Modelling and Simulation in Adaptive Designs

Alun Bedding
Director, Biostatistics Development Partners

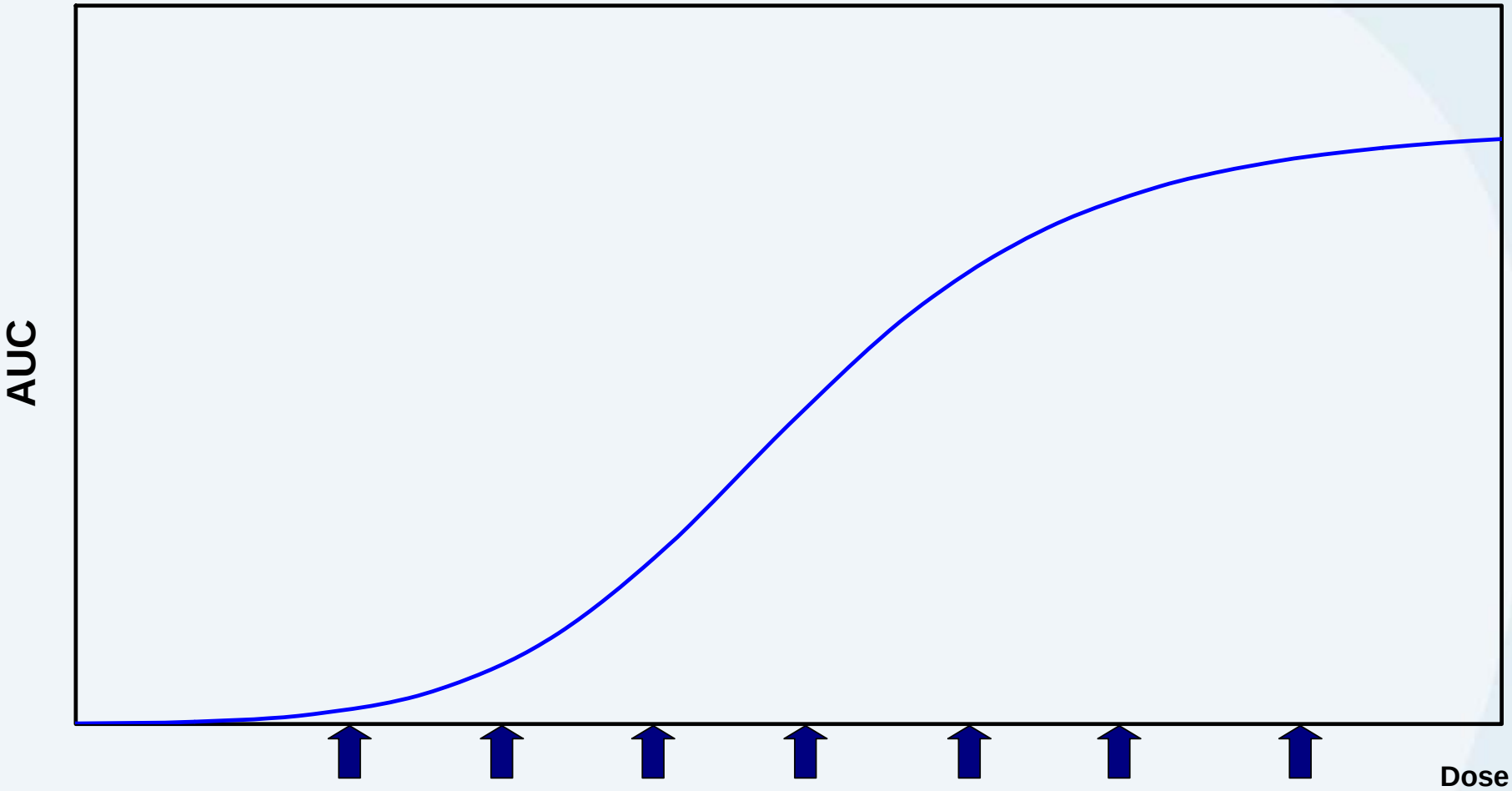
Outline

- Issues with typical dose response
- Definition of an adaptive design and possible adaptations
- Dose-escalation with
  - Single endpoint
  - Bivariate

