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

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Summary

Early phase dose-finding (EPDF) trials are key in the development of novel therapies, with their findings directly informing subsequent clinical development phases and providing valuable insights for reverse translation. Comprehensive and transparent reporting of these studies is critical for their accurate and critical interpretation, which may improve and expedite therapeutic development. However, quality of reporting of design characteristics and results from EPDF trials is often variable and incomplete. The international consensus-based CONSORT-DEFINE (Consolidated Standards for Reporting Trials Dose-finding Extension) statement, an extension of the CONSORT statement for randomised trials, was developed to improve the reporting of EPDF trials. The CONSORT-DEFINE statement introduced 21 new items and modified 19 existing CONSORT items.

This CONSORT-DEFINE Explanation and Elaboration (E&E) document provides important information to enhance understanding and facilitate the implementation of the CONSORT-DEFINE checklist. For each new or modified checklist item, we provide a detailed description and its rationale with supporting evidence, and present examples from EPDF trial reports published in peer-reviewed scientific journals. When reporting the results of EPDF trials, authors are encouraged to consult the CONSORT-DEFINE E&E document, together with the CONSORT and CONSORT-DEFINE statement papers, and adhere to their recommendations. Widespread adoption of the CONSORT-DEFINE statement is likely to enhance the reporting quality of EPDF trials, thus facilitating the peer review of such studies and their appraisal by researchers, regulators, ethics committee members, and funders.

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Keywords: Early phase trials; Phase I; Dose-finding; Dose escalation/de-escalation; Reporting guidance; CONSORT-DEFINE; CONSORT

Research in context

Evidence before this study
The CONSORT (Consolidated Standards of Reporting Trials) Statement and its extensions offer evidence-based guidelines for the essential content of clinical trial reports. Notably, the recently published CONSORT-DEFINE extension focuses on the reporting of early phase dose-finding trials.

Added value of this study
This study provides a deeper understanding of the CONSORT-DEFINE items and offers practical guidance on how to write a trial report that effectively addresses them. Examples of new and modified items in the CONSORT-DEFINE guidelines were gathered from published articles of early phase dose-finding trial results.

Implications of all the available evidence
The provided examples serve as a valuable resource for the trial community in developing their reports on early phase dose-finding trial results, aiming to greatly enhance both comprehensiveness and transparency, and thereby improve the overall quality of evidence available.

Introduction

Early phase clinical trials play a pivotal role in translating novel discoveries into therapies that enhance patient outcomes. Well-designed and properly conducted early phase dose-finding (EPDF) trials offer reliable evidence for assessing the safety and preliminary activity of healthcare interventions at an early stage, in order to advance their clinical development. However, lack of transparent reporting of the design, methods, and results of EPDF trials can lead to deceptive conclusions,

hampering subsequent clinical investigations and value for trial participants. For the scope of this work, an EPDF trial—often referred to as phase I, I/II, dose escalation or de-escalation, or dose optimisation trials—assesses different doses of an investigated intervention in groups of participants. These trials involve interim dose decisions using data on safety or tolerability (and other markers such as pharmacokinetics and activity), to determine safe and potentially active doses for further development (Supplementary Box S1).[1–4]

The ability to evaluate the quality of EPDF trials depends on complete and accurate reporting that comprehensively delineates their design, execution, and analysis. Reporting often falls short of these standards.[5–7] For example, despite the importance of well-defined objectives, a review of published reports of EPDF trials found that around 30% did not include their objectives.[7] Only around 20% of reports included a justification for the starting dose level(s)[7] despite the significance of their selection for study participants' safety.[8] The number of participants included in the main analysis, and the reasons for exclusion, were also frequently underreported (<50%).[9]

To improve the reporting of EPDF trials, the international consensus-based Consolidated Standards for Reporting Trials Dose-finding Extension (CONSORT-DEFINE) statement[10] was developed.[3] It extends the CONSORT statement for parallel group randomised trials,[11] incorporating 40 EPDF-specific items (21 new items and modifying 19 existing ones; Supplementary Figure S1). A CONSORT-DEFINE checklist for abstracts of EPDF trials was also developed, modifying five items from the CONSORT extension for journal and conference abstracts.[10] The development of the CONSORT-DEFINE checklist followed the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network's methodological framework for guideline development[12]; details of the scope and methods have been published.[2,3,10]

The CONSORT-DEFINE explanation and elaboration (E&E) document is designed to enhance understanding and facilitate the implementation of the checklist items outlined in the CONSORT-DEFINE statement.

Methods

The CONSORT-DEFINE statement recommends that, in conjunction with the existing CONSORT items,[11] 40 EPDF-specific items (21 new and 19 modified) be included in EPDF trial reports. The recommended checklist[10] of items to address in an EPDF clinical trial report is provided in Table 1.

Search strategy and selection criteria

For each new or modified item in the CONSORT-DEFINE statement, we provide at least one example sourced from a comprehensive methodological review of over 500 EPDF trials published between 2011 and 2023.[7] The examples are drawn from published EPDF trials evaluating a wide range of interventions across diverse disease contexts, encompassing pharmacological interventions (e.g., therapeutic small or large molecule drugs, vaccines, cell therapies, gene therapies) and non-pharmacological interventions (e.g., lifestyle or dietary, digital therapeutics, rehabilitation, or radiotherapy). The examples are followed by a detailed explanation of the rationale behind the checklist item, emphasising its relevance with supporting evidence, where available, and the key issues to address.

To compile these examples, we established a working group tasked with reviewing the aforementioned published EPDF trials and gathering examples that adequately illustrate each CONSORT-DEFINE item. In most cases, we provide at least two examples — one focused on oncology and one with a non-oncology or healthy volunteer context. Additionally, the examples were often selected to illustrate alternative methods of presenting the required information, offering a broader perspective on how to approach these items effectively. For a few items, where we were unable to identify suitable non-oncology or healthy volunteer examples, examples are exclusively from oncology. When adequately reported examples were not found in the initial search, recommendations were sought from co-authors and external experts. If, despite these efforts, no relevant examples could be identified in published trial reports, we sourced examples from published protocols or statistical analysis plans, or we created exemplars of good reporting practice. Subsequently, the lead authors (JR, CG, CY) selected the examples that were viewed as adequately reported for each item.

Role of the funding source

The study funders had no role in study design, data collection, analysis, interpretation, or writing of the report.

Recommendations

The explanation and rationale for new and modified CONSORT-DEFINE checklist items for the main report are provided below. Some items were elaborated on, i.e., their wording remained unchanged in reference to CONSORT, but additional CONSORT-DEFINE explanatory text was provided to clarify additional considerations for EPDF trials. Examples are quoted verbatim from the published paper. Any references cited in the quoted text are denoted by superscript [reference] to distinguish them from references in this E&E paper. For the sake of clarity, acronyms in examples are fully introduced at their first appearance, with square brackets indicating

Category and section	Standard CONSORT checklist item		CONSORT-DEFINE checklist item for EPDF Trials	
	Item No	CONSORT	Item No	CONSORT DEFINE
Title and abstract				
Title	1a	Identification as a randomised trial in the title	1a[b]	Identification as an early phase dose-finding (e.g., first-in-human, dose escalation or de-escalation, phase 1, phase 1/2, expansion, dose titration) and, if applicable, randomised trial in the title or abstract
Abstract	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts)	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT-DEFINE for abstracts)
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	2a.1[b]	Description of research question(s) and justification for undertaking the trial, including summary of relevant clinical studies (published and unpublished) examining benefits and harms for each intervention
			2a.2[a]	Summary of key findings from relevant non-clinical or preclinical research
			2a.3[a]	Summary of findings from previously generated preclinical and translational studies to support any planned biomarker substudies (where applicable)
	2b	Specific objectives or hypotheses	2b[b]	Specific objectives (e.g., relating to safety, activity, pharmacokinetics, pharmacodynamics, recommended dose(s))
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3a.1[b]	Description of trial design elements, such as dose escalation or de-escalation strategy, number of treatment groups, allocation ratio if relevant, and details of any prespecified trial adaptations
			3a.2[a]	Trial design schema to show the flow of major transition points (e.g., dose escalation to dose expansion, phase 1 to phase 2, single ascending dose to multiple ascending dose)
			3a.3[a]	Statistical methods or rationale underpinning the trial design
			3a.4[a]	Starting dose(s) with rationale
			3a.5[a]	Range of planned dose levels with rationale
			3a.6[a]	Presentation of planned dose levels (e.g., as a diagram, table, or infographic), where applicable
			3a.7[a]	Skipping of dose level(s), if applicable
			3a.8[a]	Planned cohort size(s) (e.g., fixed, flexible, adaptive)
			3a.9[a]	Dose allocation method within a dose level (including sequence and interval between dosing of participants, e.g., sentinel or staggered dosing)
			3a.10[a]	Dose expansion cohort(s), if applicable, with rationale
			3a.11[a]	Criteria for progression to the next part of the trial (e.g., phase 1 to phase 2, single ascending dose to multiple ascending dose), where applicable
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	3b[b]	Important changes to the design or methods after trial commencement (e.g., insertion of unplanned additional doses) outside the scope of the prespecified adaptive design features, with reasons
Participants	4a	Eligibility criteria for participants	4a	
	4b	Settings and locations where the data were collected	4b	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5a[b]	Interventions for each dose level (within each group) with sufficient details to allow replication, including administration route and schedule showing how and when they were actually administered
			5b[a]	Criteria for dose discontinuation, dose modifications, and dosing delays of allocated interventions for a given trial participant (e.g., dose change in response to harms, participant request, or improving or worsening disease)
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	6a[b]	Primary and secondary outcomes, including the specific measurement variable, analysis metric, method of aggregation, and time point for each outcome. Explanation of the clinical relevance of chosen outcomes is strongly recommended. Any other outcomes used to inform prespecified adaptations should be described with the rationale
	6b	Any changes to trial outcomes after the trial commenced, with reasons	6b[b]	Any unplanned changes to trial outcomes after the trial commenced, with reasons
Sample size	7a	How sample size was determined	7a[b]	Estimated number of participants (minimum, maximum, or expected range) needed to address trial objectives and how it was determined, including clinical and statistical assumptions supporting any sample size and operating characteristics
	7b	When applicable, explanation of any interim analyses and stopping guidelines	7b[b]	Prespecified interim decision making criteria or rules that guided the trial adaptation process (e.g., dosing decision to escalate or de-escalate); prespecified and actual timing and frequency of interim data reviews and the information to inform trial adaptations

(Table 1 continues on next page)

Category and section	Standard CONSORT checklist item		CONSORT-DEFINE checklist item for EPDF Trials	
	Item No	CONSORT	Item No	CONSORT DEFINE
(Continued from previous page)				
Randomisation (if applicable)				
Sequence generation	8a	Method used to generate the random allocation sequence	8a	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8b[b]	Type of randomisation; details of any restrictions (such as blocking and block size); any prespecified adaptive assignment rules or algorithm leading to adjustments in the allocation ratio, including timing and frequency of updates; any changes to the allocation rule following trial adaptation decisions
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10	
Blinding	11a	If done, who was blinded after assignment to interventions (e.g., participants, care providers, and how	11a	
	11b	If relevant, description of the similarity of interventions	11b	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12a.1[b]	Statistical methods for primary and secondary outcomes and any other outcomes used to make prespecified adaptations
			12a.2[a]	For the implemented adaptive design features, statistical methods used for estimation (e.g., safety, dose(s), treatment effects) and to make inferences
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12b[b]	Statistical methods for additional analyses (e.g., subgroup and adjusted analyses, pharmacokinetics or pharmacodynamics, biomarker correlative analyses)
			12c[a]	Analysis population(s) (e.g., evaluable population for dose-finding, safety population)
			12d[a]	Strategies for handling intercurrent events occurring after treatment initiation (e.g., how dosing adjustments were handled) that can affect either the interpretation or the existence of the measurements associated with the clinical question of interest, and any methods to handle missing data
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	13a[b]	For each group, the number of participants who were assigned to each dose level at each interim analysis (e.g., for dosing decisions), received intended treatment, and were analysed for the primary outcome and, if applicable, any other outcomes used to inform prespecified adaptations
	13b	For each group, losses and exclusions after randomisation, together with reasons	13b[b]	For each group, losses and exclusions after allocation to each dose level, together with reasons
Recruitment	14a[c]	Dates defining the periods of recruitment and follow-up	14a[c]	
	14b[c]	Why the trial ended or was stopped	14b[c]	
			14c[a]	Trial adaptation decisions made (including on what basis they were made, and when) in light of the prespecified decision making criteria and observed accrued data
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	15[b]	Baseline demographic and clinical characteristics across each dose level within each group, where appropriate
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	16[b]	For each group, the number of participants (denominator) included in each analysis across each dose level, and whether the analysis was by original assigned interventions
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	17a[b]	For each primary and secondary outcome, results for each dose level within each group, and the estimated effect size and its precision, if applicable
	17b[c]	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	17b[c]	
			17c[a]	Report interim results used to inform interim decision making such as dose escalation, de-escalation, or staying at the same dose
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	18	

(Table 1 continues on next page)

Category and section	Standard CONSORT checklist item		CONSORT-DEFINE checklist item for EPDF Trials	
	Item No	CONSORT	Item No	CONSORT DEFINE
(Continued from previous page)				
Harms	19	All important harms or unintended effects in each group (for specific guidance, see CONSORT for harms[13])	19[b]	All important harms (e.g., adverse events or effects, toxicities) reported by dose level in each group (for specific guidance, see CONSORT for Harms 2022[14])
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	20	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	21	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	22	
Other information				
Registration	23	Registration number and name of trial registry	23	
Protocol	24	Where the full trial protocol can be accessed, if available	24	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	25	
Data monitoring			26a[a]	Composition of any decision making or safety review committee or group; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details can be found (such as in a charter or protocol)
			26b[a]	Description of who had access to interim results and made the interim and final decision to terminate the trial (or part(s) of the trial, e.g., end of dose escalation), and measures to safeguard the confidentiality of interim information
Dissemination			27[a]	Specify, if applicable, whether and when results (such as safety and/or activity) were reported externally (e.g., through scientific presentations, journal publication, or the trial website) while the trial (or part(s) of the trial) was still ongoing

CONSORT, CONsolidated Standards of Reporting Trials; DEFINE, Dose-finding Extension; EPDF, early phase dose-finding. The CONSORT checklist should be used in conjunction with the CONSORT explanation and elaboration document[15] for important clarifications on the checklist items. Empty items in the CONSORT-DEFINE column indicate no modification from the standard CONSORT item. CONSORT extensions for non-pharmacological treatments and outcomes might also be relevant.[16] Note that the term "dose" in the checklist can be considered synonymous and used interchangeably with dosage, or dosing regimen (dose or schedule), or a unit dose. [a]New items that should only be applied in reference to CONSORT-DEFINE. [b]Modified items that require reference to both CONSORT and CONSORT-DEFINE. [c]Item wording remained unchanged in reference to CONSORT, but additional CONSORT-DEFINE explanatory text was provided to clarify additional considerations for early phase dose-finding trials.

