An adaptive design for dose-response using the Normal Dynamic Linear Model (NDLM)

Mike K Smith[1], Mark F. Morris[1], Ieuan Jones[1],
Andy P. Grieve[1], Keith Tan[2]

[1] Biostatistics and Reporting, PGRD Sandwich; [2] Clinical Sciences, PGRD Sandwich

Introduction

- Normal Dynamic Linear Models have been used in adaptive designs before at Pfizer.
  - ASTIN stroke trial
- There are often pragmatic reasons for simpler trial designs than fully adaptive ones.
  - Parallel group, equal allocation.
  - Usually preferred from the point of view of study conduct.
- We still want flexibility in modelling dose-response.
  - Potentially non-monotonic response.
  - Dropping ineffective doses
  - Terminating the study early due to futility.
- Suggested approach for a dose-response trial using a VAS numerical rating scale endpoint.

Model choice

- The NDLM has certain benefits as the dose-response model in this case:
  - It can easily handle a wide variety of possible dose-response curves, including non-monotonic relationships.
  - The dose-response may not be monotonic due to dropouts influencing change from baseline.
  - It is easily implemented in a Bayesian updating framework.
  - Within this framework it provides direct probabilistic statements about many features of the dose-response.

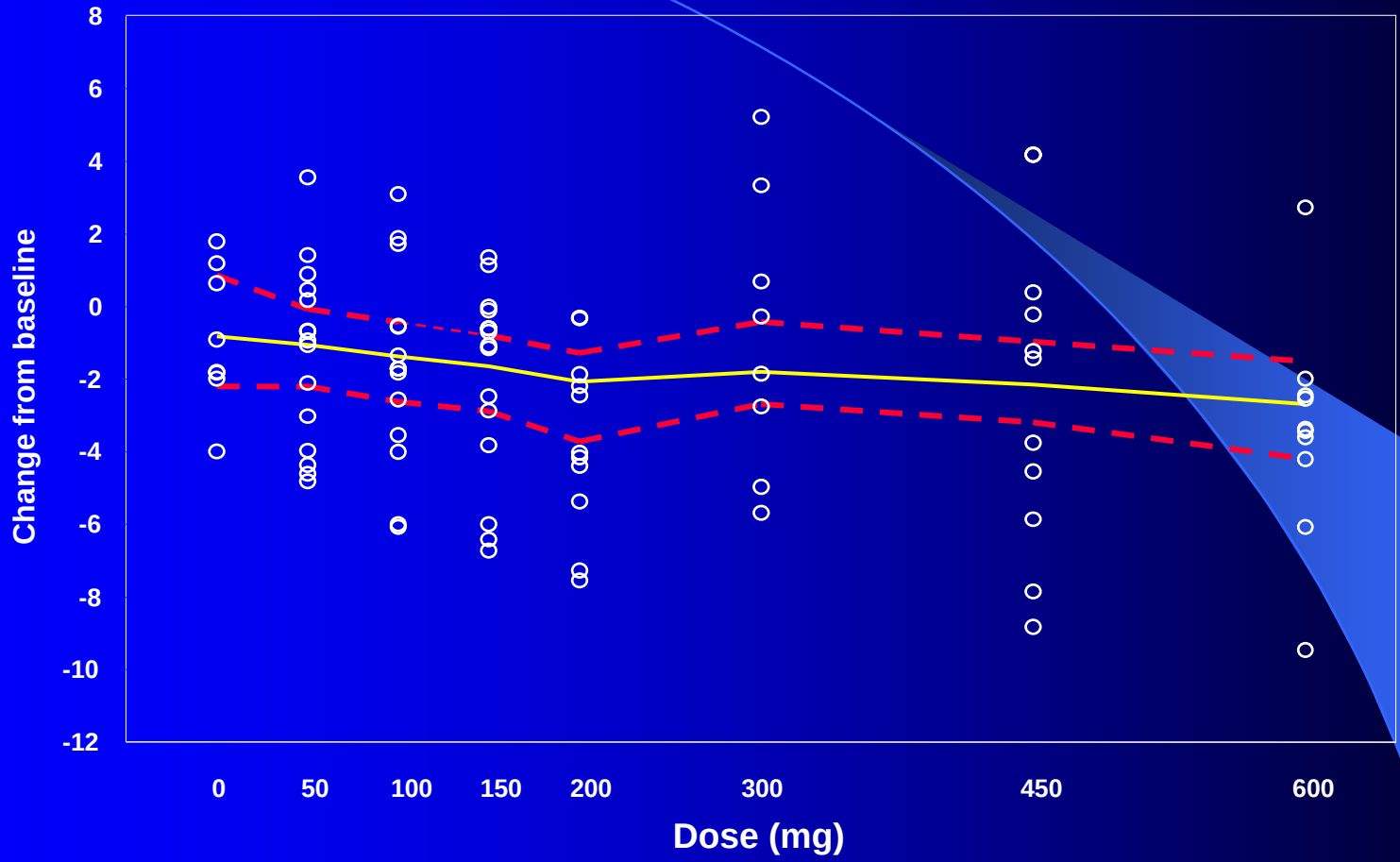
Study design and simulation

- Study objective is to find dose that gives 1.5pts improvement over placebo.
- Design:
  - 7 active doses + placebo + active comparator.
  - Parallel group
  - Equal allocation to treatments initially.
  - Interim analyses to drop ineffective doses or stop study.
- Study will run to completion as long as at least one dose shows 1.5pts improvement over placebo.

Study design and simulation

- Simulation performed to select criteria for dropping doses / terminating the study.
- When should the interim analyses be carried out?
  - Equally spaced?
  - First interim after 50% of subjects complete?
- Assess Type I error of the procedure.
- Assess the gains in efficiency over a standard parallel group study.
