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Supplementary Material

CONSORT-DEFINE explanation and elaboration: recommendations for enhancing reporting quality and impact of early phase dose-finding clinical trials

[Rekowski et al.]

Supplementary Box 1: Glossary

Activity
A measure of the physiological response that an intervention produces.

Algorithm based (rule based) design
A trial design that uses a simple set of predefined algorithms or rules to guide the decision making process for dose escalation or de-escalation. Examples include traditional 3+3, accelerated titration, and pharmacologically guided dose escalation designs.[1,2]

Biomarker substudy
A part of a clinical trial that investigates biomarkers, which are "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions. Biomarkers could include molecular, histological, radiographic, or physiological characteristics. A biomarker is not a measure of how an individual feels, functions, or survives."[3]

Clinical benefit
A favourable effect on a meaningful aspect of how a participant feels, functions, or survives as a result of an intervention.[4]

Delphi survey
A series of questionnaires used sequentially to gather diverse opinions that allow experts to develop ideas about potential future developments around an issue. The questionnaires are developed throughout the process in relation to the responses given by participants.

Dose
In this article, dose is defined broadly and can be considered synonymous with dosage or dosing regimen (dose or schedule), or a unit dose. The unit dose is the amount or intensity of an intervention (e.g., drug quantity, radiotherapy, exercise level), or the extent to which a participant might be exposed to an intervention on a single occasion. Information on dosage should include aspects of the intervention that describe how many times it was delivered and for how long—such as the number of sessions; their schedule; and their duration, intensity, or dose.[5]

Dose escalation or de-escalation
An incremental increase or decrease (or up-titration or down-titration) in the strength of any intervention (e.g., a drug or exercise intensity level) to improve its tolerability or maximise its pharmacological or clinical effect.

Dose limiting criteria
Effects or markers that are presumably related to the intervention and that either are considered unacceptable or show the desired level of effect has been achieved and a further increase in dose is not required.[6]

Dose limiting toxicity
Side effects of an intervention that are serious enough to prevent an increase in the dose of that intervention.[2]

Dosing regimen or dosage
See dose.

Early phase dose-finding trial

An early phase trial where different doses of the investigated intervention are given to groups of participants, with interim assessments of the safety/tolerability (and other markers such as activity) of the intervention.

Estimand framework

Estimands provide a structural framework to define the target of estimation for a particular clinical trial objective.[7,8] They require to specify the treatment condition of interest, the population targeted by the clinical question, the variable of interest or endpoint used to answer that question, the handling strategies for intercurrent events (ie, events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question), and a population level summary of the variable or endpoint.

Expansion cohort or dose expansion

A part of a dose escalation clinical trial that aims to accrue additional participants after an initial dose escalation part with different or targeted eligibility criteria to collect additional information on safety or activity.[9]

Group

Can refer to an intervention group or arm, or specifically defined subgroups of the targeted participant population based on, for example, participant or disease characteristics.

Harms

The totality of possible adverse consequences of an intervention or treatment; they are the direct opposite of benefits, against which they must be compared.[10] Harms can comprise of adverse events, adverse (drug) reactions, toxicities, treatment emergent adverse events, or those that are intolerable by participants.[10,11] They can also include tolerability assessment using patient reported outcomes as complementary to investigators' reporting.[12,13]

Interim analysis or review

A statistical analysis or review of accumulating data from an ongoing trial (interim data) to inform trial adaptations (before the final analysis), which might or might not involve treatment group comparisons.[14]

Model assisted design

A trial design that combines a clearly predetermined algorithm to guide the dose escalation or de-escalation as in rule based designs, and an underlying statistical model, as in model based designs.[15] Examples include the modified toxicity probability interval design[16] and the bayesian optimal interval design.[17]

Model based design

A trial design that assumes a relation between the dose of the intervention given to the participant and the likelihood of the participant experiencing an effect (such as toxicity or activity) and uses a parametric model to estimate that association. Examples include the continual reassessment method,[18] escalation with overdose control,[19] and the efficacy-toxicity trade-off based design.[20]

Multiple ascending dose

A trial design where a small number of participants (healthy volunteers or participants) receive several doses of an intervention over time to assess safety or tolerability and pharmacokinetic and pharmacodynamic profiles. Doses can remain the same or increase within a participant. The dose level is subsequently escalated for further participants according to the protocol, assuming that strict safety, effect, or pharmacokinetic criteria are met.

