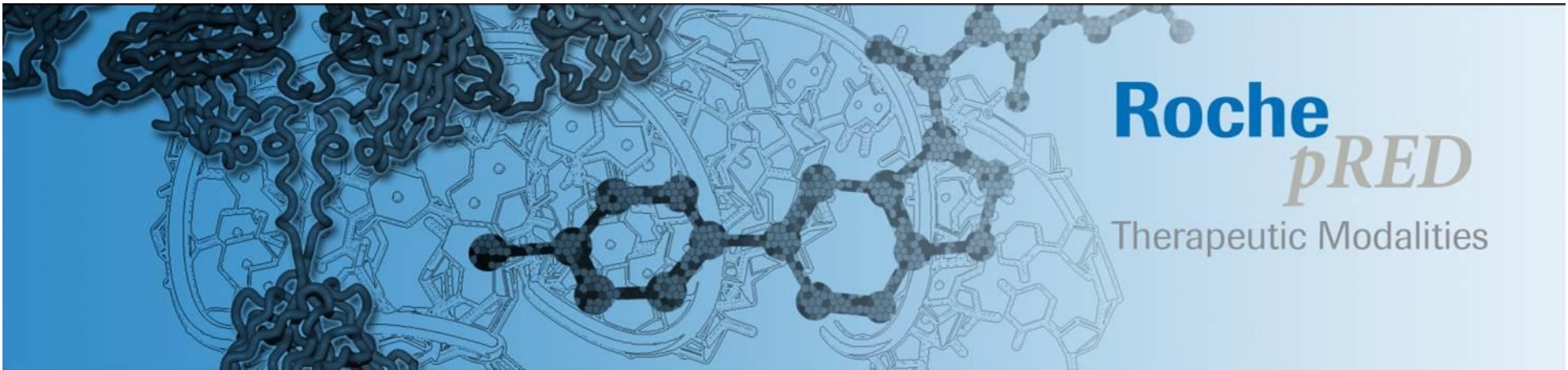
Design of First in Human Trials

Alun Bedding

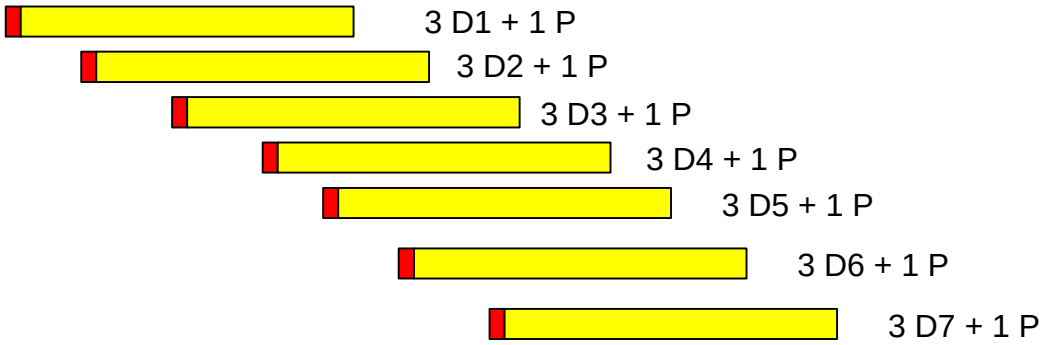


FIH - Introduction

- First time the drug is given to a human subject following extensive animal trials.
- Can be in healthy volunteers or patients.
- Doses are escalated to a scheme – which could be pre-defined.
- A single dose is given to a subject. A second study looks at multiple acsending doses (although these could be combined)
- Escalation could be within a subject or between subjects.
- Primary objective is safety and tolerability but there is an ever increasing need to look at early efficacy using biomarkers
- Drugs may be single agents or in combination

