, \ldots, d_k$ plus placebo dose group: $d_0 \rightarrow k+1$ groups.

$$Y_{ij} = \mu_{d_i} + \epsilon_{ij}, \quad \epsilon_{ij} \overset{\text{i.i.d}}{\sim} N(0, \sigma^2) \quad i = 0, ..., k, j = 1, ...n_i$$

  - μ_{d_i}: is the mean dose response at different dose levels $d_0, \ldots, d_k$
  - n_i cohort size of each dose group d_i
  - ϵ_{ij} : Error term; assumed to be independent and identically distributed.
- Mean dose response is represented as $u_{d_i} = f(d_i, \theta)$ for some dose-response model $f(.)$.
- θ: parameter vector of the unknown dose-response model f.

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MCP-Mod method

- The main aim is to find the best-fitting model(s) from the set of candidate models.
- Null hypotheses

$$H_0^m : c_m' \boldsymbol{\mu} = 0$$

for all $m \in \{1, 2, \ldots, M\}$ for some contrast c_m such that $\sum c_{mi} = 0$

- Alternative Hypotheses

$$H_1^m : \boldsymbol{c}_m' \boldsymbol{\mu} \neq 0$$

for at least one $m \in \{1, 2, \ldots, M\}$

- Single contrast test for testing the m^{th} model:

$$T_m = \frac{\boldsymbol{c}_m' \overline{\boldsymbol{Y}}}{\sqrt{S^2 \sum_{i=1}^{k} c_{mi}^2 / n_i}}, \quad m = 1, \ldots, M$$

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MCP-Mod method

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- If H_1 is true for any model m then T_m follows non-central t-distribution with non-centrality parameter.
- A significance test for the above hypotheses testing:

$$T\text{max} = \max_{m\in\{1,2,\ldots,M\}} T_m.$$

- If $T_{max} \geq q$, a significant dose response signal is established.
- q is the adjusted critical value.
- If POC is not established, that is, no significant model $=>$ stop.
- If at least one model is significant, we choose the "best" model out the set of candidate models (this the model selection approach, the model averaging approach can also be followed).

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Optimal Contrast

- Optimal contrast maximizes the chance of rejecting the associated null hypothesis, that is maximizes the non-centrality.
- Under balanced sample size allocation $n_i = n,\ i = 0, 1 \ldots, k$

$$\begin{aligned} c_m &= \frac{\boldsymbol{\mu} - \bar{\mu}\mathbf{1}}{||\boldsymbol{\mu} - \bar{\mu}\mathbf{1}||} \\ &= \frac{\boldsymbol{\mu}^0 - \bar{\mu}^0\mathbf{1}}{||\boldsymbol{\mu}^0 - \bar{\mu}^0\mathbf{1}||} \end{aligned}$$

- μ^0 is vector of standardized mean dose response.

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BMCP-Mod method

- Bayesian-MCPMod approach

$$Y_{ij} = \mu(d_i) + \epsilon_{ij}, \quad \epsilon_{ij} \overset{\text{i.i.d}}{\sim} N(0, \sigma^2) \quad i = 0, ..., k, j = 1, ...n_i$$

- Prior is considered as normal distribution

$$\boldsymbol{\mu} \sim \mathcal{N}_{K+1}\left(\boldsymbol{\theta}_0, \frac{\sigma^2}{\boldsymbol{n}_0} I\right)$$

- Posterior $\boldsymbol{\mu}$ is

$$\mu_i \mid \mathcal{Y} \sim \mathcal{N}\left(\frac{\frac{\theta_{0,}}{\sigma^2/n_{0,i}} + \frac{\bar{Y}_i}{\sigma^2/n_i}}{\frac{n_{0,}}{\sigma^2} + \frac{n_i}{\sigma^2}}, \frac{1}{\frac{n_{0,}}{\sigma^2} + \frac{n_i}{\sigma^2}}\right) = \mathcal{N}\left(\frac{n_{0,i}\theta_{0,i} + n_i\bar{y}_i}{n_{0,i} + n_i}, \frac{\sigma^2}{n_{0,i} + n_i}\right)$$

