CENTRE for STATISTICS in MEDICINE

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UNIVERSITY OF OXFORD

Embracing model-based designs for dose-finding trials

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Content

- Continual Reassessment Method – CRM
  - Benefit
  - Use
- Perceived barriers
- Recommendations for change

Phase I trial

- First in man study
- Test a new drug or treatment in a small group of people to evaluate safety, determine an acceptable dose, and identify side effects
- Aim: find maximum tolerated dose (MTD)
  - MTD is the highest (and therefore most efficacious) dose whose risk of toxicity is tolerable
- Outcome: dose-limiting toxicity (DLT)
  - DLT - Describes side effects related to the experimental treatment that are serious enough to be unacceptable and that prevent an increase in dose or level of that treatment.

Continual Reassessment Method - CRM

- Choose a target toxicity level
- Estimate the toxicity levels for each dose
- Choose a model to describe the dose toxicity relationship between the dose levels
- Update the model using all available data and calculate the best estimate of the MTD
- Allocate the next patient using the MTD estimate as a guideline

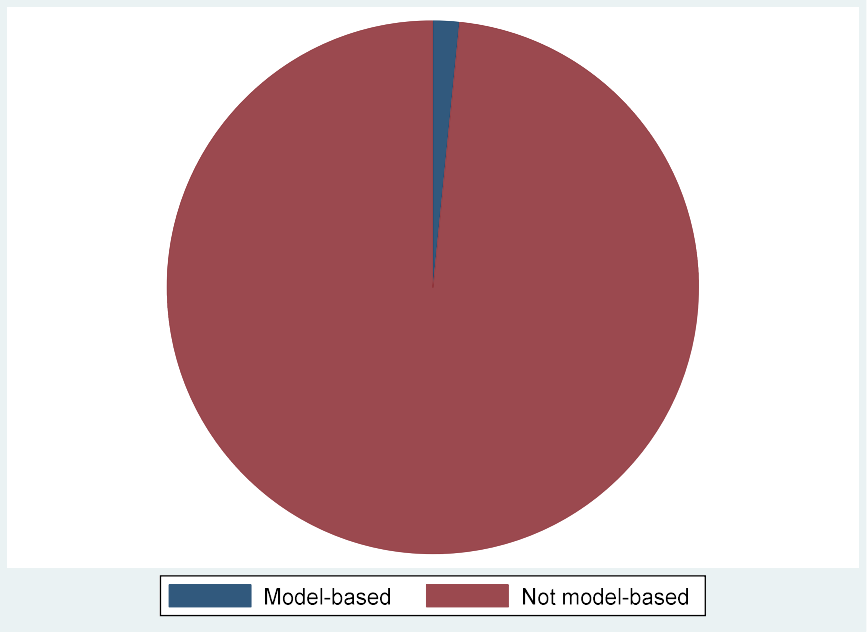
Benefits of CRM - 1

- Use data on all patients to make dose change decisions
- Treat more patients at or close to the MTD than other designs
- Select the dose with the target DLT more often then other designs

