Partial Ordering

Candidate schedules:

- d_0 : Standard of Care (SoC)
- d_1 : 1500mg BID (Total daily dose: 3000mg)
- d_2 : 1000mg TID (Total daily dose: 3000mg)
- d_3 : Asymmetric; 1500mg in the morning, 2000mg in the afternoon (Total daily dose: 3500mg)

We know that d_1 is less toxic d_3, hence, we have the following partial orderings:

1. $d_1 \to d_2 \to d_3$
2. $d_1 \to d_3 \to d_2$
3. $d_2 \to d_3 \to d_1$ (Not applicable)

Possible to apply traditional CRM and single agent Jaki et al. (2021) methods by assuming partial ordering.

Modifications to Jaki et al. (2021)

- Suppose each possible time of receiving dose is a separate agent.
- Define each dose as follows:
  - $m_j \in \{0, 1000, 1500\}$ with $j = 0, 1, 2$
  - $a_k \in \{0, 1000\}$ with $k = 0, 1$
  - $e_l \in \{0, 1000, 1500, 2000\}$ with $l = 0, 1, 2, 3$
- Schedules expressed as combinations of agents:
  - $d_0 = (m_0, a_0, e_0) = (0, 0, 0)$
  - $d_1 = (m_2, a_0, e_2) = (1500, 1500, 0)$
  - $d_2 = (m_1, a_1, e_1) = (1000, 1000, 1000)$
  - $d_3 = (m_2, a_0, e_3) = (1500, 2000, 0)$

Assuming independence of agents, the probability of DLE occurring with combination (m_j, a_k, e_l) is,

$$p_0(m_j, a_k, e_l) = 1 - (1 - p(m_j))(1 - p(a_k))(1 - p(e_l)).$$

To allow for interactions we have,

$$\begin{aligned} odds(p(m_j, a_k, e_l)) = & \, odds(p_0(m_j, a_k, e_l)) \\ & \times \exp\left(\eta_{jk} m_j a_k + \eta_{jl} m_j e_l + \eta_{kl} a_k e_l + \eta_{jkl} m_j a_k e_l\right), \end{aligned}$$

where $odds(p) = \frac{p}{1-p}$ as proposed by Neuenschwander et al. (2015) for combining three agents. Each agent has separate 2 parameter logistic model,

$$p(m_j) = \psi(\tilde{m}_j, \theta_1, \theta_{21})$$

$$p(a_k) = \psi(\tilde{a_k}, \theta_1, \theta_{22})$$

$$p(e_l) = \psi(\tilde{e}_l, \theta_1, \theta_{23})$$

Hence, the Normal prior distribution of the following must be calibrated,

$$\theta = (\theta_1, \log \theta_{21}, \log \theta_{22}, \log \theta_{23}, \eta_{jk}, \eta_{jl}, \eta_{kl}, \eta_{jkl}).$$

Following from Jaki et al. (2021), we have the following posterior of θ,

$$f_n(\theta) = \frac{f_0(\theta) \prod_{i=1}^{n} \phi(m(i), a(i), e(i), y_i, \theta)}{\int_{\mathbb{R}^8} f_0(u) \prod_{i=1}^{n} \phi(m(i), a(i), e(i), y_i, \theta) du}.$$

where,

$$\phi(m(n), a(n), e(n), y_n, \theta) = p(m(n), a(n), e(n), \theta)^{y_n} \times (1 - p(m(n), a(n), e(n)))^{1-y_n}.$$

- The given posterior is used for escalation and de-escalation decisions.
- Efficacy part of the study does not change.

Evaluation of modifications to Jaki et al. (2021)

Benefits:

- Applicable to existing AGILE platform protocols (e.g. randomisation, analysis, endpoints, etc.).
- Other approaches to handling partial ordering for multi-agent trials can be used (e.g. Wages et al. (2011) and Conway et al. (2004)).
- Statistical power of a combination approach has been shown.
- Extensible to utilise other CRM methods (e.g. EWOC, Bayesian decision analytic approach, etc.).

Drawbacks:

- Parameter calibration is computationally expensive.
- Dimensionality can get large quickly e.g. more possible schedules, less uniform schedules, multi-agent trial.

Note: Schedule space should be limited to include only schedules of interest.

Linking to the research question

- Our aim: Identify dose schedule which has toxicity closest to the TTL of 30%.
- AGILE aim: "Identify potential treatments that are safe and efficacious reliably with small to moderate sample sizes."
- Both aims are satisfied by modelling dose-toxicity relationship.
- Recommendations made via posterior distribution and stopping rules.