Table 1: **Recommended checklist items to consider in an early phase dose-finding clinical trial report from CONSORT and CONSORT-DEFINE checklists.**

additions by the authors of this article. Additional comments are provided in italics below an example, where examples may lack some details or require further elaboration. When reporting the results of EPDF trials, authors are encouraged to use the CONSORT-DEFINE E&E together with the CONSORT-DEFINE statement,[10] refer to the CONSORT statement[11] and E&E[15] (or related future updates) for unchanged items, and use any other relevant CONSORT extensions where necessary (https://www.equator-network.org/reporting-guidelines/consort/).

Access to recommended information is paramount. If the primary paper does not include recommended details, authors can, for instance, provide a summary, and indicate where full details can be found, such as in an accessible protocol, a statistical analysis plan, or a supplementary file. The rationale for not providing specific details should also be included.[10]

As variations in the terminology and definitions relating to EPDF trials exist across disciplines and geographical regions, key terms used throughout are provided in the Glossary (Supplementary Box S1).[10]

Title and abstract

Item 1a [modified] Identification as an early phase dose-finding (e.g., first-in-human, dose escalation or de-escalation, phase 1, phase 1/2, expansion, dose titration) and, if applicable, randomised trial in the title or abstract

Example 1. "Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial".[17]

Example 2. "A Phase 1 Exercise Dose Escalation Study for Stroke Survivors with Impaired Walking".[18]

Example 3. "A phase Ib dose-escalation and expansion study of the oral MEK inhibitor pimasertib and PI3K/[m]TOR inhibitor voxtalisib in patients with advanced solid tumour".[19]

Example 4. "Safety, tolerability, pharmacokinetics, and pharmacodynamics of PF-06650833, a selective interleukin-1 receptor-associated kinase 4 (IRAK4) inhibitor, in single and multiple ascending dose randomized phase 1 studies in healthy subjects".[20]

Explanation. The CONSORT statement highlighted the importance of appropriate indexing to identify randomised trials in electronic databases.[11,15] The CONSORT-DEFINE statement extends this requirement to help ensure that an EPDF trial is appropriately indexed and can be easily identified. Especially as there are various terminologies used for EPDF trials in different disease areas, providing key information in the title (where possible) or at minimum in the abstract (item 1b) is strongly encouraged.

The title or abstract should identify the main design features of the EPDF trial (e.g., first-in-human, early phase dose-finding, dose (de-)escalation, expansion, dose titration, single ascending dose, multiple ascending dose) and/or the phase of the trial (e.g., phase I, Ia, Ib, phase I/II) and, when applicable, use "randomised" if any of the participants were randomly assigned to an intervention (see Example 1 and Example 4).

Item 1b [modified] Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT-DEFINE for abstracts)

Example 1. "Background: Trastuzumab duocarmazine is a novel HER2-targeting antibody–drug conjugate comprised of trastuzumab covalently bound to a linker drug containing duocarmycin. Preclinical studies showed promising antitumour activity in various models. In this first-in-human study, we assessed the safety and activity of trastuzumab duocarmazine in patients with advanced solid tumours.

Methods: We did a phase 1 dose-escalation and dose-expansion study. The dose-escalation cohort comprised patients aged 18 years or older enrolled from three academic hospitals in Belgium, the Netherlands, and the UK with locally advanced or metastatic solid tumours with variable HER2 status who were refractory to standard cancer treatment. A separate cohort of patients were enrolled to the dose-expansion phase from 15 hospitals in Belgium, the Netherlands, Spain, and the UK. Dose-expansion cohorts included patients aged 18 years or older with breast, gastric, urothelial, or endometrial cancer with at least HER2 immunohistochemistry 1+ expression and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST). Trastuzumab duocarmazine was administered intravenously on day 1 of each 3-week cycle. In the dose-escalation phase, trastuzumab duocarmazine was given at doses of 0.3 mg/kg to 2.4 mg/kg (3 + 3 design) until disease progression or unacceptable toxicity. The primary endpoint of the dose-escalation phase was to assess safety and ascertain the recommended phase 2 dose, which would be the dose used in the dose-expansion phase. The primary endpoint of the dose-expansion phase was the proportion of patients achieving an objective response (complete response or partial response), as assessed by the investigator using RECIST version 1.1. This ongoing study is registered with ClinicalTrials.gov, number NCT02277717, and is fully recruited.

Findings: Between Oct 30, 2014, and April 2, 2018, 39 patients were enrolled and treated in the dose-escalation phase and 146 patients were enrolled and treated in the dose-expansion phase. One dose-limiting toxic effect (death from pneumonitis) occurred at the highest administered dose (2.4 mg/kg) in the dose-escalation phase. One further death occurred in the dose-escalation phase (1.5 mg/kg cohort) due to disease progression, which was attributed to general physical health decline. Grade 3–4 treatment-related adverse events reported more than once in the dose-escalation phase were keratitis (n = 3) and fatigue (n = 2). Based on all available data, the recommended phase 2 dose was set at 1.2 mg/kg. In the dose-expansion phase, treatment-related serious adverse events were reported in 16 (11%) of 146 patients, most commonly infusion-related reactions (two [1%]) and dyspnoea (two [1%]). The most common treatment-related adverse events (grades 1–4) were fatigue (48 [33%] of 146 patients), conjunctivitis (45 [31%]), and dry eye (45 [31%]). Most patients (104 [71%] of 146) had at least one ocular adverse event, with grade 3 events reported in ten (7%) of 146 patients. No patients died from treatment-related adverse events and four patients died due to disease progression, which were attributed to hepatic failure (n = 1), upper gastrointestinal haemorrhage (n = 1), neurological decompensation (n = 1), and renal failure (n = 1). In the breast cancer dose-expansion cohorts, 16 (33%, 95% CI 20.4–48.4) of 48 assessable patients with HER2-positive breast cancer achieved an objective response (all partial responses) according to RECIST. Nine (28%, 95% CI 13.8–46.8) of 32 patients with HER2-low, hormone receptor-positive breast cancer and six (40%, 16.3–67.6) of 15 patients with HER2-low, hormone receptor-negative breast cancer achieved an objective response (all partial responses). Partial responses were also observed in one (6%, 95% CI 0.2–30.2) of 16 patients with gastric cancer, four (25%, 7.3–52.4) of 16 patients with urothelial cancer, and five (39%, 13.9–68.4) of 13 patients with endometrial cancer.

Interpretation: Trastuzumab duocarmazine shows notable clinical activity in heavily pretreated patients with HER2-expressing metastatic cancer, including HER2-positive trastuzumab emtansine-resistant and HER2-low breast cancer, with a manageable safety profile. Further investigation of trastuzumab duocarmazine for HER2-positive breast cancer is ongoing and trials for HER2-low breast cancer and other HER2-expressing cancers are in preparation.

Funding: Synthon Biopharmaceuticals".[21]

Example 2. "Background: A vaccine to protect against COVID-19 is urgently needed. We aimed to assess the safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 (Ad5) vectored COVID- 19 vaccine expressing the spike glycoprotein of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strain.

Methods: This dose-escalation, single-centre, open-label, non-randomized, phase 1 trial of an Ad5 vectored COVID-19 vaccine in Wuhan, China sequentially enrolled healthy adults aged between 18 and 60 years in a pharmacological-guided design and were allocated to one of three vaccine dose groups (5×10^{10}, 1×10^{11}, and 1.5×10^{11} viral particles). The primary outcome was adverse events during 7 days post-vaccination. Safety was assessed over 28 days post-vaccination. [Specific antibodies and vaccination-induced neutralising antibodies were measured with ELISA, and neutralisation tests, respectively.] T-cell responses were assessed by enzyme-linked immunospot and flow-cytometry assays. This is a registered study (NCT04313127).

Findings: Between 16/03/2020 and 27/03/2020, we screened 195 individuals. Of them, 108 participants (51% male, 49% female; mean age 36.3 years) were [enrolled and included in the analyses (low dose, n = 36; middle dose, n = 36; high dose, n = 36). At least one adverse reaction (AR) within the first 7 days post-vaccination was reported in 87 participants (low dose group, n = 30 (83%); middle dose group, n = 30 (83%); high dose group, n = 27 (75%)). Fifty-eight (54%) participants reported pain at the injection site, and systematic ARs included fever (50 [46%]), fatigue (47 [44%]), headache (42 [39%]), and muscle pain (18 [17%]). Most reported ARs in all dose groups were mild or moderately severe. No serious adverse event was noted within 28 days post-vaccination. ELISA antibodies and neutralising antibodies increased at day 14, peaking 28 days post-vaccination. Specific T-cell response peaked at day 14 post-vaccination.

Interpretation: Humoral responses against SARS-CoV-2 peaked at day 28 post-vaccination in healthy adults, and rapid specific T-cell responses were noted from day 14 post-vaccination. Therefore, the Ad5 vectored COVID-19 vaccine is tolerable and immunogenic at 28 days post-vaccination and warrants further investigation.

Funding: National Key R&D Program of China, National Science and Technology Major Project, and CanSino Biologics."

This example was adapted from Zhu et al.[22] to reduce the word count.

Explanation. Conference and journal abstracts of EPDF trials communicate the important clinical development of a new intervention, and readers (including participants and the broader public) often base their evaluation of a trial on these abstracts.[23] As such, it is recommended that they contain clear and sufficient information on trial design, methods, results, and conclusions in relation to the EPDF trial objectives and outcomes. Numerous EPDF trials remain unpublished,[24] so abstracts presented at conferences might potentially serve as the sole source of information. Furthermore, there are often significant delays from conference presentation to full publication of such trials; hence, it is important they are well-reported as critical decisions (e.g., go/no-go decisions, decisions on new trials in other indications or of other combinations) may depend on them.[24,25]

The suggested abstract structure of the CONSORT-DEFINE statement follows a similar format as the CONSORT extension for journal and conference abstracts.[23] The modifications are made to tailor abstracts to the specific objectives of EPDF trials (see Table 2 in the CONSORT-DEFINE statement[10]). CONSORT-DEFINE outlines the recommended items that should be included in abstracts where possible, as the level of detail may be broadly dependent on the style and word count limit adopted by journals or conferences, as well as the complexity of the EPDF trial design. This extension should be used together with CONSORT for journal and conference abstracts[23] and other applicable extensions. The examples provided above include one example as it was published (Example 1) and one that was adapted to further reduce the word count (Example 2).

Introduction

Item 2a.1 [modified] Description of research question(s) and justification for undertaking the trial, including summary of relevant clinical studies (published and unpublished) examining benefits and harms for each intervention

Example 1. "A first-in-human study[reference] of CH5126766 recommended a phase 2 dose of 2.7 mg taken for four continuous days each week over 4-week cycles until disease progression, unacceptable toxicity, or patient withdrawal (whichever occurred first). Although three (7%) patients with melanoma out of the 45 patients with molecularly unselected solid tumours evaluable for response had an objective response, common adverse events in all 52 treated patients, including rash (all grades, 49 [94%] patients), elevated creatine phosphokinase (all grades, 29 [56%] patients), and diarrhoea (all grades, 27 [52%]), led to difficulties in developing this drug further. (...) The side-effects of tyrosine-kinase inhibitors have been mitigated by intermittent dosing schedules and toxicity-guided treatment interruptions (ie, so-called drug holidays) without diminishing antitumour activity[reference]. Consistent with the long half-life of CH5126766 (approximately 55 h), pharmacokinetic simulation of CH5126766 administered twice per week (on Monday and Thursday or on Tuesday and Friday) or three times per week (on Monday, Wednesday, and Friday) showed that highly intermittent schedules could provide clinically relevant

drug exposure (...)[reference]. We hypothesised that schedules of CH5126766 administered twice per week or three times per week would allow adequate drug exposure with improved toxicity profiles to facilitate the investigation of antitumour activity in biomarker-selected cohorts of patients with cancer."[26]

Example 2. "HIV-1-specific bNAbs targeting multiple epitope regions of the HIV-1 envelope trimer (Env) have demonstrated the ability to robustly reduce plasma viremia in people living with HIV not on ART [antiretroviral therapy] as well as to modestly delay viral rebound in individuals during an analytical antiretroviral treatment interruption (ATI)[reference]. Rapid selection of neutralization-resistant viral variants resulting in therapeutic failure has been observed in all referenced studies, and it has become evident that bNAb monotherapy is insufficient for viral control due to the frequent presence of pre-existing escape mutations in the substantially diverse within-host HIV quasispecies. Combination of two bNAbs with complementary epitope specificities—the CD4-binding-site (CD4bs) antibody 3BNC117 and the V3-glycan antibody 10-1074—were able to suppress viral rebound in a subset of individuals for an extended period during ATI; in contrast, viral breakthrough was observed in individuals in the presence of baseline escape or when one of the antibodies fell below the therapeutic threshold, resulting in functional monotherapy[reference].

It has, therefore, been postulated that three bNAbs targeting different epitope regions would be necessary to overcome viral variants with potentially pre-existent escape mutations and provide sufficient control of the virus to prevent development of novel resistance. Complementary viral coverage resulting in extended breadth and potency has been modeled for multiple bNAb combinations[reference], and the combination of the CD4bs antibody VRC07-523LS, the V3-glycan antibody PGT121 and the V2-apex antibody PGDM1400 has been identified to neutralize 99% of a panel of 374 cross-clade HIV-1 strains, of which 82% would be neutralized with at least two active antibodies (...)[reference].