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BMCP-Mod method

- Placebo group: $\mu_{d_0} \sim w_1 N(\theta_{0,0,1}, \sigma^2/n_{0,0,1}) + \cdots + w_4 N(\theta_{0,0,4}, \sigma^2/n_{0,0,4})$
- Active dose groups: one component conjugate normal prior

$$\boldsymbol{\mu} \sim w_1 \cdot \mathcal{N}\left(\begin{pmatrix} \theta_{0,0,1} \\ \theta_{0,1} \\ \vdots \\ \theta_{0,K} \end{pmatrix}, \begin{pmatrix} \frac{\sigma^2}{n_{0,0,1}} & \frac{\sigma^2}{n_{0,1}} & \cdots & \frac{\sigma^2}{n_{0,K}} \end{pmatrix} I\right) + \ldots +$$

$$w_L \cdot \mathcal{N}\left(\begin{pmatrix} \theta_{0,0,4} \\ \theta_{0,1} \\ \vdots \\ \theta_{0,K} \end{pmatrix}, \begin{pmatrix} \frac{\sigma^2}{n_{0,0,4}} & \frac{\sigma^2}{n_{0,1}} & \cdots & \frac{\sigma^2}{n_{0,K}} \end{pmatrix} I\right)$$

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BMCP-Mod method

$$\boldsymbol{\mu} \mid \mathcal{Y} \sim w_1^* \mathcal{N}\left(\begin{pmatrix} \frac{n_{0,0,1}\theta_{0,0,1}+n_0\bar{Y}_0}{n_{0,0,1}+n_0} \\ \frac{n_{0,1}\theta_{0,1}+n_1\bar{Y}_1}{n_{0,1}+n_1} \\ \vdots \\ \frac{n_{0,K}\theta_{0,K}+n_K\bar{Y}_K}{n_{0,K}+n_K} \end{pmatrix}, \begin{pmatrix} \frac{\sigma^2}{n_{0,0,1}+n_0} & \cdots & \frac{\sigma^2}{n_{0,K}+n_K} \end{pmatrix} I \right) + \ldots +$$

$$w_L^* \cdot \mathcal{N}\left(\underbrace{\begin{pmatrix} \frac{n_{0,0,4}\theta_{0,0,4}+n_0\bar{Y}_0}{n_{0,0,1}+n_0} \\ \frac{n_{0,1}\theta_{0,1}+n_1\bar{Y}_1}{n_{0,1}+n_1} \\ \vdots \\ \frac{n_{0,K}\theta_{0,K}+n_K\bar{Y}_K}{n_{0,K}+n_K} \end{pmatrix}}_{\theta_4}, \underbrace{\begin{pmatrix} \frac{\sigma^2}{n_{0,0,4}+n_0} & \cdots & \frac{\sigma^2}{n_{0,K}+n_K} \end{pmatrix} I}_{\tau_4} \right)$$

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BMCP-Mod method

$$\boldsymbol{c}_m^T\boldsymbol{\mu} \mid \mathcal{Y} \sim \underbrace{w_1^*\mathcal{N}\left(\boldsymbol{c}_m^T\boldsymbol{\theta}_{\mathcal{Y}}^1, \sum_{i=0}^{K} c_{m,i}^2\tau_1[i,i]\right)}_{\sim Z_1} + \cdots + \underbrace{w_4^*\mathcal{N}\left(\boldsymbol{c}_m^T\boldsymbol{\theta}_{\mathcal{Y}}^4, \sum_{i=0}^{K} c_{m,i}^2\tau_4[i,i]\right)}_{\sim Z_4}$$

$$P\left(\boldsymbol{c}_m^T\boldsymbol{\theta} > 0 \mid \mathcal{Y}\right) = \sum_{l=1}^{4} w_l^* \cdot P\left(Z_l > 0\right),$$

$$= \sum_{l=1}^{4} w_l^* \Phi\left(\frac{\boldsymbol{c}_m^T\boldsymbol{\theta}_y^l}{\sqrt{\sum_{i=0}^{K} c_{m,i}^2\tau_l^2[i,i]}}\right) = p_m^y.$$

Significant test is established if $p^* = \max_{m=1,\ldots,M} p_m^y$ is greater than an adjusted critical value $1-\alpha^*$.