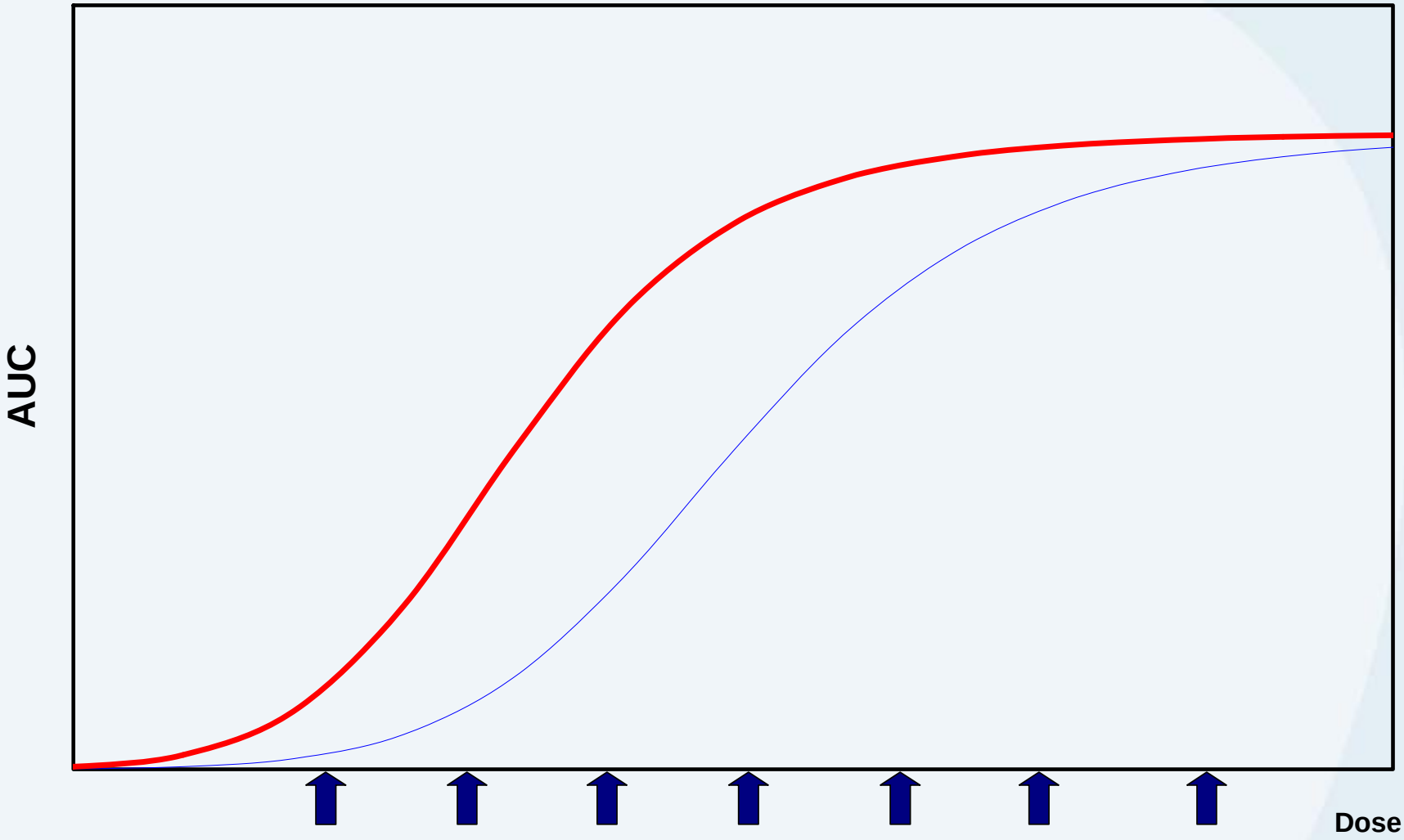
Goals of Drug Development

- Learn faster: More efficient trials
- More efficient drug/device development
- Better treatment of patients in clinical trials
  - Protect from un-safe medications

