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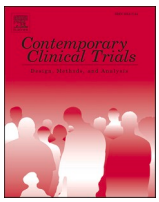

Short Communication

Reporting quality of CONSORT flow diagrams in published early phase dose-finding clinical trial reports: Improvement is needed

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ABSTRACT

Background: This project aims to: (1) assess the completeness of information in flow diagrams of published early phase dose-finding (EPDF) trials based on CONSORT recommendations, and if additional features on dose (de-) escalation were presented; (2) propose new flow diagrams presenting how doses were (de-)escalated throughout the trial.

Methods: Flow diagrams were extracted from a random sample of 259 EPDF trials, published from 2011 to 2020 indexed in PubMed. Diagrams were scored out of 15 following CONSORT recommendations with an additional score for presence of (de-)escalation. New templates were proposed for features that were deficient and presented to 39 methodologists and 11 clinical trialists in October and December 2022.

Results: 98 (38%) papers included a flow diagram. Flow diagrams were most deficient in the reporting of reasons for lost to follow up (2%) and reasons for not receiving allocated intervention (14%). Few (39%) presented sequential dose-decision stages.

Of voting methodologists, 33/38 (87%) agreed or strongly agreed that for participants recruited in cohorts, presenting the (de-)escalation steps in the flow diagram is a useful feature, also expressed by the trial investigators. Most workshop attendees (35/39, 90%) preferred a larger dose to be displayed higher up within the flow diagram than a smaller dose.

Conclusion: Most published trials do not provide a flow diagram, and for those that do, essential information is often omitted. EPDF flow diagrams capturing information on participant flow in the trial's journey, encapsulated within one figure, are highly recommended to promote transparency and interpretability of trial results.

1. Introduction

Updated in 2010, the CONSORT (CONsolidated Standards Of Reporting Trials) statement represents a minimum list of requirements recommended to standardise the reporting of randomised control trials [1]. CONSORT recommends the use of participant flow diagrams within randomised controlled trials to present the journey of patients through a trial, with the aim of supporting reader's critical appraisal of the internal and external validity of a trial [2] by reducing the time required to determine the quality of the study [3].

Though there is on-going development to extend CONSORT 2010 for early phase dose-finding (EPDF) trials [4,5], there is no guidance on what should be included in flow diagrams for such trials. EPDF trials are highly adaptive by nature, with several sequential dose escalation or de-escalation steps throughout the trial. Intuitive and clear flow diagrams which have the potential to present how doses were adapted, patient withdrawals and analysis populations will increase transparency of trial details and facilitate better assessment of trial results. As EPDF clinical trials sample a very small number of participants, indicating participant flow from enrolment to analysis could determine whether participants are representative of a larger eligible population.

The aim of our study was to determine the current uptake and completeness of participant flow diagrams in published EPDF papers, and to provide recommendations on how their flow diagrams can be improved.

2. Methods

Eligible trials were identified by electronically searching the bibliographic database MEDLINE (via PubMed) in April 2021. Early phase dose-finding phase I or I/II trials with dose escalation/de-escalation elements published in English from 2011 to 2020 were included and