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Simulation Study

Example:

- $k = 4$ active dose groups and a placebo group: $d_0 = 0$, $d_1 = \frac{1}{30}$, $d_2 = \frac{3}{30}$, $d_3 = \frac{10}{30}$, $d_4 = 1$
- Standard deviation $\sigma = 1.1$
- $M = 6$ candidate models
  - Three different Emax models
  - One Exponential model
  - One Linear model
  - One Logistic model
- $\alpha = 0.05$
- Overall sample size $n = 300$

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Simulation Study

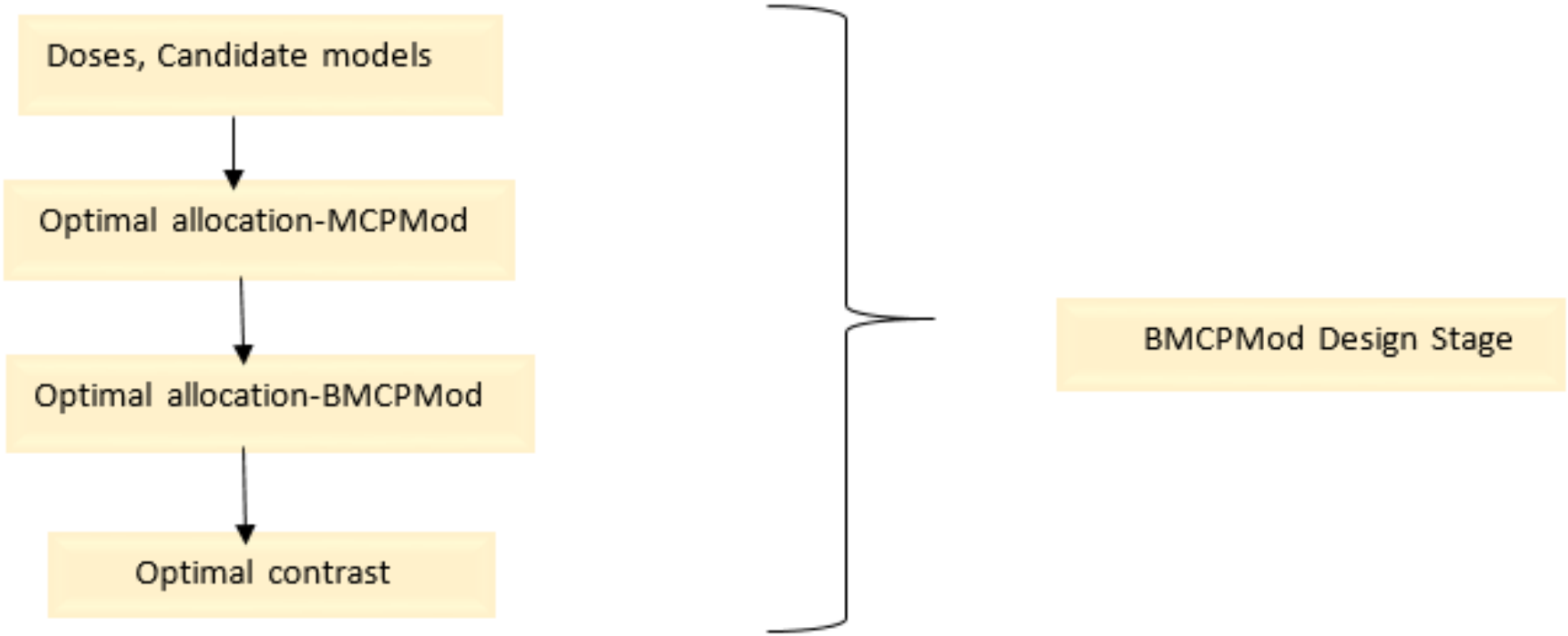

Figure: BMCPMod Design Stage

Simulation Study

Prior Information:

- **Placebo group** has three different conjugate priors

prior	weights	Mean($\theta_{0,0,i}$)	ESS($n_{0,0,i}$)	ESS_{elir}
informative	0.5	0	30	9.5
weakly informative 1	0.25	0.25	2	
weakly informative 2	0.25	-0.25	2	

Table: Placebo prior information

- We consider vaguely informative prior for active groups.
- **active dose groups:** prior mean: $\theta_{0,i} = 0$, ESS: $n_{0,i} = 1$

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Simulation Study

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Expected local-information-ratio effective sample size

- $ESS_{elir} = E_{\mu}(\frac{i(p(\mu))}{i_F(\mu)})$
- $i_F(\mu) = -\sum_i n_i E(\frac{\partial^2}{\partial \mu^2} log f(y_{i1}|\mu))$ is the Fisher information of the sampling model
- $i(p(\mu)) = -\frac{d^2 \log p(\mu)}{d\mu^2}$ is the prior distribution of μ.
- If the prior is a k components mixture distribution, $p(\mu) = \sum_{j=1}^{K} w_j p_j(\mu)$
- ESS_{elir} is calculated using function `ess` of `RBesT` package in R.