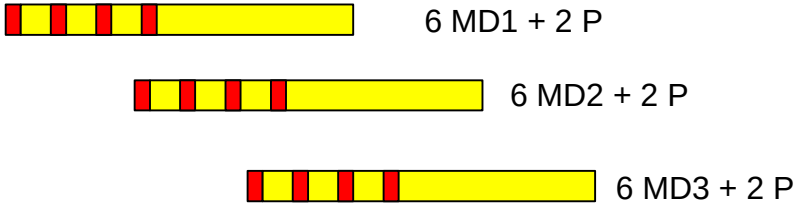
Typical looking First in Human Studies

Single Ascending Dose – 7 doses in cohorts



Total n = 28

Multiple Ascending Dose – 3 doses in cohorts



Total n = 24

Dose Escalation – Continual Reassessment Method – mainly used in Oncology

- The Continual Reassessment Method (CRM) was proposed by O'Quigley, Pepe and Fisher (1990) for the Phase I dose finding trials in cancer, to address concerns in standard designs (3 +3) that were in use:
- Inactivity of the treatment at low doses
- Severe toxic effects expected at high doses
- Poor knowledge of the dose toxicity relationship at the start of the trial
- Potential therapeutic benefit for the patient
- **Need for efficient design with a small number of patients**

Background to the CRM

- The CRM, as its name suggests, is a continually adapting design, but just for binary data
- Uses all data accumulated so far to determine the target dose, reassessing the target dose after each subject provides data
- Assumes dose toxicity follows some montonic relationship
- Also uses prior information, employing Bayesian methodology
- Initially designed for toxicity studies, but equally applicable to efficacy, or both efficacy and toxicity in the bivariate CRM
- Toxicity study targets the Maximum Tolerated Dose (MTD)
- Efficacy study targets the Minimum Efficacious Dose (MED)

Neuenschwander et al (2008)

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Critical aspects of the Bayesian approach to phase I cancer trials

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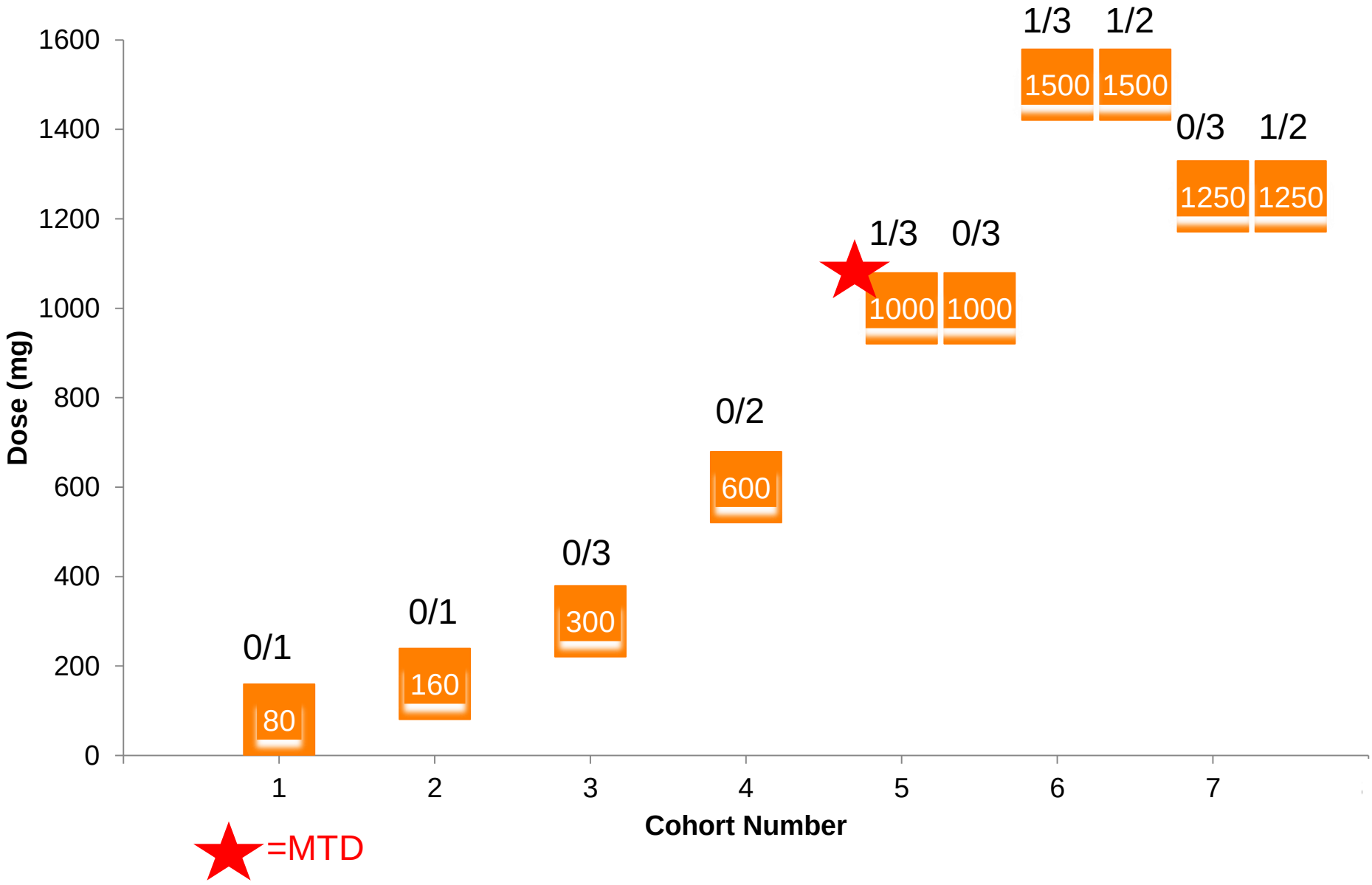
SUMMARY

