Simulating Adaptive Dose Finding Designs

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PSI Meeting on Modelling and Simulation

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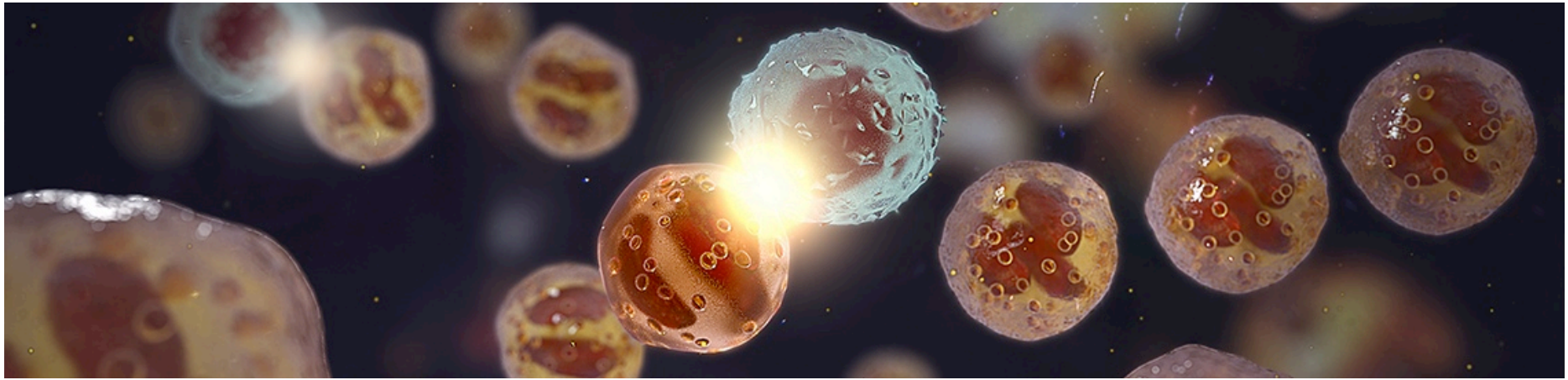
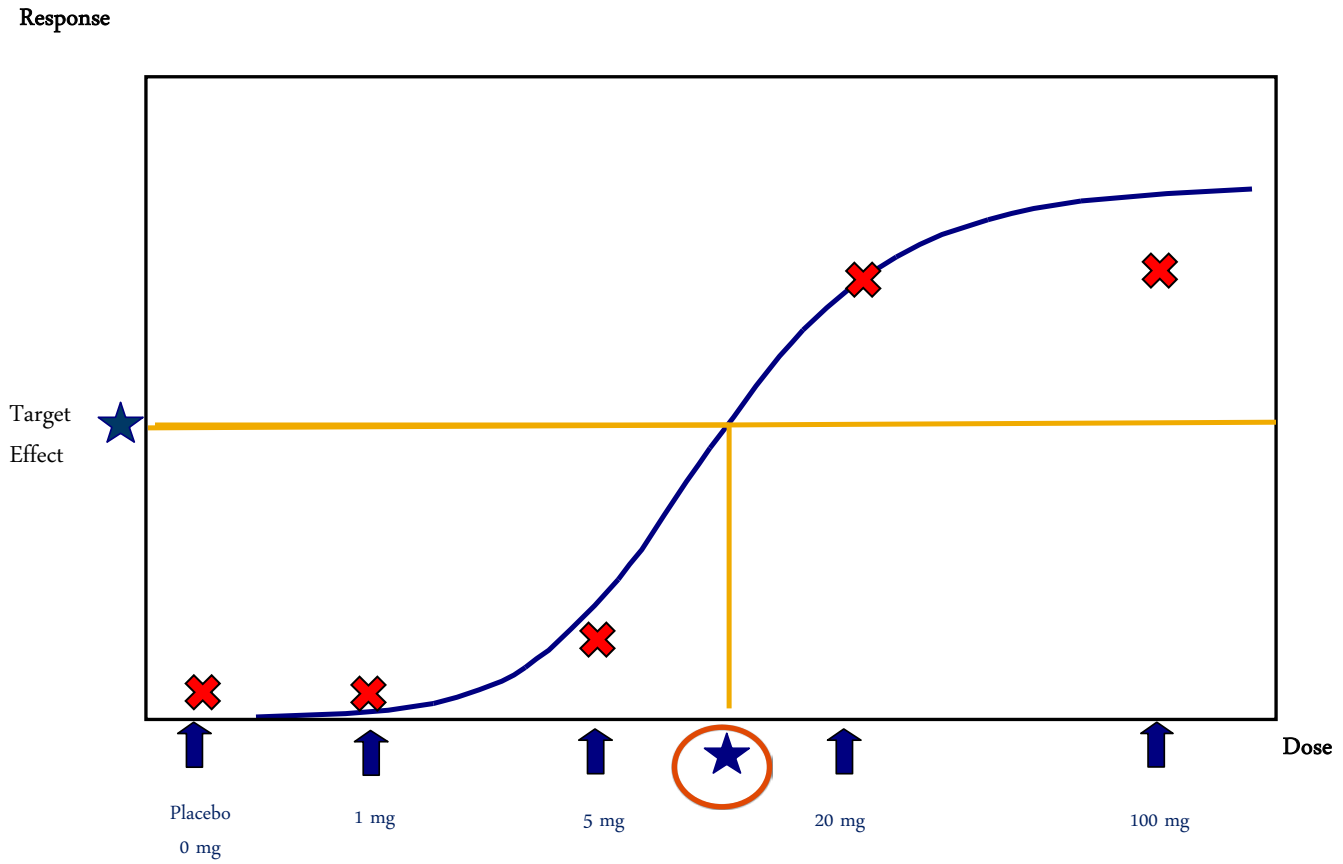


