Case studies of Bayesian adaptive designs using various amounts of prior information

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Synposis

- Previous examples / experiences
- New examples / building on past experiences.
- Conclusions / Discussion.

Previous examples:

- **ASTIN**
  - Stroke
  - Very little prior information
  - Adaptive design, finding optimal dose for next subject.
  - Normal Dynamic Linear Model (NDLM).
  - Phase III-esque.

Reference:

Berry, D., Mueller, P., Grieve, A., Smith, M., Parke, T., Blazek, R., Mitchard, N., and Krams, M. (2001). Adaptive Bayesian designs for dose-ranging drug trials. In *Case Studies in Bayesian Statistics, Volume V*, (ed. C. Gatsonis, B. Carlin, and A. Carriquiry), pp. 99–181. Springer-Verlag, New York.

Previous examples:

- **PD-217,014**
  - Pain
  - Prior information on Placebo and active comparator.
  - Adaptive design at cohort level, dropping doses.
  - Normal Dynamic Linear Model (NDLM).

Reference:

Smith MK, Jones I, Morris, MF, Grieve AP, Tan K. (2006) Implementation of a Bayesian adaptive design in a proof of concept study. *Pharmaceutical Statistics*. **5**; 39-50.

Previous examples:

- New treatment versus existing treatment.
  - **Lots** of prior information on existing treatment.
  - Summarise using Emax dose-response model.
  - Calculate ED50 of new treatment compared to existing treatment (Relative potency).
  - Bias randomisation towards new treatment.

Reference:

Smith MK, Marshall S. (2006) A Bayesian design and analysis for dose-response using informative prior information. *J. Biopharmaceutical Statistics*. **16**; 695-709.

Building on past experience

- Example with little or no prior information.
  - “NDLM” with Poisson data = DGLM
  - Dynamic Generalised Linear Model.
- Example with some prior information but gaps in our knowledge.
  - Using what information we have
  - Using optimal design theory.
- Example with LOTS of prior information.
  - Do we even need to collect more data from the existing treatment or comparator?

