Optimising First In Human (FIH) Studies

ITT5

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The Problem

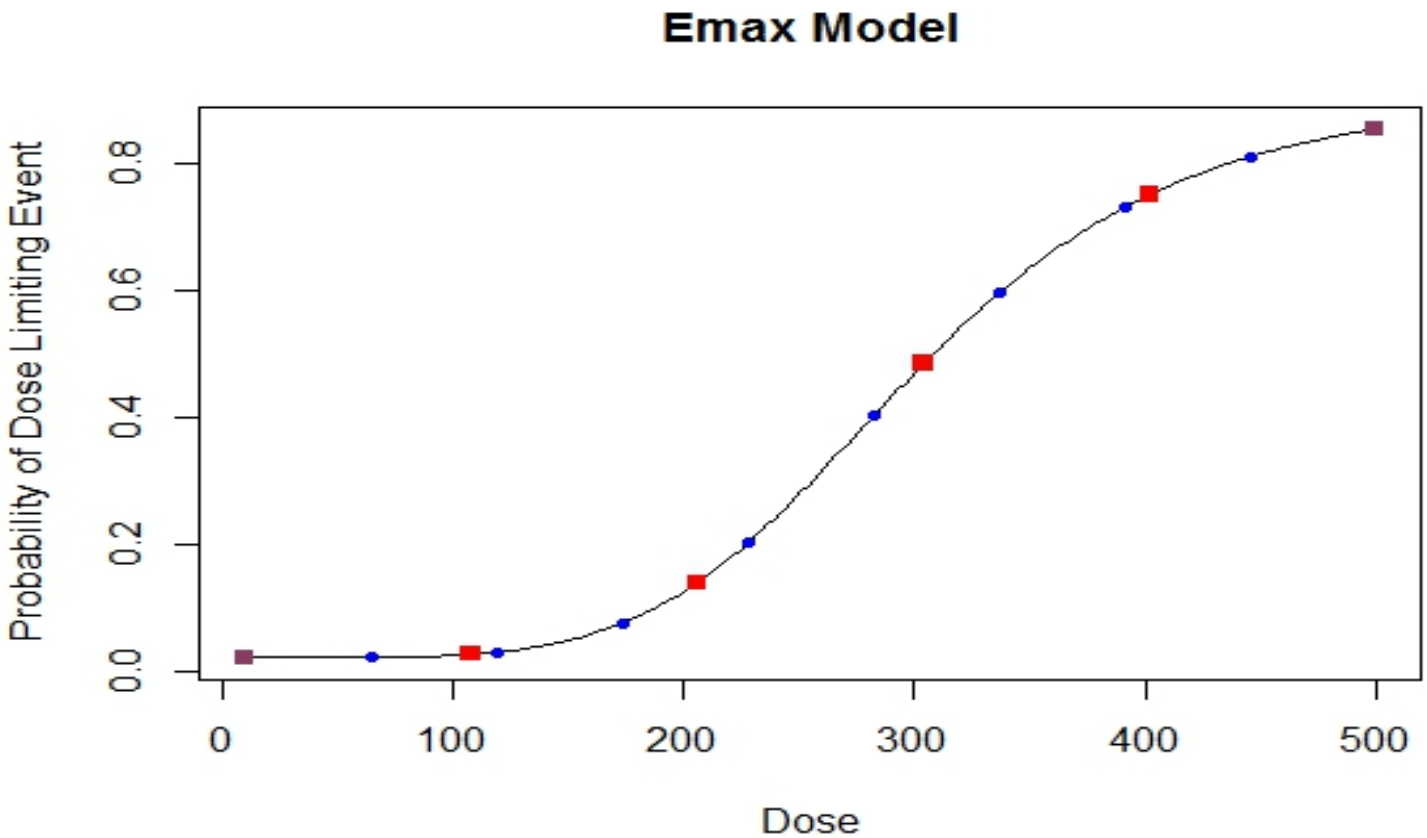
Question

How can we optimise First In Human studies?