Outline

- Metrics from an adaptive dose finding design
- Example 1 – Respiratory
- Example 2 – Infectious Disease
- Example 3 – Ulcerative Colitis
- Conclusions

Dose Finding



Some Suggested Metrics for Adaptive Dose Finding

Key Metrics	Purpose
Mean number of subjects in the trial	Quantify benefits of stopping for futility or early success
Proportion of outcomes: • Early or late success • Early or Late futility	High level characterization of the expected outcome for the dose-response scenario.
Proportion of time each dose is selected as a target (e.g. target is EDx, MED, Dmax)	For a given dose-response scenario, these proportions may be assessed against the "correct" selection (e.g., which dose is the true MED)
Mean number of subjects per dose	Assess how the adaptive allocation assigns subjects to address the research question (e.g., to find MED)
Mean (standard deviation of) response at each dose	Assess the accuracy of the dose-response estimation
Bias and Root Mean Squared Error of response at each dose	Assess the accuracy of the dose-response estimation
Mean probability of clinically significant difference for each dose	Quantifies the predictive probabilities of achieving a pre-specified treatment effect over control
Predicted probability of achieving statistical significance in Phase 3 for a given design	Quantifies the chance of being successful in a Phase 3 trial with a given number of subjects and required significance level, assuming the same treatment effect as the one observed in the current study.

Example 1 – Respiratory

Example 1 - Respiratory

- A Phase IIb study in the treatment of moderate or severe asthmatics
  - Determine the minimum efficacious dose
  - Gain an understanding of the dose response

- Can we use a flexible design in this situation?
  - Increase the chances of a successful trial
  - Reduce the chances of a failed study
  - Increase the probability of stopping a poor drug early