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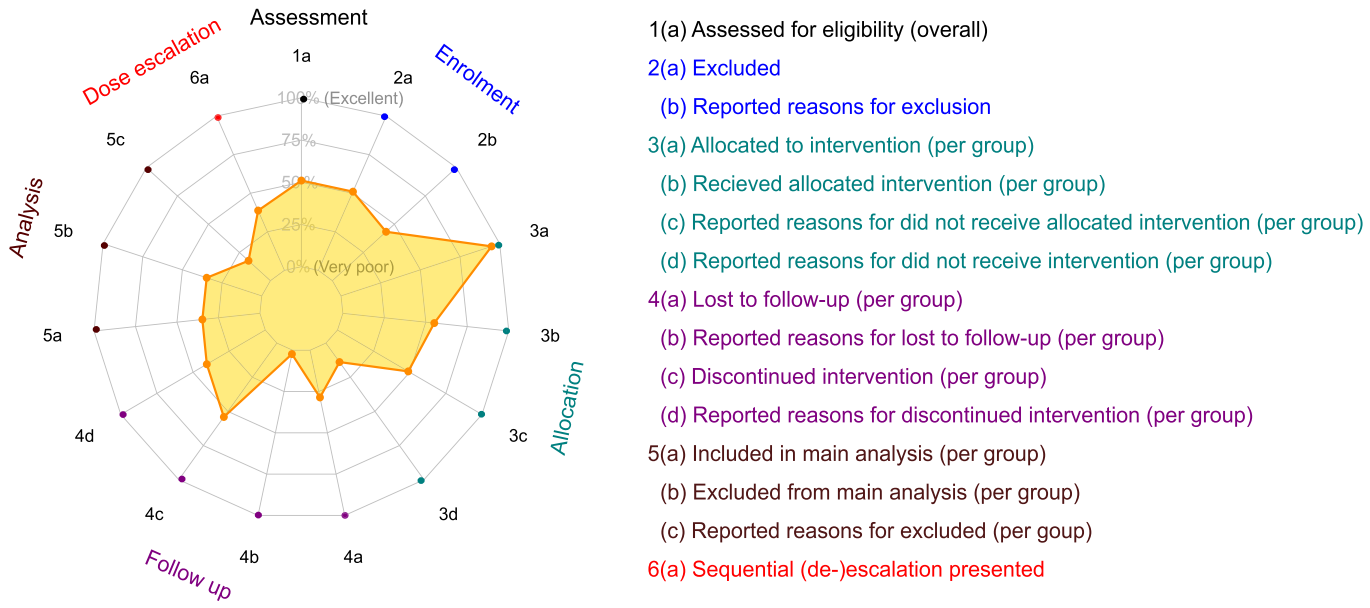

Fig. 1. Radar plot presenting the proportion of extracted flow diagrams which reported each feature.

eligible if they were: (a) a study with a human population, (b) a full text publication in a peer-reviewed PubMed-indexed journal, (c) published in English, (d) early phase (phase I, phase II or phase I/II) trial; (f) presented at least one dose (de-)escalation component; and (g) determining safe dosages for further investigation. Details of identification, screening and eligibility have been presented previously [6]. Reviewers (EA and YZ) independently screened papers for flow diagrams and extracted data from included papers. The two reviewers discussed differences, with an additional arbitrator if required (CY). To support reviewers in their assessment, a method document was created to minimise discrepancies.

For each eligible report, we extracted an accompanying flow diagram and information on trial demographics including trial design, trial area (oncology/non-oncology), funding, centre (multi/single), and allocation (randomised/non-randomised).

To determine the current quality of flow diagrams, we used the assessment criteria presented in Fig. 1 (containing a maximum of 15 points). Scoring was inspired by Hopewell and colleagues' [7] criteria to assess the completeness of flow diagrams presented within randomised controlled trials. To tailor the criteria to the EPDF setting, we included an additional mark for a graphical or written attempt to present the dose (de-)escalation within the trial. As 62% of trials were not randomised, we did not evaluate number randomised. Each reporting feature was marked out of zero or one except for provision of reasons which could be not applicable. Data was extracted from the flow diagram if it was mentioned directly or inferable from the information provided within the figure. When a paper presented more than one flow diagram, we extracted the flow diagram which provided the most information.

To assess the trend in prevalence and reporting quality of flow diagrams over time, a linear regression model was fitted. The number of flow diagrams and the average score of each diagram was fitted with year as the independent variable. R version 4·2·1 was used for the statistical analysis.

Once areas for improvement were recognised, new templates were designed to support publications with the structure of their flow diagram. These templates were presented and voted on by 39 methodologists at the 7th Early Phase Adaptive Trials Workshop held at the MRC Biostatistics Unit in October 2022 and 11 members of the Drug Development Unit (DDU) team at The Institute of Cancer Research in December 2022.

Table 1
Mean proportion of features presented within a participant flow diagram partitioned by trial characteristics.