Aims

- SAD: Optimise the dosing scheme based on safety endpoints
- MAD: Incorporate efficacy endpoints

Optimising Single Ascending Dose (SAD) Studies - Model



Optimising Single Ascending Dose (SAD) Studies - Simulation with fixed Emax parameters

$$\begin{array}{lcll} \text{Dose current cohort} & \rightarrow & \hat{\mathbb{P}}(\text{DLE}) \geq \gamma & \rightarrow \quad \text{Stop} \\ & & \hat{\mathbb{P}}(\text{DLE}) < \gamma & \rightarrow \quad \text{Increase} \end{array}$$

Dose Escalation Rule

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Dose Escalation Rule

Model Comparison - Utility Function

$$|p - \gamma| \; \beta_1 \mathbb{I}\{p > \gamma\} + |p - \gamma| \; \beta_2 \mathbb{I}\{p < \gamma\}$$

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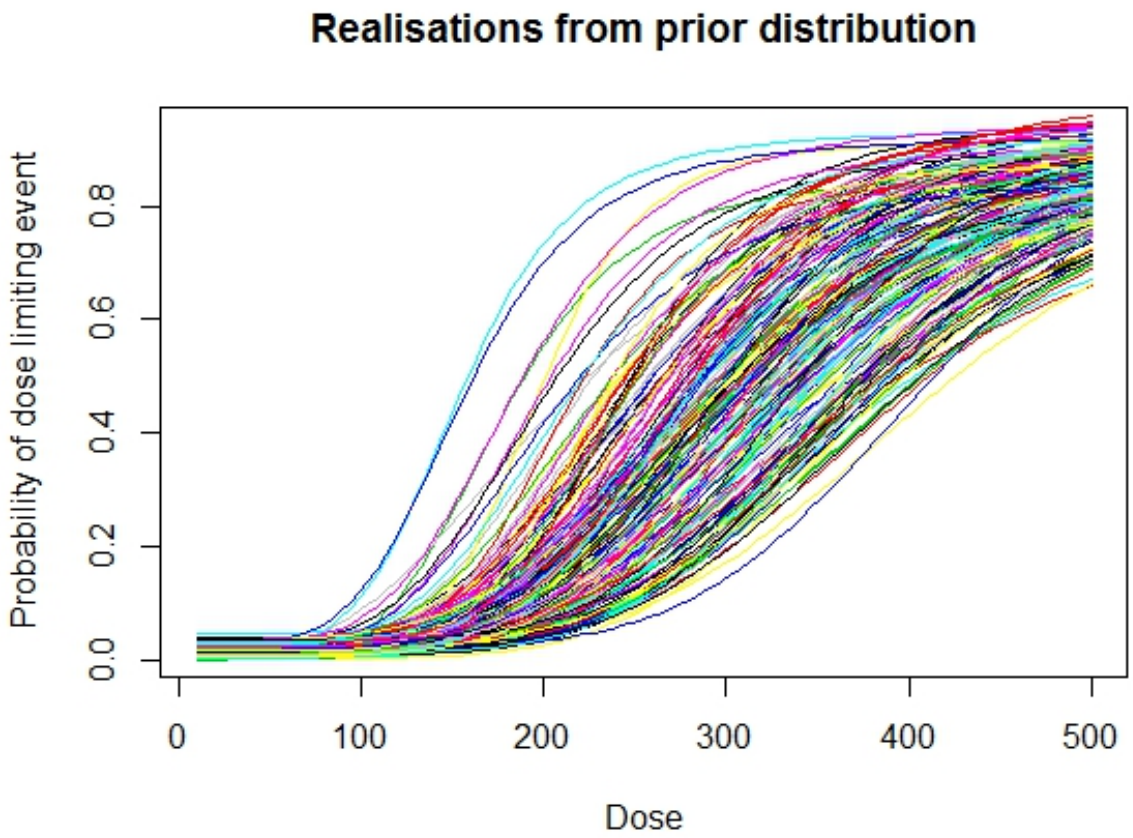
Number of doses	2	3	5	6	10
$\mathbb{E}$(Utility)	0.420	0.256	**0.237**	0.259	0.300

Optimising Single Ascending Dose (SAD) Studies - Simulation - with prior for Emax parameters



