Decision making in drug development: Choosing a biomarker for Phase II and predicting the outcome of Phase III

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Phase II biomarker trials

Is a new treatment promising?

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- Evidence is sought for further investigation (Phase III)
- Pr(success in Phase III) can be estimated based on Phase II data
  - Stallard, Whitehead and Cleall (2005)
- Clinical Endpoint of Interest (CEI) is not always possible to be measured in Phase II

Predictive ability
Notation

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- X binary CEI, B biomarker
- Binary biomarker: $\text{PPV} = \text{P}(X = 1|B = 1)$, $\text{NPV}=\text{P}(X = 0|B = 0)$
- Continuous biomarker: logistic model predicting CEI $\rightarrow$ $\text{PPV}_l = \text{P}(X = 1|B > d)$, $\text{NPV}_l=\text{P}(X = 0|B < d)$
  - PPV_l and NPV_l are the correct classification probabilities

Example

Designing Neonatal Encephalopathy (NE) Phase II trial

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- CEI is neurodevelopmental outcome (good or bad) after 18 months
- Possible biomarkers
  - MRI scans (normal or abnormal)
  - Time for aEEG trace to return to normal (TTNT)

Stallard et al.'s approach

Illustration

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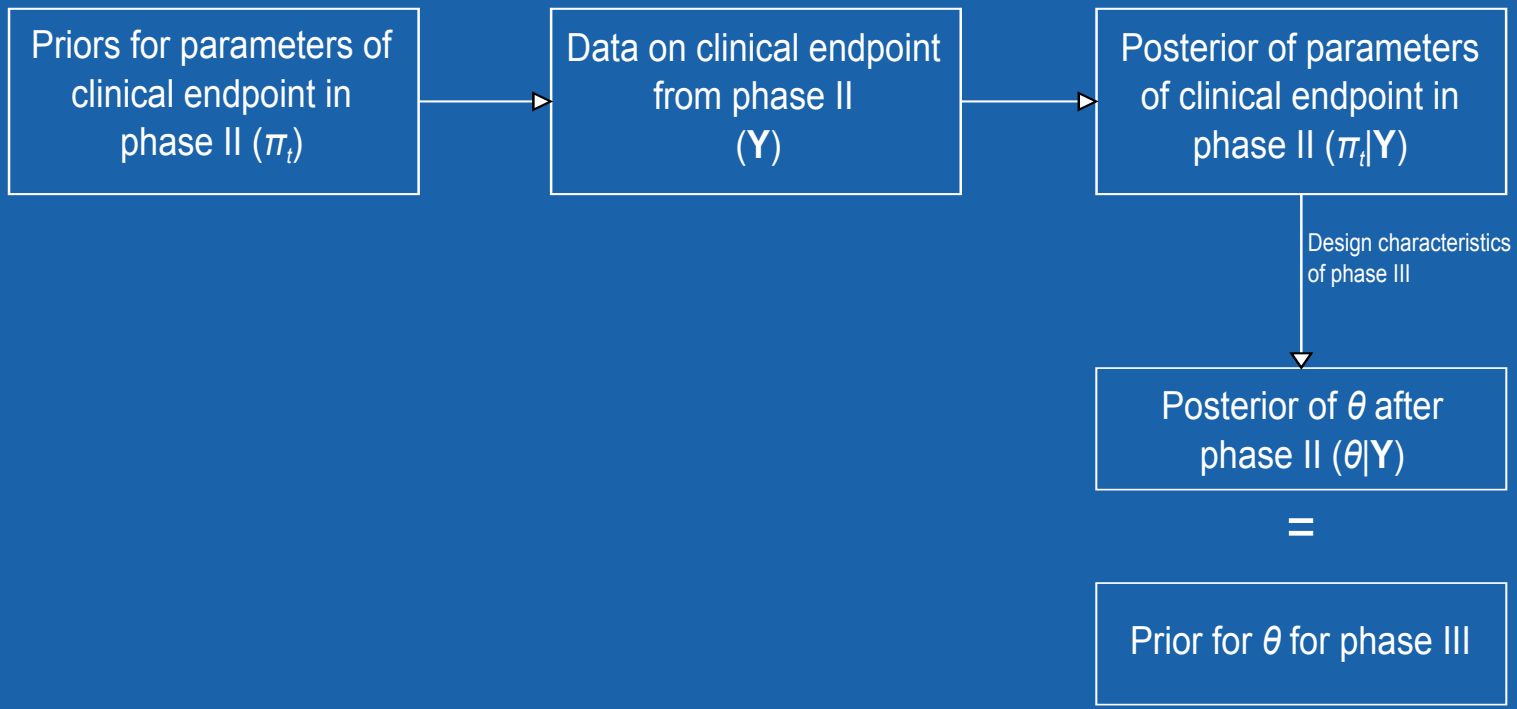

