Continual Reassessment Method for Phase I Trials of Combined Drugs

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Phase I Trials

- Initial safety trials
- Goal is to recommend a dose for further testing for efficacy in Phase II from a set of doses
- The highest dose with an "acceptable" rate of **dose-limiting toxicity (DLT)**, defined by protocol specific adverse events
  - Known as the **maximum tolerated dose (MTD)**
- Ultimate goal is to locate the MTD, while adhering to certain ethical considerations

Continual Reassessment Method (CRM)

- A statistical procedure that updates the information on the probabilities of dose-limiting toxicity (DLT) in light of the results obtained for **all** patients already observed
- Allocation rule to sequentially assign **each** incoming patient to one of the possible doses, with the intent of assigning doses ever closer to, and eventually recommending, the **(MTD)**

*Gasparini and Eisele, *Biometrics* 2000; **56**: 609–615.

Attributes of CRM

- Working mathematical dose-toxicity model is assumed

$$\Pr(\text{DLT at dose } i) \approx p_i^{\exp(\theta)}$$

- After each inclusion, update dose-toxicity curve based on accumulated data (# patients observed, # patients with DLT) at various dose levels.
- Assign next inclusion to dose with DLT rate estimated to be closest to target DLT rate
- After n patients, estimated MTD is dose recommended to the $(n+1)$th patient

Drug Combination Studies

- Fundamental assumption in single-agent trials
  - Increase dose $\rightarrow$ greater chance of DLT
  - Toxicity probabilities follow a "complete order"
- In trials combining more than one drug, fundamental assumption may not hold for every dose pair
  - Increase dose drug A, decrease dose drug B $\rightarrow$?? chance of DLT
  - Toxicity probabilities now follow a "partial order"

Example 1

- Phase I trial of a toll-like receptor (TLR) agonists with or without a form of incomplete Freund's adjuvant (IFA) for the treatment of melanoma.
- **Primary objective**: determine the highest dose of the combination (i.e. MTD combination)

	Doses of TLR	Doses of IFA		
		0	0.5	3
Toxicity increases ↑ ↑	1600			
	400			
	100			
	25			
	Toxicity increases ⟶			

PI: Craig Slingluff, MD

Example 1

- Know some information regarding dose-toxicity relationship between available combinations.
- TLR dose 25 and IFA 0 is less toxic than all other combinations

Doses of TLR	IFA		
	0	0.5	3
1600			most
400			
100			
25	least		

Example 1

- Know some information regarding dose-toxicity relationship between available combinations.
- TLR dose 400 and IFA 0.5 is less toxic than TLR dose 1600 and IFA 0.5

Doses of TLR	IFA		
	0	0.5	3
1600		more	
400		less	
100			
25			

Example 1

- Know some information regarding dose-toxicity relationship between available combinations.
- TLR dose 1600 and IFA 0.5 is less toxic than TLR dose 1600 and IFA 3

Doses of TLR	IFA		
	0	0.5	3
1600		less	more
400			
100			
25			

Example 1

- Do not know some information regarding dose-toxicity relationship between available combinations.
- Which is more toxic? TLR dose 100 and IFA 0 or TLR dose 25 and IFA 0.5

Doses of TLR	IFA		
	0	0.5	3
1600			
400			
100	??		
25		??	

Example 1

- Do not know some information regarding dose-toxicity relationship between available combinations.
- Which is more toxic? TLR dose 100 and IFA 0 or TLR dose 25 and IFA 0.5

Doses of TLR	IFA		
	0	0.5	3
1600			
400	more		
100	less	more	
25		less	more

Overall Strategy

- Determine between which combinations order relationships are known
- Formulate **possible** orders of the combination-toxicity curve
- **Goal:** use known ordering information to choose a "proper" subset of orderings.
  - Intuition: if we knew which order was "correct," we could simply use CRM

Example 2

- Phase I combination trial for pancreatic cancer patients
- Not all combinations need to options

Doses of Drug A (mg/day)	Doses of Drug B (mg/day)				
	500	750	1000	1250	1500
2					
1.5					
1					
0.5					

