Outline

1. Phase I Oncology Trials
2. Rule Based Designs
3. CRM
4. EffTox
5. Combination Therapy
6. Summary
Phase I Oncology Trials

Rule Based Designs

CRM

EffTox

Combination Therapy

Summary
Phases of Drug Development

- Phase 1: Safety trials
- Phase 2: Efficacy trials
- Phase 3: Confirmatory trials
- Phase 4: Post-marketing surveillance
Goals of Phase 1

- First application of a new drug in humans
- Establish safety profile of a new drug
- Pharmacokinetics and pharmacodynamics
- Determine appropriate dosing for future studies
Why are Oncology trials different?

- Healthy volunteers are used when a new drug is expected to be relatively nontoxic
- Cytotoxic agents are known to be toxic
- Phase 1 oncology trials include patients for whom standard treatments have failed
- Goals:
  - Limit toxicities
  - Maximize the number of patients that receive a therapeutic dose
- We are interested in the probability of dose limiting toxicity (DLT) for each dose
- For cytotoxic agents, we assume that as dose increases, the probability of DLT and the probability of efficacy will also increase
- Goal is to find the maximum tolerated dose (MTD): Highest dose with probability of DLT less than some pre-specified cut-off (usually 0.2 or 0.33)
The dose-toxicity curve
1 Phase I Oncology Trials

2 Rule Based Designs

3 CRM

4 EffTox

5 Combination Therapy

6 Summary
Rule-based designs: 3+3 design

- **Step 1**: Enter first cohort of 3 patients at the lowest dose
- **Step 2**: Observe toxicity outcomes
  - if 0/3 DLT, treat next cohort of 3 patients at next highest dose
  - if 1/3 DLT, treat next cohort of 3 patients at same dose
    - if 1/3 + 0/3 DLT, treat next cohort of 3 patients at next highest dose
    - if 1/3 + 1/3 DLT, define dose as MTD
    - if 1/3 + 2/3 or 3/3 DLT, dose exceeds MTD
  - if 2/3 or 3/3 DLT, dose exceeds MTD
- **Step 3**: Repeat until MTD is reached.
- **Step 4**: MTD is defined as a dose with \( \leq 2/6 \) DLT
• Cohort 1: dose level 1, 0/3 DLT
• Cohort 2: dose level 2, 0/3 DLT
• Cohort 3: dose level 3, 1/3 DLT
• Cohort 4: dose level 3, 0/3 DLT
• Cohort 5: dose level 4, 2/3 DLT

Conclude that dose level 3 is the MTD
Pros and Cons of the 3+3 design

- Pros
  - Simple!
- Cons
  - ad hoc
  - imprecise
  - only allows for a target DLT probability of .33
  - treats a maximum of 6 patients at the MTD
The continual reassessment method (CRM) was the first Bayesian adaptive phase 1 design (O’Quigley, Pepe and Fisher, 1990).

The CRM uses a one-parameter parametric model for the probability of DLT at each dose.
Let $p(d) = P(DLT|dose = d)$

- **Power Model**
  $$p(d) = d^{\exp(a)}$$

- **Logistic Model**
  $$p(d) = \frac{\exp(3 + ad)}{1 + \exp(3 + ad)}$$

- **Hyperbolic Tangent Model**
  $$p(d) = \left(\frac{\exp(d)}{\exp(d) + \exp(-d)}\right)^a$$
As a model based method, we are able to estimate the probability of DLT for each dose using standard Bayesian methods. Assuming prior distribution, \( \pi(a) \),

\[
\pi(a | \bar{y}) \propto L(\bar{y} | a) \pi(a),
\]

where,

\[
L(\bar{y} | a) = \prod_{i=1}^{n} p(d_i)^{y_i} (1 - p(d_i))^{1-y_i}.
\]

The posterior is generally not available in closed form and must be estimated using numerical methods (i.e. MCMC).
CRM algorithm

- **Step 1**: Assume a vague or fully non-informative prior for an
- **Step 2**: Treat 1 patient at the level closest to the current estimate of MTD
- **Step 3**: Observe toxicity outcome
- **Step 4**: Update posterior for an
- **Step 5**: Treat next patient at the level closest to the current estimate of MTD based on posterior for an
- **Step 6**: Repeat 1-5 until maximum sample size is reached
The standard CRM dose-escalation can be too aggressive. The following modifications have been suggested as a remedy:

- Start at the lowest dose and do not skip untried doses
- Treat patients in cohorts greater than 1 (2 or 3)
- No dose escalation until all treatment in patients from previous doses are completed
- More aggressive stopping rules for safety
Advantages and disadvantages to the CRM