Operating characteristics

Characteristics that relate to the statistical behaviour or performance of the trial design in answering research questions. These might include the probability of correctly selecting the correct dose, statistical power, false positive error rate, bias in estimation of treatment effect, or probability of each adaptation taking place.[14,21]

Pharmacodynamics

Described as what a drug does to the body; pharmacodynamics refer to how the drug works and how it affects the body.

Pharmacokinetics

Described as what the body does to a drug; pharmacokinetics refer to the movement of the drug into, through, and out of the body. It includes the analysis of chemical metabolism and the measurement or modelling of a substance from the moment that it is used up to the point when it is completely eliminated from the body.

Prespecified decision making criteria

Planned or prespecified rules to guide decisions, describing whether, how, and when the proposed trial adaptations will be used during the trial. The criteria involve prespecifying a set of actions guiding how decisions about implementing the trial adaptations are made given interim observed data (decision rules). They also involve prespecifying limits or parameters to trigger trial adaptations (decision boundaries), for example, stopping boundaries that relate to prespecified limits regarding decisions to stop the trial or any treatment arms early.

Single ascending dose

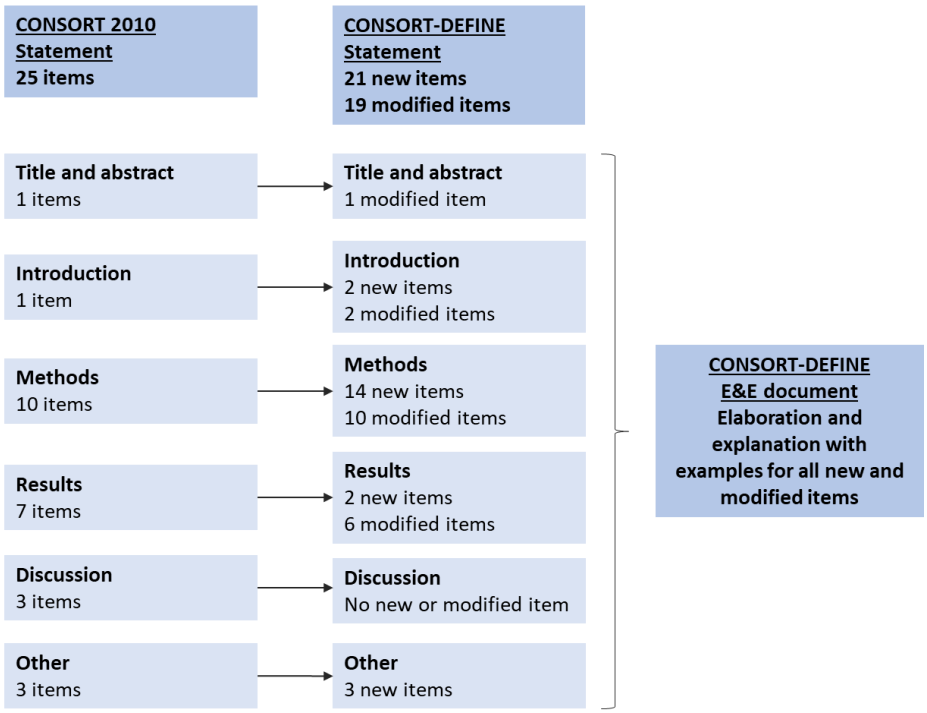
A trial design in which a small number of participants receive one dose of a therapeutic intervention at a given dose level to assess safety or tolerability and characterise the pharmacodynamics and pharmacokinetics of the intervention. Single ascending dose trials are often conducted in a small number of healthy volunteers, although some trials recruit participants with a disease of interest. The dose is subsequently escalated for further participants according to the protocol, assuming that strict safety, effect, or pharmacokinetic criteria are met.

Transition points

The points or parts in a clinical trial when the decision can be made to proceed to the next stage or phase, such as from dose escalation to dose expansion, from phase 1 to phase 2, or from a single ascending dose to multiple ascending dose.

Trial (design) adaptations

Prespecified changes or modifications (defined in advance) that can be made to various aspects of a trial while it is ongoing without undermining the trial's validity and integrity.[22] These prespecified modifications are driven by accruing interim data.[23] Examples include adjusting the doses; changing the predetermined sample size; stopping the trial early for efficacy, futility, or safety; and switching the allocated treatment of participants owing to a lack of benefit or safety issues.[14]



Supplementary Figure 1 Evolution from CONSORT 2010 to CONSORT-DEFINE and CONSORT-DEFINE elaboration and explanation (E&E) document with an overview of new and modified items in the CONSORT-DEFINE statement by section.