PI: Hanna Sanoff, MD

CRM for Drug Combinations

- "Two-parameter" version of CRM*
  1. Estimate which ordering is most likely to represent the "correct" dose-toxicity curve
  2. Within the chosen ordering, use CRM to estimate DLT probabilities and allocate combinations
- The "CRM-like" working model for the probability of DLT at combination i in possible ordering m is

$$\Pr(\text{DLT at combination } i) \approx p_{im}^{\exp(\theta_m)}$$

*Wages, Conaway, O'Quigley. *Biometrics* 2011; **67**: 1555–63.

*Wages, Conaway, O'Quigley. *Clin Trials* 2011; **8**: 380–89.

CRM for Drug Combinations

- After each cohort inclusion, estimate θ_m for each of the orderings by maximum likelihood
  - Choose ordering with largest likelihood
  - Using chosen ordering, update estimates of DLT probabilities for all combinations
  - Next patient goes on combination with estimated DLT probability closest to the target DLT rate

Implementation in Drug Combo Trials

- Three investigator-initiated (FDA/IRB approved) studies at UVA Cancer Center (1 multi-site with MD Anderson)
- Consultation with biostatisticians at three other university cancer centers
- Statistical software available in `R`* (package `pocrm`) can be used for
  - implementation in actual trials
  - simulation of operating characteristics

*Wages, Varhegyi. *Computer Methods & Programs in Biomedicine* 2013; **112**: 211–218

Grouping Combinations Into Zones

- Know dose-toxicity relationship between combinations in different zones
  - Toxicity increases from Zone 1 to Zone 6
- Don't know dose-toxicity relationship between combinations within zones

Doses of TLR	IFA		
	0	0.5	3
1600	Zone 4	Zone 5	Zone 6
400	Zone 3	Zone 4	Zone 5
100	Zone 2	Zone 3	Zone 4
25	Zone 1	Zone 2	Zone 3

Grouping Combinations Into Zones

- Combination A is the least toxic combination
- B $<$ C or C $<$ B
- D $<$ E $<$ F or F $<$ E $<$ D, etc.

Doses of TLR	IFA		
	0	0.5	3
1600	I	K	L
400	F	H	J
100	C	E	G
25	A	B	D

How To Choose Possible Dose-toxicity Relationships

- Use zones as a guide to specifying possible dose-toxicity relationships
- There may be many possibilities; not feasible to specify **all**
  - Begin by ordering according to rows and columns
  - Use diagonals as a guide for determining other orders
  - Clinical information can help reduce the number
- A generic set can be used that works well in many situations*

*Wages, Conaway. *Pharm Stats* 2013; **12**: 217–224

Getting Trial Underway

- Mathematically, we need at least one DLT and one non-DLT in order to estimate DLT probabilities
- Use an initial escalation scheme (Stage 1) until first DLT is observed
- Use zones to guide allocation in Stage 1

Stage 1 in Example 1

1. Patients enrolled in cohorts of 2
2. Begin in Zone 1; if deemed safe (no DLT's), escalate to Zone 2
3. If more than one combination contained within a zone, randomly assign cohort to combination within the zone
4. Escalation to higher zone only occurs when all combos in lower zone have been tried and deemed safe
5. Once there is at least one DLT and one non-DLT, Stage 1 ends

Stage 2 in Example 1

1. Stage 2 uses a set of 6 possible dose-tox relationships to model DLT probabilities
2. Uses dose-toxicity curve that best fits *all* accumulated data
3. Within chosen dose-toxicity curve, use CRM to estimate DLT probabilities at each dose-combination
4. Process is repeated after each included patient in Stage 2 until maximum sample size is reached or until stopping rule takes effect

Concluding Remarks

- Overall, the proposed design is competitive with existing methods for dose-finding in multi-agent trials
- Simple extension of the well-known CRM
- Excellent properties when it is possible to write down all possible orderings (not shown)
- Good properties when a “proper” subset of orderings is used

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