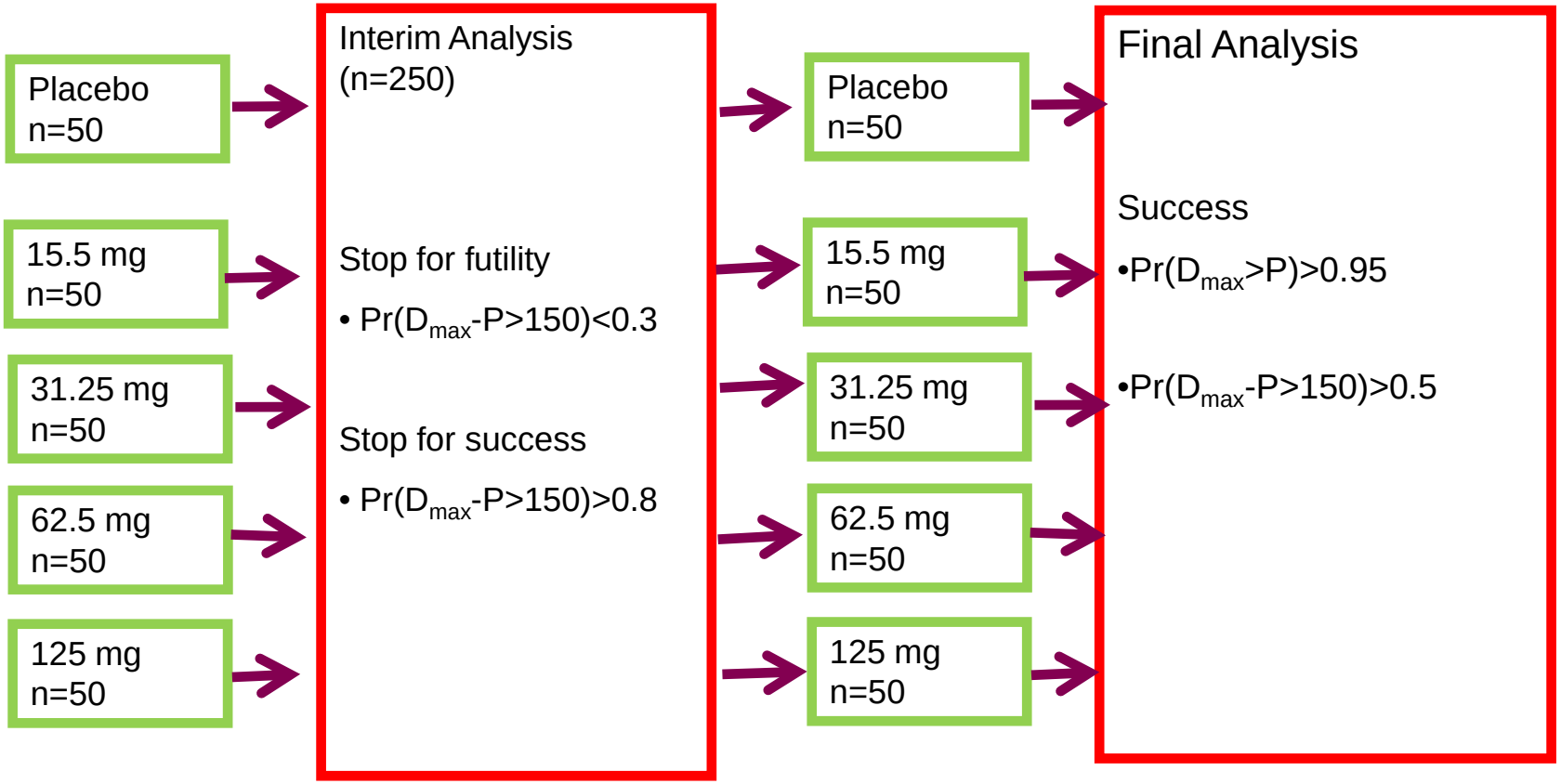
Study design

- Single dose, placebo controlled, parallel group
- Primary endpoint of FEV1 – Objective to find a dose which gives an increase in FEV1 of 150 mL (SD – 350 mL)
- Placebo response = 100 mL
- Decisions to be made using Bayesian probabilities - Pr(D-P) > 150
- Maximum number of subjects to be recruited – 500
- Time of endpoint – 7 days
- Recruitment rate – 5 patients per week
- Study already conducted in COPD suggests that doses – 15, 30, 60, 120 mg should be sufficient to characterise the dose response curve

Non-Adaptive Design Sample Size

Design	Total N	Power for Superiority of Dose vs Placebo		
		Pairwise Comparisons	Emax model	Linear model
5 Trt Parallel Group	500 (100/arm)	0.86	0.90	0.94