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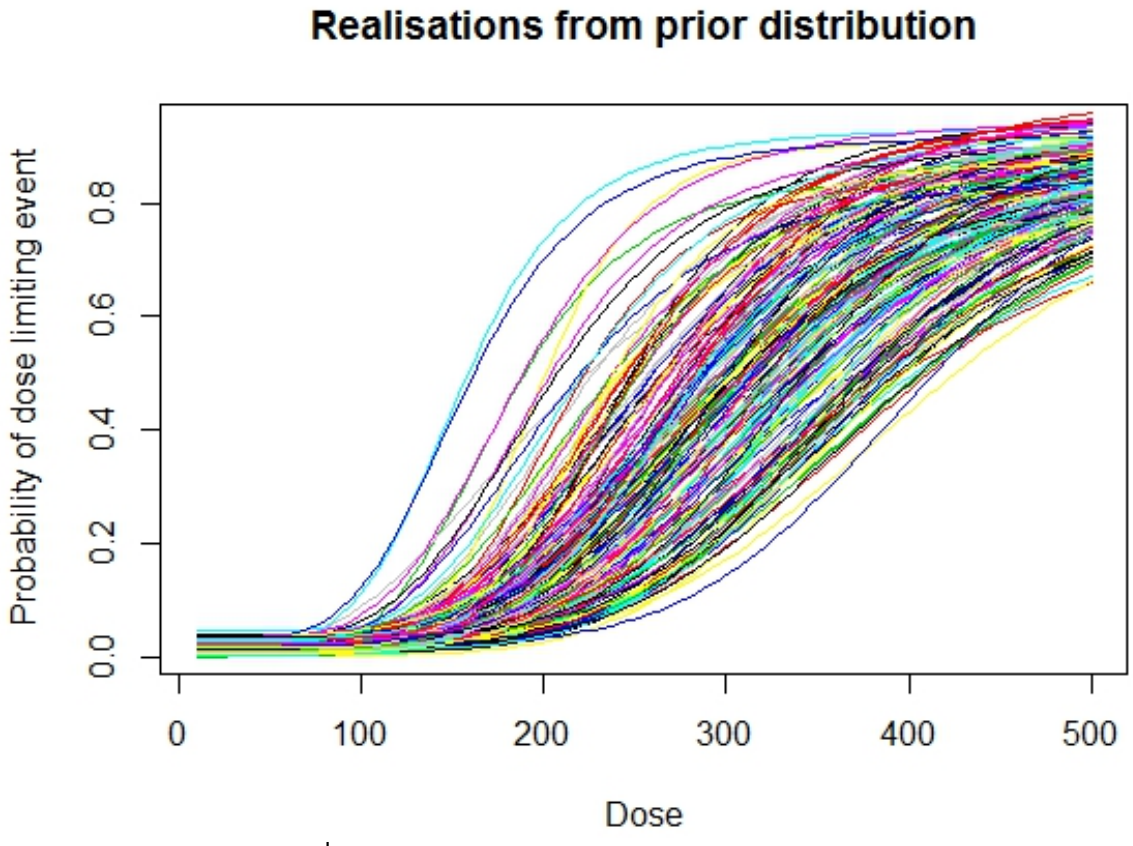

Number of doses	2	3	5	6	10
$\mathbb{E}$(Utility)	0.420	0.256	**0.237**	0.259	0.300
$\mathbb{E}_\pi$(Utility)	0.419	0.310	0.278	**0.236**	0.297

Optimising Single Ascending Dose (SAD) Studies - Extensions

- Investigate different dosing strategies

Choose next dose based on observed data:

- Simple estimation of probabilities
- Model-based choice of dose

- Increasing/decreasing one dose level
- Dose jumping

Optimising Multiple Ascending Dose (MAD) Studies

- Study Aim: Assess safety when dosed multiple times

Directions for Optimisation

- Parallel to SAD optimisation framework
- Incorporate PD biomarker into utility function
  - Model separately, just collecting PD biomarker info, optimising based on safety
  - Model jointly, optimise based on both.
- Combination therapies

Thanks!

Thanks for listening!
Any questions?