Scenario		Dose -3	Dose -2	Dose -1	Dose 0	Dose 1	Dose 2	Dose 3	Dose 4	Requiring Extension (%)	Sample Size
	Prior DLT		0.03	0.07	0.12	0.2	0.3	0.4	0.6		
1	True DLT rate		**0.2**	0.36	0.45	0.55	0.6	0.7	0.8	1.6	21[15,24]
	P(select)	0.09	**0.7**	0.17	0.03	0	0	0	0		
2	True DLT rate		0.07	**0.2**	0.36	0.45	0.55	0.6	0.7	3.38	24[21,27]
	P(select)	0	0.24	**0.5**	0.23	0.02	0	0	0		
3	True DLT rate		0.05	0.07	**0.2**	0.36	0.45	0.55	0.6	2.66	24[21,27]
	P(select)	0	0.02	0.17	**0.6**	0.18	0.02	0	0		
4	True DLT rate		0.03	0.05	0.07	**0.2**	0.36	0.45	0.55	2.36	24[21,27]
	P(select)	0	0	0.01	0.19	**0.6**	0.18	0.02	0		
5	True DLT rate		0.01	0.03	0.05	0.07	**0.2**	0.36	0.45	4.54	24[21,27]
	P(select)	0	0	0	0.02	0.21	**0.57**	0.18	0.01		
6	True DLT rate		0.01	0.01	0.03	0.05	0.07	**0.2**	0.36	5.5	27[24,27]
	P(select)	0	0	0	0	0.03	0.22	**0.62**	0.12		
7	True DLT rate		0	0.01	0.01	0.03	0.05	0.07	**0.2**	5.94	24[24,27]
	P(select)	0	0	0	0	0.01	0.04	0.37	**0.58**		
8	True DLT rate		0.5	0.6	0.65	0.7	0.75	0.8	0.9	0	9[6,15]
	P(select)	**0.81**	0.19	0	0	0	0	0	0		

Supplementary Figure 2 Table A8.1 from the trial protocol of Craddock et al.[24], used under CC BY 4.0.

Characteristic	Single ascending dose						Multiple ascending dose				
	500 mg (*n* = 8)	1000 mg (*n* = 8)	2000 mg (*n* = 8)	4000 mg (*n* = 8)	Overall (*n* = 32)	Placebo (*n* = 8)	250 mg BID (*n* = 8)	500 mg BID (*n* = 8)	1000 mg BID (*n* = 8)	Overall (*n* = 24)	Placebo (*n* = 6)
Age (years)											
Mean ± SD	47.6 ± 14.94	42.0 ± 20.47	41.5 ± 15.58	40.6 ± 18.55	42.9 ± 16.89	28.3 ± 13.25	43.3 ± 10.43	47.9 ± 14.93	51.8 ± 13.51	47.6 ± 13.00	48.8 ± 20.91
Median	47.50	37.00	41.50	35.50	43.00	25.00	47.00	53.00	50.50	50.50	50.50
Min, max	23.0, 66.0	19.0, 67.0	21.0, 62.0	21.0, 69.0	19.0, 69.0	18.0, 58.0	27.0, 53.0	20.0, 69.0	29.0, 70.0	20.0, 70.0	25.0, 70.0
Sex, n (%)											
Male	4 (50.0)	4 (50.0)	4 (50.0)	4 (50.0)	16 (50.0)	4 (50.0)	4 (50.0)	4 (50.0)	4 (50.0)	12 (50.0)	3 (50.0)
Race, n (%)											
Asian	0	0	1 (12.5)	2 (25.0)	3 (9.4)	0	1 (12.5)	0	0	1 (4.2)	2 (33.3)
Black	2 (25.0)	2 (25.0)	1 (12.5)	0	5 (15.6)	2 (25.0)	1 (12.5)	2 (25.0)	2 (25.0)	5 (20.8)	1 (16.7)
White	6 (75.0)	5 (62.5)	6 (75.0)	6 (75.0)	23 (71.9)	6 (75.0)	6 (75.0)	6 (75.0)	6 (75.0)	18 (75.0)	3 (50.0)
Other	0	1 (12.5)	0	0	1 (3.1)	0	0	0	0	0	0
BMI (kg/m^2)											
Mean ± SD	26.2 ± 4.11	24.0 ± 4.11	23.0 ± 2.83	28.7 ± 4.73	25.5 ± 4.41	23.9 ± 4.02	27.6 ± 1.28	27.8 ± 4.37	26.8 ± 3.15	27.4 ± 3.08	25.8 ± 4.48
Median	24.29	25.31	22.37	27.51	25.50	22.17	27.70	27.80	25.90	27.40	25.55
Min, max	22.7, 32.4	17.9, 28.3	19.8, 27.6	22.0, 25.3	17.9, 35.3	20.2, 32.2	25.5, 29.7	21.6, 35.2	23.6, 32.7	21.6, 35.2	19.8, 31.7

Supplementary Figure 3 Table 1 from Chandorkar et al.[25], used under CC BY 4.0.