• Advantages
  • In general, the CRM is more likely to find the true MTD than 3+3
  • Can be adapted for target probabilities other than .33
  • Model-based methods uses all date to model the dose-toxicity curve
  • Treats more patients with doses close to the MTD (i.e. patients more likely to receive efficacious dose)

• Disadvantages
  • More complicated (for clinicians, at least)
  • Model misspecification is a potential concern
1. Phase I Oncology Trials
2. Rule Based Designs
3. CRM
4. EffTox
5. Combination Therapy
6. Summary
Simultaneously considering Efficacy and Toxicity

- Standard Phase I designs only consider toxicity
- This is not ideal in some situations
  - MTD has unacceptable efficacy
  - Efficacy does not continue to increase as dose increases
EffTox (Thall and Cook, 2004) is a Bayesian adaptive phase 1 design that simultaneously considers toxicity and efficacy.

- EffTox considers two binary outcomes:
  - Toxicity: $Y_T$
  - Efficacy: $Y_E$

- We must model the joint probability of efficacy and toxicity:

$$\pi_{a,b}(x, \theta) = Pr(Y_E = a, Y_T = b | x, \theta)$$
Thall and Cook (2004) consider logistic regression models for the marginal probabilities of efficacy and toxicity:

- The marginal probabilities for efficacy and toxicity are:
  \[ \pi_E (x, \theta) = \pi_{1,0} (x, \theta) + \pi_{1,1} (x, \theta) \]
  \[ \pi_T (x, \theta) = \pi_{0,1} (x, \theta) + \pi_{1,1} (x, \theta) \]

- We fit the following logistic regression models for the marginal probabilities:
  \[ \text{logit} (\pi_E (x, \theta)) = \beta_{0,E} + x\beta_{1,E} + x^2\beta_{2,E}, \]
  \[ \text{logit} (\pi_T (x, \theta)) = \beta_{0,T} + x\beta_{1,T}, \]
The joint probability of efficacy and toxicity is modeled using a copula model

\[ \pi_{a,b} = \pi_E^a (1 - \pi_E)^{1-a} \pi_T^b (1 - \pi_T)^{1-b} + (-1)^{a+b} \pi_E (1 - \pi_E) \pi_T (1 - \pi_T) \frac{e^{\psi} - 1}{e^{\psi} + 1} \]

- \( \psi \) characterizes the correlation between efficacy and toxicity
- \( \psi = 0 \) indicates that efficacy and toxicity are independent
Estimating the parameters

The likelihood, \( L(Y_E, Y_T|x, \theta) \), for a patient at dose \( x \) is

\[
\pi_{1,1}(x, \theta)^{Y_E Y_T} \pi_{1,0}(x, \theta)^{Y_E(1-Y_T)} \pi_{0,1}(x, \theta)^{(1-Y_E)Y_T} \pi_{0,0}(x, \theta)^{(1-Y_E)(1-Y_T)}
\]

- Specify priors for all parameters
- Proceed with standard Bayesian inference using MCMC
Clinicians are asked to specify three points:

- \((\pi^*_E, 0)\) - minimum efficacy with no toxicity
- \((1, \pi^*_T)\) - maximum toxicity with perfect efficacy
- \(\left(\pi'_E, \pi'_T\right)\) - a point that is equally desirable to the first two
Acceptable Doses

Dose levels are considered acceptable if

$$\Pr \left( \pi_E (x, \theta) > \pi_E^* | Y_E, Y_T \right) > p_E$$

and

$$\Pr \left( \pi_T (x, \theta) < \pi_T^* | Y_E, Y_T \right) > p_T$$
A dose with probability of efficacy, $\pi_E$, and probability toxicity, $\pi_T$, has desirability $\delta = 1 - r$ where

$$r = \left( \left( \frac{1 - \pi_E}{1 - \pi_E^*} \right)^p + \left( \frac{\pi_T}{\pi_T^*} \right)^p \right)^{1/p}$$

where $p$ is found by plugging $(\pi'_E, \pi'_T)$ in for $(\pi_E, \pi_T)$, setting $r = 1$ and solving for $p$. 
EffTox Algorithm

- **Step 1**: Treat the first cohort (2 or 3 patients) at the lowest dose level
- **Step 2**: Observe the efficacy and toxicity outcomes
- **Step 3**: Update posterior and calculate posterior means, $E(\pi_E(x, \theta) | Y_E, Y_t)$ and $E(\pi_T(x, \theta) | Y_E, Y_t)$ for each dose level
- **Step 4**: Determine the acceptable doses
- **Step 5**: Compute desirability index for all acceptable doses
- **Step 7**: Terminate the trial if no doses are acceptable, otherwise, treat the next cohort at the most desirable dose under the restriction that no untried doses may be skipped
- **Step 8**: Continue until the maximum sample size is reached. The dose with the highest desirability is selected for further evaluation
Advantages and Disadvantages of EffTox