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Optimal allocation

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- Experimental optimal design is represented as

$$\xi = \{(d_1 \cdots d_k), (w_1 \cdots w_k)\}$$

- Fishers Information matrix is $M(\xi, \theta) = \sum_{i=1}^{k} w_i \frac{\partial f(d,\theta)}{\partial \theta} \frac{\partial f(d,\theta)^\top}{\partial \theta}$
- D-optimal Design using General Equivalence Theorem (GET)
  - Design maximizes $log\{\det[\boldsymbol{M}(\xi)]\}$
  - $d(x, \xi) = f(x)^T [\boldsymbol{M}(\xi)]^{-1} f(x) \leq p$
- Optimal allocation is calculated using function `optDesign` of `DoseFinding` package in `R`.

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Simulation Study

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- Optimal allocation for MCPMod:

Dose	0	$\frac{1}{30}$	$\frac{3}{30}$	$\frac{10}{30}$	1
N=300	80	33	44	48	95

- Optimal allocation for BMCPMod:

Dose	0	$\frac{1}{30}$	$\frac{3}{30}$	$\frac{10}{30}$	1
N=300	72	34	46	50	98

Optimal Contrast

- Optimal contrast for unbalanced sample size:

$$\boldsymbol{c}_m \propto \boldsymbol{S}^{-1}\left(\boldsymbol{\mu}_m^0 - \frac{\boldsymbol{\mu}_m^{0\prime}\boldsymbol{S}^{-1}\mathbf{1}}{\mathbf{1}'\boldsymbol{S}^{-1}\mathbf{1}}\right)$$

  - μ_m^0 is the vector of standardized mean dose response.
  - S = diag$(n_0, n_1, \ldots, n_k)$ is the matrix of inverse of the cohort sizes.
  - We normalize the optimal contrast so that $||c_m||$=1.

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Simulation Study

Optimal contrast for BMCPMod allocation:

	Emax1	Emax2	Emax3	exponential	logistic	linear
0	-0.685	-0.837	-0.613	-0.379	-0.499	-0.425
0.03	-0.182	-0.006	-0.204	-0.172	-0.229	-0.186
0.1	-0.021	0.142	-0.094	-0.206	-0.262	-0.201
0.33	0.215	0.221	0.174	-0.120	0.231	-0.050
1	0.672	0.480	0.737	0.877	0.759	0.861

Table: BMCPMod Optimal Contrast

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Simulation Study

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- The posterior probabilities for $M = 6$ models

Models	posterior probabilities
Emax1	0.3107429
Emax2	0.4103961
Emax3	0.2813772
Exponential	0.2122869
Linear	0.2528265
Logistic	0.2225135

Table: Posterior Probabilities

- Adjusted critical value is 0.14823
- $0.4103961 \geq 0.14823$ POC is established.

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References

[1] Frank Bretz et al. "Dose finding–a challenge in statistics". In: BiometricalJournal: Journal of Mathematical Methods in Biosciences 50.4 (2008),pp. 480–504.

[2] Frank Bretz, Jos ´e C Pinheiro, and Michael Branson. "Combining multiplecomparisons and modeling techniques in dose-response studies". In: Biometrics 61.3 (2005), pp. 738–748.

[3] Fleischer, Frank and Bossert, Sebastian and Deng, Qiqi and Loley, Christina and Gierse, Jana. Bayesian MCP-Mod. Journal of Statistical Planning and Inference. Pharmaceutical Statistics Journal (2022).

[4] Pinheiro, J., Bornkamp, B., Glimm, E., & Bretz, F. (2014). Model[U+2010]based dose finding under model uncertainty using general parametric models. Statistics in medicine, 33(10), 1646-1661.

[5] Introduction to dose response models. Slides prepared by dose response working group. GSK Asia Private Limited. 2020;

Thank You