Assessing the Effect of Practical Considerations when using the CRM in Dose Finding Studies

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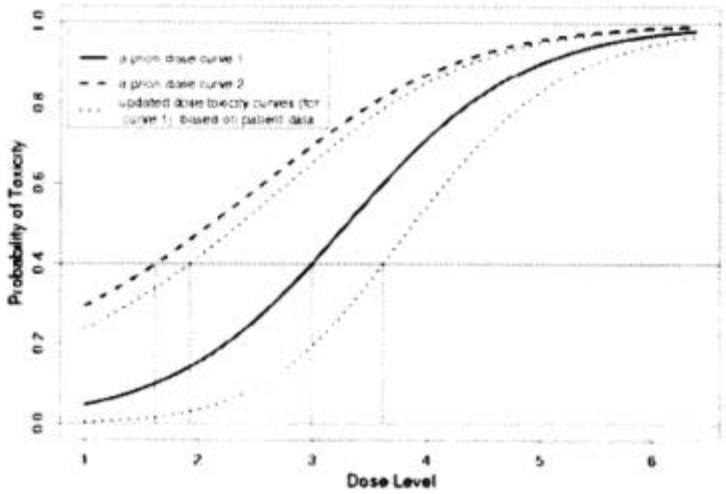
Agenda

- Introduction to Phase I Studies & Continual Reassessment Method (CRM)
- Motivation & Set-up
- Simulation Results and Conclusions

Phase I (Dose-Finding) Studies

- Broad class of early development trial designs
- Purpose: find a dose of treatment that is optimal with respect to simple criteria, such as toxicity and efficacy
- Often the first time the drug is being tested in humans
- Traditional approach: 3 + 3 Method
- Modern approach: Continual Reassessment Method (CRM)

Continual Reassessment Method (CRM)



- Target Toxicity Rate
- Dose Limiting Toxicity – DLT (Toxicity)
- Maximum Tolerated Dose – MTD

Choosing a CRM design

Dose-Toxicity Model
- One-Parameter Models
- Two-Parameter Models

Dose Levels
- Should reflect preclinical information
- Series of doses that increase in increments determined in a predictable fashion

Cohort Size
- Usually 2-4 patients
- Typically around 30 total patients

Target Toxicity Rate
- The maximum probability of Dose Limiting Toxicities that is considered acceptable in the trial
- Depends on the length of the study as well as the disease being studied

Stopping Criteria
- Set a fixed number of patients at trial onset
- Stop once a fixed number of patients have been treated at a dose
- Stop when target dose changes by less than 10%

Motivation: Pfizer Research

Continual Reassessment Method for First-in-Human Trial: From Design to Trial Implementation

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Why Pfizer?

Cohort	Dose (mg)	Evaluable Patients	Patients with DLTs	CRM-estimated MTD (mg)	Dose Recomm. by CRM (mg)	Next Dose Assigned (mg)
1	10	4	0	222	21	21
2	21	4	0	266	43	43
3	43	3	0	266	89	89
4	89	4	0	266	185	154[a]
5	154	4	0	266	266	266[b]
6	266	4	1	383	383	319[c]
7	319	4	2	266	266	266
8	266	4	2	222	222	222
9	222	2	1	222	222	222
10	222	4	4	128	128	154[d]
11	154	4	0	154	154	154
12	154	4	1	154	154	NA[e]

[a] Out of caution: 154mg was maximum allowed at the time
[b] Model switch occurred after this cohort
[c] Other (non-DLT) AE's and investigators' input
[d] Based on cohort 5 (154 mg) safety results
[e] 154mg declared MTD, Part 1 concluded

*Data first presented in Tabernero et al. (2011)

Model change

Human Oversight

MTD

Research Questions

- Does dropping doses affect CRM performance?
- Does the sample size affect CRM performance?
- Does the number of doses considered affect CRM performance?