Expanding Stallard et al.'s approach

Illustration

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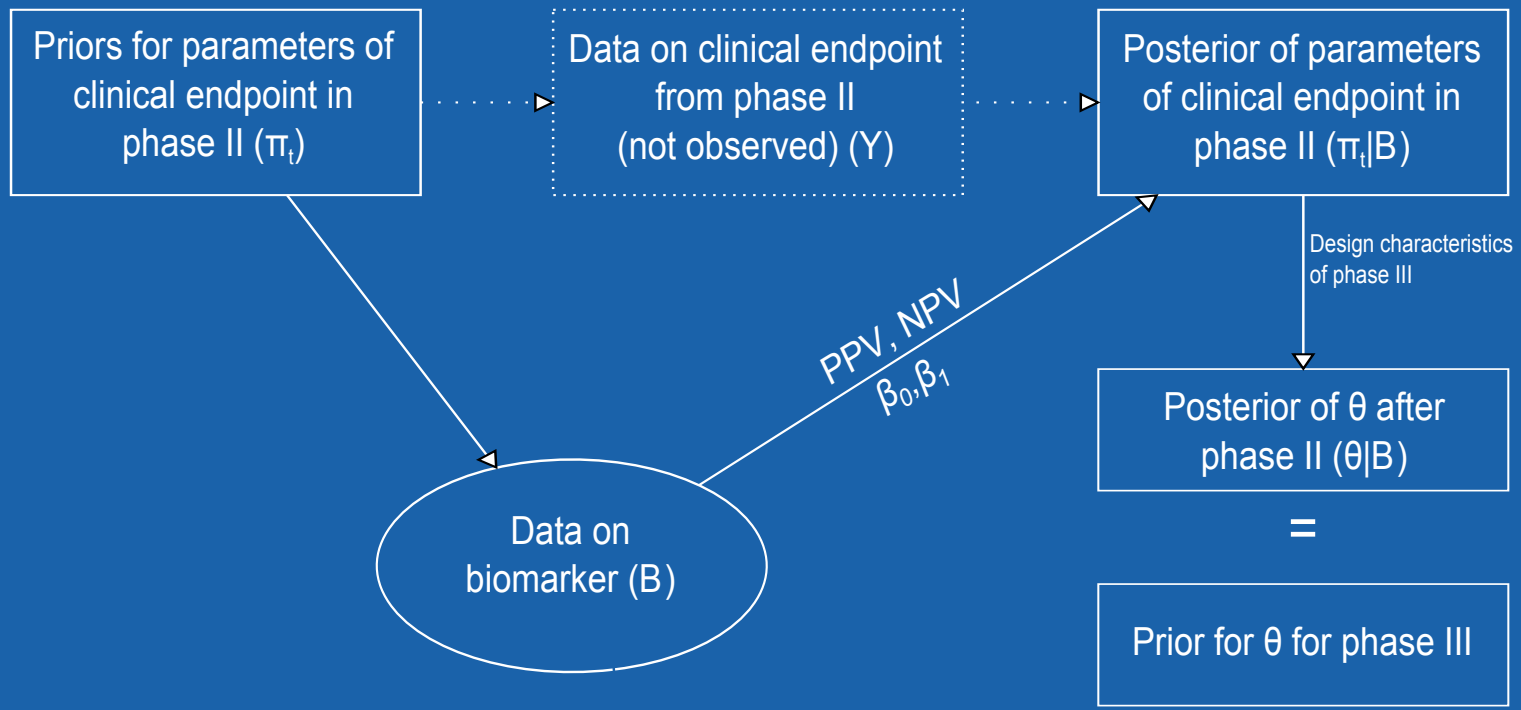