Demographic variables	Placebo $n = 10$	Oxa 0.25 mg $n = 6$	Oxa 0.5 mg $n = 6$	Oxa 1.5 mg $n = 6$	Oxa 2.5 mg $n = 6$	Oxa 5 mg $n = 6$
Age, years						
Mean	23.7	21.0	22.5	24.0	23.3	22.8
SD	3.9	3.1	2.6	4.6	3.9	2.4
Range	20–32	18–25	18–26	19–31	19–28	20–26
Height (cm)						
Mean	183.6	181.1	182.7	183.8	186.0	186.8
SD	5.0	9.2	6.7	8.7	11.2	4.0
Range	175.8–192.3	171.8–195.0	175.9–191.4	170.0–191.7	174.4–204.2	181.6–191.1
Weight (kg)						
Mean	77.7	73.1	79.4	71.9	73.8	76.8
SD	8.4	10.9	11.3	9.0	11.1	5.6
Range	67.7–94.9	61.7–84.9	68.4–96.5	61.2–86.2	60.2–85.8	68.5–82.8
Body mass index (kg/m^2)						
Mean	23.1	22.4	23.7	21.3	21.2	22.0
SD	1.9	3.7	2.3	1.6	1.3	1.0
Range	19.9–26.8	18.3–27.2	21.5–26.8	19.6–24.1	19.8–22.9	20.8–23.0

Supplementary Figure 4 Table 1 from Dijkstra et al.[26], reprinted from British Journal of Clinical Pharmacology with permission from John Wiley and Sons.

System organ class/preferred term	Number (%) of subjects					
	Placebo $n = 10$	Cohort 4 Oxa 0.25 $n = 6$	Cohort 1 Oxa 0.5 $n = 6$	Cohort 5 Oxa 1.5 $n = 6$	Cohort 2 Oxa 2.5 $n = 6$	Cohort 3 Oxa 5.0 $n = 6$
Any event	2 (20)	2 (33)	1 (16.7)	6 (100)	6 (100)	6 (100)
Ear and labyrinth disorders						
Tinnitus					1 (16.7)	
Eye disorders						
Asthenopia					1 (16.7)	1 (16.7)
Gastrointestinal disorders						
Nausea	1 (10.0)			3 (50.0)	2 (33.3)	2 (33.3)
Vomiting				1 (16.7)		
General disorders and administration site conditions						
Asthenia				1 (16.7)		
Fatigue	1 (10.0)				3 (50.0)	1 (16.7)
Feeling abnormal				1 (16.7)		1 (16.7)
Feeling of relaxation		1 (16.7)				
Nervous systems disorders						
Balance disorder					1 (16.7)	
Disturbance in attention				1 (16.7)		
Dizziness		1 (16.7)			1 (16.7)	
Dysarthria					1 (16.7)	
Headache	1 (10.0)			1 (16.7)	1 (16.7)	
Paraesthesia		1 (16.7)				
Somnolence	2 (20.0)	1 (16.7)	1 (16.7)	1 (16.7)	2 (33.3)	1 (16.7)
Tremor				1 (16.7)		
Vision blurred				2 (33.3)	2 (33.3)	2 (33.3)
Psychiatric disorders						
Disturbance in attention						1 (16.7)
Euphoric mood					1 (16.7)	2 (33.3)
Hallucination, visual						4 (66.7)
Vascular disorders						
Dizziness		1 (16.7)		4 (66.7)	3 (50.0)	6 (100.0)
Flushing				1 (16.7)		
Hypotension				3 (50.0)		
Orthostatic hypotension				1 (16.7)	2 (33.3)	
Pallor				1 (16.7)		
Syncope						1 (16.7)

Supplementary Figure 5 Table 3 from Dijkstra et al.[26], reprinted from British Journal of Clinical Pharmacology with permission from John Wiley and Sons.