Although both VRC07-523LS and PGT121 have demonstrated robust antiviral activity in viremic people living with HIV, PGDM1400 has not been evaluated in humans thus far. This antibody was originally identified in donor 84 of the International AIDS Vaccine Initiative (IAVI) Protocol G cohort and is exceptionally broad and potent, covering 83% of a panel of 106 cross-clade pseudoviruses at a median 50% inhibitory concentration (IC50) of 0.003 μg mL–1, being ten-to 100-fold more potent than CD4bs antibodies such as VRC01 and 3BNC117[reference]. Indeed, PGDM1400 provided highly potent antiviral activity in non-human primate simian–human immunodeficiency virus (SHIV) SF162P3 challenge studies[reference]. Here, we evaluated the safety, tolerability and pharmacokinetics of PGDM1400 when given intravenously, alone or in combination with PGT121 and VRC07-523LS, in adults without HIV and determined the antiviral activity of all three bNAbs in viremic adults living with HIV not on ART."[27]

This example states the research question, justification for conducting the trial, a summary of the relevant clinical studies, and the potential benefits. However, it lacks a description of the potential harms of the combination of the interventions.

Explanation. Details on the research question(s) and a justification of the rationale for the trial are important as EPDF trials, compared to later phase trials, generally harbour greater uncertainties around the risk-benefit ratio given the limited available information. These studies are often the first time a new intervention is tested in healthy volunteers, patients, or specific participant subgroups. Consequently, these studies also impose a greater burden for participants and those conducting the study due to the increased need to monitor closely, and to collect samples and data.[28,29] Readers need sufficient information to understand the significance of the clinical problem and to assess the ethical and scientific rationale justifying conducting the trial.[28] Clearly defined research questions also shape the objectives, trial design, analyses, and interpretation of the results.[30]

There should be a description of the importance of the research question(s) and a justification of the rationale for the trial. This item focuses on the justification for the trial in the context of available evidence from relevant clinical trials examining the potential benefits and harms,[15] whereas item 2a.2 focuses on the relevant non-clinical or preclinical research. It is strongly recommended that the justification for undertaking the trial includes any systematic review of previous similar trials or an indication of the absence of such trials.[15]

Item 2a.2 [new] Summary of key findings from relevant non-clinical or preclinical research

Example 1. "Seliciclib is an orally available cyclin-dependent kinase (CDK) inhibitor under development for oncology indications. Seliciclib suppresses synovial fibroblast proliferation, not only by inhibiting CDK2, but also by inducing expression of the endogenous CDK inhibitor p21, which is otherwise downregulated in synovial fibroblasts in patients with rheumatoid arthritis[reference]. In addition, inhibition of CDK7 and CDK9 by seliciclib reduces transcription of the B-cell lymphoma-2 (BCL-2) family member MCL1, leading to impaired viability of neutrophils, synovial macrophages, and synovial fibroblasts[reference]. Seliciclib and related CDK inhibitors have shown efficacy and potency in preclinical arthritis models[reference]. Unlike other CDK inhibitors, seliciclib is not myelosuppressive[reference];

its reported toxicity profile is otherwise similar to that of existing conventional synthetic disease-modifying antirheumatic drugs (DMARDs).

These observations, together with evidence from genetic studies that suggest CDK inhibition as a plausible therapeutic strategy in rheumatoid arthritis[reference] (…)."[31]

Example 2. "FS118 is a first-in-class tetravalent bispecific (mAb 2 format) mAb against LAG-3 and PD-L1[reference]. A LAG-3–binding site was introduced into the fragment crystallizable (Fc) region of a full-length human IgG1 PD-L1 mAb[reference], in addition to two mutations to abrogate Fcγ receptor binding[reference]. FS118-mediated blockade of LAG-3 and PD-L1 enhanced T-cell activity in vitro, and a mouse surrogate of FS118 significantly suppressed mouse tumor growth[reference]. Interestingly, a mouse surrogate of FS118 reduced cell-surface LAG-3 on T cells and increased soluble LAG-3 in the serum of mice, whereas the combination of mAbs targeting LAG-3 and PD-L1 increased LAG-3 expression in vivo. Given the compensatory upregulation of LAG-3 in response to anti–PD-(L)1 failures, and the mechanism of FS118-mediated shedding of cell-surface LAG-3 to overcome immune-mediated suppression, these data indicate that FS118 may extend clinical benefit beyond anti–PD-(L)1 monotherapy, providing rationale for this phase 1 clinical trial."[32]

Explanation. Non-clinical research relates to in vitro laboratory studies, in vivo studies in animals, and in silico studies.[8,33,34] Preclinical research is a subgroup of non-clinical research that relates to any non-clinical research that is performed before a treatment is first administered to humans. Non-clinical/preclinical data in pharmacokinetics, pharmacodynamics, and toxicology and their translation to humans are essential for the planning and conduct of EPDF trials–especially for first-in-human trials. These data are frequently used to determine the starting dose(s) and dose increments, and to identify potential safety issues, particularly when clinical evidence has not yet been gathered.

Where applicable, a summary of the key non-clinical data and results should be provided, focusing on: The relevance of the experimental model(s) (e.g., the relevance of the animal model for the specific clinical translational question); the properties of the target; pharmacodynamics; pharmacokinetics and toxicokinetics; safety pharmacology; and toxicology studies.[8] If relevant, reporting of specific aspects such as details on biologically active metabolites as well as drug–drug interactions should also be considered. If not provided, information on why non-clinical or preclinical research were not relevant for planning the trial should be provided, such as if planning of the trial was based on available clinical evidence in other settings (e.g., diseases or participant populations) (see item 2a.1). Where available and relevant, supportive findings from other non-clinical studies of drugs of the same class or that may have shared effects should also be considered.

Item 2a.3 [new] Summary of findings from previously generated preclinical and translational studies to support any planned biomarker substudies (where applicable)

Example 1. "Pembrolizumab, a highly selective, humanized monoclonal IgG4 kappa isotype antibody against PD-1, can disrupt the engagement of PD-1 with its ligands and impede inhibitory signals in T cells, with resultant tumor recognition by cytotoxic T cells. In clinical trials, anti–PD-1 and anti–PD-L1 antibodies produce durable responses in approximately 20% of unselected patients with advanced non–small-cell lung cancer[reference]. Developing reliable, validated biomarkers that identify patients with an increased probability of response to these antibodies remains a challenge[reference]. Because the PD-1 pathway may be a key mechanism of immune escape in a subgroup of patients with non–small-cell lung cancer, PD-L1 expression in tumor or inflammatory cells is a candidate biomarker. However, PD-L1 expression has not been formally validated as a biomarker in contemporaneously collected tumor tissue. As part of the large, international, phase 1 KEYNOTE-001 trial, we evaluated the side effects, safety, and antitumor activity of pembrolizumab in patients with advanced non–small-cell lung cancer. We also sought to define and validate a tumor PD-L1 expression level associated with an enhanced likelihood of benefit from pembrolizumab."[35]

This example provides rationale for conducting the planned biomarker substudy using PD-L1 expression based on known mechanisms of PD-L1 function (presumably based on preclinical and/or clinical studies), but it lacks specific details about preclinical and translational studies supporting this approach.

Example 2. "In preclinical and early clinical studies, ATR inhibition has been shown to be synthetically lethal with LOF [loss-of-function] of the ataxia telangiectasia-mutated (ATM) kinase[reference]. Although early clinical studies investigating ATR inhibition in tumors harboring ATM mutations or lacking ATM protein expression have shown preliminary signals of antitumor activity, the optimal method for identifying ATM LOF in a broader population remains to be established. We hypothesize that the accurate diagnosis and treatment of ATM LOF tumors requires the determination of allelic status (biallelic versus non-biallelic) and the exclusion of ATM LOF alterations stemming from clonal hematopoiesis. Furthermore, we

hypothesize that ATR inhibition results in anti-tumor activity in DDR [DNA damage response] alterations beyond ATM, such as BRCA1/2 and others. Specifically, the clinical activity of ATR inhibition in PARP inhibitor (PARPi)-resistant tumors, including cancers with BRCA1/2 reversion mutations, has not been reported. (...)

Multiple ATR inhibitor (ATRi)-sensitizing cancer alterations have been proposed by means of RNA interference-enabled or CRISPR–Cas9-enabled forward chemogenomic screening[reference]. We used these chemogenomic CRISPR-enabled screen datasets, together with internal and published preclinical validation data, to identify ATRi-sensitizing DDR alterations as the rational basis for patient selection for treatment with camonsertib (RP-3500) (...)[reference].

Here we report results of a phase 1 clinical trial (Treatment Enabled by SNIPRx (SyNthetic Lethal Interactions for Precision Therapeutics platform) (TRESR)) of camonsertib in patients with DDR biomarker-selected advanced solid tumors (NCT04497116). (...) A key requirement for trial eligibility was the presence of an ATRi-sensitizing gene alteration (LOF of ATM, ATRIP, BRCA1, BRCA2, CDK12, CHTF8, FZR1, MRE11, NBN, PALB2, RAD17, RAD50, RAD51 B/C/D, REV3L, RNASEH2A, RNASEH2B or SETD2; Fig. 1a). Several of the eligibility genes, such as SETD2 and RNASEH2B, are distinct from the canonical homologous recombination repair (HRR) genes associated with sensitivity to PARPi. Preplanned translational analyses were designed to (1) define the context in which solid tumors are sensitive to camonsertib, including tumor type and genomic profile; (2) test the hypothesis that biallelic LOF of the gene alteration would enrich for clinical benefit to camonsertib; and (3) define if early ctDNA [circulating tumor DNA] dynamics predict clinical outcomes to camonsertib."[36]

Explanation. There is growing interest in the use of biomarkers to aid the evaluation of new therapies in EPDF trials.[37,38] Biomarkers may help to define the recommended dose(s) for subsequent testing, confirm mechanisms of action, serve as intermediate endpoints for clinical benefit or harm, or define participant subgroups that may respond better to targeted treatments. To optimise success in biomarker studies, researchers need to present a clear study concept supported by existing findings from previous studies on the planned biomarkers.[38]

If applicable, there should be provision of background information to support each biomarker substudy planned for the trial. This should include biomarker assay validation and performance data, and biological and clinical rationale. Correlative studies should align with exploratory (correlative) research objectives. For example, this could include analyses to determine if the expression of a specific marker (e.g., genetic or protein) is associated with response to or toxicity of the intervention.[39]

Item 2b [modified] Specific objectives (e.g., relating to safety, activity, pharmacokinetics, pharmacodynamics, recommended dose(s))

Example 1. "The primary objective was to determine dose-limiting toxicity (DLT) and the maximum-tolerated dose (MTD) of AG-013736. Secondary objectives were to (1) evaluate the pharmacokinetics (PK) of oral AG-013736, (2) conduct a pilot evaluation of the effect of food on AG-013736 PK, (3) conduct a pilot evaluation of the effect of an antacid on the PK of AG-013736, and (4) document preliminary evidence of antitumor activity."[40]

Example 2. "The purpose of this first-in-human (FIH) clinical trial of ABBV-3373 was to characterize the pharmacokinetics (PK), immunogenicity including anti-drug antibody (ADA) incidence and titre measurement, and pharmacodynamics (PD) including an assessment of serum cortisol levels as a safety PD marker, safety and tolerability of ABBV-3373 following single ascending doses in healthy adults to help guide future clinical studies."[41]

Example 3. "The primary objectives of the SAD [single ascending dose] study were to assess the safety and tolerability of single oral doses of V-7404 administered to healthy adult volunteers and to assess the plasma PK [pharmacokinetics] of V-7404 after administration of single oral doses. The secondary objective of the SAD [single ascending dose] study was to assess the effects of food on the safety, tolerability, and single-dose PK of V-7404. The primary objectives of the MAD [multiple ascending dose] study were to assess the safety and tolerability of multiple oral doses of V-7404 administered to healthy adult volunteers, both QD [once a day] or BID [twice a day], for 14 days, and to assess the PK of V-7404 after administration of single and multiple oral doses."[42]

Example 4. "We undertook a dose escalation study to identify the maximum tolerated dose of targeted multimodal exercise in a group of community-dwelling stroke survivors with impaired balance and walking."[18]

Explanation. Research objectives are at the heart of any clinical trial as they inform the trial design (e.g., outcomes) and analysis methods, and facilitate the subsequent interpretation of trial findings.[30] This modified CONSORT-DEFINE item additionally highlights that participant well-being is usually the primary consideration in EPDF trials.

EPDF trials should describe any research objectives to address the specific scientific question(s) the trial was intended to answer. The objectives should encompass safety, toxicity, activity (e.g., preliminary measures of efficacy), pharmacokinetics, pharmacodynamics, feasibility assessment, recommended dose(s), or some combination thereof.[1,43–45] Primary objectives should be distinguished from secondary or exploratory objectives to emphasise the main aim(s) of the trial and support the interpretation of the results (see Example 1 and Example 3). For EPDF trials with formal testing of hypotheses, these should be stated, providing insight into the conclusions relating to research questions that may be anticipated.