The Bayesian approach to finding the maximum-tolerated dose in phase I cancer trials is discussed. The suggested approach relies on a realistic dose–toxicity model, allows one to include prior information, and supports clinical decision making by presenting within-trial information in a transparent way. The modeling and decision-making components are flexible enough to be extendable to more complex settings. Critical aspects are emphasized and a comparison with the continual reassessment method (CRM) is performed with data from an actual trial and a simulation study. The comparison revealed similar operating characteristics while avoiding some of the difficulties encountered in the actual trial when applying the CRM.

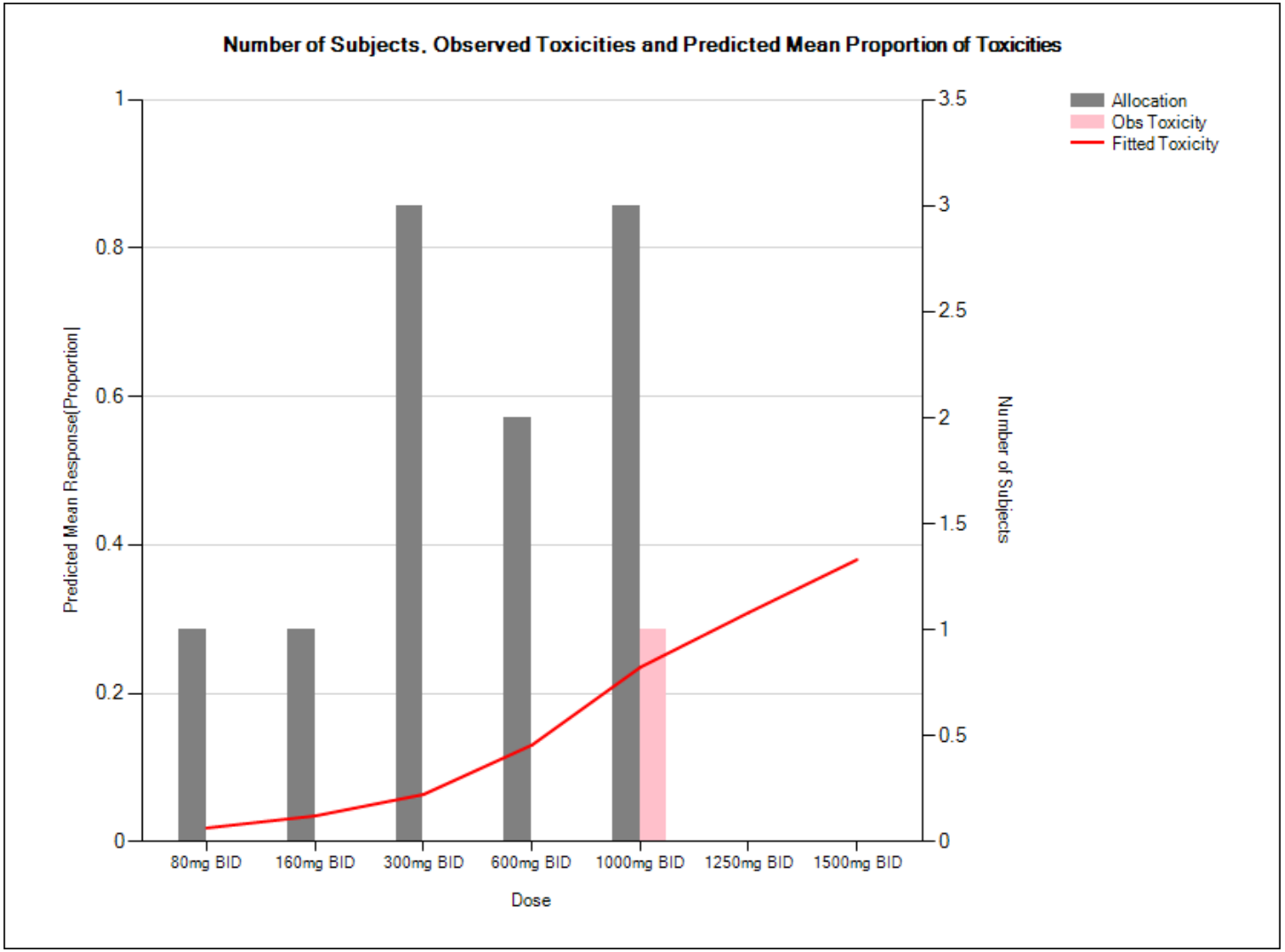
KEY WORDS: maximum-tolerated dose; continual reassessment method; logistic model