		Mean proportion (SD) %
Trial Area	Cancer (n = 28)	34.3 (27.1)
	Non-Cancer (n = 70)	46.9 (28.0)
Trial design	3 + 3 and variants (n = 26)	33.5 (27.8)
	Rolling 6 (n = 1)	40.0 (–)
	Accelerated titration design (n = 1)	33.3 (–)
	Model assisted/Model-based design (n = 1)	61.5 (–)
	SAD (n = 18)	54.5 (29.3)
	MAD (n = 30)	48.5 (.27.6)
	SAD+MAD (n = 21)	38.1 (26.9)
Funding	Government(s) (n = 13)	64.2 (24.2)
	Internal funding (institution) (n = 2)	33.3 (28.3)
	Mixed (n = 10)	58.6 (30.3)
	Private-for-profit (companies/entities) (n = 64)	35.6 (26.0)
	Private not-for-profit (organisations/ philanthropies) (n = 5)	36.9 (21.6)
	Not reported (n = 4)	73.3 (15.2)
Centre type	Multi-centre (n = 50)	38.5 (24.8)
	Single-centre (n = 34)	48.3 (29.4)
	Unclear (n = 14)	48.3 (34.9)
Allocation	Randomised (n = 43)	45.8 (28.6)
	Non-randomised (n = 55)	40.0 (27.7)

SAD: Single ascending dose; MAD: Multiple ascending dose.

3. Results

A random sample of 259 full text articles were identified and reviewed. Only 38% (98/259) of articles included a flow diagram. The median sample size of patients allocated to intervention was 45 (Q1-Q3: 30–75.25).

Allocation to intervention (95%), received allocated intervention (55%) and did not receive allocated intervention (49%) were generally well reported and compared favourably to those of Hopewell and colleagues' [7] similar review within randomised control trials. However, reported reasons for: did not receive allocated intervention (14%), lost to follow-up (2%) and excluded in main analysis (18%) were reported poorly and were substandard in comparison to RCT flow diagram publications. The stage at which patients were withdrawn or discontinued treatment was rarely displayed and often collated together in the