Methods: Trial design

Item 3a.1 [modified] Description of trial design elements, such as dose escalation or de-escalation strategy, number of treatment groups, allocation ratio if relevant, and details of any prespecified trial adaptations

Example 1. "In this Phase IB, open-label, dose-determining study (CBHQ880A2102; NCT00741377), patients with relapsed or refractory MM [multiple myeloma] with ≥1 prior SRE [skeletal-related event] received BHQ880 (Novartis) in combination with zoledronic acid (Zometa®; Novartis) and anti-myeloma therapy. (...) The dose–DLT [dose–dose-limiting toxicity] relationship, estimated by a two-parameter Bayesian Logistic Regression Model (BLRM), along with the principal of escalation with overdose control (EWOC), was used to guide dose escalation and estimate the MTD [maximum tolerated dose]."[46]

Example 2. "This phase 1, randomized, observer-blinded, placebo-controlled, single and multiple ascending-dose study (...) was conducted in two parts (...) at a single clinical site in the United States (...). Part A consisted of 5 single ascending-dose (SAD) cohorts of healthy volunteers who received the following doses of BITS7201A: (A) 30-mg subcutaneous (SC), (B) 90-mg SC, (C) 300-mg SC, (D) 300-mg IV [intravenous], and (E) 750-mg IV (...). Part B consisted of multiple ascending-dose (MAD) cohorts of healthy volunteers who each received a total of 3 doses of BITS7201A once every 4 weeks as (F) 150-mg SC, (G) 300-mg SC, or (H) 600-mg SC on Days 1, 29, and 57 (...). The treatment allocation for these cohorts was 6 active: 2 placebo, for a planned enrollment of 40 subjects and 24 subjects in Parts A and B, respectively. Part B was to begin after safety data review of the 300-mg SC cohort in Part A. For Part B, we also planned an additional cohort of 16 patients with mild atopic asthma (Cohort I; 12 active: 4 placebo), who were to receive multiple doses of 600-mg BITS7201A SC, or the maximally tolerated dose based on the MAD, healthy volunteer cohorts."[47]

Example 3. "This was a multicenter, open-label, Phase I, multiple ascending dose-escalation trial of single agent idasanutlin in a microprecipitate bulk powder (MBP) formulation in patients with advanced malignancies other than leukemia (...). (...) The dose-escalation phase involved single-patient cohorts until grade 2 related adverse events (AE) were reported (...). Based on these AE criteria, subsequent dose escalation involved 3-patient cohorts in a modified continual-reassessment-method EWOC [escalation with overdose control] design."[48]

Explanation. The CONSORT statement,[11,15] with related extensions, reflects on trial design features focusing on randomised trials. For example, the Adaptive designs CONSORT Extension (ACE) statement[49] covers trial design features relating to randomised adaptive designs. EPDF trials may or may not be randomised,[7] but all use intra-participant or inter-participant dose (de-)escalation strategies, and by nature incorporate trial adaptations (e.g., dose levels can be escalated, de-escalated, or dropped based on observed interim toxicity and activity data).[50,51] All of these aspects influence the choice of the study design and statistical methods. Specification of planned opportunities for adaptations and their scope is essential to preserve the trial and data integrity of adaptive designs and to facilitate regulatory assessments, regardless of whether they were triggered during the trial.[49] Hence, adequately describing these important features of the trial design will enable readers to understand how the trial was set up.

There should be a brief description of the main elements and features of the dose-finding trial design used, along with details of the prespecified trial adaptations. These aspects include.

- Phase of clinical research (e.g., I, I/II, first-in-human, first-in-child);
- Specific design features (e.g., open-label, double-blinded, placebo-controlled, dose escalation or de-escalation, expansion cohort, or intra-participant dose escalation);
- Number of groups (which could be treatment groups or specifically defined [targeted] subgroups based on, for example, age or disease type);
- Prespecified trial adaptations, such as,
  - Dose adaptations based on type of (de-)escalation design strategies (e.g., algorithm-based, model-based, model-assisted designs, single ascending dose, multiple ascending dose, or intra-participant dose escalation),
  - Other adaptations (e.g., safety, futility, efficacy, enrichment), regardless of whether they were triggered.[49–51]

Specific details of design features are addressed in items 3a.2 to 3a.11.

Item 3a.2 [new] Trial design schema to show the flow of major transition points (e.g., dose escalation to dose expansion, phase 1 to phase 2, single ascending dose to multiple ascending dose)

Example 1. *This example is from Figure 1a in Zhang et al.,[52] used under CC BY 4.0, cropped from original (Fig. 1a).*

Example 2. *This example is from Online Resource 1 in Lee et al.,[53] used under CC BY 4.0 (Fig. 1b).*

Explanation. Planning dosing strategies in EPDF trials can be complex depending on the research context, adaptive trial design features, and methods considered. EPDF trials are increasingly designed to seamlessly address multiple objectives that span multiple transition points of clinical research (e.g., dose escalation to [multiple] expansion cohort(s), phase I to II, single ascending dose to multiple ascending dose).[8,55,56] The increasing complexity of trial design and dosing strategies can be challenging for readers to comprehend.

Hence, authors are encouraged to provide a graphical representation of the overall schema of the proposed trial, when possible, to show the timing of major reviews and decision points, highlighting any overlap between study cohorts and parts to help the reader interpret the logical stages of the process (see Example 2).[8] When a trial consists of different parts, the trial design schema should show the timing and criteria of major transition or progression points (e.g., dose escalation to expansion, dose escalation to dose optimisation (particularly as outlined in projects like the FDA Optimus project, which focuses on selected tolerable doses to ensure they are active and tolerable),[1,4] phase I to phase II, single ascending dose to multiple ascending dose, stage 1 to stage 2 with a formal interim analysis for futility/activity, monotherapy to combination regimen, or exploration of an alternative administration schedule or route).[57]

Item 3a.3 [new] Statistical methods or rationale underpinning the trial design

Example 1. "Activity and toxicity data were used to update an EffTox model to establish the optimal dose of ponatinib with FLAG-IDA [fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin], the trial's primary endpoint. The adaptive Bayesian EffTox method and its application to MATCHPOINT and operating characteristics have been described previously (including a discussion of alternative methods)[reference]. In summary, bivariate binary outcomes were incorporated into the model seeking probability of activity of 45% or more and probability of dose-limiting toxicity of 40% or less. Activity was modelled using a quadratic form, allowing for a non-monotonic dose–response relationship, such as a plateau of activity at higher doses. Toxicity was incorporated into the model using a linear form. The prior probabilities of activity and toxicity were agreed by consensus of the trial management group (...). Dose transition pathways were incorporated alongside the EffTox method to visualise all potential dose pathways, be it escalation or de-escalation, remaining at the same dose, or stopping early[reference]. The dose transition pathways provided a simple means of assessing the effect of different data permutations of outcomes for future patients on the EffTox recommendations during the progress of trial. Additionally they would prove a useful design calibration tool to ensure the EffTox design would behave as anticipated given its chosen design parameters[reference]."[58]

Example 2. "Dose escalation was done using a modified Bayesian optimal interval design, which provided greater flexibility than the standard 3 + 3 design (...)[reference].

In this trial, the target rate for dose-limiting toxic effects was set at 30% with a boundary for dose escalation of 23.6% and a boundary for dose de-escalation of 35.9%. The modification of Bayesian optimal interval escalation and de-escalation rules includes exemptions in the case of six or nine patients evaluable for dose-limiting toxic effects, and use of both accelerated and standard titration parts.

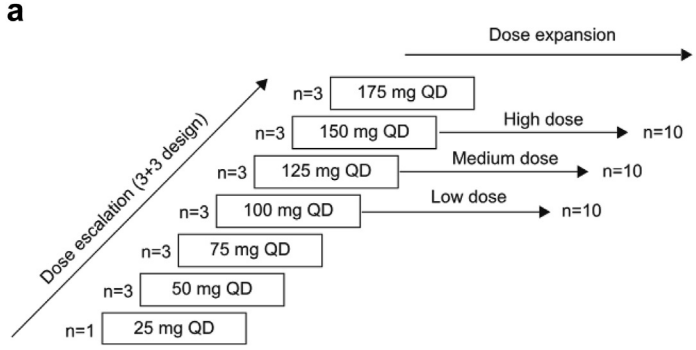
The decision to escalate to the next highest dose was made by comparing the observed rate of dose-limiting toxic effects with the two predetermined fixed boundaries (23.6% and 35.9%), with the target rate of dose-limiting toxic effects of 30% falling between the two boundaries. Details related to dose-escalation stopping criteria are outlined in Appendix (...). The evaluation period for dose-limiting toxicity spanned the first 4 weeks (ie, 28 days) after the first administration of subcutaneous epcoritamab. (...)

Dose escalation was stopped if the maximum sample size had been reached; if there were nine dose-limiting toxicity (DLT)–evaluable patients at the current dose level, and the decision would be to remain on the same dose level based on the dose-escalation rules; if the lowest dose was disallowed; or if there were six DLT– 2 evaluable patients with ≤1 DLT on the current dose level provided that a higher dose level had already been evaluated and the number of DLTs at the higher dose level had led to a de-escalation."[54]

The trial design described in this example is illustrated in Supplementary Figure S1 in the online Supplementary Appendix of Hutchings et al.,[54] reprinted from The Lancet with permission from Elsevier (Fig. 1c).

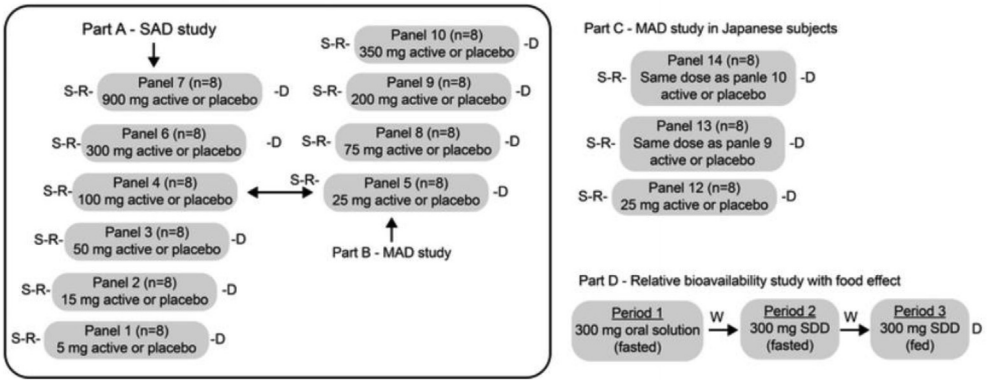
Example 3. "This is the first phase I trial in children to use the rolling-six design, which allows enrollment of up to 6 patients at a dose level versus the standard 3, in an attempt to shorten overall study duration by

a



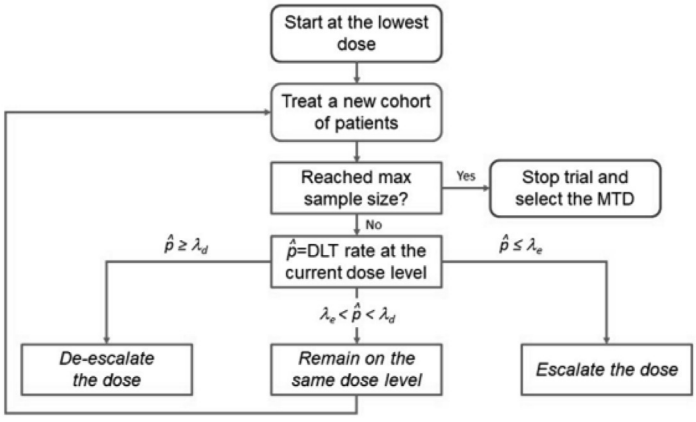
QD: once a day.

b



D: study discharge; MAD: multiple ascending dose; R: randomisation; S: screening; SAD: single ascending dose; SDD: spray dried dispersion; W: washout.

c



λ_d and λ_e indicate DLT rate boundaries for dose de-escalation and dose escalation, respectively; p represents the estimated DLT rate at the time of decision making. DLT: dose-limiting toxicity; max: maximum; MTD: maximum tolerated dose.

Fig. 1: **(a)** Item 3a.2, trial design schema to show the flow of major transition points, Example 1—obtained from Figure 1a in Zhang et al.,[52] used under CC BY 4.0, cropped from original; **(b)** Item 3a.2, trial design schema to show the flow of major transition points, Example 2—obtained from Online Resource 1 in Lee et al.,[53] used under CC BY 4.0; **(c)** Item 3a.3, statistical methods or rationale underpinning the trial design, Example 2—obtained from Supplementary Figure S1 in the online Supplementary Appendix of Hutchings et al.,[54] reprinted from *The Lancet* with permission from Elsevier.

eliminating the observation period when a cohort is expanded from 3 to 6."[59]

Example 4. "The cisplatin dose was assigned using the TITE-CRM [time-to-event continual reassessment method] to establish the rate of DLT [dose-limiting toxicity], while maximizing the number of patients treated at doses likely to be efficacious and maintaining the trial open to enrollment[reference]. Dose levels and prior estimates of the probability of DLT, based on previous experience with radiochemotherapy involving gemcitabine, are presented in Table 1[reference]. The goal of the trial was to determine the dose of cisplatin associated with a 20% probability of DLT (a target rate of 0.20). The initial dose level of cisplatin was 30 mg/m^2. When a patient was eligible for enrollment, the probability of DLT was estimated for each dose, based on the trial experience up to that time and the prior expectations of toxicity. In the TITE-CRM paradigm, patients who had enrolled in the trial but had not experienced DLT were included in the probability calculation with a weight equal to the proportion of the 9-week acute toxicity observation period they had completed; patients who experienced toxicity or completed the observation period without toxicity were assigned full weight. Each new patient was assigned to the currently estimated target dose, defined as the dose having an estimated probability of toxicity closest to but not greater than the target rate, subject to the restriction that two patients must have completed therapy at the lower dose before the first patient was assigned to a higher dose. The prior distribution of the dose-toxicity model was chosen to control the expected number of toxicities in the trial under a variety of scenarios about the true relationship between dose and toxicity[reference]."[60]

Explanation. The statistical methods that underpin the trial design are central to achieving the research objectives. EPDF trials are adaptive by nature. Reporting how the information is gathered and used to direct prespecified adaptations at interim analyses, in accordance with prespecified decision-making criteria or rules (item 7b) in EPDF trials is essential. This enables readers to assess the appropriateness of statistical methods used to evaluate the operating characteristics of the adaptive design (item 7a) and for performing statistical inference (item 12a.2).[49]

The reasoning or logical basis for selecting the trial design should be presented. This includes rule-based designs (such as 3 + 3, Rolling 6,[61] single ascending dose, or multiple ascending dose).[55] Descriptions of statistical methods used to set up and implement the adaptive design should be provided. Detailed analytical derivations of statistical information that guide planned adaptations utilising statistical models or formulas should be presented to enhance reproducibility.[49] For dose adaptations based on model-based and model-assisted dose-finding designs,[62,63] comprehensive details and explanations of the statistical methods should be provided. This includes, where applicable, model assumptions, mathematical form of the model, choice of model parameters, Bayesian prior distribution and its elicitation, and the rationale for choosing a target risk/toxicity rate or acceptable range for the recommended dose(s).[44,64,65] For other adaptations, such as early stopping for futility, the statistical methods used (such as conditional power, predictive power, and posterior probability of treatment effect) should be clearly described.[44,49] It is good scientific practice to provide details of statistical software and packages with versions (if applicable) used for design and parameter choices (e.g., via simulation).[44,49]

Item 3a.4 [new] Starting dose(s) with rationale

Example 1. "Based on preclinical results in experimental animal models, a clinically relevant plasma concentration of IRL790 is around 1 mM. The NOAEL [no-observed-adverse-effect level] in dogs given twice-daily oral doses IRL790 is 18 mg/kg/day (9 mg/kg orally twice daily), corresponding to Cmax of about 9 mM. Calculations based on oral administration in dogs suggested that the starting dose in humans, 5 mg, would yield a peak plasma concentration of about 0.12 mM and 1.3% of the plasma concentration of the NOAEL in the most sensitive species studied. The dose selection in the SAD [single ascending dose] part of the study was based on sub-and supra-clinical doses. Hence, the 40 mg dose was calculated to yield peak plasma concentrations of about 1 mM and the top dose, 160 mg, 4 mM, well below the NOAEL level in dogs. Since dose-limiting AEs [adverse events] were expected to be central nervous system (CNS) related, it was our experience that humans could be more sensitive to such AEs, doses selected for the study did not a priori aim for an maximum tolerated dose level following single oral administration, but rather to cover a relevant plasma concentration range."[66]

Example 2. "The starting dose of JNJ-54175446 (50 mg) for this multiple-dose study was predicted to result in an average 50% inhibition of the central P2X7 receptor confirmed by data from preceding single-dose studies[reference]."[67]

Example 3. "In the SAD [single ascending dose] part, the starting dose of 1 mg was selected based on the no-observed-adverse-effect-level (NOAEL), in compliance with FDA [The United States Food and Drug Administration] and European Medicines Agency (EMA) guidance[reference]. This dose provided a safety margin of 621 for the most appropriate toxicology species (dog[reference]) and was expected to be pharmacologically

inactive. (...) The starting dose of 10 mg twice daily (b.i.d.). for 5.5 days was chosen in the MAD [multiple ascending dose] part based on blinded PK [pharmacokinetics] data from the SAD part."[41]

Explanation. Reporting the starting dose and its rationale is crucial for understanding the basis of dose selection, which enhances transparency and reproducibility, aids regulatory evaluations, and allows evaluation of whether a given method was useful in a particular setting.[68] Additionally, this information is essential for contextualising and interpreting trial results, from the beginning through subsequent interim and to final dose adjustments, in response to accumulating observed outcomes.