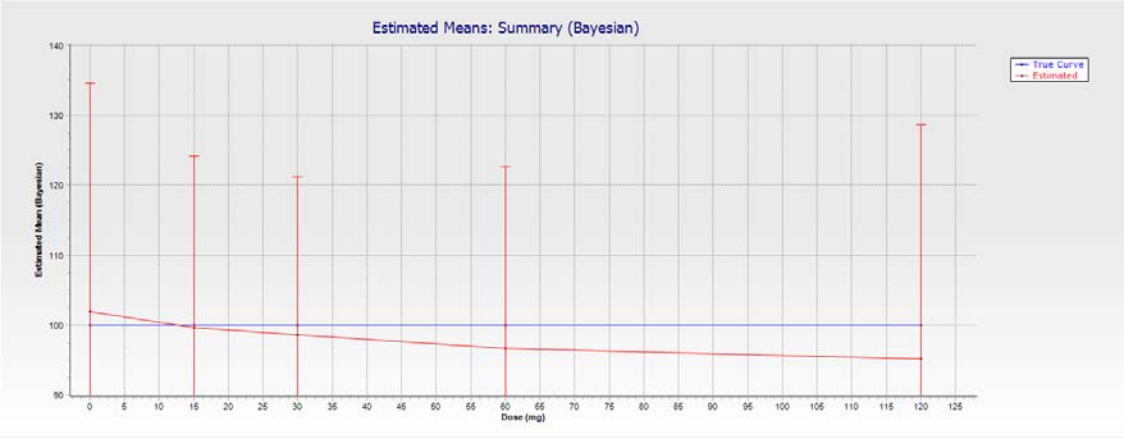
Design Details

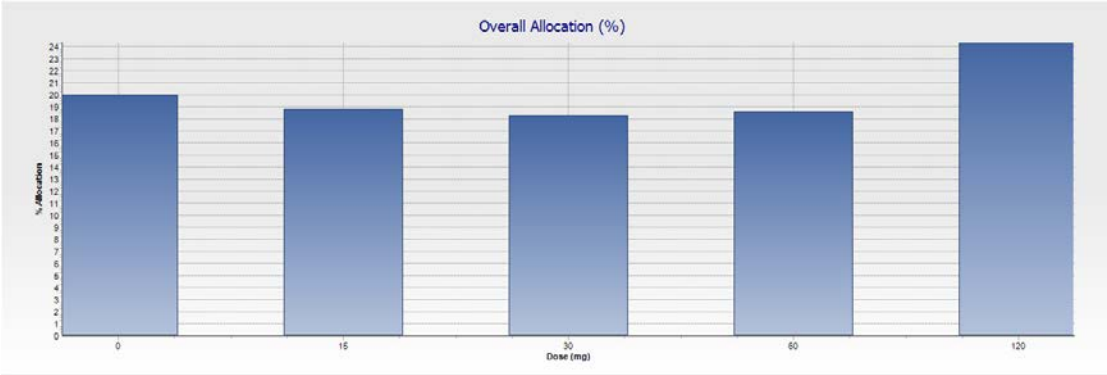


Inputs to the simulations

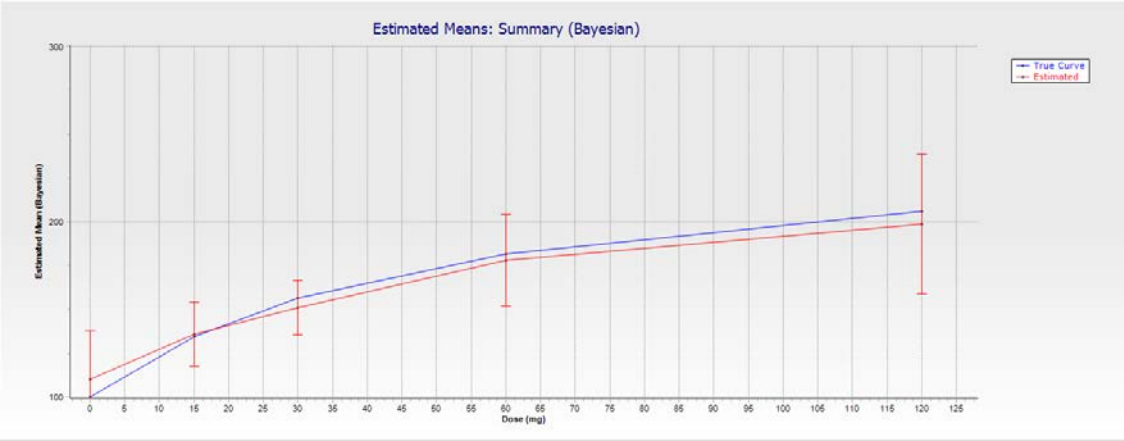
- Model for the dose response – E_{max}
- Prior information
  - Use of non-informative prior makes it equivalent to the frequentist analysis.
  - Bayesian analysis allows us to use the correct probability statements
- Scenarios
  - Null – all doses have the same effect as placebo
  - Monotonic dose response with low response at high dose
  - Monotonic dose response with very high response at high dose

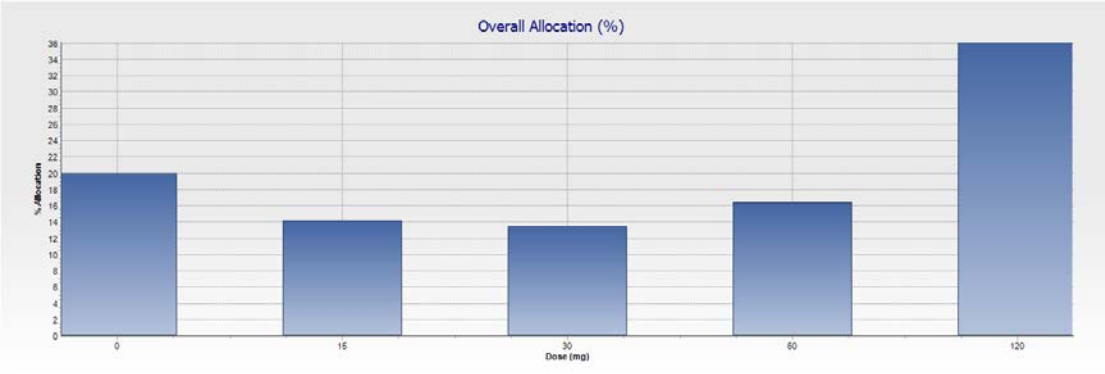
Simulation Results – Null





Simulation Results – Low Effect





Simulation Results – Very High Effect

Simulation Results

Simulation Scenario	Average Sample Size	Trials stopping for futility (%)	Trials Stopping for Success (%)	Trials Declaring Success (%)	Average Duration of Trial (weeks)
Null Effect	275	90	0	4	56
Low effect	408	32	5	52	83
Very large effect	365	1	53	95	74