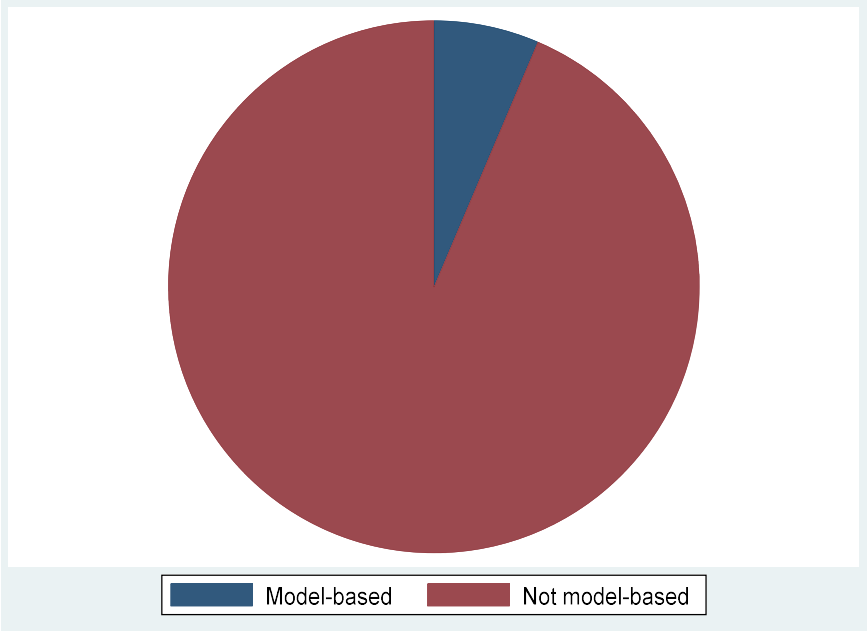
Benefits of CRM - 2

- Flexibility
  - Defining a DLT rate
  - MTD can be estimated with a required degree of precision
  - Dose-response curve shape
  - Doses can be skipped and new doses added
- Extended scope
  - Combination treatments
  - Non-binary end points
  - Time to event information

Use of CRM



1.6% of phase I cancer trials published 1991-2006[1]



6.4% of trials addressing small-molecule targeted therapies and dose-escalation published 2012-2014[2]

Use of CRM

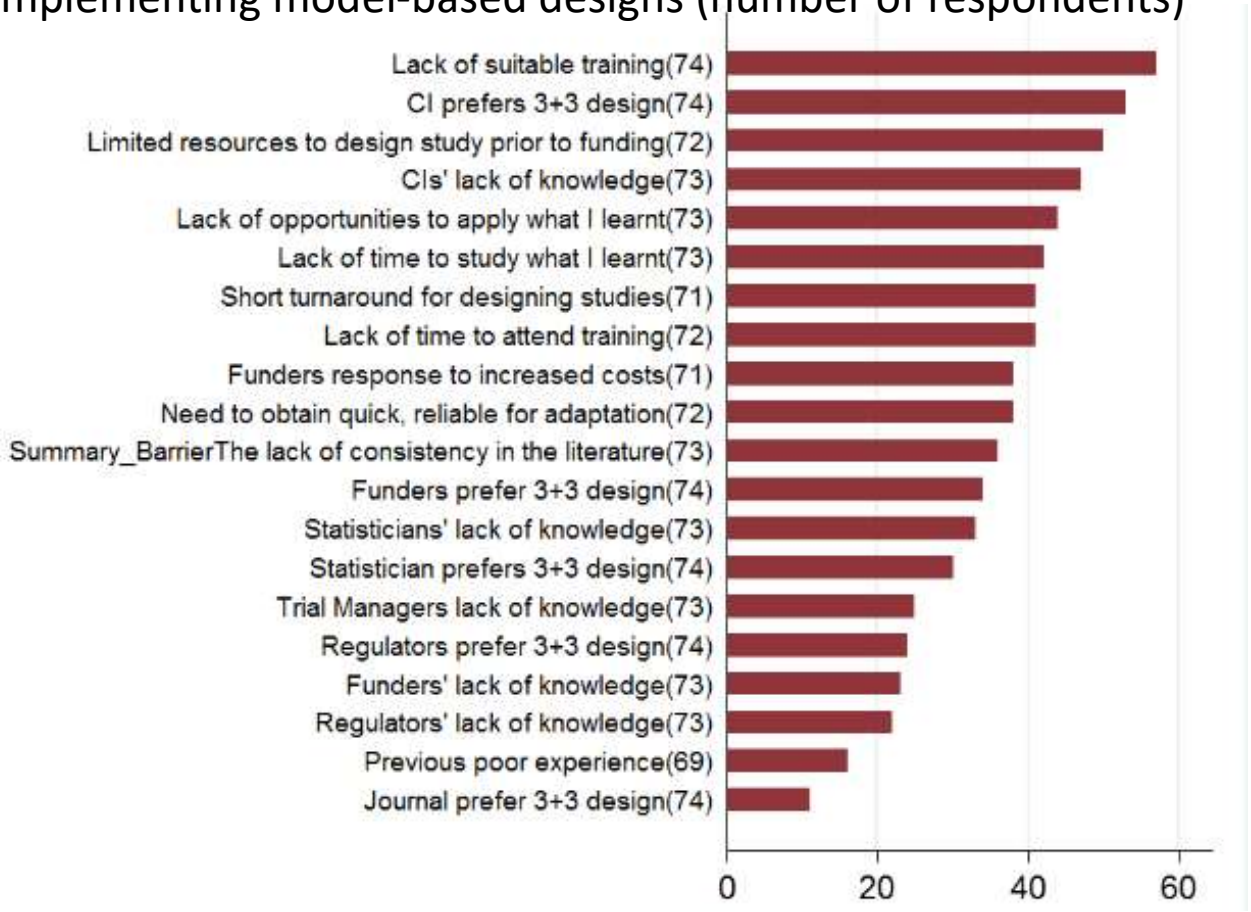
- 1.6% of phase I cancer trials published 1991-2006[1]
- 6.4% of trials addressing small-molecule targeted therapies and dose-escalation published 2012-2014[2]