Our Study Design

Without Dropping Doses	Consecutive Stopping Criteria	High MTD
		Medium MTD
		Low MTD
		No MTD
	No Consecutive Stopping Criteria	High MTD
		Medium MTD
		Low MTD
		No MTD
Dropping Doses	Consecutive Stopping Criteria	High MTD
		Medium MTD
		Low MTD
		No MTD
	No Consecutive Stopping Criteria	High MTD
		Medium MTD
		Low MTD
		No MTD

Study Comparison

Our Simulation

- Target Toxicity Rate: .30
- Sample Size: 30, 45, 60
- Cohort Size: 3
- Max Escalation: 3
- Dose Levels: 5, 10, 20
- Stopping Condition:
  - Consecutive Doses
  - Specified Sample Size
  - All Estimated Toxicities > Target Toxicity Rate

Pfizer's Study

- Target Toxicity Rate: .25
- Sample Size: 50
- Cohort Size: 4
- Max Escalation: 3
- Dose Levels: 22 (10mg-319mg)
- Stopping Condition:
  - Consecutive Doses
  - Specified Sample Size
  - All Estimated Toxicities > Target Toxicity Rate

Our Simulation Data: Toxicity Profiles

Dose	1. High MTD	2. Medium MTD	3. Low MTD	4. All Toxic
1	0.01	0.01	0.01	0.35
2	0.02	0.02	0.05	0.40
3	0.04	0.04	0.10	0.55
4	0.06	0.06	0.20	0.75
5	0.08	0.08	**0.30**	0.85
6	0.10	0.10	0.40	0.90
7	0.12	0.15	0.55	0.95
8	0.14	0.20	0.75	0.99
9	0.16	0.25	0.85	0.99
10	0.18	**0.30**	0.90	0.99
11	0.20	0.35	0.95	0.99
12	0.22	0.40	0.99	0.99
13	0.24	0.45	0.99	0.99
14	0.26	0.55	0.99	0.99
15	**0.30**	0.75	0.99	0.99
16	0.34	0.85	0.99	0.99
17	0.38	0.90	0.99	0.99
18	0.45	0.95	0.99	0.99
19	0.55	0.99	0.99	0.99
20	0.75	0.99	0.99	0.99

Results: Regarding Pfizer

With respect to dropping unused doses late in the study

Carrying all Doses Through Entire Study

Percentage of CRM Simulations Selecting MTD or MTD-1 Stopping for Consecutive Dose Criteria

High MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	100	91	60
Number of Subjects = 45	100	97	71
Number of Subjects = 60	100	98	77

Dropping Doses Late in Study

Percentage of CRM Simulations Selecting MTD or MTD-1 Stopping for Consecutive Dose Criteria

High MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	100	89	69
Number of Subjects = 45	100	96	73
Number of Subjects = 60	100	98	78

Further Evidence – Carrying Through vs Dropping Doses

Carrying all Doses Through Entire Study

Percentage of CRM Simulations Selecting MTD or MTD-1
Not Stopping for Consecutive Dose Criteria

Low MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	96	66	38
Number of Subjects = 45	98	78	41
Number of Subjects = 60	98	84	49

Dropping Doses Late in Study

Percentage of CRM Simulations Selecting MTD or MTD-1
Not Stopping for Consecutive Dose Criteria

Low MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	90	65	24
Number of Subjects = 45	95	76	39
Number of Subjects = 60	98	81	47

Results: More Regarding Pfizer

With respect to sample size

Dropping Doses Late in Study
Percentage of CRM Simulations Selecting MTD or MTD-1
Stopping for Consecutive Dose Criteria

Low MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	91	62	26
Number of Subjects = 45	93	64	40
Number of Subjects = 60	93	66	44

Dropping Doses Late in Study
Percentage of CRM Simulations Selecting MTD or MTD-1
Stopping for Consecutive Dose Criteria

High MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	100	89	69
Number of Subjects = 45	100	96	73
Number of Subjects = 60	100	98	78

Further Evidence – Sample Size

Dropping Doses Late in Study
Percentage of CRM Simulations Selecting Dose > MTD
Stopping for Consecutive Dose Criteria

Low MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	2	25	34
Number of Subjects = 45	1	26	34
Number of Subjects = 60	1	25	34

Dropping Doses Late in Study
Percentage of CRM Simulations Selecting Dose > MTD
Stopping for Consecutive Dose Criteria

Medium MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	1	27	40
Number of Subjects = 45	0	28	38
Number of Subjects = 60	0	27	32

Results: General Comments on CRM Performance

When possible, reduce the number of doses considered prior to beginning the trial

Carrying all Doses Through Entire Study
Percentage of CRM Simulations Selecting MTD
Stopping for Consecutive Dose Criteria