Non-adaptive – n = 500, power = 90%, alpha=0.05, duration = 121 weeks

Conclusions from the simulations

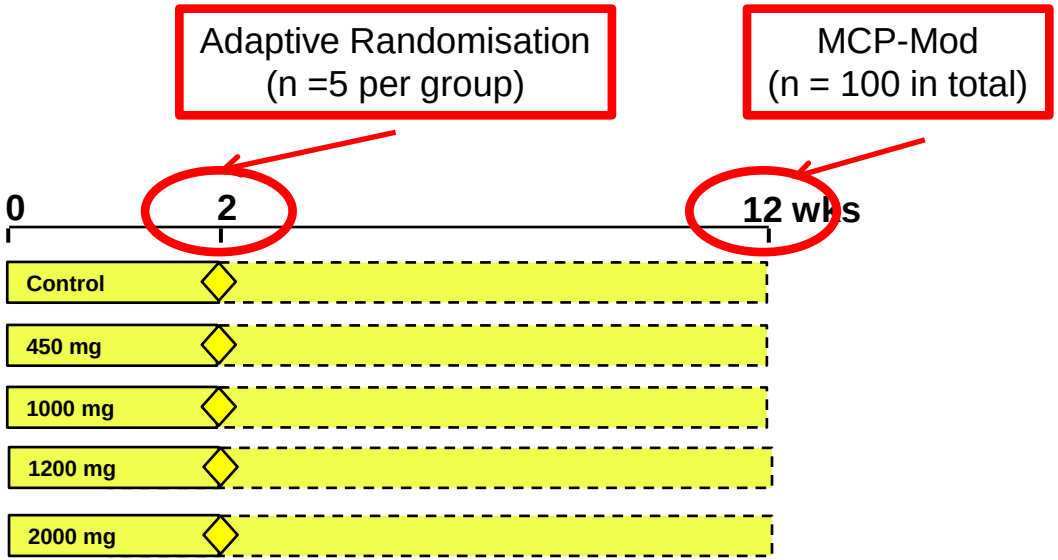
- Adaptive design performs as well as the fixed design but:
- Less subjects
- Shorter duration
- If drug does not work then stops early – fixed design cannot
- If the drug does work then can stop early as well – fixed design cannot
- Be careful with curtailment – might be biased by early responses

Example 2 – Anti-Infectives

Phase 2b Adaptive Design in Anti-Infectives

- Objective is to find a dose which gives a 0.5 decline in log viral load
- Five treatments – 4 doses and control
- 100 total subjects
- Adaptive randomization after n=5 according to week 2 DNA decline
- MCP-Mod analysis for dose-response curve at the end of week 12 based on viral load (n=20)
- Assume that the DNA decline at week 2 is predictive of the viral load at week 12 and that the dose response is similar

