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
Introduction SAD MAD

Optimising Single Ascending Dose (SAD) Studies - Model

Emax Model

Probability of Dose Limiting Event

0.0 0.2 0.4 0.6 0.8

Dose

0 100 200 300 400 500
Optimising Single Ascending Dose (SAD) Studies - Simulation with fixed Emax parameters

Dose current cohort \( \to \hat{P}(\text{DLE}) \geq \gamma \to \text{Stop} \)
\( \hat{P}(\text{DLE}) < \gamma \to \text{Increase} \)

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

Dose current cohort $\rightarrow \hat{P}(DLE) \geq \gamma \rightarrow$ Stop
$\hat{P}(DLE) < \gamma \rightarrow$ Increase

Dose Escalation Rule

Model Comparison - Utility Function

$$|p - \gamma| \beta_1 I\{p > \gamma\} + |p - \gamma| \beta_2 I\{p < \gamma\}$$
Optimising Single Ascending Dose (SAD) Studies - Simulation with fixed Emax parameters

Dose current cohort  $\rightarrow \hat{P}(\text{DLE}) \geq \gamma \rightarrow \text{Stop}$
$\hat{P}(\text{DLE}) < \gamma \rightarrow \text{Increase}$

Dose Escalation Rule

Model Comparison - Utility Function

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

<table>
<thead>
<tr>
<th>Number of doses</th>
<th>2</th>
<th>3</th>
<th>5</th>
<th>6</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mathbb{E}$(Utility)</td>
<td>0.420</td>
<td>0.256</td>
<td>0.237</td>
<td>0.259</td>
<td>0.300</td>
</tr>
</tbody>
</table>
Optimising Single Ascending Dose (SAD) Studies - Simulation - with prior for Emax parameters

Realisations from prior distribution

- Number of doses: 2, 3, 5, 6, 10
- E(utility): 0.420, 0.256, 0.237, 0.259, 0.300
- E(π): 0.419, 0.310, 0.278, 0.236, 0.297
Optimising Single Ascending Dose (SAD) Studies - Simulation - with prior for Emax parameters

<table>
<thead>
<tr>
<th>Number of doses</th>
<th>2</th>
<th>3</th>
<th>5</th>
<th>6</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mathbb{E}(\text{Utility})$</td>
<td>0.420</td>
<td>0.256</td>
<td><strong>0.237</strong></td>
<td>0.259</td>
<td>0.300</td>
</tr>
<tr>
<td>$\mathbb{E}_\pi(\text{Utility})$</td>
<td>0.419</td>
<td>0.310</td>
<td>0.278</td>
<td><strong>0.236</strong></td>
<td>0.297</td>
</tr>
</tbody>
</table>
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 for listening!
Any questions?