Medium MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	68	33	20
Number of Subjects = 45	67	34	21
Number of Subjects = 60	70	36	28

Dropping Doses Late in Study
Percentage of CRM Simulations Selecting MTD
Not Stopping for Consecutive Dose Criteria

Low MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	56	26	11
Number of Subjects = 45	55	37	20
Number of Subjects = 60	51	42	22

Determining the Number of Doses to be Considered

Too Many Doses

- Increased Cost and Subjects Needed
- Lower probability of selecting MTD

Too Few Doses

- Escalation increments are higher
- Dose toxicity range may not contain target toxicity level

Issues with Smaller Numbers of Doses

Carrying Doses Through Entire Study
Percentage of CRM Simulations Recommending No MTD
Stopping for Consecutive Dose Criteria

No MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	67	74	86
Number of Subjects = 45	67	75	89
Number of Subjects = 60	71	75	88

Carrying Doses Through Entire Study
Percentage of CRM Simulations Recommending No MTD
Not Stopping for Consecutive Dose Criteria

No MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	85	88	87
Number of Subjects = 45	94	94	91
Number of Subjects = 60	96	95	94

Why Does This Occur?

- Reason 1
  - When all doses are very toxic, the CRM will rarely recommend escalation.
  - Imposing stopping conditions for consecutive doses forces the study to stop very early.
  - Because of this, the a priori toxicity estimates carry greater weight.
  - Based mostly on a priori estimates, the CRM tends to select an MTD, even when none is present.

- Reason 2
  - With fewer doses, we can not gather sufficient data.
  - Observed toxicities may not be representative of true toxicity probabilities.

Suggested Solution

- When a small number of doses is being considered, consecutive stopping criteria should be delayed until the study is at least partially finished.

Conclusions

- Pfizer's study
  - Dropping doses likely did not impact their results.
- General CRM Design
  - Dose Effect
  - Sample Size Effect
- Ideal Scenario:
  - Large Sample Size
  - Low Number of Considered Doses
  - Delayed Stopping Criteria

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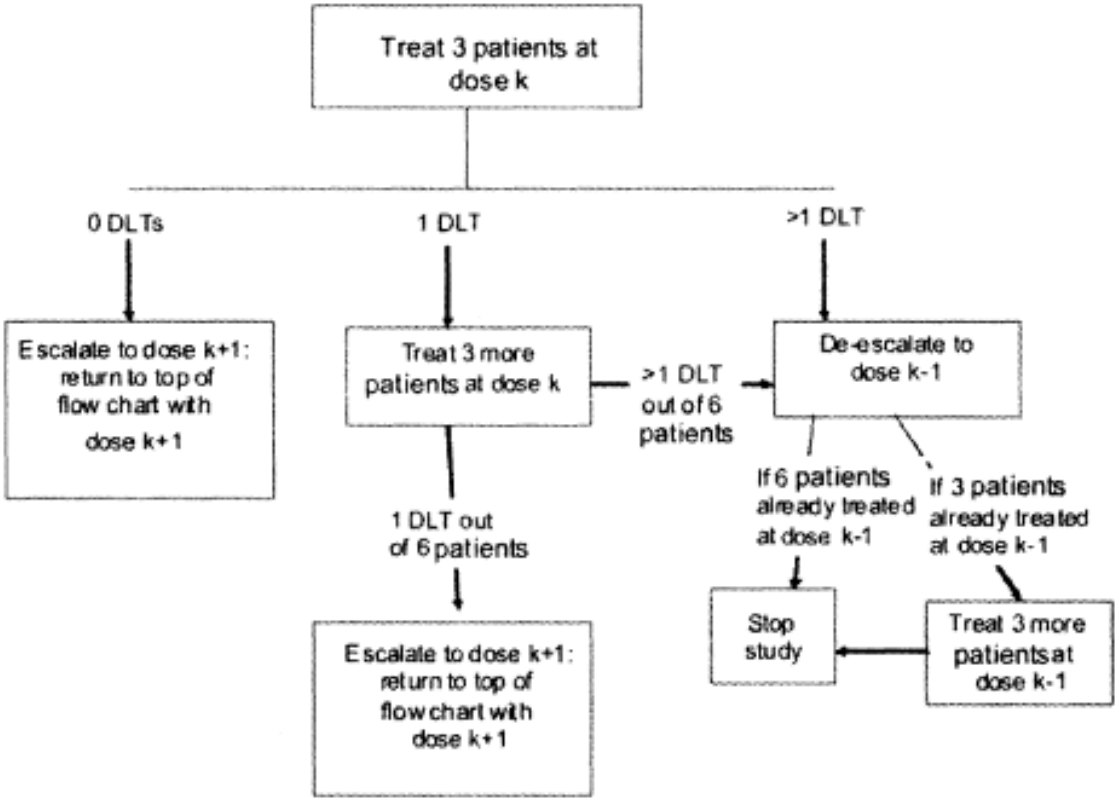
3 + 3 Method