Phase 2 12 Week Patient Study



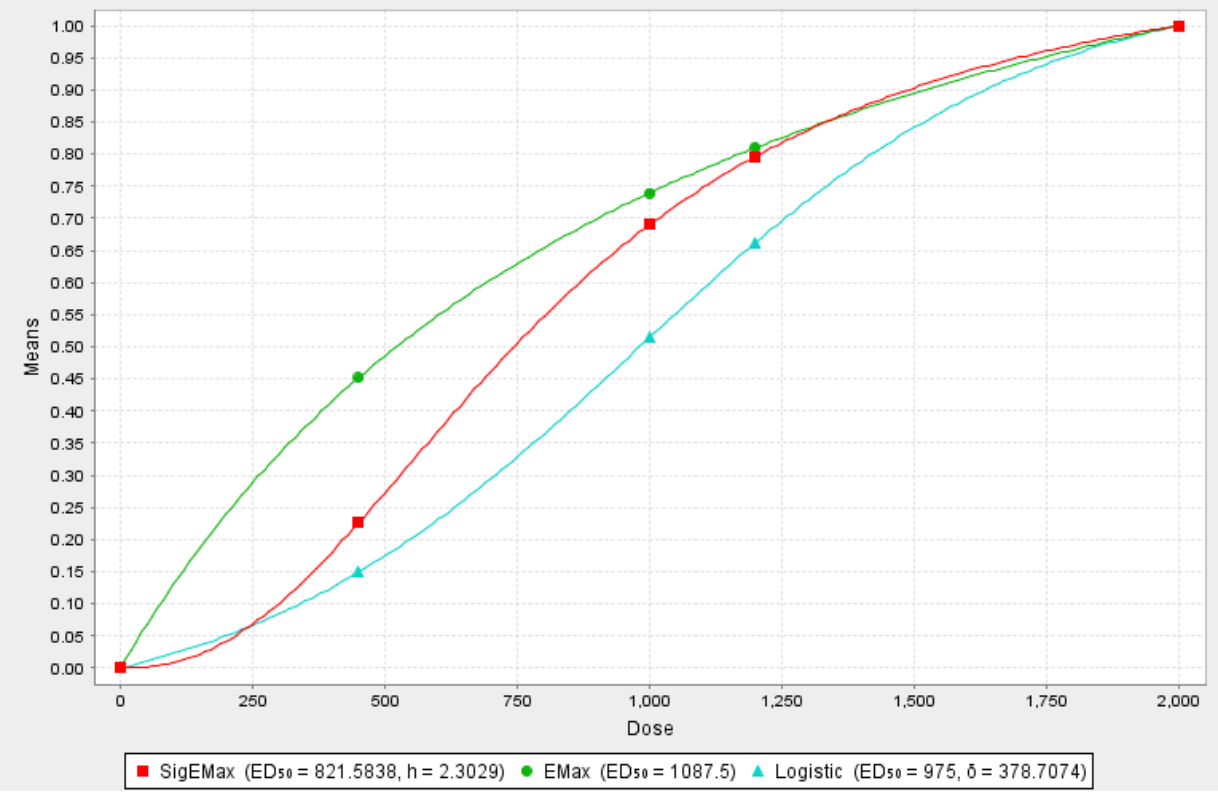
Assumptions

- **Adaptive Randomisation at Week 2**
    - Target Log DNA decline: 0.5
    - SD: 0.5
    - N = 5 is adequate to characterise the dose response curve and choose the optimal doses for stage 2
    - Assume a number of potential response shapes and optimise on those
- **MCP-Mod at Week 12**
    - Target Log viral load decline: 0.5
    - SD: 2.5
    - Total N = 100

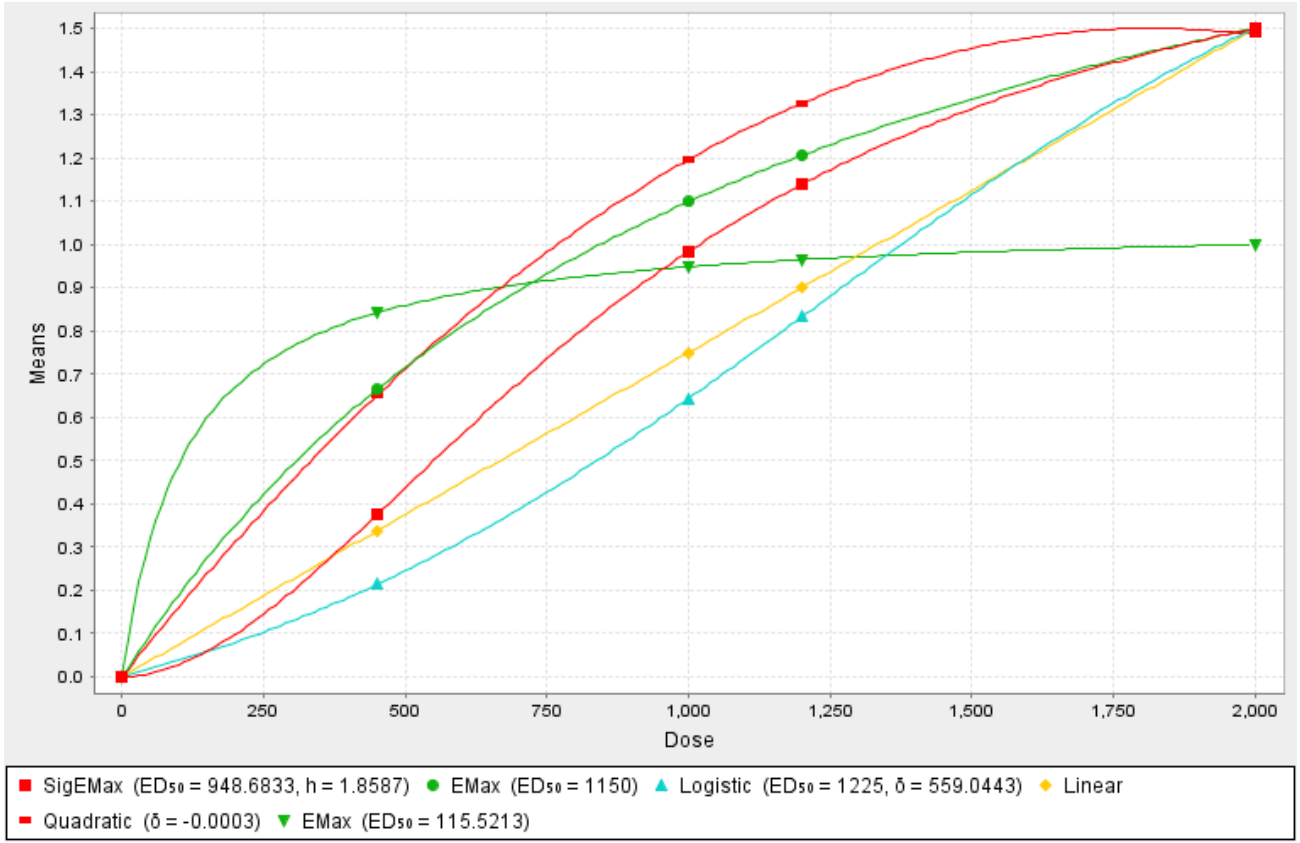
Compare Three Approaches

- MCP-Mod Only
  - No adaptation and equal randomisation
  - Analysis at the end of the study using MCP-Mod
- Optimal MCP-Mod
  - Interim carried out at 5 subjects per group and then use D and C Optimality to determine the randomisation of the next subjects
  - Analysis at the end of the study using MCP-Mod (even though you have a good idea of the dose response)
- Adaptive Design – Best Intention
  - Interim carried out at 5 subjects per group
  - Allocate remaining subjects according to what dose has the highest probability of being the target dose.
  - Analysis at the end Bayesian Pr(delta > 0)
- Then for interest compare to Dunnett contrasts and model based contrasts

