Assessing the reporting quality of early phase dose-finding trials (#247)

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Background

Incomplete, unclear, or inaccurate reporting of the design, conduct and analysis of early phase dose-finding trials can hinder interpretability, reproducibility and impact on timely clinical development and lead to erroneous conclusions on tolerability and efficacy. There currently exists no work that comprehensively assesses the reporting quality in this setting. We conducted a rapid methodological review to address this gap by investigating the quality of published trials using broadly the CONSORT 2010 checklist with added items specific to dose-finding trials.

Methods

Data Extraction Items: Drawn from guidance documents (including CONSORT 2010 [1], Adaptive designs CONSORT Extension (ACE), SPIRIT 2013) with added items specific to early phase dose-finding trials from relevant published literature.

Selection of Clinical Trials Papers: MEDLINE via PubMed was searched for articles published in English, from 2011 to 2020.

Key Inclusion Criteria: 1) Phase I or I/II clinical trials, where interim dosing decisions have to be undertaken (escalate, de-escalate, stay at the current level or stop a trial early), with the aim of identifying a recommended dosing regimen(s) for further testing; 2) reported main analysis of a trial.

476 trials (238 oncology and 238 non-oncology) were randomly selected over three stages, with a sample validated by independent reviewers.

Results

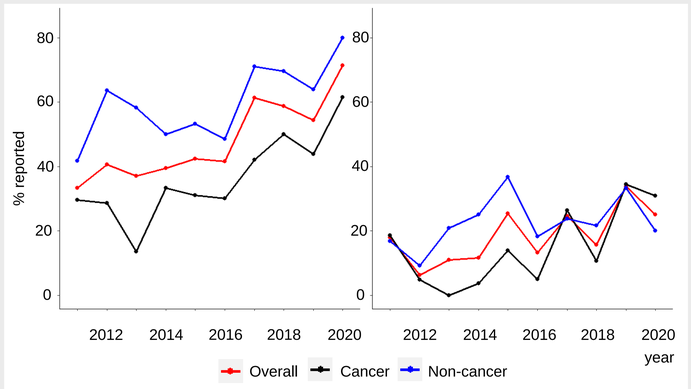
We noticed the difference in describing the dose-escalation component in oncology and non-oncology settings:	n (%) reported: cancer (n = 238)	non-cancer (n = 238)
Definition of dose-limiting toxicity (DLT) or safety measures used to inform dose-decisions provided, if applicable	199 (84%)	50 (29%)
DLT assessment period provided, if applicable	172 (74%)	29 (35%)
Provided escalation and de-escalation criteria/rules (at least, partially)	200 (84%)	95 (40%)
Definition of maximum tolerated dose (MTD) or recommended dose(s), if applicable	163 (72%)	9 (6%)

We also looked at access to Protocol, Statistical Analysis Plan (SAP) and lay summary. Those are **rarely reported**. For overall 476 trials: Protocol (6.3%), SAP (3.8%), lay summary (1.5%).

The key items that are frequently **not** reported in both oncology and non-oncology settings include:

	n (%) reported: cancer (n = 238)	non-cancer (n = 238)
Methods		
Planned/maximum sample size	69 (29%)	104 (44%)
with justification	35 (15%)	58 (24%)
Recruitment method	19 (8%)	51 (21%)
Oversight committees	39 (16%)	89 (37%)
roles and structure	17 (7%)	40 (17%)
Who makes dose decisions	10 (4%)	39 (16%)
Definition of analysis population:		
dose-determination	108 (45%)	111 (47%)
safety	114 (48%)	129 (54%)
key outcomes	100 (42%)	131 (56%)
Rationale for starting dose	52 (22%)	42 (18%)
Results		
Baseline demographic and clinical characteristics by each dose level	70 (29%)	148 (62%)
Settings and locations where data were collected	86 (36%)	150 (63%)
Participant flow diagram/table	85 (36%)	144 (61%)
Losses/exclusions for each dose level	30 (13%)	85 (36%)

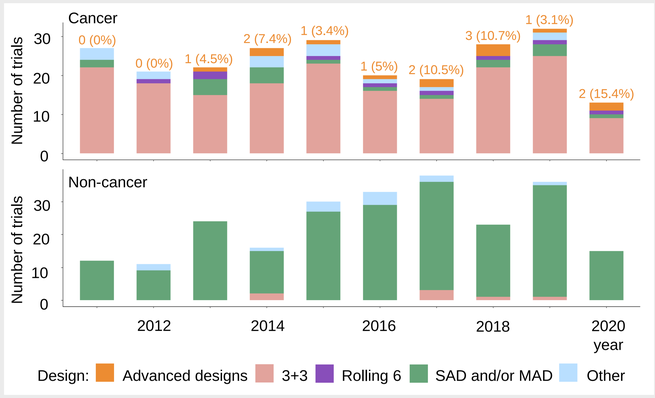
There is a positive trend in the reporting of some items including participant flow (flow diagram/table) and sample size justification.



Participant flow chart provided by a flow diagram and/or a table

Planned/maximum sample size justified

The prevailing designs were 3+3 for the oncology settings and single ascending dose (SAD) and/or multiple ascending dose (MAD) for non-oncology settings. The percentage of oncology trials using advanced designs has increased over time. The advanced designs include model-based designs (e.g. continual reassessment method) and model-assisted designs (e.g. modified toxicity probability interval method).



Conclusions

Important methodological features in design, conduct and analysis are frequently omitted. Overall, non-cancer trials appear to be better reported, as mainly randomised, they may have adopted CONSORT 2010 guidance. This review confirms the need for robust consensus-driven guidance for researchers and journals reporting dose-finding trials, to allow accurate assessment of their results to reduce research waste [2].

The Executive Committee would like to invite interested stakeholders to register their interest in taking part in the Delphi Survey process [3] via https://icr.onlinesurveys.ac.uk/df-delphi-survey-interest

We can **do more** to **reduce research waste**

References

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3. Dose-finding CONSORT Extension project website. http://www.icr.ac.uk/our-research/researchers-and-teams/professor-christina-yap/dose-finding-consort-extension-project (Assessed: 14 February 2022)

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