Example with no prior information

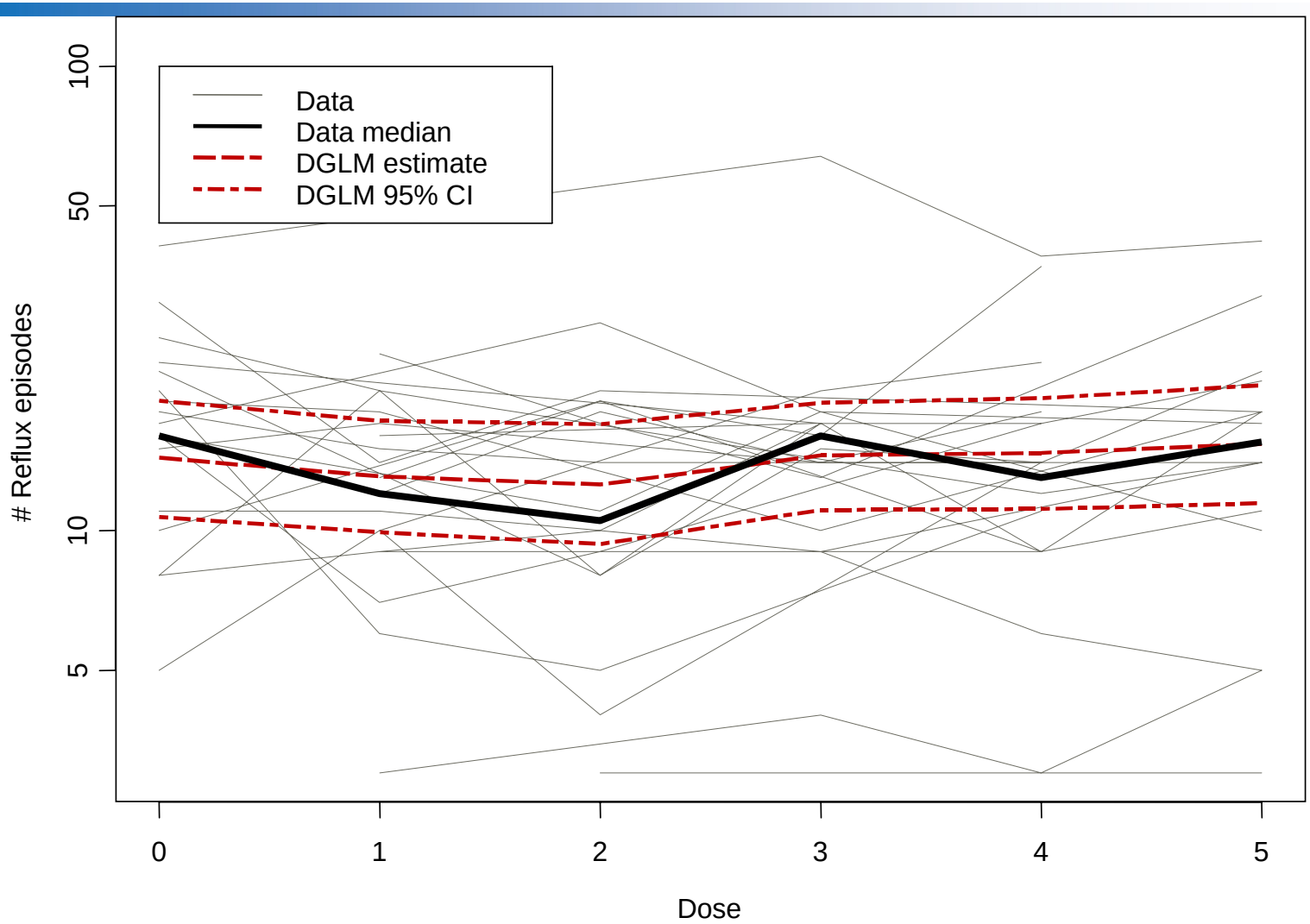
Setting

- New compound for Gastro-esophogeal reflux disorder (GERD).
  - Endpoint: # of reflux episodes (count).
- New mode of action.
- Preclinical results show promise, but little known of how this will work in humans.
- Some concern about the possibility of non-monotonic dose-response.

Methods

- Normal Dynamic Linear Model (NDLM) used in stroke, pain for continuous outcomes.
  - Flexible, data-driven smoother.
  - Allows for non-monotonicity.
- Dynamic Generalised Linear Model (DGLM) developed for count data.
  - Same basic structure.

DGLM results



Discussion

- Pros:
  - Flexible model.
  - Doesn’t need much prior information up front.
  - Few assumptions.
  - Doesn’t assume monotonicity.
- Cons:
  - No pharmacological meaning.
  - More doses than standard design.

Example with some prior information but gaps in our knowledge.