Recommended approaches exist for determining the appropriate starting dose(s) for first-in-human and early phase clinical trials.[8,55,69–71] Regardless of the approach used, the starting dose level(s) should be stated, and a scientific rationale for the choice for each investigated intervention or study population should be provided. The rationale should include, but not be limited to, key findings from relevant non-clinical/preclinical studies (for first-in-human trials) and/or clinical experience with the intervention(s) justifying the dose chosen or, if applicable, dose rationale for similar interventions in other disease areas and (sub) populations.[72,73]

Item 3a.5 [new] Range of planned dose levels with rationale

Example 1. "Participants could receive 200 mg, 400 mg, 600 mg, 800 mg, or 1000 mg, taken daily for 4 consecutive days every week over a 4-week treatment period. Dose range and schedule were predetermined on the basis of healthy control and oncology studies in which more than 450 participants had previously received seliciclib[reference]."[31]

Example 2. "A first-in-human study[reference]of CH5126766 recommended a phase 2 dose of 2.7 mg taken for four continuous days each week over 4-week cycles until disease progression, unacceptable toxicity, or patient withdrawal (whichever occurred first). Although three (7%) patients with melanoma out of the 45 patients with molecularly unselected solid tumours evaluable for response had an objective response, common adverse events in all 52 treated patients (...) led to difficulties in developing this drug further (...).

The side-effects of tyrosine-kinase inhibitors have been mitigated by intermittent dosing schedules and toxicity-guided treatment interruptions (...) without diminishing antitumour activity[reference]. Consistent with the long half-life of CH5126766 (approximately 55 h), pharmacokinetic simulation of CH5126766 administered twice per week (...) or three times per week (...) showed that highly intermittent schedules could provide clinically relevant drug exposure. (...)

In the dose-escalation phase, patients received oral schedules of 4.0 mg CH5126766 twice per week (...) or 4.0 mg CH5126766 three times per week (...) delivered in cycles of 28 days."[26]

Explanation. Careful selection of doses for an intervention, with rationale, in EPDF trials is key to safeguard participants and to evaluate the activity of the intervention, and should be clearly described for regulatory assessment and for readers to understand how they were chosen. Whether the doses and the number of dose levels are prespecified or may be adjusted based on accrued data can affect dosing decisions and trial findings. Hence, it is important that such information be adequately described to enhance reproducibility and the interpretation of findings, regardless of the research context.

Authors should specify the planned doses (whether single or combination therapies) considered, with rationale, and provide details on associated boundaries of maximum dose, maximum expected exposure, desired pharmacological activity, and/or intra-patient dose adaptations, where applicable. They should indicate if the doses and the number of dose levels are prespecified or may be adapted in accordance with safety and tolerability, as well as pharmacokinetic/pharmacodynamic data as applicable.[55,57] The maximum allowed increment between dose levels should be provided.[8,57] For interventions given in combination,[74,75] authors should clarify whether interventions were planned to be given in parallel or in a prespecified sequence and the maximum allowed increases in each component of the combination. The specific ways an intervention is administered are covered in item 5a.

Item 3a.6 [new] Presentation of planned dose levels (e.g., as a diagram, table, or infographic), where applicable

Example 1. *This example is from Figure 1 in Gadgeel et al.,[76] reprinted from The Lancet Oncology with permission from Elsevier (Fig. 2a).*

Example 2. *This example is from Figure 1* in Yang et al.,[77] *reprinted from Clinical Pharmacology in Drug Development with permission from John Wiley and Sons (Fig. 2b).*

Explanation. Most EPDF trials use multiple dose levels (in monotherapy or in combination with other therapies) and complex dosing strategies.[79] Hence, using a form of visual aid to present the planned dose levels (where applicable) will help readers better understand and evaluate the results of the trial. It can also help to increase the transparency and reproducibility of trial results and facilitate comparisons across different studies.

Visual aids like a diagram, table, or infographic can be utilised for providing a clear presentation of the dose levels in item 3a.5; there is no specific, prescribed

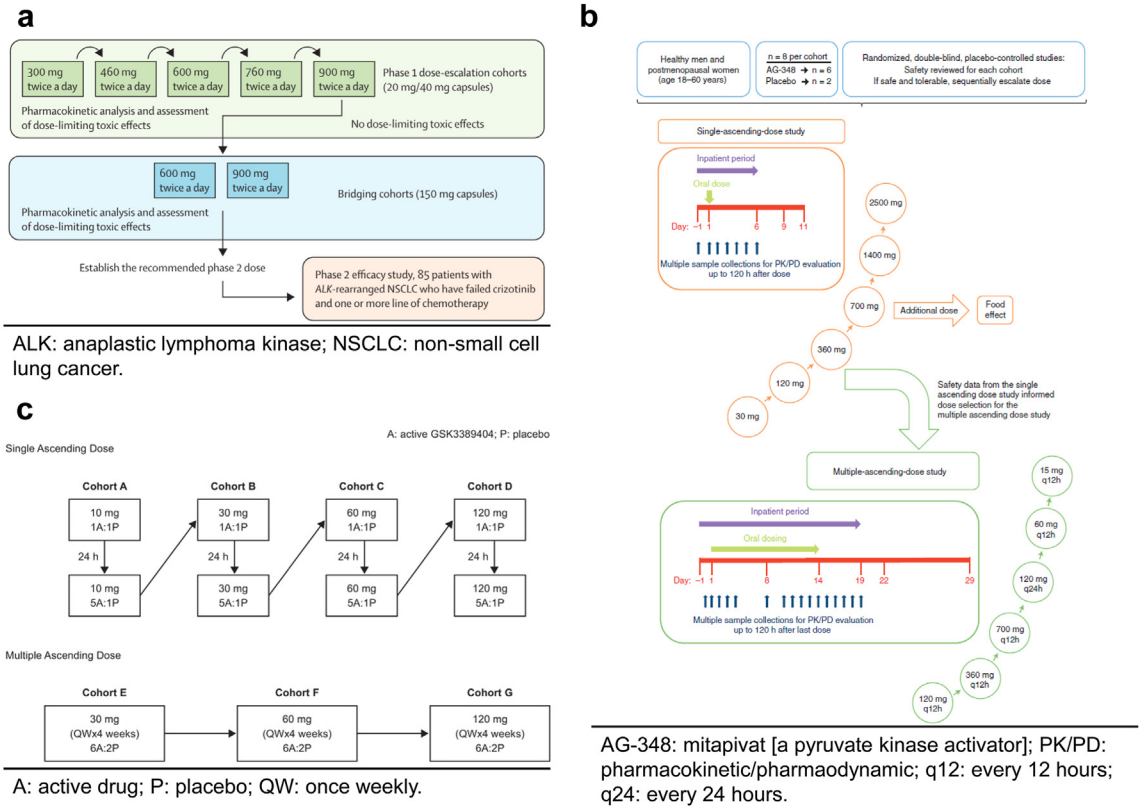


Fig. 2: **(a)** Item 3a.6, presentation of planned dose levels, Example 1—obtained from Figure 1 in Gadgeel et al.,[76] reprinted from *The Lancet Oncology* with permission from Elsevier; **(b)** Item 3a.6, presentation of planned dose levels, Example 1—obtained from Figure 1 in Yang et al.,[77] reprinted from *Clinical Pharmacology in Drug Development* with permission from John Wiley and Sons; **(c)** Item 3a.11, criteria for progression to the next part of the trial, Example 1—obtained from Figure 2 in Han et al.,[78] used under CC BY-NC 4.0.

format.[44,45,80,81] A graphical or tabular presentation may not be necessary when the dose levels are not predefined or are very simple (e.g., details can be presented in the text for a few dose levels or when using simpler dosing strategies).

Item 3a.7 [new] Skipping of dose level(s), if applicable

Example 1a (protocol publication). "For both groups, dosing starts at level 0 and allows for possible escalation to two higher levels, or deescalation to a lower dose, as recommended by the TITE-CRM [time-to-event continual reassessment method], without skipping untried doses in escalation."[82]

Example 1b. "However, in adherence to the modified TITE-CRM design, which specifies that no untried doses are skipped, the next recommended dose was dose level 1 for subsequent recruitment of Cohort 2 patients in Group A."[83]

This example was extracted from the Supplementary Appendix, which is available as an online supplement to the publication of the trial results. The trial results paper (example 1b) referenced the publication of the protocol (example 1a).

Example 2 (trial design publication). "The recommended dose (…) for each of the subsequent cohorts is determined using the CRM [continual reassessment method] incorporating all of the accumulated DLT [dose limiting toxicity] outcomes but for added safety, the design includes a restriction to prevent skipping of untested doses when escalating."[84]

Example 3. "Skipping of dose levels was not permitted and so in the absence of dose-limiting toxicity, doses were considered sequentially with three patients per dose level."[85]

Explanation. Dose adaptation strategies in EPDF trials may allow skipping of dose level(s),[62] and as this feature impacts the design's performance, reproducibility, and interpretation, it is important that this is specified. For example, allowing for skipping in escalation can result in faster attainment of pharmacologically and/or clinically active dose levels, the maximum allowed dose, or treatment exposure if the recommended dose(s) is at the upper end of the investigated dose range, but it may introduce a risk of overdosing.

In settings with predefined dose levels, it is useful to specify whether the design allowed skipping of predefined dose levels in escalation or de-escalation, e.g., from dose level 3 to level 5. This may not be applicable in settings where dose levels were not predefined (e.g., where the next dose level would have been determined after observing the tolerability data at previous dose levels). Referencing published literature containing the required information (e.g., trial design papers in examples 1a and 2) or providing supplementary material or an accessible protocol is adequate.

Item 3a.8 [new] Planned cohort size(s) (e.g., fixed, flexible, adaptive)

Example 1. "At least three patients had to be assigned to a cohort, unless two evaluable patients in the cohort experienced a DLT [dose limiting toxicity] before the third patient was enrolled, in which case the model was re-evaluated before additional patients were enrolled to the cohort."[86]

Example 2. "In 18 patients (3 cohorts of 6 patients each) with SAH [subarachnoid haemorrhage] from a ruptured cerebral aneurysm, nitrite (3 patients) or saline (3 patients) was infused. Sodium nitrite and saline were delivered intravenously for 14 days, and a dose-escalation scheme was used for the nitrite, with a maximum dose of 64 nmol/kg/min."[87]

Explanation. In EPDF trials, safety assessment and dose decision reviews are usually assessed after each cohort.[45] Cohort sizes in EPDF trials vary greatly and are often chosen subjectively based on precedence and preference.[88] In placebo-controlled EPDF trials, there is also great variability in the number and ratio of active and placebo-treated participants in each cohort.[55] As the accrued data are reviewed after each cohort of participants, the cohort size has a direct effect on the timing of interim analyses and any trial adaptations, the credibility of the decisions that would be made and the statistical performance of the design.

Whether the planned cohort size was fixed (e.g., cohorts of three participants) or variable should be stated,[89] and any amendments to the protocol affecting this should be clearly reported. For cohort sizes that are not fixed, it should be specified what determined the cohort size during the trial. For randomised EPDF trials, including those with a control or placebo group, it is important to provide details on how many participants in each cohort were assigned to the respective groups.