[1]Regatko A et al (2007), J Clin Oncol 25(31); 4982-4986

[2]van Brummelen EMJ et al (2016), J Pharmacokinet Pharmacodyn 43: 235-242

Barriers

Percentage of respondents identifying each item as a barrier to implementing model-based designs (number of respondents)



Recommendations 1 of 3

Misconception	CI's disillusioned with the idea that model based ideas are more efficient	Address perceptions of 'efficiency' for model-based designs. Communicate that this means more often accurately identifying the correct dose rather than meaning an individual study will be shorter in duration or have a lower sample size
	Perception that regulators prefer 3+3	Communicate that UK regulators do endorse other trial designs and European regulatory guidance does not dictate use of a particular trial design

Recommendations 2 of 3

Training	Supporting uptake of model-based designs by statisticians and CIs	While training courses for utilising bespoke expensive software exist, training courses providing a broad academic introduction to the field and utilising free or inexpensive software need to be developed.
		More publications on the practicalities of setting up and running model-based trials
	Appraisal of studies by funding bodies and ethics committees	Develop tailored training sessions for key partners to support a thorough scientific appraisal of proposed designs of phase I trials
	Model-based dose-finding experienced statisticians contact	Develop a forum for contacting experienced statisticians

Recommendations 3 of 3

Design and evaluation	Lack of time to design and evaluate a model-based approach	Promote the need for early discussions between CI and statisticians to allow time to develop and evaluate
		Develop software and protocol templates
Funding	Question routine use of 3+3 designs	Encourage funders to question the use of algorithm-based designs and embrace the idea of more efficient model-based studies.
	Lack of statistical review for applications	Include statistical representation on funding boards for phase I trials.

Summary

- There is overwhelming evidence for the benefits of CRM.
- Many leading pharmaceutical companies routinely implement model-based designs.
- Our analysis identified multiple barriers for academic statisticians and clinical academics in mirroring the progress industry has made in trial design.
- Unified support from funders, regulators, and journal editors is needed to change practice and result in more accurate doses for later-phase testing, and increase the efficiency and success of clinical drug development.

Based on published paper

Embracing model-based designs for dose-finding trials.