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Main Objective

Posterior distribution for CEI after Phase II, based on the biomarker data

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- If Y_t^{II} total number of successes on **binary** CEI is observed, $\pi_t^{II} | Y_t^{IIobs} \sim \text{Beta}(\alpha_t + Y_t^{IIobs}, \beta_t + n_t^{II} - Y_t^{IIobs})$
- Parameters of posterior Beta distribution have a direct interpretation
- Translating the successes on a biomarker into posterior parameters for the CEI is informative for decision making

From biomarker data to posterior of CEI

Combining biomarker data and predictive accuracy

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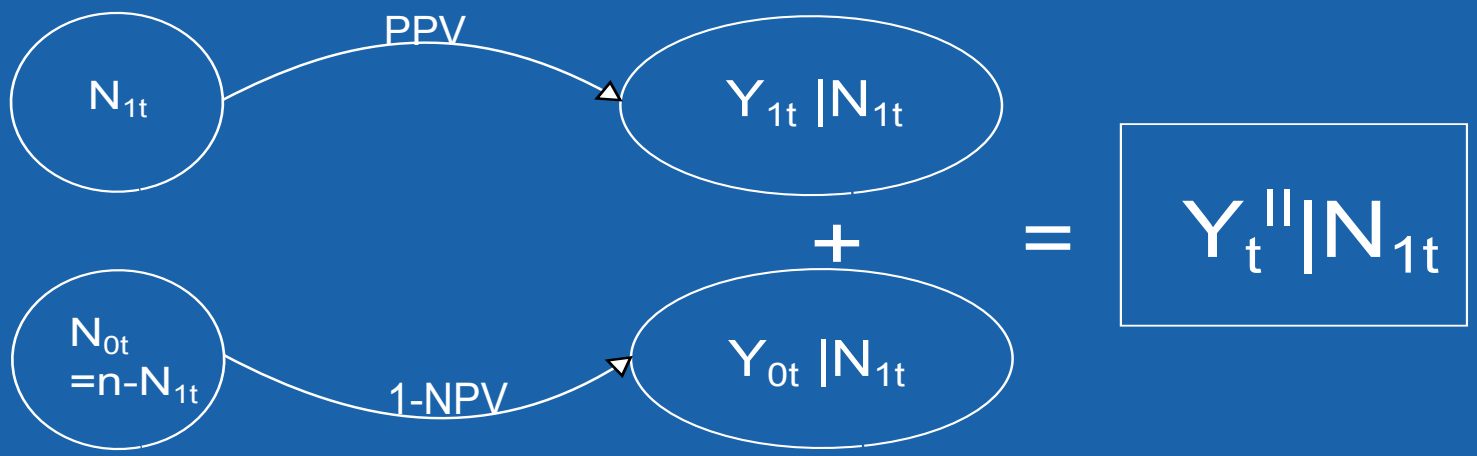
- For every success or failure on the biomarker, the probability of success in the CEI is known
  - PPV and NPV are treated as known and fixed

N_{1t}= # successes on biomarker
N_{0t}= # failures on biomarker



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From biomarker data to posterior of CEI

Approximate posterior Beta distribution

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- Distribution of $\pi_t^{II}|Y_t^{II}$ is known (Beta)
- Distribution of $Y_t^{II}|N_{1t}$ is known (Poisson-Binomial)
- Distribution of $\pi_t^{II}|N_{1t}$ is approximately Beta(γ, δ)
  - Parameters estimated by the method of moments
- Distribution of log(OR) ($\theta|N_{1t}$) will be approximately N(θ^*, τ^2)

Beta parameters

Translation of biomarker results and predictive accuracy

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γ and δ parameters of suggested Beta distributions for several scenarios, when prior parameters $\alpha = \beta = 1$ are used.