Box 1 A standard "3 + 3" dose escalation design starting at dose k. The maximum tolerated dose (MTD) is usually defined as the highest dose at which 0 or 1 dose-limiting toxicities (DLTs) are observed in six patients (although some "3 + 3" rules call the highest dose with two or fewer dose-limiting toxicities in six patients the MTD). If de-escalation occurs at the first dose level, then the study is discontinued.



3+3 Methods Pros and Cons

Pros

- Simple
- Familiar

Cons

- Tends to treat many patients at low, ineffective doses
- Large uncertainty about MTD

Continual Reassessment Method (CRM)

Pros

- Incurs fewer toxic events
- More accurately estimates MTD

Cons

- Safety Concerns
- “Complicated”
- Unfamiliar

Our Study Design

- Going through study without dropping doses
  - Implementing a consecutive stopping criteria
    - High MTD, Medium MTD, Low MTD, No, MTD
  - Not implementing a consecutive stopping criteria
    - High MTD, Medium MTD, Low MTD, No MTD

- Going through study dropping doses
  - Implementing a consecutive stopping criteria
    - High MTD, Medium MTD, Low MTD, No MTD
  - Not implementing a consecutive stopping criteria
    - High MTD, Medium MTD, Low MTD, No MTD

Interpreting Results

Carrying All Doses Through Entire Study
Percentage of CRM Simulations Selecting MTD
Stopping for Consecutive Dose Criteria

High MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	78	55	31
Number of Subjects = 45	82	66	37
Number of Subjects = 60	82	68	44

- Carrying Doses vs Dropping Doses
- Percentages of Simulations Selecting: MTD, MTD or MTD-1, >MTD, No MTD
- Implementation of Stopping Criterion for Consecutive Doses
- MTD Profile
- Doses Under Consideration
- Number of Subjects

Determining the Number of Doses to be Considered

Too Many Doses

- Increased Cost and Subjects Needed
- Lower probability of selecting MTD

Dropping Doses Late in Study
Percentage of CRM Simulations Selecting MTD
Stopping for Consecutive Dose Criteria

High MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	100	89	69
Number of Subjects = 45	100	96	73
Number of Subjects = 60	100	98	78

Too Few Doses

- Escalation increments are higher
- Dose toxicity range may not contain target toxicity level

Evidence

Carrying All Doses Through Entire Study

Percentage of CRM Simulations Treating All Subjects at Dose 1

Stopping for Consecutive Dose Criteria

No MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	69	55	31
Number of Subjects = 45	69	58	28
Number of Subjects = 60	72	57	28

Not Stopping for Consecutive Dose Criteria

No MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	70	58	27
Number of Subjects = 45	68	56	29
Number of Subjects = 60	70	57	30

Dropping Doses Toward End of Study

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	70	60	30
Number of Subjects = 45	68	59	27
Number of Subjects = 60	69	58	31

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	66	57	27
Number of Subjects = 45	69	60	28
Number of Subjects = 60	70	57	27

Further Evidence – Small Numbers of Doses and Related Issues

Dropping Doses Late in Study
Percentage of CRM Simulations Recommending No MTD
Stopping for Consecutive Dose Criteria

No MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	68	75	86
Number of Subjects = 45	67	74	86
Number of Subjects = 60	65	74	87

Dropping Doses Late in Study
Percentage of CRM Simulations Recommending No MTD
Not Stopping for Consecutive Dose Criteria

No MTD Profile

	Doses Under Consideration		
	5 Doses	10 Doses	20 Doses
Number of Subjects = 30	86	89	88
Number of Subjects = 45	91	93	92
Number of Subjects = 60	93	96	94