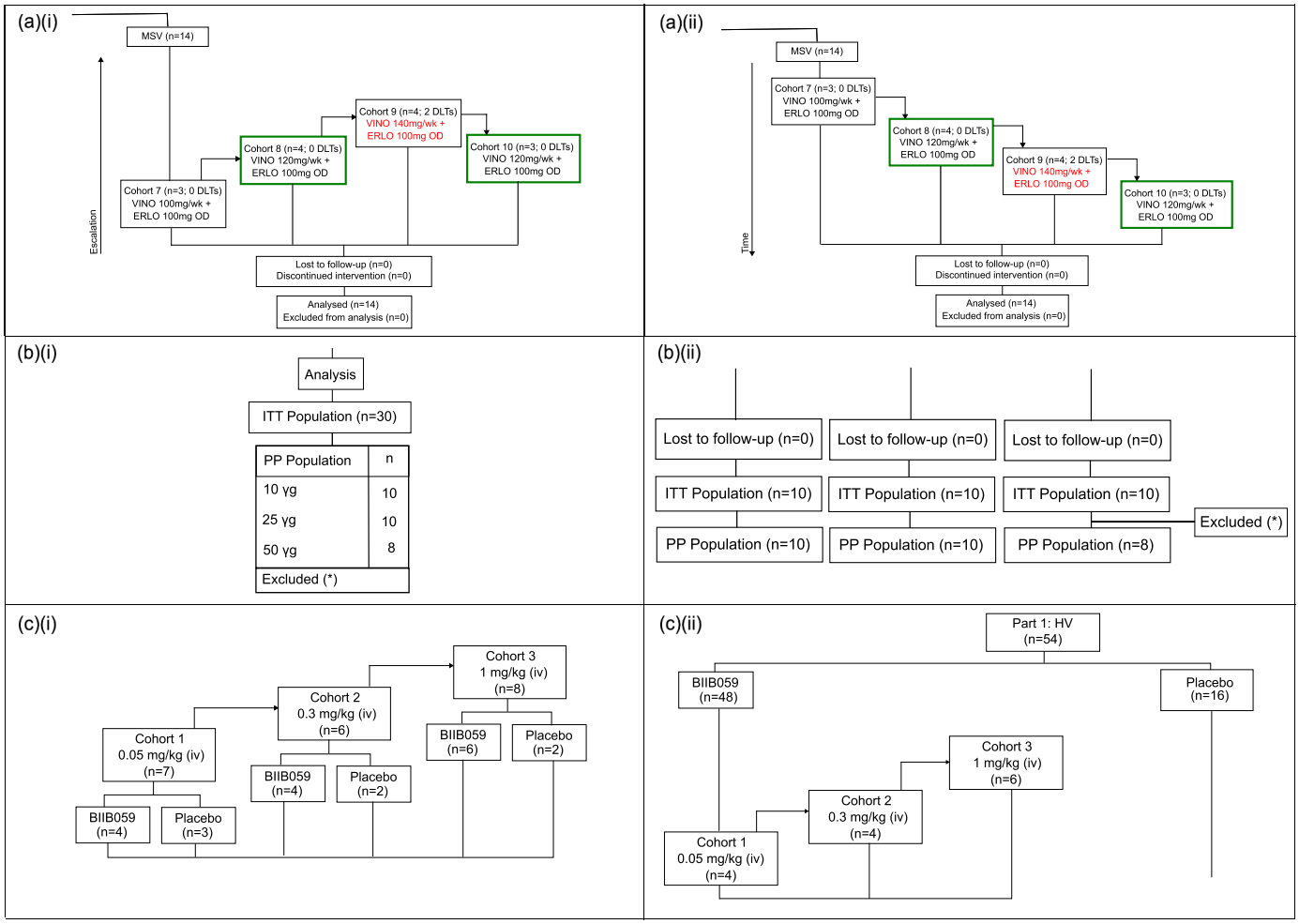

Fig. 2. Novel flow diagram templates with: (a) [9] height used to capture (i)(de-)escalation and (ii) time, (b) [10] analysis (i)separated by cohort and (ii) summarised across cohorts, and (c) [11] placebo (i) separated by cohort, (ii) summarised across cohorts. Additional colour is used to represent dosages with DLTs (red) and recommended MTD (green) for the dose-finding trial described in (a). For the dose-finding trial presented in (c) no serious adverse events were observed, nor dosages recommended for later phase trials. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

diagram. Few diagrams (39%) made any attempt at presenting each dose-decision stage. These results are summarised in the radar plot presented in Fig. 1.

In Table 1, we present the quality of flow diagrams across various trial demographics. Non-cancer trials presented a higher quality flow diagram compared to cancer trials, with government funded trials presenting the best quality flow-diagram of all the identified funding pathways. There was a significant increase in the prevalence of flow diagrams presented within EPDF trials over time (4.3% increase/year, 95% CI: 2.2%–6.4%). However, there is no improvement in the mean proportion of features presented in flow diagrams over time (1.1% increase/year, 95% CI: −1.9%-4.1%).

We devised a series of novel templates to improve features which were poorly reported within this review, presented in Fig. 2. Of the 39 voting methodologists at the 7th Early Phase Adaptive Trials Workshop, 33 (85%) agreed or strongly agreed that for participants recruited in cohorts, presenting the (de-)escalation steps within the flow diagram is a useful feature. This was mirrored within the DDU team. Height was preferably used to showcase dose-escalation (90%) in comparison to time of dose administration (Fig. 2(a)(i) and (a)(ii) respectively). Workshop feedback suggested that the methodologists preferred analysis to be tabulated within one table (54%) in comparison to being separated by each cohort (Fig. 2(b)(i) and (b)(ii)). Methodologists also preferred placebos presented within each respective dose cohort (62%) in comparison to combining the placebo into its own separate arm (Fig. 2(c)(i) and 2(c)(ii)). Within the DDU team, there was no clear preference on how to present larger dosage. However, the team preferred to combine the information for all dose levels into one box for both dose level analysis (8/11, 73%) and allocation of placebo (7/10, 70%). Further suggestions from the DDU Team recommended the use of colour to highlight important dose levels, such as the MTD (Fig. 2(a)).