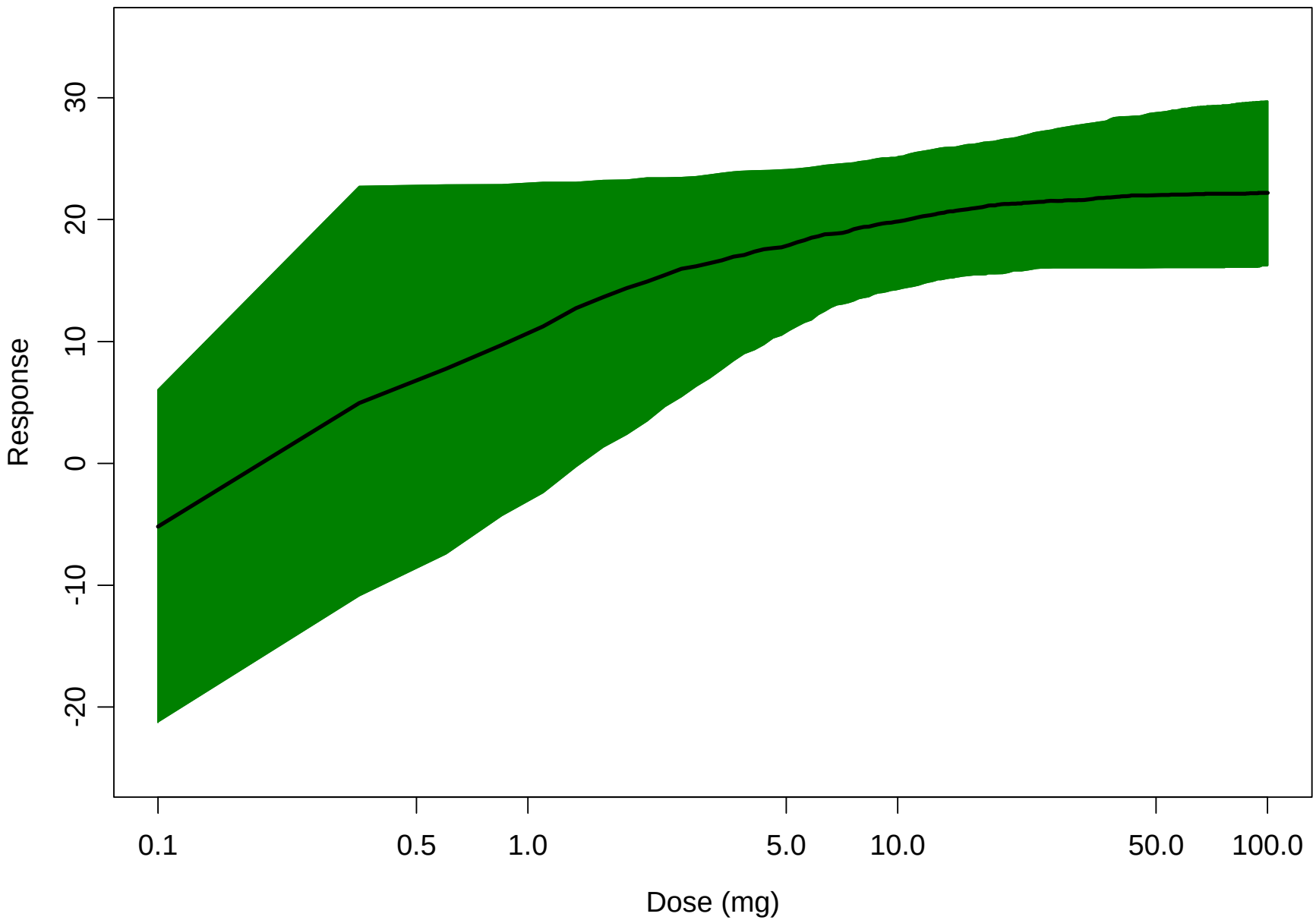
Prior information.

- Doses: 0, 3, 10, 30 & 100 mg
- 3 way XO
- 24 patients

- Now planning next Phase II study.

Model fitted to existing data

- Emax model fitted.
- E0 and Emax parameters well estimated.
- ED50 parameter not well characterised.
  - BUT we know what range it is in.
- Need to find design to better estimate this parameter.
- AND robust to model uncertainty.


Model fit ± 90 % C.I.
Response
30
20
10
0
-10
-20
0.1
0.5
1.0
5.0
10.0
50.0
100.0
Dose (mg)

Dosing options

- Fixed: PLAC & 75 mg
- Select 3 doses from:

1, 2, 3, 5, 10, 15, 20, 25 & 50 mg

(120 dosing permutations)

