MRC Biostatistics Unit

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Dose-escalation designs for combination & dose-schedule studies

Lecture 9: Designs for combination trials with one agent being fixed

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Motivation

- So, far we have considered the setting with several agent being escalated simultaneously.
- There are trials that study the escalating doses of one drug with another one being (semi-) fixed (e.g. at established, approved, currently receiving dose);
- Such trials might require their own approaches.
- In this lecture, we will consider a number of settings for which a model-based design can provide a natural solution.

Setting 1

- Increasing doses of one experimental agent, $d_1, d_2, \ldots, d_j$;
- **One/two doses** of the backbone agent;
- **Experimental might be administered as mono**;
- The toxicity increases within each agent;
- Agents will have either additive or synergistic effect on toxicity
- The objective is to find the MTD with the given **overall** TTL;

A model for Setting 1

- One can build on the the **single-agent BLRM design**
  - to benefit from the monotonicity assumption within each agent;
  - to keep the complexity of estimation problem to its minimum

For example,

- experimental agent can be administered as a mono or a combo;
- two doses of the backbone, $f_1 < f_2$

$$logit(p(d_j, f_k)) = \alpha_0 + \alpha_1 \times \log(d_j / D_*) + \alpha_2 \times I[f \geq f_1] + \alpha_3 \times I[f \geq f_2]$$

Covariates if administered as mono: $(d_j, 0, 0)$

Covariate if administered in combination with f_1: $(d_j, 1, 0)$

Covariate if administered in combination with f_2: $(d_j, 1, 1)$

A comment on Setting 1

- Similar modelling can be used in problems with several (but few) administration schedules of the monotherapy drug is being studied.

  For example,

  - experimental agent can be administered under continuous dosing;

    or

  - experimental agent can be administered under 3w on / 1w off;

Setting 2

- Increasing doses of one experimental agent, $d_1, d_2, \ldots, d_j$;
- **One fixed** dose of the backbone agent
  (the same for all patients in the trial);
- The toxicity increases within each agent;
- Agents will have either additive or synergistic effect on toxicity
- The objective is to find the MTD with the given **additional** TTL
  (over the backbone agent);

Motivating example I

- The standard of care is chemo (the full dose) and an immune-checkpoint blocker (PD-1) is dose-escalated.
  - Only a slight increase in toxicity, τ, over the toxicity of the chemo is tolerable.
- The objective is to identify the maximum tolerated combination in terms of the target additional toxicity rate;

Motivating example II

- The standard of care for COVID-19 is to be combined with an antiviral agent
  - For a new (and constantly evolving disease), it might be hard to attribute the dose-limiting event to the drug or to the disease itself;
  - Interested in the additional toxicity rate over the disease one/standard of care;

  The primary goal of the dose-escalation is formulated in terms of the **additional risk of a dose limiting toxicity** (ADLT).

Setting 2 (Ctd)

- Increasing doses of one experimental agent, $d_1, d_2, \ldots, d_j$;
- Let $d_0 = 0$ be a dose of zero of the treatment, **control arm**.
- p_j is probability of DLT if given dose d_j, $p_0 \leq p_1 \leq \ldots \leq p_m$;
- Prior information for the DLT risk of the control, p_0, is available.
- We seek to identify dose that correspond to the ADLT risk of TTL with corresponds to finding the dose $d_{j^\star}$ such that

$$j^\star = \arg \min_{j=0,\ldots,m} |\left(p_j - p_0\right) - TTL|.$$

- Patients are **randomised** between experimental and control.

A model for Setting 2

- The model:

$$\textit{logit}\ p(\tilde{d}_j, \alpha_1, \alpha_2) = \alpha_1 + \alpha_2 \tilde{d}_j$$

- $\tilde{d}_j$ is a standardized dose level corresponding to dose j
- α_1 and α_2 are unknown parameters;
- We require $\tilde{d}_0 = 0$ which will guarantee that
  - a sequential update of the slope parameter α_1 will not contribute to the DLE probability estimation on the control, yet
  - all data are used for the parameters estimation

A model for Setting 2

- The prior distribution of the parameters – $f_0(.)$.
- $\hat{p}_j^{(0)}$ are prior estimates of the DLT probabilities associated with doses d_j $j = 0, \ldots, m$

$$\tilde{d}_j = \frac{\text{logit}(\hat{p}_j^{(0)}) - \hat{\alpha}_1^{(0)}}{\hat{\alpha}_2^{(0)}}$$

- $\hat{\alpha}_1^{(0)}$, $\hat{\alpha}_2^{(0)}$ are prior point estimates of the model parameters;
- To satisfy $\tilde{d}_0 = 0$, the prior needs to be chosen such that $\text{logit}(\hat{p}_0^{(0)}) = \hat{\alpha}_1^{(0)}$.