Fig. 3 provides an example of an enhanced flow diagram, with modifications to the original diagram [8], displaying a combination of informative features in Fig. 2. This flow diagram depicts the use of a modified 3 + 3 design to guide escalation and de-escalation decisions. In this trial, 1 DLT out of 6 patients was observed at the starting dose in Cohort 1. Cohort 2 was given a higher dose (indicated by a higher height), where 2 DLTs were observed out of 4 patients. This led to a de-escalated dose (lower height) for Cohort 3 and so on. The final maximum tolerated dose was given to Cohort 5 and highlighted in green.

4. Conclusions

Whilst the use of flow diagrams within EPDF publications is increasing over time, the reporting and quality of these figures remains poor. Our study represents a minimal necessary assessment of the presence and completeness of flow diagrams within EPDF clinical trials. In Hopewell's review [7], over half (56%) of trials presented a flow diagram. Within CONSORT endorsing journals, flow diagrams are a requirement for RCTs, which may provide insight as to why participant

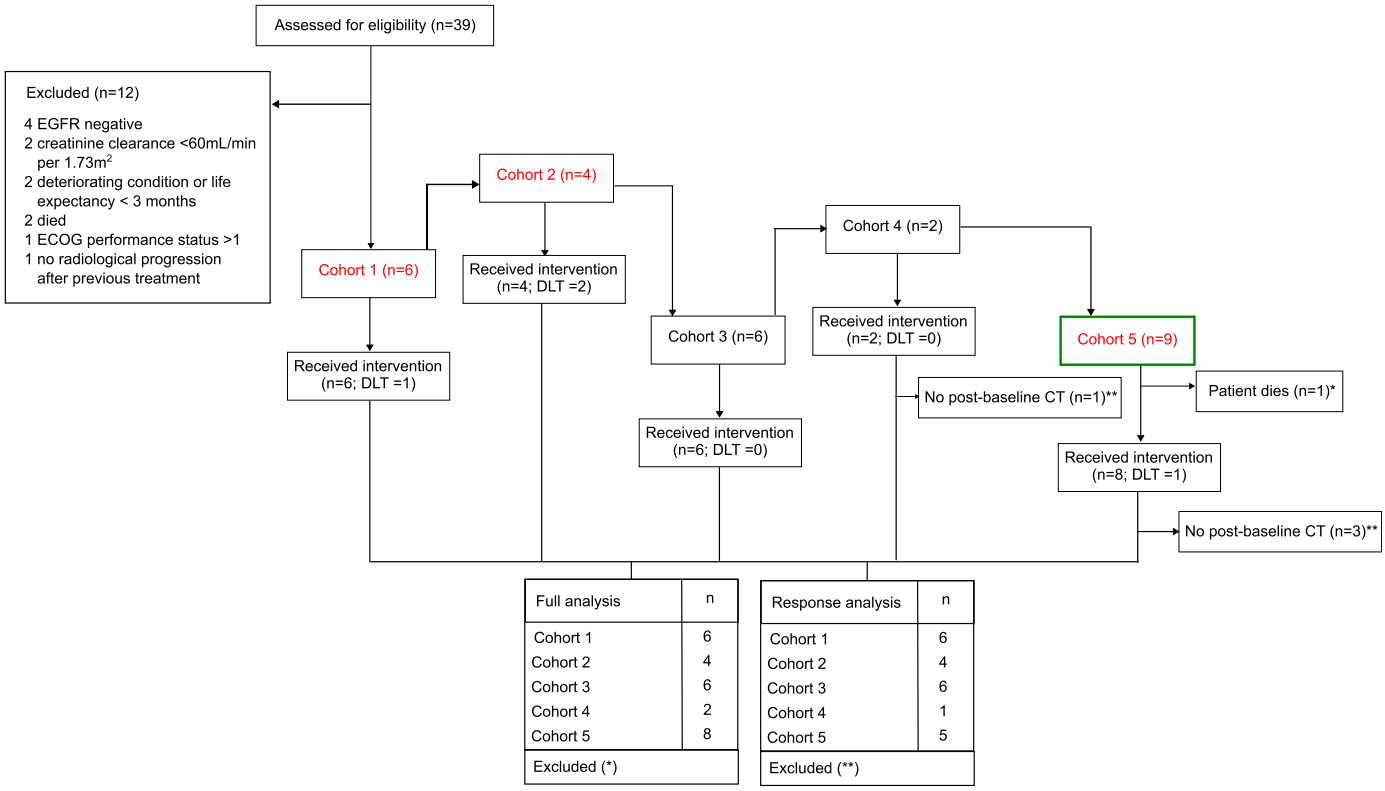

Fig. 3. An example of an enhanced flow diagram for an early phase dose-finding clinical trial using a modified 3 + 3 dose-finding design. [8] A patient was included in the response analysis population if they underwent a baseline assessment and at least one scheduled post-baseline tumour assessment by CT and PET–CT. [8] Details of the study dosing cohorts are provided in the manuscript's Panel description [8].

flow diagrams appear in 18% more papers within Hopewell's review [7] than within this review.

The number of patients allocated to intervention (EPDF/RCTs (%): 95/94), received allocated intervention (55/40) and did not receive allocated intervention (49/38) were more often presented within EPDF flow diagrams than in RCTs [7]. However, most other features were more poorly reported within EPDF flow diagrams compared to their RCT counterparts.

It was often unknown if a patient withdrew before or after treatment was administered. This inflated the proportion of flow diagrams which indicated the number of patients discontinuing treatment (54%). In many cases, the inference required by the reader to distinguish between discontinued intervention and did not receive allocated intervention negated the advantage of a flow diagram to present the information clearly and succinctly to readers.

4.1. Implications for practice