Dose-selection

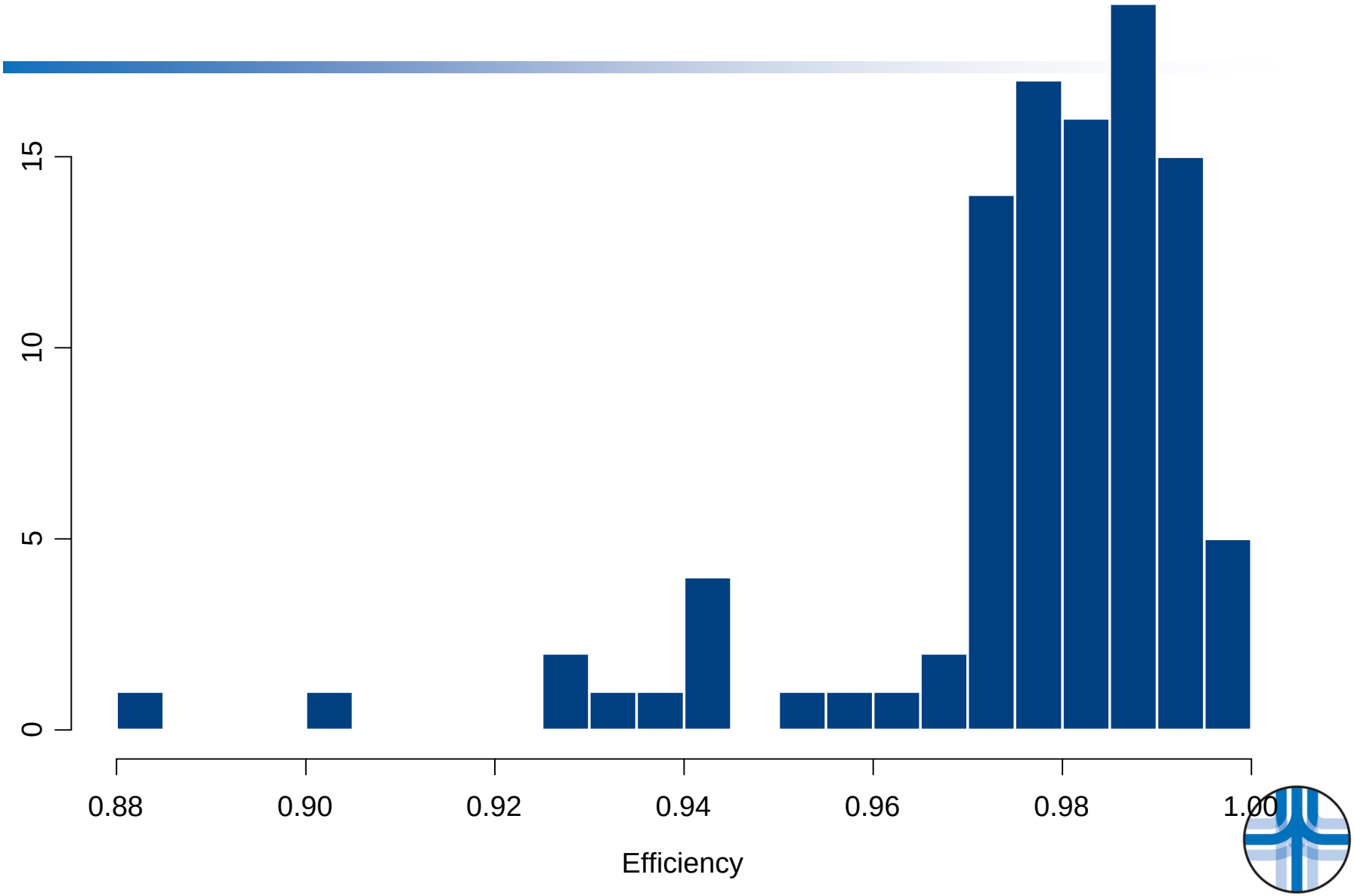
- For each dosing combination:
  - Add prior Ph IIa data
  - Use PFIM1.2 algorithm[1] to assess optimality criteria.
  - Select design which is most robust to model uncertainty.

[1] Retout & Mentré (2003). Optimisation of individual and population designs using Splus. *J. Pharmacokinet. Pharmacodyn.*, 30(6): 417-443.