• Advantages
  • Efficacy and toxicity considered simultaneously
  • Considers MTD undesirable if the MTD has unacceptable efficacy
  • Does not escalate unless there is an efficacy benefit

• Disadvantages
  • Complicated!
  • Requires a larger sample size than standard phase 1 designs
Phase I Oncology Trials

Rule Based Designs

CRM

EffTox

Combination Therapy

Summary
Combination Therapy

- It is increasingly common that our interest lies in the safety profile for a combination of two drugs.
- This requires dose finding with two agents.
- Yin and Yuan (2009) describe a Bayesian adaptive design for two-agent dose finding.
• Let $A_1, \ldots, A_J$ be the dose levels for drug A and $B_1, \ldots, B_K$ be the dose levels for drug B.

• Let $X_{jk}$ and $Y_{jk}$ be binary indicators for whether or not a patient experienced a toxicity from drugs A and B, respectively, from combination $A_j$ and $B_k$.

• Yin and Yuan use a similar approach to the EffTox design in that they directly model the marginal probabilities and combine them using a copula model.
Yin and Yuan use the one-parameter power model for the marginal probabilities

\[ P(DLT \text{ from Drug } A | \text{dose} = j) = p_j^\alpha \]

and

\[ P(DLT \text{ from Drug } B | \text{dose} = j) = q_k^\beta \]
The joint probability of efficacy and toxicity is modeled using a copula model

$$\pi_{j,k}^{(x,y)} = p_j^{\alpha_x} (1 - p_j^{\alpha})^{1-x} q_k^{\beta_y} (1 - q_k)^{1-y} + (-1)^{x+y} p_j^{\alpha} (1 - p_j^{\alpha}) q_k^{\beta} (1 - q_k) \frac{e^{\psi} - 1}{e^{\psi} + 1}$$

- $\psi$ characterizes the correlation between drug A and drug B
- $\psi = 0$ indicates that drug A and drug B are independent
Estimating the parameters

The Likelihood for Yin and Yuan’s model is

\[
\prod_{j=1}^{J} \prod_{k=1}^{K} \left( \pi_{j,k}^{(0,0)} \right)^{n_{j,k}^{(0,0)}} \left( \pi_{j,k}^{(0,1)} \right)^{n_{j,k}^{(0,1)}} \left( \pi_{j,k}^{(1,0)} \right)^{n_{j,k}^{(1,0)}} \left( \pi_{j,k}^{(1,1)} \right)^{n_{j,k}^{(1,1)}}
\]

- Specify priors for \( \alpha, \beta \) and \( \psi \)
- Proceed with standard Bayesian inference using MCMC
- A problem arises if we are unable to assign DLTs to a specific drug
- In this case, we only observe whether or not a DLT occurs
- To accommodate, we alter the likelihood to

\[
\prod_{j=1}^{J} \prod_{k=1}^{K} \left( \pi_{j,k}^{(0,0)} \right)^{n_{j,k}^{(0,0)}} \left( 1 - \pi_{j,k}^{(0,0)} \right)^{n_{j,k} - n_{j,k}^{(0,0)}}
\]
Combination dose-finding algorithm

- **Step 1**: Treat patients in the first cohort at the lowest dose combination

- **Step 2**: If for the current dose \((j, k)\) we have
  \[
P \left( \pi_{j,k} > \pi_* | Data \right) < c_e
  \]
  escalate to an adjacent dose level with probability of toxicity greater than that for the current dose level.

- **Step 3**: If for the current dose \((j, k)\) we have
  \[
P \left( \pi_{j,k} > \pi_* | Data \right) > c_d
  \]
  de-escalate to an adjacent dose level with probability of toxicity lower than that for the current dose level.

- **Step 5**: The MTD is the dose level with probability of DLT closest to the target when the maximum sample size is reached.
1 Phase I Oncology Trials

2 Rule Based Designs

3 CRM

4 EffTox

5 Combination Therapy

6 Summary
Summary

• The goal of a phase 1 clinical trial is to assess the safety profile of a new drug and determine the optimal dose for further investigation.

• Phase 1 oncology trials are unique for enrolling cancer patients who’s previous treatments have failed.

• We would like to treat as many patients as possible at therapeutic dose levels while identifying the MTD.

• Bayesian adaptive designs allow us to treat more patients at therapeutic dose levels while identifying the true MTD at a higher rate than standard designs.

• Bayesian adaptive designs provide the flexibility to accommodate deviations from standard phase 1 designs (toxicity and efficacy, two drugs, etc.)