- Uses a two parameter logistic model instead of one-parameter
- Targets an acceptable region and has restrictions on other regions:
  - Under dosing, excessive toxicity and unacceptable toxicity

Example Escalation



You might then fit a model



Example Adaptive FIH Study

Rationale and study design of the Adaptive study of IL-2 dose on regulatory T cells in type 1 diabetes (DILT1D): a non-randomised, open label, adaptive dose finding trial

Frank Waldron-Lynch,[1] Paula Kareclas,[2] Kathryn Irons,[2] Neil M Walker,[1] Adrian Mander,[3] Linda S Wicker,[1] John A Todd,[1] Simon Bond[2,3]

What was the design of this study?

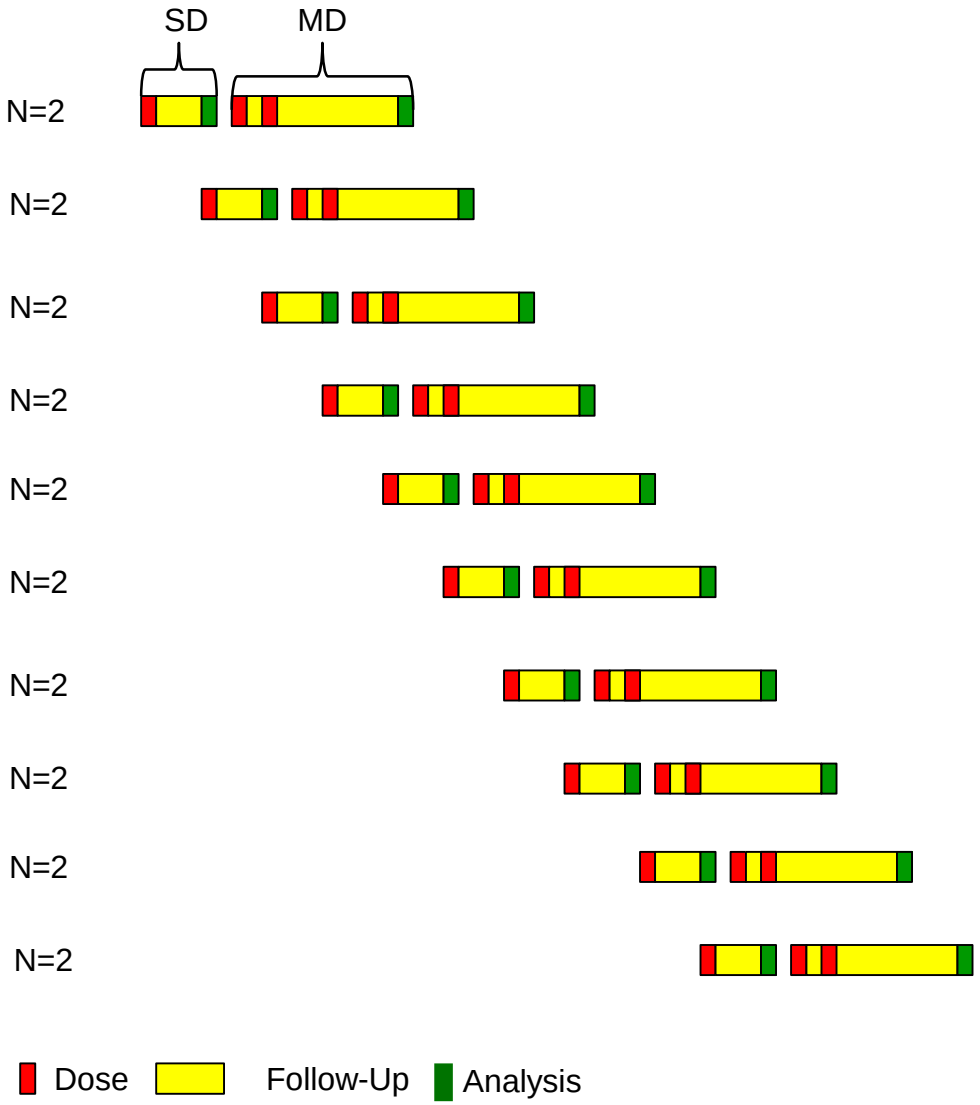
- Primary outcome – dose response of the maximum % increase in regulatory T-cells over baseline.
- Two parts – learning phase, adaptive phase
- Learning phase
  - First 10 patients receive doses 0.04, 0.16, 0.6,1, 1.5 IU/m^2 in ascending order.
  - Two targets are identified – maximal and minimal T-reg increase.
- Adaptive phase
  - Interim analysis after every patient to determine the optimal dose for the next patient.
  - Based on minimizing the variance-covariance matrix of the targets
- Total sample size was 40.