		PPV and NPV (equal)					
		0.50		0.75		1	
Sample size (n)	successes (n_1)	γ	δ	γ	δ	γ	δ
$n = 30$	n_1=3	8.0	8.0	5.4	11.8	4.0	28.0
	n_1=9	8.0	8.0	7.3	10.7	10.0	22.0
	n_1=15	8.0	8.0	9.2	9.2	16.0	16.0

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NE trial

Choosing a biomarker for primary outcome

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- Phase II study criteria
  - 80% power to detect a clinically relevant effect at a 10% one-sided significance level
- TTNT more appealing to show a significant effect with a smaller sample size
  - TTNT requires 46 patients per group while MRI 82 (62% power with 46 patients)
  - TTNT has also higher predictive accuracy

NE trial

Probability of a successful Phase III for assumed effect sizes

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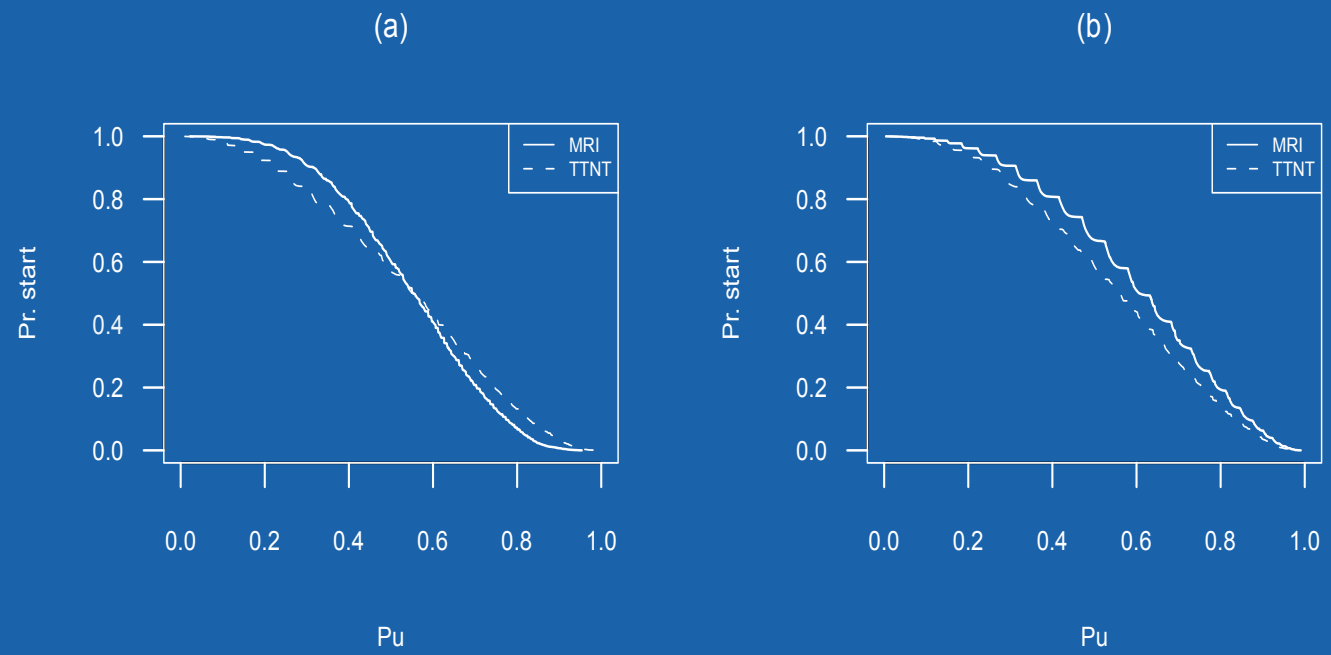
- Two scenarios studied, assuming 46 patients per treatment arm
  - (a) published $PPV_{(I)}$ and $NPV_{(I)}$
  - (b) equal $PPV_{(I)}$ and $NPV_{(I)}$=0.92



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Discussion

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- Expanding Stallard et al.'s (2005) methodology - different endpoints
- Data and predictive accuracy of biomarker are combined and quantified
- Biomarker's predictive accuracy should be substantially high
- A decision framework for jointly designing the two phases - allocation of resources

References

Stallard, N., Whitehead, J., and Cleall, S. (2005). Decision-making in a phase II clinical trial: a new approach combining Bayesian and frequentist concepts. *Pharmaceutical Statistics*, 4:119- 128.

Thank you