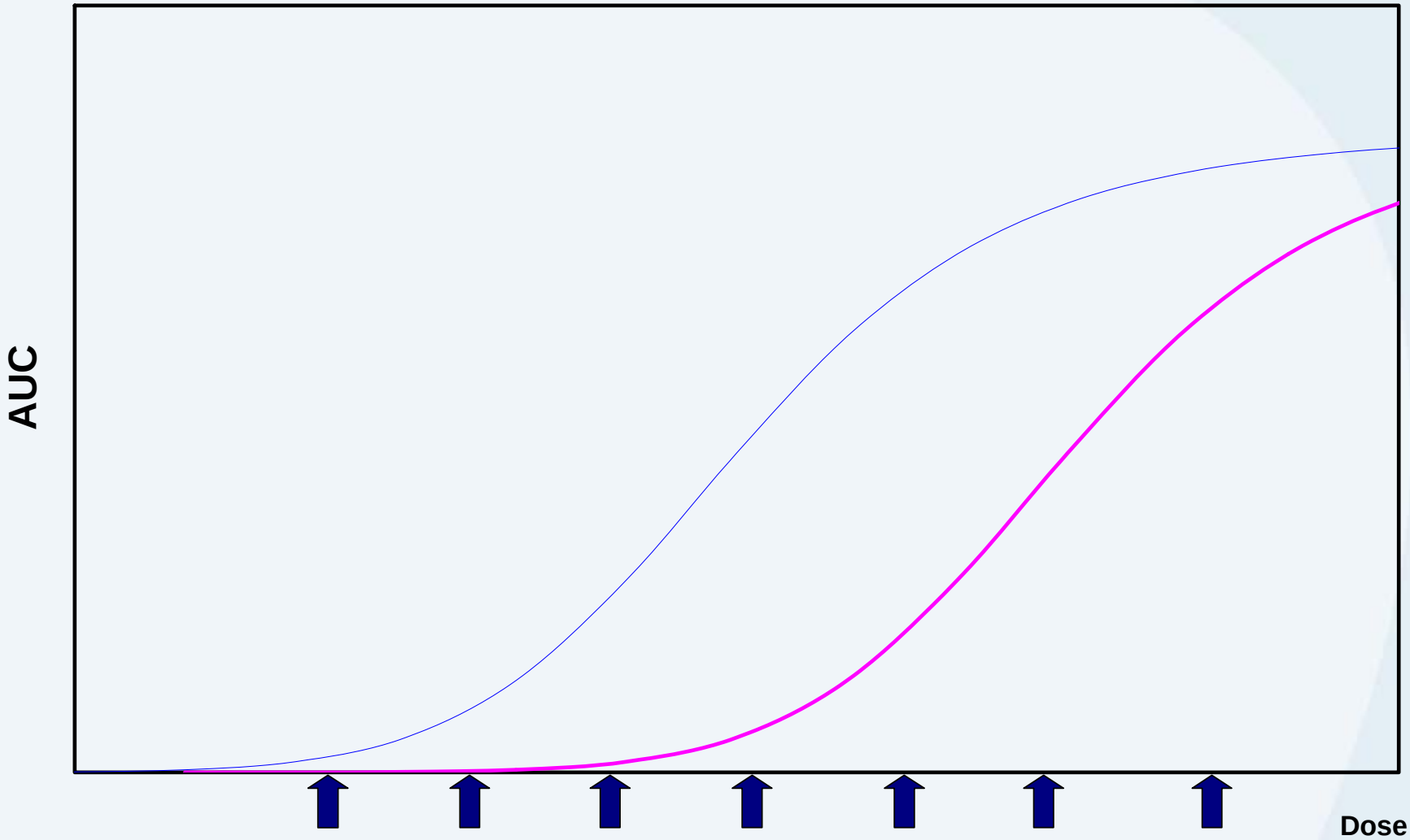
Dose/Exposure Curve



Dose/Exposure Curve – Safety Concern



Dose/Exposure Curve – Lack of Effect Concern



Definition of an Adaptive Design

- **<u>Adaptive Design</u> – any design which uses accumulating data to decide how to modify aspects of the study without undermining the *validity* and *integrity* of the trial.**
  - Should be adaptive by "design", not remedy for poor planning
  - Numerous types of adaptive designs
- More likely adaptations in Exploratory Phases
  - **Randomization**
  - Add/drop treatment arms
  - Sample size
  - Stopping development of a compound
  - Combine Phase I and II trials
  - Study hypotheses
  - Ordering of hypotheses
  - Primary endpoint
  - Study population

Ethical issues

- Efficient in terms of obtaining maximum information with as few subjects as possible.
- Subjects should be protected from highly toxic dose levels.
- Do not know what subjects are going to be getting before the study.
- State maximum dose.
- Pullman and Wang - Controlled Clinical Trials (2001)
  - Conclude that adaptive designs perform better ethically.
  - Adaptive designs are ethically justified in desperate medical situations.
  - In this situation may be morally required.