A design for Setting 2

- The first cohort of $c_1 + c_2$ patients is assigned to the first dose and to the control arm, respectively.
- DLT outcomes are collected, the posterior is updated;
- The set of safe doses is found as

$$\mathbb{P}\left(p_j - p_0 \geq TTL + 2\epsilon\right) < c_{\text{overdose}}$$

  where ϵ is the width of the interval of DLT risk which we consider acceptable, c_{overdose} is overdosing threshold;

- Amongst them, the next experimental patients receive dose such that

$$\mathbb{P}\left(p_j - p_0 \in [TTL - \epsilon, TTL + \epsilon]\right) \tag{1}$$

- The design proceeds until the maximum number of patients is reached or the study is stopped earlier for safety.

Comments on Setting 2

- Randomised BLRM was applied in a COVID-19 trial (UK National Early Phase Platform Trial[1])
- There could be other reasons to have a control arm in Phase I (e.g. non primary safety analysis);
- One can benefit from including this information into the toxicity model.

[1] Griffiths et.al., 2021. AGILE: a seamless phase I/IIa platform for the rapid evaluation of candidates for COVID-19 treatment. Trials, 22(1)

Setting 3

- Increasing doses of one experimental agent, $d_1, d_2, \ldots, d_j$;
- Dose of the backbone agent is **fixed but different** for each patients (eg assigned by treating clinician);
- The toxicity increases within each agent;
- The objective is to find the **dosing function**, i.e. individual MTDs given the assigned dose of the backbone agent.

Motivating Trial

- An opiate detoxification trial in opiate dependent individuals.
- Current treatment: opiate substitution therapy (methadone) but few opiate addicts successfully complete detoxification;
- Hypothesis: baclofen likely to improve withdrawal symptoms
- Dual-agent combinations of four doses of baclofen and continuous doses of methadone
- Dose of methadone is **patient-specific** and defined externally (prescribed by the treating clinician).
- The objective is to define the **dosing function** that for each patient will recommend the dose of baclofen associated with 15-25% risk of DLT.

A model for Setting 3

- 2BLRM
  - To tackle the uncertainty in the ordering;
  - To have flexibility in the continuous dose modelling;
  - To fit combination-toxicity curve;

A design for Setting 3

1. The lowest dose of B_k is allocated to the first cohort.
2. After the DLTs are evaluated, the posterior is updated.
3. When the next patient comes, the set of safe admissible doses of baclofen (given the methadone dose) is found

$$\mathbb{P}\left(p(M = M', B_k) > TTL + \epsilon\right) < c_{overdose}.$$

4. Among safe admissible doses, the dose of B such that

$$\mathbb{P}\left(p(M = M', B_k) \in (TTL - \epsilon, TTL + \epsilon)\right)$$

   is maximised is assigned to the next patient.
5. Steps 2–4 are repeated until the maximum number of patients is reached or trial-specific early stopping criteria are met.

Numerical Evaluation: Performance Metrics

- We need to ensure that it can reliably recommends patient-specific baclofen and safeguards the patients.
- Requires assumption on the distribution of the externally defined doses
- We are interested in the
  - how accurate the design recommendations are;
  - how many patients are assigned in the trial;
  - how many of them experience a DLT.

Accuracy Performance Metric

- There is a **contour of the target combinations** – for each given dose of M, there is a target dose of the B compound
- One can report how well this contour is fitted across doses of M by the end of the trial $\rightarrow$ challenging to communicate;
- Evaluate the performance of the design in terms of its **predictive properties** for patients in subsequent Phase II.
- Accuracy in terms of the proportion of patients (out the total hypothetical sample size in Phase 2 trial) that
  - will be recommended their target combination
  - will be recommended a combination that is safe for them.

Comments on the Settings

- No two trials are the same, but
- Model-based approaches can offer an elegant solution to many problems;
- While ensuring the effecient use of the whole information in the trial, and
- Ensuring that the design answers the right question.