Supplementary material

Supplementary table A

Pubmed search strategy for Continual Reassessment Method and 3+3

1. "Continual Reassessment Method" [tiab] OR "Continual Reassessment Methods" [tiab] (204)
2. "continual reassessment" [tiab] OR "continuous reassessment" [tiab] (274)
3. CRM [tiab] (2517)
4. TITE-CRM [tiab] (15)
5. mCRM [tiab] (12)
6. B-CRM [tiab] (3)
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6 (2694)
8. "3 + 3" [tiab] (118334)
9. "A + B design" [tiab] OR "A + B designs" [tiab] (65)
10. "rolling six" [tiab] OR "rolling-6" [tiab] OR "rolling 6" [tiab] OR "rolling-six" [tiab] (22)
11. "algorithm based" [tiab] OR "algorithm-based" [tiab] (4553)
12. "rule based" [tiab] OR "rule-based" [tiab] (2380)
13. "adaptive design" [tiab] OR "adaptive designs" [tiab] (483)
14. "traditional escalation rule" [tiab] (0)
15. "standard design" OR "standard designs" [tiab] (220)
16. "algorithmic design" OR "algorithmic designs" [tiab] (23)
17. #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 (126009)
18. #7 AND #17 (61)
19. Clinical Trials, Phase I as Topic [mh] OR Clinical Trial, Phase I [pt] (18782)
20. "phase I" [tiab] OR "phase one" [tiab] OR "phase 1" [tiab] OR "first-in-man" [tiab] OR "first-in-human" [tiab] OR "first in man" [tiab] OR "first in human" [tiab] OR "first-in-person" [tiab] OR "first in person" [tiab] OR "initial human" [tiab] OR "dose-finding trial" [tiab] OR "dose-finding trials" [tiab] OR "dose-finding study" [tiab] OR "dose-finding studies" [tiab] OR "dose-finding design" [tiab] OR "dose escalation trial" [tiab] OR "dose escalation trials" [tiab] OR "dose escalation study" [tiab] OR "dose escalation studies" [tiab] OR "dose escalation design" [tiab] OR "dose-ranging clinical trial" [tiab] OR "dose-ranging clinical trials" [tiab] OR "dose-ranging trial" [tiab] OR "dose-ranging trials" [tiab] (46574)
21. #19 OR #20 (51905)
22. #18 AND #21 (38)

Supplementary table B

Embase search strategy for Continual Reassessment Method and 3+3

1. Continual Reassessment Method/ (37)
2. (continual adj reassessment adj method$).ti,ab. (321)
3. ((continual OR continuous) adj reassessment).ti,ab. (425)
4. Quasi-CRM.ti,ab. (4)
5. CRM.ti,ab. (3403)
6. TITE-CRM.ti,ab. (30)
7. mCRM.ti,ab. (15)
8. B-CRM.ti,ab. (4)
9. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 (3688)
10. "3+3".ti,ab. (45474)
11. "3 plus 3".ti,ab. (13)
12. "A+B design$".ti,ab. (80)
13. "rolling six".ti,ab. (24)
14. "rolling-six".ti,ab. (24)
15. "rolling 6".ti,ab. (28)
16. "rolling-6".ti,ab. (28)
17. (algorithm adj based).ti,ab. (5850)
18. (algorithm-based).ti,ab. (5850)
19. "rule based".ti,ab. (2683)
20. "rule-based".ti,ab. (2683)
21. (adaptive adj design$).ti,ab. (720)
22. (traditional adj escalation adj rule).ti,ab. (1)
23. (standard adj design$).ti,ab. (416)
24. (algorithmic adj design$).ti,ab. (20)
25. (empirically adj based adj traditional adj method$).ti,ab. (1)
26. (empirically-based adj traditional adj method$).ti,ab. (1)
27. 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 (55237)
28. 9 AND 27 (80)
29. "Phase 1 clinical trial (topic)"/ (9214)
30. Phase I Clinical Trial/ (29437)
31. "phase I".ti,ab. (47733)
32. "phase 1".ti,ab. (15020)
33. "phase one".ti,ab. (1459)
34. "first-in-man".ti,ab. (1169)
35. "first in man".ti,ab. (1169)