Candidate Models for MCP-Mod



Assumed Response Shapes



Sample Sizes for Each Dose Under the Three Designs – Maximum Sample Size = 100

Design	Control	450 mg	1000 mg	1200 mg	2000 mg
MCP-Mod	20	20	20	20	20
Optimal MCP-Mod	31	27	9	16	17
Best Intention	34	11	8	9	38

- Do we want/need equipoise?
- What is our objective in Phase II – find appropriate dose for Phase III and optimise shape of the dose response curve

Power Under the Three Designs (and Dunnett or Model Based Contrasts)

- Power – to detect at least one dose significantly different to placebo at the 10% significance level

Design	Power	Type I error
MCP-Mod	80%	11%
Optimal MCP-Mod	84%	11%
Best Intention	81%	9%
Dunnett	71%	10%
Model Based Contrasts	80%	10%

Not the whole story – find a dose which gives log viral decline of 0.5

Design	P(Correct)
MCP-Mod	90%
Optimal MCP-Mod	92%
Best Intention	72%

Message

Not much to choose between MCP-Mod and optimal MCP-Mod or model based and optimal model based.

Better than best intention

Pairwise tests cannot estimate the true dose !!!!!!

And What About the Model Fit

Design	MSE
MCP-Mod	0.1946
Optimal MCP-Mod	0.1907
Best Intention	0.3452

Message
Not much to choose between MCP-Mod and optimal MCP-Mod or model based and optimal model based.