Love SB, Brown S, Weir CJ, Harbron C, Yap C, Gaschler-Markefski B, Matcham J, Caffrey L, McKevitt C, Clive S, Craddock C, Spicer J, Cornelius V

British Journal of Cancer (2017), 117, 332-339

Number	Question	Response options					
Q1_all	Are you:	Chief Investigator	Statistician	Trial Manager	Funder	Other	Please specify
Q2	How long have you worked with dose finding studies?	I have never worked with dose finding studies	0-2 years	3-5 years	6-10 years	11-20 years	20+ years
Q3	Have you ever been involved in a dose finding study that, rather than using 3+3 or another rule-based design, used an alternative?	yes	no	don't know			
Q4_Stats	Do you have access to software to support alternative approaches to 3+3 and other rule-based designs?	yes	no	don't know			
Q4_others	Is appropriate statistical support available to you to undertake alternative approaches to 3+3 and other rule-based designs?	yes	no	don't know			
Q5_Stats	When designing a trial, how often do you consider alternatives to 3+3 and rule-based designs	always	often	not very often	never	don't know	
Q5_others	When designing a trial, how often is there discussion about alternative designs to the 3+3 or other rule-based designs?	always	often	not very often	never	don't know	

Number	Question		Response options				
Q6	In your experience, how often is the following a barrier to using alternative approaches to 3+3 and other rule-based designs ?	CI prefers 3 + 3 design	always	often	not very often	never	don't know
		Statistician prefers 3 + 3 design	always	often	not very often	never	don't know
		Funder prefers 3 + 3 design	always	often	not very often	never	don't know
		Journal prefers 3 + 3 design	always	often	not very often	never	don't know
		Regulator prefers 3 + 3 design	always	often	not very often	never	don't know
Q7	In your experience, how often is the following a barrier to using alternative approaches to 3+3 and other rule-based designs ?	Statisticians' lack of knowledge about alternatives to 3+3 -	always	often	not very often	never	don't know
		CIs' lack of knowledge about alternatives to 3+3	always	often	not very often	never	don't know
		Regulators' lack of knowledge about alternatives to 3+3	always	often	not very often	never	don't know
		Funders' lack of knowledge about alternatives to 3+3	always	often	not very often	never	don't know
		Trial Managers' lack of knowledge about alternatives to 3+3	always	often	not very often	never	don't know

Number	Question		Response options				
Q8	In my experience the following is a barrier to using alternative approaches to 3+3 and other rule-based designs:	Lack of suitable training - Strongly agree	strongly agree	agree	disagree	strongly disagree	don't know
		Lack of time to attend training - Strongly agree	strongly agree	agree	disagree	strongly disagree	don't know
		Lack of time to study what I learnt about alternative approaches - Strongly agree	strongly agree	agree	disagree	strongly disagree	don't know
		Lack of opportunities to apply what I learnt - Strongly agree	strongly agree	agree	disagree	strongly disagree	don't know
Q9	In my experience, the requirement to obtain quick, reliable data to inform adaptation forms a particular barrier to using alternatives to 3+3 and other rule-based designs?		strongly agree	agree	disagree	strongly disagree	don't know
Q10	In my experience, the lack of consistency in the literature supporting alternatives to 3+3 and other rule-based designs is a barrier to using them		strongly agree	agree	disagree	strongly disagree	don't know
Q11	In my experience, the limited resources available to design a study prior to funding constrain our ability to use alternatives to 3+3 and other rule-based designs		strongly agree	agree	disagree	strongly disagree	don't know

Number	Question		Response options				
Q12	In my experience, funders do not respond positively to the increased costs involved in the implementation of designs that are more complex than 3+3 and other rule-based designs		strongly agree	agree	disagree	strongly disagree	don't know
Q13	In my experience, the short turnaround for designing studies is a barrier to considering alternatives to 3+3 and other rule-based designs?		strongly agree	agree	disagree	strongly disagree	don't know
Q14	I previously had a poor experience of using an alternative approach to 3+3/rule-based designs		Yes	No	Please provide brief details		
Q15	Do you have any other concerns about using alternative approaches to 3+3/rule-based designs?		Yes	No	Please specify		