References

1. Araujo DV, Oliva M, Li K, Fazelzad R, Liu ZA, Siu LL. Contemporary dose-escalation methods for early phase studies in the immunotherapeutics era. *European Journal of Cancer* 2021; **158**: 85-98.
2. Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in phase I cancer clinical trials. *J Natl Cancer Inst* 2009; **101**(10): 708-20.
3. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools). 2016. https://www.ncbi.nlm.nih.gov/books/NBK326791/ (accessed 10 June 2024).
4. Hufnagel SB. Defining and Assessing Clinical Benefit: A Regulatory Perspective. 2019. https://www.fda.gov/media/131585/download (accessed 31 March 2023).
5. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014; **348**(mar07 3): g1687-g.
6. Dalton EJ, Churilov L, Lannin NA, Corbett D, Campbell BCV, Hayward KS. Multidimensional Phase I Dose Ranging Trials for Stroke Recovery Interventions: Key Challenges and How to Address Them. *Neurorehabilitation and Neural Repair* 2021; **35**(8): 663-79.
7. Lynggaard H, Bell J, Lösch C, et al. Principles and recommendations for incorporating estimands into clinical study protocol templates. *Trials* 2022; **23**(1).
8. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials E9(R1). 2019. https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf (accessed 21 June 2024).
9. Iasonos A, O'Quigley J. Dose expansion cohorts in Phase I trials. *Stat Biopharm Res* 2016; **8**(2): 161-70.
10. Ioannidis JPA. Better Reporting of Harms in Randomized Trials: An Extension of the CONSORT Statement. *Annals of Internal Medicine* 2004; **141**(10): 781.
11. European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man. 2017. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf (accessed 21 June 2024).
12. Basch E, Yap C. Patient-Reported Outcomes for Tolerability Assessment in Phase I Cancer Clinical Trials. *J Natl Cancer Inst* 2021; **113**(8): 943-4.
13. Retzer A, Sivell S, Scott H, et al. Development of a core outcome set and identification of patient-reportable outcomes for primary brain tumour trials: protocol for the COBra study. *BMJ Open* 2022; **12**(9): e057712-e.
14. Dimairo M, Pallmann P, Wason J, et al. The Adaptive designs CONSORT Extension (ACE) statement: a checklist with explanation and elaboration guideline for reporting randomised trials that use an adaptive design. *BMJ* 2020; **369**: m115-m.
15. Kurzrock R, Lin C-C, Wu T-C, Hobbs BP, Pestana RC, Hong DS. Moving Beyond 3+3: The Future of Clinical Trial Design. *American Society of Clinical Oncology Educational Book* 2021; (41): e133-e44.
16. Ji Y, Wang S-J. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. *J Clin Oncol* 2013; **31**(14): 1785-91.
17. Yuan Y, Hess KR, Hilsenbeck SG, Gilbert MR. Bayesian Optimal Interval Design: A Simple and Well-Performing Design for Phase I Oncology Trials. *Clin Cancer Res* 2016; **22**(17): 4291-301.
18. O'Quigley J, Pepe M, Fisher L. Continual Reassessment Method: A Practical Design for Phase 1 Clinical Trials in Cancer. *Biometrics* 1990; **46**(1): 33.
19. Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. *Statistics in Medicine* 1998; **17**(10): 1103-20.
20. Thall PF, Cook JD. Dose-Finding Based on Efficacy-Toxicity Trade-Offs. *Biometrics* 2004; **60**(3): 684-93.
21. Wages NA, Horton BJ, Conaway MR, Petroni GR. Operating characteristics are needed to properly evaluate the scientific validity of phase I protocols. *Contemporary clinical trials* 2021; **108**: 106517-.
22. Lorch U, O'Kane M, Taubel J. Three steps to writing adaptive study protocols in the early phase clinical development of new medicines. *BMC Med Res Methodol* 2014; **14**: 84-.
23. Chow S-C, Chang M, Pong A. Statistical Consideration of Adaptive Methods in Clinical Development. *Journal of Biopharmaceutical Statistics* 2005; **15**(4): 575-91.
24. Craddock C, Slade D, De Santo C, et al. Combination Lenalidomide and Azacitidine: A Novel Salvage Therapy in Patients Who Relapse After Allogeneic Stem-Cell Transplantation for Acute Myeloid Leukemia. *Journal of Clinical Oncology* 2019; **37**(7): 580-8.
25. Chandorkar G, Zhan Q, Donovan J, Rege S, Patino H. Pharmacokinetics of surotomycin from phase 1 single and multiple ascending dose studies in healthy volunteers. *BMC Pharmacol Toxicol* 2017; **18**(1): 24.
26. Dijkstra FM, Zuiker RGJA, Heuberger JAAC, et al. Administration of oxathridine, a first-in-class histamine-3 receptor partial agonist in healthy male volunteers: Central nervous system depression and pseudo-hallucinations. *Br J Clin Pharmacol* 2024; **90**(1): 321-35.