Many of the areas appearing deficient within EPDF participant flow diagrams align with CONSORT's recommended remit of features. EPDF papers should take inspiration from CONSORT's flow diagram template to increase the quality of flow diagrams being published.

Flow diagrams are essential to succinctly present basic trial information, encouraging readers to make efficient validity assessments and corroborate trial conclusions. Presenting study design within a flow diagram can help authors reduce the word count of their paper, crucial within a word-constrained journal article, whilst still presenting the trial transparently.

Within RCTs, flow diagrams can effectively present the journey of a patient through a trial: including the number of patients allocated to treatment, information regarding patient discontinuation, and the number of patients included in each analysis population. EPDF trials often have many unique dose escalation schedules, determined by increasingly complex statistical designs. As well as presenting the journey of a patient in a trial, the goal of flow diagrams in the early phase setting is to present a visual illustration of a trial's sequential dose adaptation decisions and participant flow, and the evaluation of safety and tolerability. To encapsulate the adaptive nature of dose-finding designs, we encourage EPDF flow diagrams to identify whether subsequent dosages are (de-)escalations of previously explored dosages in the trial.

Our study highlights a current deficiency of participant flow diagrams within early phase publications. When flow diagrams are included, they are often significantly incomplete. With these omissions, it is challenging for readers to assess the eligibility of the trial population and has the potential to introduce selection bias into the conclusions and results of the trial [12].

With the wide array of trial designs and continued development of novel designs, publications would benefit from endorsed designs and templates to inspire their diagrams. Future work exploring creation of templates or web-based flow diagram generators that include all essential information would help to improve the quality, transparency, and efficiency of clinical trials.

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CRediT authorship contribution statement

Emily Alger: Investigation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing, Visualization. **Yuqi Zhang:** Validation, Writing – review & editing. **Christina Yap:** Conceptualization, Investigation, Methodology, Visualization, Writing – review &

editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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