Item 3a.9 [new] Dose allocation method within a dose level (including sequence and interval between dosing of participants, e.g., sentinel or staggered dosing)

Example 1. "At each dose escalation, one participant was inoculated, followed by the rest of the group one week later, together with the first participant of the next group. (…) Allocation to dosage and combination with MF59-adjuvant was by sequence of enrolment. The predefined escalation schedule started with 6 μg (groups 1A and 1B), followed by 12 μg (groups 2A and 2B), 25 μg (groups 3A, 3B, and 6), 50 μg (groups 4 and 7), and 70 μg (group 5) ABNCoV2. Dose escalation occurred in groups of six participants, starting with split groups for the first three lowest doses, in which half (n = 3) of the participants received the non-adjuvanted vaccine (groups 1A, 2A, and 3A) and half received the MF59-adjuvanted vaccine (groups 1B, 2B, and 3B)."[90]

Example 2. "The first three participants in each arm and at each dose level in Part A and Part B were enrolled as open-label sentinels. The purpose of the sentinel groups was to identify potential toxicities prior to enrollment of the randomized expansion cohorts. (…) Part A included three sequential treatment arms of 25 μg, 100 μg and 200 μg doses. Each treatment arm consisted of three sentinel participants and 24 expansion cohort participants (18 active and 6 placebo) (…). Safety data from the sentinel cohort within each treatment arm in Part A were reviewed by the investigator in consultation with the sponsor prior to dosing the expansion cohort. Once the final participant in a treatment arm was dosed and completed the Day 8 evaluation, the safety monitoring committee (SMC) reviewed the safety data from the sentinel and expansion cohorts prior to escalation to the next treatment arm."[91]

Example 3. "The planned dose levels were 30, 40, 50, 60, 70, 80 and 90 mg/m^2/day, with the increases to be made in a stepwise fashion in cohorts of at least three patients. A treatment course was defined as 5 consecutive days of CPT-11 administration, and a treatment cycle was a treatment course plus the time needed for recovery from any toxicities. A minimum of 1 week was required between the entry of the first patient and the entry of the subsequent two patients at any given dose-level. Before dose escalation, all three patients had to receive at least one treatment cycle. The first patient was observed for cumulative toxicity or any new grade 2 toxicity for at least 1 week into the second cycle. If toxicity occurred, an extra week of observation was required prior to dose escalation. The second and third patients were observed for at least 3 weeks from the start of the treatment cycle."[92]

Example 4. "In each dose group (or subgroup), 2 sentinel participants were randomized at a ratio of 1:1 to receive ABBV-3373 or matching placebo and monitored for 24 h prior to dosing the remaining participants in each group."[41]

Explanation. The planned dose allocation strategy should be described for ethical reasons. For example, it aids safety evaluation by researchers, trial monitoring groups, regulators, ethics committee members, and funders to know how many participants were planned to receive the same dose or be exposed to a new dose level at a given time. These considerations will be most applicable to first-in-human trials, where there is little information on the toxicity profile of the new treatment.

Authors should describe how participants were allocated to each dose and specify whether sentinel or staggered dosing was implemented. A sentinel participant is the first to be dosed before the entire trial or before a cohort of participants is treated, with allowance for a minimum amount of time to elapse for review prior to dosing subsequent participants at the same dose level. Staggered dosing describes an approach where all participants are dosed with minimum intervals between them.[8]

Item 3a.10 [new] Dose expansion cohort(s), if applicable, with rationale

Example 1. "MAGE-A4 is expressed in solid cancers, including synovial sarcoma (SS), myxoid/round cell liposarcoma (MRCLS), non-small-cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC) and ovarian, urothelial, melanoma and gastroesophageal cancers. (…)

This phase 1 trial was conducted using a 3 + 3 design and involved dose escalation of afami-celacross dose Groups 1–3 and an expansion group. Dose ranges (…) were (…) 1.2 × 109 to 10 × 109 cells for the expansion group (n = 29, one EGJ [esophagogastric junction], one esophageal, three head and neck, one melanoma, five MRCLS, two ovarian, 15 SS and two urothelial) [*to further characterise safety and objective response rate in patients with MAGE-A4 positive tumours*]."[93]

Enhancements in italics to address the rationale for the expansion group.

Example 2. "Owing to concerns about the long-term tolerability of the 3 mg daily dose, 2 mg and 2.5 mg once a day were assessed further in expansion cohorts to aid determination of the recommended phase 2 dose."[94]

Example 3. "We used a modified 3 + 3 design, in which we enrolled three patients initially to a dose-escalation cohort and assessed them for dose-limiting toxic effects. To enable robust characterisation of the pharmacokinetic profile, up to seven patients in total were enrolled to every dose-escalation cohort."[76]

Explanation. Expansion cohorts can enhance understanding of the toxicity profile, pharmacology, or effects on other biomarkers. They may also be used to obtain preliminary evidence of activity to justify progression to future studies (e.g., phase I to II).[56] Expansion cohorts could allocate more participants to selected dose levels or subgroup/disease-specific cohorts. Clearly stating the objectives of the expansion cohort(s), as well as providing information on whether their sample size is statistically justified (item 7a) and whether predefined criteria to inform go/no-go decisions (item 7b) about the clinical development of the intervention exist, will help the reader to understand the questions that the expansion cohorts are designed to answer.[95]

Authors should specify how they determined which dose(s) to expand, how many participants were treated at the selected dose(s) in each expansion cohort and the objectives of the expansion cohort(s). They should state whether backfill cohorts (defined as additional participants being allocated to doses already deemed safe to collect further information on safety profile, pharmacokinetic/pharmacodynamic, or activity)[96] were permitted to be opened in parallel to the dose-finding part and how their data would be used to inform subsequent interim trial adaptations and the final recommended dose(s).[95,97]

Item 3a.11 [modified] Criteria for progression to the next part of the trial (e.g., phase 1 to phase 2, single ascending dose to multiple ascending dose), where applicable

Example 1. "Doses were escalated in a sequential fashion contingent on the safety and PK [pharmacokinetics] profiles of at least 4 subjects who had received GSK3389404 at the previous dose levels up to and including day 4 postdose. Once all subjects in cohort D had reached day 4 with an acceptable safety profile, part 2 of the study was initiated."[78]

The criteria for progressing to the next part of the trial as described in this example are supplemented by a trial design schema in Figure 2 in Han et al.,[78] used under CC BY-NC 4.0 (Fig. 2c).

Example 2 (trial design publication). "TRAFIC has a phase I dose-finding trial rolling into a single-arm, single-stage phase II trial. The full trial protocol has been previously published[reference]. The primary objective of phase I is to determine the maximum tolerated dose (MTD) of seliciclib over a 4-week treatment period when given in addition to an existing TNF [tumour necrosis factor] inhibitor with or without sDMARDs [synthetic disease-modifying anti-rheumatic drugs]. Phase I is planned to roll into phase II for which the primary objective is to assess the potential efficacy of seliciclib following 12 weeks of treatment when administered at the MTD established in phase I; efficacy is based on a composite response measure."[84]

Explanation. This item is linked to item 3a.2. Increasingly, EPDF trials have combined or integrated parts (such as phases Ia/Ib/II) as they can be time and cost-effective, leading to accelerated clinical

development.[8,55] Transparent reporting of criteria for transitioning from one phase to another phase of the same study is critical as these criteria inform the decision to progress to the next part of the trial, affecting the credibility of the decisions on transitioning to the next part of the trial, and the interpretation of the study findings.

Authors should specify clear criteria for major transition points of progression to the next part of the trial (including the minimum data requirements), highlighting any overlap between the different parts, where applicable.[8] Such major transitions may include progression from dose escalation to expansion cohorts after dose(s) have been selected for further testing; from phase I to phase II (see Example 2); or from a single ascending dose to multiple ascending doses (see Example 1). Whether data from one part would contribute to decision-making in subsequent parts of the trial should be clearly stated.

Item 3b [modified] Important changes to the design or methods after trial commencement (e.g., insertion of unplanned additional doses) outside the scope of the prespecified adaptive design features, with reasons

Example 1. "The DLT [dose limiting toxicity] of hyperphosphatemia and the observation that most patients treated with doses ≥100 mg experienced AEs [adverse events] of hyperphosphatemia (…) prompted the initiation of additional analyses to evaluate BGJ398 dose/schedule adjustment. Hyperphosphatemia was managed through dietary restrictions, phosphate-lowering therapy, and drug interruptions. Earlier data from 43 patients treated at 125 mg once daily revealed a median time to first dose interruption of 22 days and a median duration of interruption of 7 days. Considering these data and the properties of BGJ398 PK [pharmacokinetics], an intermittent 3-weeks-on/1-week-off schedule of 125 mg once daily was introduced as a dose-expansion arm in a protocol amendment."[98]

Example 2. "Immune responses in this group of 20 [vaccine recipients] were evaluated in a blinded manner, to determine if there was sufficient response to consider a lower dose study. The combination of safety and immunogenicity results led to redesign of the protocol to examine lower doses ranging from 0.3 to 3 μg. The amendment provided for an on-site observation period of 4 h following the first dose of vaccine for all participants and follow up in clinic on Days 1 and 29 for safety assessment, safety laboratory studies and brief physical examination."[99]

Example 3. "Due to toxicities that occurred outside of the dose-limiting toxicity period, the protocol was amended on Jan 30, 2019, to include a cohort expansion accrued at the recommended phase 2 dose on 5-day instead of 10-day schedule that was used for finding the maximum tolerated dose and recommended phase 2 dose. This amendment was approved by the institutional review boards at all study sites. We evaluated a 5-day schedule because it was expected to be less toxic than the 10-day schedule and likely to improve the safety profile of the regimen. As a safeguard, we first enrolled three patients at the recommended phase 2 dose on the 5-day schedule. If no more than one patient experienced a dose-limiting toxicity, we planned to enrol an additional nine patients at the recommended phase 2 dose. During this cohort expansion phase, the Bayesian optimal interval dose elimination rule was used to monitor toxicity."[100]

Explanation. Given the uncertainties around EPDF trials, they are at higher risk of experiencing unplanned changes to the design or methods after trial commencement.[1,101] The CONSORT,[11,15] ACE,[49] and CONSERVE[102] statements emphasise the need to report such unplanned major changes as, depending on the nature and reason for the changes, they may introduce biases that compromise trial credibility, render the planned statistical methods invalid, or complicate the interpretation of results.[103]

Consistent with the ACE statement,[49] authors should describe major unplanned changes and their potential effect on the trial design or methods (including unplanned decision-making criteria) after the commencement of the trial. Authors should clarify whether unplanned changes were made following access to key trial information, such as interim data, to help readers assess potential sources of bias and implications for the interpretation of results. For EPDF trials, such changes may include changes in eligibility criteria, the insertion of additional doses not considered at the start of the trial (see Example 2), or dose decisions for the next cohort being made based on fewer participants than planned. As these trials are typically planned with adaptations,[50,51] it is important to distinguish unplanned changes from prespecified adaptations (covered in items 3a.1, 7b). There may also be unexpected logistical or practical challenges that impose changes on trial conduct (e.g., changes in funding, slow accrual, new scientific knowledge that impacts an aspect of the trial).

Methods: Participants, interventions, and outcomes

Item 5a [modified] Interventions for each dose level (within each group) with sufficient details to allow replication, including administration route and schedule showing how and when they were actually administered

Example 1. "Sunitinib was supplied as capsules of 25 mg and 50 mg for oral administration. Sunitinib was administered continuously for 4 weeks followed by 2 weeks off treatment. This 6-week time period was defined as a treatment cycle. (…) [The] starting oral dose

of sunitinib was 30 mg/m^2 every 2 days. (...) At the time of the study, only 25-mg and 50-mg capsules were available, and therefore the total dose was rounded up to the nearest 25 mg according to BSA [body surface area]."[104]

Example 2. "Treatments consisted of 25 mL oxathridine solution or a matching placebo for oral administration. The solution was administered with purified water and blackcurrant syrup to a volume of 100 mL for masking purposes. Planned dose levels were 0.5, 2.5, 10, 25, 40, 60, 80 and 100 mg. Volunteers were in a fasted state from 10 h prior to dosing and were allowed to eat from 3 h after dosing. Volunteers were allowed to drink water ad libitum, except for 1 h before and 2 h after dosing when drinking water was not allowed."[105]

Example 3. "Subjects in the SAD [single ascending dose] cohorts were randomized to receive a single IV [intravenous] dose of active PF-06480605 1 mg, 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 600 mg or 800 mg, or placebo. Subjects in the MAD [multiple ascending dose] cohort were randomized to receive single SC [subcutaneous] doses of active PF-06480605 30 mg, 100 mg or 300 mg, or placebo, or [intravenous] doses of active PF-06480605 500 mg or placebo administered once every 2 weeks for a total of three doses."[106]

Explanation. As there is a high level of uncertainty about the adequate dosing of the interventions in EPDF trials due to their early exploratory stage in the clinical development process,[29] unforeseen modifications of the interventions (e.g., changes in formulation) or the set of dose levels considered may occur. It is important that such modifications are reported to ensure reproducibility and guide decision-making about the dose(s) for subsequent trials (cf. item 3b).

This item partially overlaps with items 3a.4 and 3a.5, which cover the specification of the preplanned range of doses, including the starting dose(s) of the interventions, as key elements of the EPDF trial design. This item, however, specifically focuses on the complete description of the interventions, including the doses that were planned (items 3a.4 and 3a.5) and actually administered (item 13a), as well as the route of administration, consistent with the Template for Intervention Description and Replication (TIDieR) checklist,[107] an extension of CONSORT item 5a.[11] The proportion of the intervention that was administered per dose level should be reported.

Item 5b [new] Criteria for dose discontinuation, dose modifications, and dosing delays of allocated interventions for a given trial participant (e.g., dose change in response to harms, participant request, or improving or worsening disease)

Example 1. "Patients received oral schedules of 4.0 mg CH5126766 twice per week (...) or 4.0 mg CH5126766 three times per week (...) delivered in cycles of 28 days. (...) Patients who had grade 2 or worse treatment-related toxicity, with the exception of grade 2 rash and grade 2 creatine phosphokinase elevation, had dose interruptions until the toxicity improved to grade 1 or less. Patients who had dose interruptions for grade 3 or worse rash or grade 3 or worse creatine phosphokinase elevation were able to resume treatment upon improvement of the toxicities to grade 2 or less. After the first dose delay, treatment continued at the same dose; however, if it was necessary to delay dosing again, the patient was allowed a 0.8 mg dose reduction (ie, to 3.2 mg or 2.4 mg). The maximum permitted dose interruption was 14 days. Given that rash was a common side-effect, we recommended the use of topical steroids, and where necessary, oral steroids, as well as dose interruptions for recurrent rash or grade 3 or worse rash and prompt dermatological consultation."[26]

In this example, although the maximum duration for dose interruption is stated, implying treatment would be stopped if dose interruption exceeded the specified duration, it does not explicitly state the criteria for dose discontinuation.