Healthy Volunteer Studies

- Whitehead et al "Easy-to-implement Bayesian methods for dose-escalation studies in healthy volunteers" *Biostatistics 2001*
- Conventional dose escalation design for first cohort:

Period	Subject 1	Subject 2	Subject 3	Subject 4
1	d_1	d_1	d_1	Placebo
2	d_2	d_2	Placebo	d_1
3	d_3	Placebo	d_2	d_2
4	Placebo	d_3	d_3	d_3

- Where d1<d2<d3
- Data collected for each dose and modelled.
- Can be used for binary or continuous endpoints
- Needs a model for dose-response or exposure-response
  - Linear, non-linear, non-parametric etc…..

Apply Bayesian Decision Theory

- Updating:
- In any given period, decision to be made as to which doses should be administered to three out of four subjects (fourth to receive placebo) based on current information about dose response
- Subject to dose being considered safe
- No pre-determined randomisation
  - Is this a problem?
  - We are trying to learn as much as possible

- First period - dose based on prior information or lowest possible dose
- Response observed – model fitted - optimal choice for second period.
- Use of a gain or utility function

Gain Functions

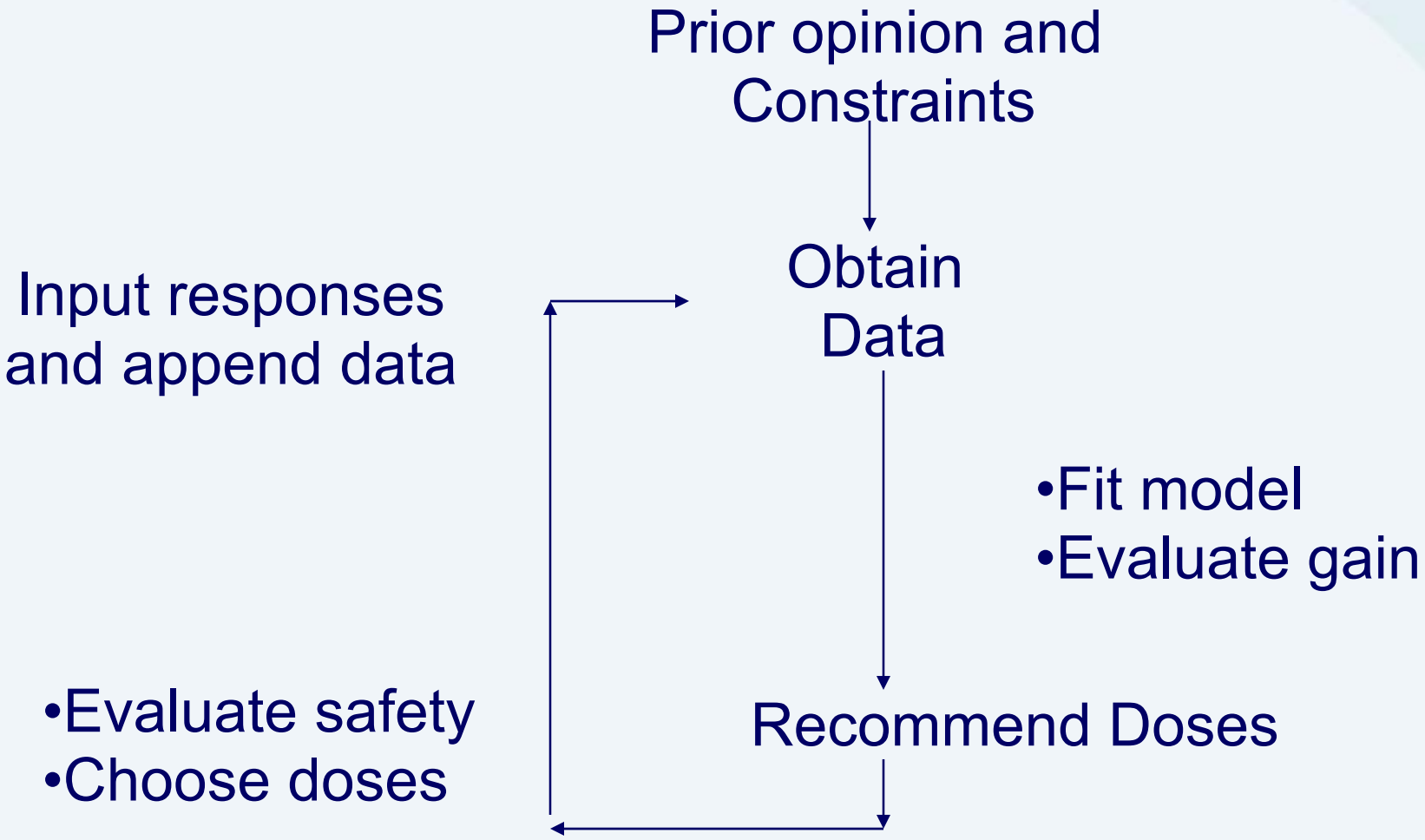
- Maxsafe
  - Simply treats each subject at the highest permissible dose given the safety constraint.
  - Gathers information about both the maximum dose and the response to it.
- Optsafe
  - Estimates the parameters in the model as precisely as possible.
  - Choice of doses which minimises the determinant of the variance-covariance matrix of the posterior distribution of the parameters.
- Variance
  - Minimises the variance of the estimate of interest