- Investigate across a variety of different simulated dose-response curves.
- NDLM implemented in WinBUGS v1.4 with data handling and manipulation in SAS.

Simulation results - NDLM



- NDLM characterises the underlying dose-response with interval estimates around the model estimates.

Simulation results – P(Futility)

- Probability of achieving <1.5pts difference over placebo at each dose.
  - i.e. Probability of futility = P(Futility).
- Drop two lowest doses with P(Futility) >0.8
- Highest doses show some evidence of an effect
  - P(Futility)<<0.8

Simulation results – # Interims

Simulation Scenario *Power (average n)*	0 (No dose response)	1 (Modest improvement)	2 (Clinically important improvement)
0 interims	0 (280)	0.42 (280)	0.83 (280)
1 interim	0 (156)	0.41 (247)	0.84 (265)
2 interims	0 (118)	0.42 (225)	0.81 (256)
3 interims	0 (97)	0.41 (209)	0.83 (249)

- P(At least one dose >1.5pts improvement)
  - If a clinically important effect exists, this is picked up in the study.
- 280 is maximum sample size if study runs to completion.
- Average n shows that if there is little or no effect the average sample size decreases
  - Stopping early, or dropping ineffective doses.

Simulation results – Cost savings

Simulation Scenario	0 (No dose response)	1 (Modest improvement)	2 (Clinically important improvement)
Average total sample size from simulations	118	225	256
Saving in sample size (vs. 280 randomised)	162	55	24
Financial Saving at ($3K/subject)	$ 486,000	$ 165,000	$ 72,000

- Direct cost savings can be made.
  - Indirect savings are greater: Reduced time to decision, reallocating resource to new candidates.

Conclusions

- A combination of flexible dose-response model and an adaptive design with interim analyses has been shown to be effective in simulations.
  - Good characterisation of the dose-response.
  - Useful inferences about effect at each dose.
- Real cost and resource savings are possible.
- Pragmatic and easily implemented design.
- Direct link between simulation framework (SAS / WinBUGS) and reporting system.
- Can easily be implemented in other projects and indications.