Example 2. "Regorafenib was orally administered at a dose of 120 mg per patient once daily after meals for 3 weeks (day 1–21), followed by a 1-week off-treatment period (day 22–28). This 4-week period was considered one cycle. Dose reduction or interruption was allowed during treatment based on the severity of the regorafenib-related AEs [adverse events]. Dose modification was initiated for AEs > grade 2, except for hand-foot skin reaction, hypertension, and increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin (T-Bil) (Supplementary Table S1). For patients who required a dose interruption, regorafenib treatment was only resumed during the oral administration period of each cycle (day 1–21). If AEs ≥ grade 2 were not observed in cycle 1, a dose increase to 160 mg/day in cycle 2 and beyond was allowed. However, when only AEs ≥ grade 1 for AST, ALT, or bilirubin increases were newly observed, the regorafenib dose was not increased. Treatment continued until tumour progression, unacceptable side-effects, or withdrawal of consent occurred. Antitumor response was evaluated by each investigator every 8 weeks according to the RECIST [response evaluation criteria in solid tumors] guidelines. AEs were assessed by investigators and reported according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 4.0)[reference]."[108]

The criteria for dose discontinuation are stated in Supplementary Table S1.

Explanation. In EPDF trials, dosing discontinuations, modifications, or delays can occur for a given participant

for several reasons. EPDF trials are often designed with preplanned criteria to guide them for a given participant. Transparency and complete reporting of the criteria enable readers to assess the implications when they are followed or overruled, which may impact the clinical interpretation of their findings and the credibility of the trial.

Authors should specify criteria used to discontinue, modify, or delay the allocation of an intervention to a given trial participant. Examples include dose changes in response to an adverse event, participant request, or improving/worsening health status. It should be stated whether the criteria differ within or outside the predefined safety/tolerability assessment period. A dose modification and dosing delays can be visually presented (e.g., in a table) to present study-specific adverse event dose modifications.[39] In contrast to item 7b.1, which specifies stopping rules for the trial level or a given cohort, the focus here is on the individual participant.[109]

Item 6a [modified] Primary and secondary outcomes, including the specific measurement variable, analysis metric, method of aggregation, and time point for each outcome. Explanation of the clinical relevance of chosen outcomes is strongly recommended. Any other outcomes used to inform prespecified adaptations should be described with the rationale

Example 1. "The primary endpoint of the phase 1b study was the occurrence of dose-limiting toxicity (caused by both non-immune-related and immune-related adverse events) *[during the 28-days dose limiting toxicity observation period]* in order to define the safety and tolerability of escalating doses of ALT-803 used in combination with nivolumab and to establish a recommended phase 2 dose; the appendix provides a full definition of dose-limiting toxicity. The secondary endpoints of the phase 1b study included duration of response, progression-free survival, overall survival, pharmacokinetics (ALT-803 Cmax and area under the curve), immunogenicity, plasma cytokine concentration, and lymphocyte subpopulation characterisation. In cases of pseudoprogression, this was defined as a more than 20% increase in tumour burden as measured by irRECIST [immune-related response evaluation criteria in solid tumors] 1.1 at timepoints up to 12 weeks previous to a partial or complete response. Progression-free survival and overall survival were measured from start of treatment to time of progression or death, respectively. Objective responses were defined as complete and partial responses as determined using RECIST [response evaluation criteria in solid tumors] (version 1.1)."[108]

Enhancements in italics to address the time window of the dose limiting toxicity period. Note that the time point or assessment window is not clear for the other endpoints either. This example lacks an explanation of the clinical relevance of the chosen outcomes in both the main paper and the protocol provided as a supplementary document.

Example 2. "The primary safety endpoint of this trial was the number of at least possibly related grade 3 adverse events and SAEs [serious adverse events] from time of first ABNCoV2 administration to the end of the follow-up period. The secondary safety endpoint was the number and severity of solicited adverse events within 1 week following administration of ABNCoV2. Solicited local adverse events were defined as pain, tenderness, erythema, and induration at the injection site. Solicited systemic adverse events were defined as headache, fatigue, fever, drowsiness, and chills. Causality to the study interventions was graded by the investigators (...) as unrelated, unlikely related, possibly, probably, or definitely related. Severity of adverse events was graded as mild (grade 1), moderate (grade 2), or severe (grade 3). Verbatim-recorded adverse events were coded using the Medical Dictionary for Regulatory Activities (version 24.1). For solicited and laboratory adverse events, the US Food and Drug Administration toxicity grading scale was used (...).

The primary immunogenicity endpoint was the concentration of vaccine-specific IgG [immunoglobulin G] antibodies 14 days after first vaccination. Exploratory immunogenicity endpoints included the concentration of vaccine-specific antibodies at baseline, during immunisation, and at follow-up. RBD-specific [receptor binding domain-specific] total IgG titres were measured by ELISA [enzyme-linked immunosorbent assay], as previously described (...)[reference]. RBD-specific CD4+ and CD8+ T cells were measured by flow cytometry following peptide stimulation (...)."[90]

This example lacks an explanation of the clinical relevance of the chosen outcomes.

Explanation. The importance of a clear and complete description of outcomes is well acknowledged, regardless of trial context.[110] Like the ACE statement,[49] this modified CONSORT-DEFINE item addresses the need to prespecify outcomes that were planned to inform prespecified adaptations. In combination with the primary outcome, such outcomes influence the adaptation process and the operating characteristics of the statistical design.[49]

Authors should clearly describe prespecified outcomes used to assess research objectives (Item 2b), including how and when they were assessed. Similarly, this description applies to outcomes used to inform prespecified adaptations (item 3a.1). The clinical relevance of chosen outcomes should be explained,[111] or readers should be directed to where this information can be found. In some situations, adaptations may be based on an early observed outcome considered

informative for the primary outcome[112] or a combination of an early outcome and the primary outcome.[110] In such cases, there should be a clinical rationale supporting the use of an adaptation outcome that is different from the primary outcome(s) to aid in the clinical interpretation of results.[49] For example, tolerability and activity could both be used to inform dose adaptations or early stopping (for safety and/or futility), and activity data at an earlier assessment point could be used as an early outcome.[113]

Item 6b [modified] Any unplanned changes to trial outcomes after the trial commenced, with reasons

Example. "Another exploratory endpoint was virus neutralisation of the ancestral isolate FR-4286 (B.1) and variants of concern: alpha (B.1.1.7), beta (B.1.351), and delta (B.1.617.2). We assessed serum from baseline and during immunisation and follow-up in a 50% plaque reduction neutralisation test ($PRNT_{50}$). The incidence of infection with omicron variants increased sharply after the completion of the trial. Therefore, measurement of omicron (BA.1) virus neutralisation was amended to the assay list and compared with an ancestral (D614G) variant and delta variants. These measurements were done independently of the originally planned virus neutralisation panel. Virus neutralisation assays were done as previously described (...)[reference]."[90]

Explanation. Similar to item 3b, transparently reporting unplanned changes to trial outcomes with accompanying justifications enables readers to distinguish between unplanned changes and prespecified adaptations, aiding in assessing outcome reporting bias,[49,110] and helping to maintain the trial's credibility and integrity.

Authors should clearly report any changes to outcomes (including how they were assessed or measured) deviating from the prespecified adaptations, including an explanation of why such changes occurred in line with the CONSORT statement and their potential impact. By their nature, EPDF trials are associated with uncertainties around their outcomes due to limited evidence.[29] As such, changes to trial outcomes specified in the protocol (or their aspects, such as how they are assessed, item 6a) may occur for several reasons. For instance, the assessment period of toxicity, or the grading of specific safety or activity events, may have been refined based on emerging data. Similarly, an emerging important outcome can be added, and the order of importance of outcomes to address research objectives can be amended.

Item 7a [modified] Estimated number of participants (minimum, maximum, or expected range) needed to address trial objectives and how it was determined, including clinical and statistical assumptions supporting any sample size and operating characteristics

Example 1. "Sample sizes were based on clinical considerations (estimated number required to provide safety, tolerability, and pharmacological information and to minimize exposure to healthy subjects at each dose level) rather than statistical considerations. For study 1, the required total sample size was approximately 40 subjects (10 per cohort); for study 2, the required total sample size was approximately 80 subjects (10 per cohort). In study 1, a sample size of 6 subjects was sufficient to provide >90% power to detect a food effect-related 2-fold increase of maximum observed concentration (Cmax) or area under the concentration–time profile curve (AUC) and 80% power to detect a 1.6-fold increase in both PK [pharmacokinetics] parameters for all doses except 1000 mg, assuming that the predicted within-subject PK variability would not change with food intake."[20]

Example 2. "The single-dose portion of the study was exploratory in nature, and therefore, no formal statistical tests were used to select sample size. (...) The sample size for the repeat-dose cohort was determined based on a noninformative Bayesian analysis of the percentage lean body mass change from baseline as measured by DXA [dual-energy X-ray absorptiometry]. The repeat-dose cohort was limited to 15 subjects, 9 receiving domagrozumab and 6 receiving placebo, and the sample size was determined sufficient to support a preliminary assessment in percentage lean body mass change from baseline by DXA. Under the Bayesian decision rule, with 9 subjects receiving domagrozumab and 6 subjects receiving placebo, and assuming a 5% standard deviation, the probabilities of declaring statistical difference were 27% without a treatment difference from placebo; 70% with a 3% difference from placebo; and 90% with a 5% difference from placebo. This was a secondary objective for the repeat-dose cohort."[114]

Example 3 (protocol). "Operating Characteristics of the Modified CRM [continual reassessment method] based on 5000 simulations on 7 different scenarios. Numbers in bold indicate the pre-specified target toxicity (20%) and probability of selecting that dose as the correct dose. DLT: Dose-limiting toxicity. P(Select): Probability of selecting a dose as the MTD [maximum tolerated dose]. LQ: lower quartile, UQ: upper quartile. The trial requires a further recruitment of 3 patients (i.e., giving a total of 30 patients) 0–6% of the time, depending on the underlying scenarios. If Dose −3 is selected, this indicates that the MTD is below the lowest dose. Note: this table was created using the original prior of (0.03, 0.07, 0.12, 0.20, 0.30, 0.40, 0.60).

This design with 27 patients (with a possible extension of 3 patients in 0–6% of the time) correctly selects the MTD with probabilities of at least 50% in scenarios 1–7 (...). In particular, there is a 60% probability of correctly selecting Dose 1 as the MTD under scenario 4, which we consider to be the most probable scenario. More importantly, given that our prime focus is safety in

this study, the probability of choosing a dose with true probability of DLT of 36% or higher is 25% or less. The probability of choosing a dose which would cause severe overdosing (where true DLT is at least 45%) is at most 3%. In the scenario where the lowest dose is too toxic (scenario 8), there is a high chance of 81% that the CRM will recommend early stopping and indicate that the MTD is below the lowest dose. By allowing the trial to stop early if it meets the stopping early criteria that there are already 12 patients at the proposed MTD, the trial would, on average, stop earlier by at least 3 patients, except in Scenario 6 and 8. This could potentially reduce the trial duration for this Phase I component by at about 2.5 months. In the case of excess toxicity, the trial will only recruit an average of 9 patients before recommending early termination."[115]

This example was extracted from the trial protocol, which is available as an online supplement to the publication of the trial results. The operating characteristics of the trial design are provided in Table A8.1 in the trial protocol of Craddock et al.,[115] used under CC BY 4.0 (Supplementary Figure S2).

Explanation. Details of the sample size and the statistical performance of the trial design are important to assess its ability to address the research objectives and summarise any limitations to aid interpretation. For example, operating characteristics can indicate poor statistical performance of the design when it exposes a high proportion of participants to overly toxic doses, has a low probability of correctly identifying the maximum tolerable dose or recommended dose(s), or results in inappropriate early termination of the trial or dose levels.[116] The actual total sample size may be challenging to specify in advance in EPDF trials.[45] However, it is possible to decide upon a maximum sample size, estimate the possible range of participant numbers required, or define a rule that ends recruitment. Such estimates can be informed by design operating characteristics, often determined by statistical simulation results, but may also be restricted by feasibility (e.g., by the number of participants that may be recruited in the planned time frame or by the cost of the intervention).

Authors should provide a justification for the sample size, e.g., generating operating characteristics to assess the performance of the adaptive design under a variety of situations. The assumptions and details of the methods used should be specified (item 3a), for example, relating to the choice of parameters, simulated scenarios, and decision thresholds (see Example 3).[44] If applicable, plans should be outlined for managing the sample size to ensure there are sufficient evaluable participants (e.g., through the replacement of participants who are not evaluable for the primary endpoint (item 12c)). It is useful to provide a summary of the statistical performance of the design, regardless of whether the design used has a statistical basis (e.g., algorithm-based 3 + 3 design), as this enhances the interpretation of results and highlights key limitations (see Example 1).

Item 7b [modified] Prespecified interim decision making criteria or rules that guided the trial adaptation process (e.g., dosing decision to escalate or de-escalate); prespecified and actual timing and frequency of interim data reviews and the information to inform trial adaptations

Example 1. "Dose escalation of irinotecan included two periods: initial dose escalation period and Escalation with Overdose Control (EWOC)[reference] dose escalation period. During the initial dose escalation period, one patient was assigned to each dose level beginning at the lowest dose level. This cohort size was maintained until a dose-limiting toxicity (DLT) was observed, when the cohort size was increased to two patients and the EWOC dose escalation period began. The toxicity data of all patients previously enrolled in the trial were used to update the dose–toxicity relationship and to guide the next escalation/de-escalation. During this EWOC dose escalation period, a cohort of two patients was assigned to a dose level and the next dose level for enrollment was calculated using EWOC software with a target DLT probability of 25% and overdose controlled to be less than 30%. The posterior distribution of the MTD [maximum tolerated dose] and the 85% confidence interval of the MTD were calculated after each patient's toxicity report was available. If the magnitude of the change in the estimate of the Bayesian confidence interval of MTD and posterior distribution between successive patients was small, specifically the width of the confidence interval estimated MTD did not change by 5% between three successive patients, the study would terminate if there were already six patients treated at the estimated MTD or continue until there were six patients treated at that level."[117]

Example 2. "For any given dose, escalation to the next higher dose proceeded if the DSMB [data safety monitoring board] did not identify safety and tolerability concerns after reviewing safety data, especially for dose-limiting toxicity (DLT), which was defined as any adverse event of grade 3 or more based on the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (except for changes in activated partial thromboplastin time (…) or any confirmed thrombotic event [e.g., deep vein thrombosis or pulmonary embolism]). The following dose escalation rules guided the DSMB: (i) if none of three subjects receiving BAY 86-6150 at a given dose developed DLT, the dose was to be increased for the next cohort; and (ii) if one of three subjects at a given dose developed DLT, four additional subjects were to be enrolled at the same dose (3:1; BAY 86-6150/placebo). If additional DLTs were not observed

in this expanded cohort, the dose was to be increased; if two or more of six subjects developed DLT, dose escalation was halted; and (iii) if two or more of three subjects at a given dose developed DLT, dose escalation or expansion was halted. Dose escalation was also halted, pending review by the DSMB, if any patient developed deep vein thrombosis, pulmonary embolism, or any other confirmed thrombotic event (e.g., myocardial infarction or stroke).