Learnings from this trial

- The adaptive design was more than flexible enough to quantify the dose response curve and identify the dose which achieve the targets.
- However, the team thought it could have been done with less patients.

- The following is an idea of a design !!!!!

Example Combined SAD and MAD trial



Adaptive Randomisation (applied at every analysis)

- The process for adaptation uses the methods as outlined by the paper "Dose-Finding Based On Efficacy-Toxicity Trade-Offs" by Peter F. Thall and John D. Cook, Biometrics Sep 2004.
- Dose response models updated after every patient has PD and safety data after both single and multiple dose.
- For this study the utility is a balance PD effect (clinically relevant effect = 15%) and safety:
  - For PD we assign the utility U_{PD}
  - PD < 0 then $U_{PD} = 0$
  - $0 \leq PD \leq 15\%$ then $U_{PD} = PD * 6.67$
  - PD > 15% then $U_{PD} = PD$
  - Then for each safety parameter (1 to X) we assign the following utility (U_{Sx}):
  - Pr(safety exceeding threshold) < 20% then $U_{Sx} = 1$
  - Pr(safety exceeding threshold) ≥ 20% then $U_{Sx} = 0$
- Then the joint utility or gain is: $U_{PD} * U_{S1} * U_{S2} \ldots\ldots * U_{Sx}$ where X is the total number of safety endpoints.
- Pick the next dose which has the highest probability of having the highest utility.

Escalation could be within a subject instead of between subjects

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

Period	Subject 1	Subject 2	Subject 3	Subject 4
1	d_1	d_1	d_1	Placebo
2	d_2	d_2	Placebo	d_2
3	d_3	Placebo	d_3	d_3
4	Placebo	d_4	d_4	d_4

Model within subject dose escalation

$$Y_{ij} = \theta_1 + \theta_2 \ell_{ij} + S_i + \varepsilon_{ij}$$

Where

$$Y_{ij} = Log(AUC)$$

$$\ell_{ij} = Log(Dose)$$

$S_i \sim N(0, \tau^2)$ – random effect for ith subject

$$\varepsilon_{ij} \sim N(0, \sigma^2)$$

$$\rho = \tau^2 / (\sigma^2 + \tau^2)$$

Other things to take think about

- Should escalation be done only on toxicity? Could we use some bivariate – biomarker and toxicity – some work done by Thomas Jaki at Lancaster
- TGN1412 Story – taking this into account
- Combinations – PIPE designs by Adrian Mander (MRC) but are these the best approach?
- We don’t use pre-clinical information well – can we incorporate this into a prior of some sort?

Doing now what patients need next