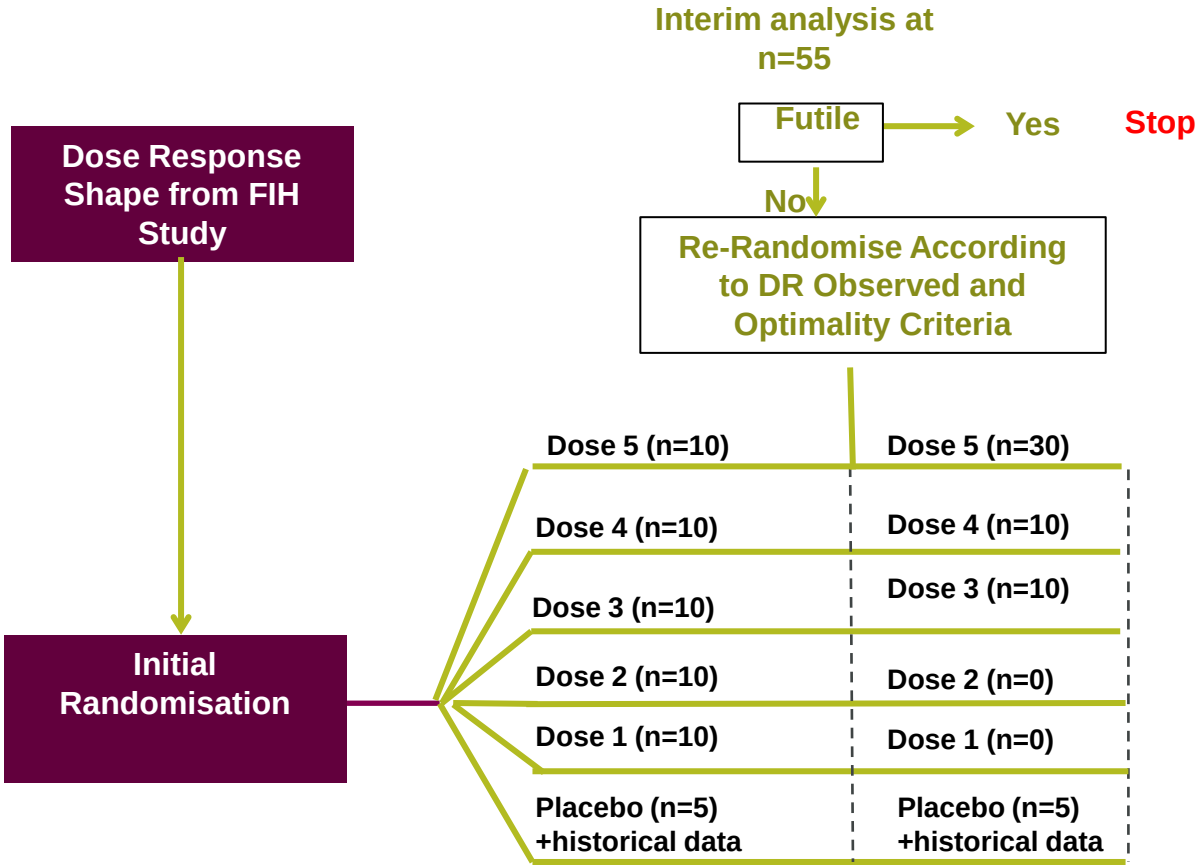
Better than best intention

Example 3 – Ulcerative Colitis

Dose Finding Phase 2b Trial

- Adaptive two stage design with a single dose compared to placebo (plus historical data).
- 5 doses versus placebo – 12 weeks dosing followed by 8 follow-up
- The primary endpoint will be proportion of patients in clinical remission at week 12.
- Clinical significant effect is 30 percentage points above placebo, assuming placebo rate is 10%
- N = 110 with 2:1 randomisation ratio (active:control).
- Historical data will be used to enrich the control arm.
- An interim analysis will be conducted once 55 patients reach week 12.
  - The study will stop for futility if Pr(Difference ≥30%) <0.1 for all doses.
- At the end of the study success will be declared if:
  - Success will be declared if Pr(Difference ≥30%) > 0.7
  - Futility declared if Pr(Difference ≥30%) <0.1 for all doses

POC/DF Design

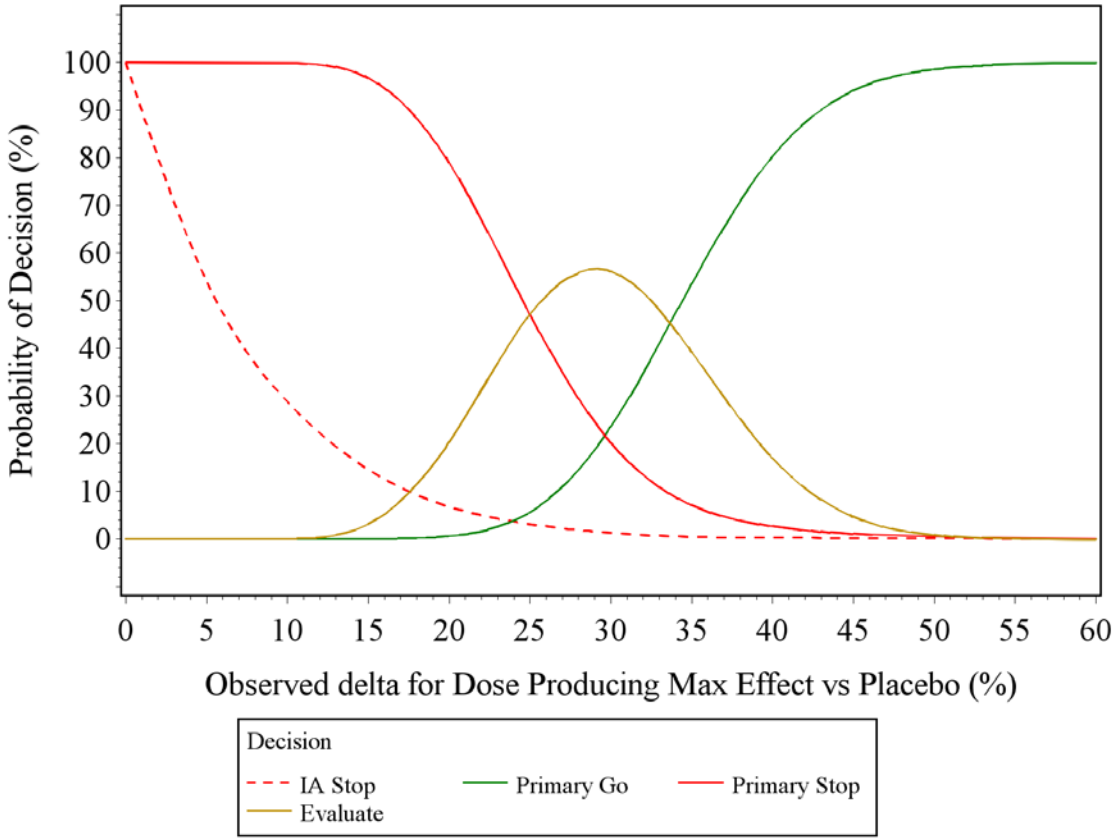


Statistical Assumptions and Decision Criteria

- Historical placebo are exchangeable with trial placebo
- Prior dose response shape for the clinical endpoint assumed to be similar as that for PD endpoint in the FIH study
- Randomisation following interim determined by stage 1 dose response with patients being randomised to most informative doses using a combination of C and D-Optimality and fixed rate allocated to placebo.

	INTERIM ANALYSIS N=55	FINAL ANALYSIS N=110
DECISION CRITERIA	No Go – Pr(Δ ≥30%) <0.1 for all doses.	Go - Pr(Δ ≥30%) > 0.7 Otherwise evaluate No Go – Pr(Δ ≥30%) <0.1

Plot of Operating Characteristics



Conclusions

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- Simulation is imperative with adaptive dose finding designs to understand the operating characteristics.
- Remember what is important may not significance or power in the true sense but more probability of making the right or wrong decision.
- Make sure you run adequate number of simulations and explain the assumptions under which the simulations are run.

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