Using D-optimality criteria (at MLEs)

FIX 1	D1	D2	D3	FIX 2	Criterion
0	**1**	**30**	**50**	75	5.51
0	**1**	**25**	**50**	75	5.49
0	**1**	**20**	**50**	75	5.47
0	**1**	**2**	**50**	75	5.46
0	**1**	**25**	**30**	75	5.45
….					
0	**25**	**30**	**50**	75	1.83

Across model uncertainty



Taking into account uncertainty

FIX1	D1	D2	D3	FIX2	Efficiency		
					5%	50%	95%
0	**1**	**30**	**50**	75	0.82	0.98	1.00
0	**1**	**25**	**50**	75	0.82	0.98	1.00
0	**1**	**20**	**50**	75	0.85	0.97	1.00
0	**1**	**2**	**50**	75	0.96	0.99	1.00
0	**1**	**25**	**30**	75	0.82	0.97	1.00
…							
0	**25**	**30**	**50**	75	0.03	0.36	0.57

Discussion

- Not used here in an adaptive trial…
- BUT could be used easily in a trial with a planned interim.
- Using formal optimality criteria for learning about model parameters rather than “dose effectiveness”.
- Assumes Emax function & monotonicity.
  - BUT D-optimality for any parametric model could be evaluated within PFIM.

Example with lots of prior information.

Lead to Backup development

- Lots of prior information on lead compound.
  - Phase II and Phase III efficacy.
- Developing backup
  - Same class of compound.
- Fitted Emax model to Lead compound.
  - Assuming same slope / Hill coefficient between lead and backup.

Model

- 3-parameter Emax model.

$$Response_i = E0 - \frac{(Emax * dose_i)}{((ED50x / RP) + dose_i)} + e_i$$

$$e_i \sim N(0, \sigma^2)$$

- RP = Relative potency
  = $ED50_{lead}$ / $ED50_{backup}$

Design

- VERY limited budget
  - Exploratory efficacy study for the backup compound.
- Don’t want to “waste” resources by restudying lead compound.
  - Objective endpoint / biomarker.
- Rely on prior information for lead compound.
  - Estimate relative potency for backup.
  - “Historical control” (!).

Designs considered

Scenario	Dose Levels for backup	Number of Subjects Per Dose	Total N
1	MEDIUM	6	6
2	MEDIUM	8	8
3	MEDIUM	10	10
4	LOW and HIGH	4	8
5	LOW and HIGH	6	12
6	LOW, HIGH and MTD	6	18

Simulations

- Simulations run accounting for uncertainty in model parameters.
  - Examine robustness of designs.
  - Look for bias, precision of relative potency estimate (given known “true” value).
  - Examine sensitivity to departures from assumptions.

Simulation results

Scenario	Dose Levels for backup	Number of Subjects Per Dose	%CV of ED50 estimate	Total N
1	MEDIUM	6	**76.2**	6
2	MEDIUM	8	**72.2**	8
3	MEDIUM	10	**70.5**	10
4	LOW and HIGH	4	**63.9**	8
5	LOW and HIGH	6	**59.4**	12
6	LOW, HIGH and MTD	6	**48.7**	18

Conclusions

- We can recover sufficient information from designs with less than 3 doses to fit Emax models (with 3 parameters).
  - Depends on level of confidence required.
- Relies heavily on informative prior information for certain parameters e.g. E0, Emax.
- Again, this study not run as adaptive, but it ***could*** be…

Discussion.

- **ASSUMPTION:** Nothing has changed since lead compound was developed.
  - If this assumption does ***not*** hold then AVOID this type of design!!
- If emerging data appear to be “different” from our prior experience then we ***should*** adapt to recover information about E0, Emax from the lead compound.

Conclusions

Conclusions

- Even a little prior information goes a long way…
- Especially in adaptive designs
  - Refining the dose-range as you go along.
  - Dropping doses.
  - Finding “optimal” design points.
  - Accumulating knowledge from the current trial.
  - Reusing information from previous compounds.
  - Efficient trial designs.
  - Adapting to salvage information when prior assumptions do not hold.

…And in practice?

- Adaptive designs are great at killing drugs.
- LOTS of examples where we stop early and conclude no effect.
- FEW examples where we find very positive outcomes early.