Safety constraint and Constrained Optimality

- Limiting level of response in Log AUC (L) such that values larger are considered undesirable.
- Allow the constraint that $\Pr(Y_{if} > L) \leq C_0$
- Where Y_{if} is the future response to dose d_f predicted from the fitted model in the adaptive design

- Predictive distribution provides safety criterion which d_f must satisfy before being considered.
- Then for those combinations allowable the one which estimates the slope and intercept most precisely will be recommended or treat with the highest dose allowable.
- Continue until all subjects/periods used or some other criteria around the estimates.

Computational flow of an Adaptive Design



First Human Dose Study

- Potential Doses in the Study: 2, 5, 10, 20, 40, 80, 120 mg
- Fit linear model to the data – Bayesian results:

  Intercept = -2.30

  Slope = 2.071

  W-S Variance = 0.19

  B-S Variance = 0.28
- Prior information from previous studies

  Dose - 2 10

  AUC - 1 9
- Safety cut-off: L=400, $\Pr(Y_{if} > 400) \leq 0.05$
- Sample size = 60

Study Data – Using Maxsafe

Cohort	Period	Dose, AUC								d^*_f
		Subject 1		Subject 2		Subject 3		Subject 4		
1	1	**2**	0.44	**2**	0.21	**2**	0.41	**0**		20.86
	2	**20**	71.27	**20**	78.03	**0**		**20**	24.67	20.14
	3	**20**	98.17	**0**		**20**	105.77	**2**	0.68	19.76
	4	**0**		**20**	18.07	**2**	0.47	**2**	0.43	22.26
		Subject 5		Subject 6		Subject 7		Subject 8		
2	1	**20**	40.51	**20**	13.85	**20**	39.12	**0**		26.67
	2	**2**	0.31	**2**	0.13	**0**		**2**	0.48	27.99
	3	**20**	37.52	**0**		**2**	0.39	**20**	24.70	30.44
	4	**0**		**40**	209.38	**2**	0.61	**2**	0.44	28.79
		Subject 9		Subject 10		Subject 11		Subject 12		
3	1	**20**	57.71	**20**	45.62	**20**	32.84	**0**		28.62
	2	**2**	0.77	**2**	0.22	**0**		**2**	0.87	29.80
	3	**20**	58.63	**0**		**2**	0.39	**20**	76.60	29.13
	4	**0**		**40**	496.62	**2**	0.47	**2**	0.65	29.50

Table of the maximum likelihood estimates

	θ_1	θ_2	τ^2	σ^2
Traditional	-2.34 (0.248)	2.074 (0.09)	0	0.313
Bayesian using maxsafe	-2.30 (0.180)	2.071 (0.06)	0.28	0.19

Applying to Multiple Endpoints

- Zhou et al (2006) - Bayesian Decision Procedures for Binary and Continuous Dose-Escalation Studies, Pharmaceutical Statistics
- Paper looks at a bivariate outcome
  - Dose limiting event (DLE)
  - Desirable outcome (DO)
- Looks at modelling based on a conditional idea
  - DO given no DLE
- Set of doses available for administration to successive cohorts
- Selection criteria – choose dose that maximizes therapeutic effects and minimizes side effects
- Gain – magnitude y of the DO without a DLE – let this equal y^*
- Give next cohort dose which is seen to maximise the expected value of y^*

Summary

- Adaptive designs are well-accepted in earlier phase exploratory development
- Can be used for binary, continuous or a combination of the two
  - With single endpoints trying to maximise a gain
    - What is the highest dose to give
    - Optimise the parameters of the model
  - With bivariate endpoints look at what dose(s) maximise the desirable outcome whilst keeping dose limiting event low?
- Caution
    - Needs planning – look at the operating characteristics
      - Type I and type II error
    - Think about drug supply
    - Make sure decision can be made quickly