36. "first-in-human".ti,ab. (1654)
37. "first in human".ti,ab. (1654)
38. "first-in-person".ti,ab. (8)
39. "first in person".ti,ab. (8)
40. (initial adj human).ti,ab. (344)
41. "dose-finding trial$".ti,ab. (301)
42. "dose-finding stud$".ti,ab. (2024)
43. "dose-finding design$".ti,ab. (82)
44. "dose escalation trial$".ti,ab. (1051)
45. "dose escalation stud$".ti,ab. (3333)
46. "dose escalation design$".ti,ab. (486)
47. "dose-ranging clinical trial$".ti,ab. (33)
48. "dose-ranging trial$".ti,ab. (254)
49. Drug Dose Escalation/ (16490)
50. Radiation Dose Escalation/ (386)
51. 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 (95153)
52. 28 AND 51 (66)

Supplementary Table C: Barriers to embracing model based design questionnaire

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	
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	always	often	not very often	never	don't know
		Funders' lack of knowledge about alternatives to 3+3 - Always	always	often	not very often	never	don't know
		Trial Managers' lack of knowledge about alternatives to 3+3 - Always	always	often	not very often	never	don't know
		Lack of suitable training - Strongly agree	strongly agree	agree	disagree	strongly disagree	don't know
Q8	In my experience the following is a barrier to using alternative approaches to 3+3 and other rule-based designs:	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
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		

Supplementary Table D: Free text response to Q14 and Q15

Two prior bad experiences: 1) Bayesian method which estimated the next dose level - we opened several dose cohorts over several months all around the MTD when this could have been determined faster by 3+3 ii) CRM method where some of the participating sites did not turnaround eCRF data entry in a timely manner e.g. 21 days instead of 5 which delayed dose decisions.
CRM / Bayesian methods require real time data capture which may not be resourced in an academic centre, real time PK analysis and real time statistical support
We are often looking for data (whether tolerability or pharmacodynamic) at multiple does levels and whilst model-based approaches fit a curve (and estimate optimal dose most accurately), the information at others doses can be limited to demonstrate a dose-effect or investigate exploratory biomarkers that may give a better readout of optimal dose. We can then recruit more patients at those other levels but then lose some of the efficiency gains.
As a phase I trialist I have used a variety of designs, 3+3 has the advantage that it is reliable and works
Not yet convinced they provide more reliable dose finding
I have only experience of one true alternative trial design in phase I and it actually worked well but (1) I don't think it saved time or reduced the number of cohorts studied (2) on one occasion at least the investigators and study staff over-ruled the next dose level, feeling it was too high and not safe enough (3) it as very complex (only one person seemed to know what the next dose level would be for a patient)
I would like to use more efficient approaches more frequently. However, with FIM studies of novel agents in oncology, nowadays, there are often too many unknowns to make ambitious dose escalation schemes acceptable (eg. PK, PD and toxicities not predictable). The other main barrier is lack of availability of good statisticians to advise on design
have had good experiences using rolling 6, CRM and other adaptive designs
main issue is 'selling' them to some funders and fellow clinicians
the trial took much, much longer and far too many patients were recruited into the lower doses compared to a 3+3
Lack of dedicated statistical support and experience of e.g. Bayesian designs that led to slow trials and far too many patients for a phase 1
In various discussions with other CIs etc., there seems to be a consensus that there is no current design which is consistently superior to 3+3
Although I have never used an alternative approach I am currently in the process of incorporating 'alternative' elements into a phase I design so have awareness of the issues.
Much slower and binary based on DLTs with too little flexibility to use other toxicity data, PD and PK data
To what extend the rule-based designs can be accepted by the PI? How to standardize procedure of rule-based designs?
Need to be confident enough to design, analyse, write up, persuade CI, and communicate all of that with non-statistical audiences - easier if working in an environment where others are doing this regularly, for support - but accessible training materials / software / literature would help
Not involved in such studies, but if required to be I would want a generally-accepted theoretical approach with easily accessible software (much more of an issue for those who don't normally do these studies than for experts). The 3+3 design meets these requirements