It is recognized that no specific hemostasis marker has been shown to correlate with efficacy or safety outcomes upon treatment with rFVIIa, and the mechanism of action of BAY 86-6150 is believed to be identical to that of rFVIIa. Hence, hemostasis markers could not be prespecified for decisions regarding dose escalation or cessation. However, quantitative changes in these markers in relation to predose status were carefully evaluated, and could be used by the DSMB to guide decisions regarding dose escalation."[118]

Explanation. EPDF trials, by their nature, use adaptive designs.[50] The importance of transparency and complete reporting of prespecified decision-making criteria in adaptive designs is highlighted in the ACE statement.[49] Complete reporting of interim decision-making criteria, timing, and frequency, as well as the information used to inform the adaptations, is vital, as it directly impacts the operating characteristics of the design (item 7a) and the clinical interpretation of the findings.

For EPDF trials, authors should specify.

(1) Prespecified guidance or rules for trial adaptations (item 3a.1), which could be:
   - Dose adaptations, such as dosing decision to escalate or de-escalate (e.g., based on observing fewer than x events out of y participants or targeting a toxicity/risk probability of say 15%–25%);
   - Other trial adaptations, such as guidelines for stopping due to safety concerns, futility, or efficacy;
(2) Planned timing and frequency of interim data looks (e.g., at set time intervals or after a certain number of participants have been observed for a specified period) and;
(3) Observed data (such as toxicity, activity, pharmacokinetic or pharmacodynamic data, either singularly or in combination) or statistical information used to inform the trial adaptations (item 3a.3).

An explanation should be provided if the interim decision-making criteria/rules were not prespecified (item 3b).

In EPDF trials, the prespecified and actual timing and frequency of the interim analyses could differ, particularly if the interim analyses are conducted after each cohort and the cohort size (item 3a.8) is not fixed. In such cases, it should be clearly indicated what actually happened.[49] Whether stopping rules were binding or non-binding should also be indicated to facilitate assessment of the implications in the case when they were overruled or ignored.[49]

Methods: Assignment of interventions

Item 8b [modified] Type of randomisation; details of any restrictions (such as blocking and block size); any prespecified adaptive assignment rules or algorithm leading to adjustments in the allocation ratio, including timing and frequency of updates; any changes to the allocation rule following trial adaptation decisions

Example 1. "The second stage allocated eligible participants based on a CRM [continual reassessment method] modeling approach that accounts for both toxicity and immune response in combinations of agents. Toxicity assessment was based on the occurrence of DLTs [dose limiting toxicities], and immune response assessment was based on achievement of dRsp [durable CD4+ T cell immune response]. The estimated DLT [dose limiting toxicity] probabilities at each arm were used to adaptively define an 'acceptable' set of safe arms, based on which arms had estimated DLT rates below the 25% DLT threshold with high confidence. Once the set of acceptable arms was determined after each new accrual, the recommended arm for the next accrual was chosen at random from the safe set, with each acceptable arm weighted by its estimated dRsp probability [*defined as a CD4+ T cell response to the vaccine in peripheral blood mononuclear cells over two consecutive time points during vaccination (days 0–85)*]. This weighted randomization scheme was employed for the first one-third of the trial. In the latter portion of the trial, the recommended arm for the next accrual was the acceptable arm with the maximum estimated dRsp probability. Additional details regarding the modeling approach have been summarized in a prior report."[119]

Enhancements in italics to include the definition of durable CD4+ T cell immune response, which was taken from another section of the paper.

Example 2. "Prospectively generated permuted block randomization[reference] using four blocks of size four each and an allocation ratio of 3:1 within each block (treatment:no treatment) was used to create three dose cohorts of five to six patients each. In each dose cohort, four patients were randomized to IDDD [intrathecal drug delivery device] implantation plus administration of idursulfase-IT [idursulfase-intrathecal] once monthly (every 28 ± 7 days) for 6 months, and in each dose cohort one or two patients were randomized to no treatment. Those randomized to treatment in the first, second, and third cohorts received 10-mg, 30-mg, and 1-mg idursulfase-IT monthly, respectively. In total, 16 patients were randomized—four IT-treated patients per dose group and four patients in the no treatment group."[120]

Explanation. The reporting of randomisation features before activation of trial adaptations should follow CONSORT items 8a and 8b. This item focuses on additional considerations where the allocation ratio changes for adaptive designs. Changes in the allocation ratio influence the efficiency and the operating characteristics of the design. For instance, the performance of 1:1:1 throughout is different from 1:1:1 followed by 1:3:2 after the adaptation. Currently, adaptive randomisation is infrequently used in EPDF trials.[7]

Authors should state whether the allocation ratio(s) remained fixed throughout or was altered during the trial as a consequence of prespecified adaptations (e.g., when modifying randomisation to favour treatments that appear to be more promising or when a new arm is added to an ongoing trial).[49] Any unplanned changes to the allocation ratio should also be reported.

Methods: Data collection, management, and analysis

Item 12a.1 [modified] Statistical methods for primary and secondary outcomes and any other outcomes used to make prespecified adaptations

Example 1. "During this EWOC [escalation with overdose control] dose escalation period, a cohort of two patients was assigned to a dose level and the next dose level for enrollment was calculated using EWOC software with a target DLT [dose-limiting toxicity] probability of 25% and overdose controlled to be less than 30%. The posterior distribution of the MTD [maximum tolerated dose] and the 85% confidence interval of the MTD were calculated after each patient's toxicity report was available. If the magnitude of the change in the estimate of the Bayesian confidence interval of MTD and posterior distribution between successive patients was small, specifically the width of the confidence interval estimated MTD did not change by 5% between three successive patients, the study would terminate if there were already six patients treated at the estimated MTD or continue until there were six patients treated at that level."[117]

Example 2. "A CRM [continual reassessment method][reference] directed enrollment in the second stage. This method used a selected set of possible orderings of combinations for the DLT [dose-limiting toxicity] probabilities and a working model for the DLT probabilities under each ordering. The CRM model was used to fit the working model with the accumulated data. In the event of a tie between the likelihood values of two or more orderings, then the selected order of combinations was chosen at random from among the tied orderings. The DLT probabilities defined a set of acceptable combinations with a toxicity tolerance of 33%. Assuming at least one optimal combination existed, up to 52 evaluable participants could have been accrued to determine the optimal combination. (…)

The study was not designed to make statistical comparisons between arms. Frequency and magnitude of TRAEs [treatment-related adverse events] were summarized by arm. IRR [immune response rate] for defined categories was estimated as point estimates with 90% exact CIs [confidence intervals]. Graphical representations were used to present study outcomes. Fisher's exact test was used to assess associations of maximum immune response to maximum TRAE [treatment-related adverse event] grade and other select AEs [adverse events]. (…) Disease-free survival and overall survival distributions were estimated by the product-limit method of Kaplan and Meier."[121]

Example 3. "Noribogaine and noribogaine glucuronide concentrations above the limit of quantification were used to calculate pharmacokinetic parameters using model independent methods. The maximum plasma concentration (Cmax) and time to maximum plasma concentration (Tmax) were the observed values. Plasma concentration data in the post-distribution phase of the plasma concentration–time plot were fitted using linear regression to the formula ln C = ln C_o—t. Kel, where C_o was the zero-time intercept of the extrapolated terminal phase and Kel was the terminal elimination rate constant. The half life ($t_{1/2}$) was determined using the formula $t_{1/2}$ = 0.693/Kel. The area under the concentration–time curve (AUC) from time zero to the last determined concentration–time point (tf) in the post-distribution phase was calculated using the trapezoidal rule. The area under the curve from the last concentration–time point in the post distribution phase (C_{tf}) to time infinity was calculated from $AUC_{t\text{-}\infty}$ = C_{tf}/Kel. The concentration used for C_{tf} was the last determined value above the LLOQ [lower limit of quantitation] at the time point. The total $AUC_{0-\infty}$ was obtained by adding AUC_{tf} and $AUC_{t-\infty}$. Noribogaine apparent clearance (CL/F) was determined using the formula CL/F = Dose/$AUC_{0-\infty}$ x 1,000, and apparent volume of distribution (Vd/F) was determined using the formula Vd/F=(CL/F)/Kel. Total urine noribogaine was the sum of both analytes.

Summary statistics (means, standard deviations, and coefficients of variation) were determined for each dose group for safety laboratory test data, ECG [electrocardiography] and pharmacokinetic parameters, and pharmacodynamic variables. Categorical variables were analyzed using counts and percentages. Dose proportionality of AUC and Cmax was assessed using linear regression. The effect of dose on pharmacodynamic parameter values over time was assessed using two-factor analysis of variance (ANOVA). Pairwise comparisons (with Tukey–Kramer adjustment) between each dose group to the placebo were conducted at each time

point using the least-squares estimates obtained from the ANOVA, using SAS Proc Mixed (...)."[122]

Explanation. The CONSORT statement[11] and E&E[15] address the importance of describing statistical methods to analyse primary and secondary outcomes at the end of the trial. This CONSORT-DEFINE modified item extends this to require a similar description for statistical methods used for interim analyses, which might not necessarily include the comparison between different doses or interventions. Providing adequate information will ensure that the findings can be replicated based on the description of the methods used, enhancing transparency and interpretation. Providing information about the statistical software and packages (if applicable), including the version number, used for analyses (e.g., dose (de-)escalation decisions and biomarker analyses) is good practice to enable the key results of the trial to be reproduced.[44,49]

There should be a detailed description of the statistical methods used to address the objectives (item 2b) of an EPDF trial with their prespecified adaptations (item 3a.1). These methods could be based on descriptive statistics (e.g., frequencies, percentages, and means) or narrative descriptions (e.g., a description of adverse events experienced), or statistical models, or a combination of both, used for interim analyses for dose (de-) escalation decisions or other trial adaptations; for example, determining the next participant's dose level or stopping the trial early for poor safety or futility. Methods using statistical models (item 3a.3) to analyse any adaptation outcomes (item 6a) should be detailed for reproducibility and transparency of the adaptation process and results. This may include statistical methods for safety monitoring or data-driven pharmacokinetic/pharmacodynamic modelling if either was used to inform prespecified adaptations. Authors should specify whether a frequentist or Bayesian framework was used and report indications of uncertainty (e.g., using confidence intervals or credible intervals) as appropriate.[44] For Bayesian methods, it is recommended that details on the description of the prior distributions of model parameters be provided in accordance with item 3a.3.

Item 12a.2 [new] For the implemented adaptive design features, statistical methods used for estimation (e.g., safety, dose(s), treatment effects) and to make inferences

Example 1. An empirical dose-toxicity model was used to calculate estimates of the probability of occurrence of DLT [dose-limiting toxicity] for the investigated doses and recommended dose escalation/de-escalation on the basis of the investigators' experience and published data. (...) A normal prior of mean 0 and variance 0.75 for the slope parameter was assumed. The MTD [maximum tolerated dose] was defined as the dose level with an estimated DLT rate closest to 20% (target) with its associated DLT rate and 90% probability interval.[115]

Example 2 (protocol). We will employ the BOIN [Bayesian optimal interval] design[reference] to find the MTD [maximum tolerated dose]. (...) After the trial is completed, we select the MTD based on isotonic regression as specified previously[reference]. Specifically, we select as the MTD the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, we select the higher dose level when the isotonic estimate is lower than the target toxicity rate; and we select the lower dose level when the isotonic estimate is greater than the target toxicity rate.[123]

This example was extracted from the trial protocol, which is available as an online supplement to the publication of the trial results.

Explanation. In EPDF trials, a common key objective is the estimation of the recommended dose(s), which can be informed by statistical methods estimating toxicity, activity, a combination of both, or other parameters of interest. There is also an increasing use of seamless phase I/II designs with initial dose (de-)escalation, which may then be followed by dose expansion or a randomised dose-ranging part to explore potential promising dose(s) that are tolerable and active.[1,4] For the dose-ranging part, see the ACE statement,[49] which discusses several statistical issues that may arise when using an adaptive randomised design to estimate treatment effects for key outcomes. Such issues include estimation bias that may result if conventional estimates of treatment effect based on fixed design methods are used.[49] Similar issues arise for single-arm multi-stage designs.[124] Results and conclusions may differ when different analysis methods are used. Hence, there should be a description of the statistical methods used to estimate measures of treatment effects with associated uncertainty and a *p*-value (when prespecified in the analysis plans) to aid interpretation and reproducibility.

There should be a description of the statistical methods used for estimation of the parameters of interest (such as safety and treatment effects) with associated uncertainty (e.g., confidence intervals or credible intervals). Typical key parameters in EPDF trials include toxicity rates, treatment effects, or recommended dose(s). For instance, the statistical methods and criteria used to select the recommended dose (such as a dose with dose limiting toxicity closest to a prespecified threshold, see both examples) should be described. Authors should specify whether a frequentist or Bayesian framework was used to make inferences and what indications of uncertainty (e.g., confidence intervals or credible intervals) were calculated. Hypothesis tests that are powered to make inferences should be performed and reported if they were prespecified in the

protocol. If different statistical methods were used for interim and final analyses, it is importantly to explicitly state that. For rule-based designs, where no statistical methods are utilised for estimation or to make inferences, this item is not applicable.

Item 12b [modified] Statistical methods for additional analyses (e.g., subgroup and adjusted analyses, pharmacokinetics or pharmacodynamics, biomarker correlative analyses)

Example 1. "Pharmacokinetic analysis was performed using non-linear mixed effects modeling (NONMEM). A four-compartment model was used, and estimated model parameters included oral bioavailability of irinotecan (F), absorption rate constant for irinotecan (ka), volume of the central compartment for irinotecan (VCPT11L) and apparent volume of distribution for SN-38 lactone (VSN-38L), the intercompartmental rate constants (k12 and k21), conversion of irinotecan to SN-38 (k13), and the SN-38 elimination rate constant (k30). Secondary parameters calculated during data fitting included apparent oral clearance of irinotecan, CLCPT11L and apparent oral clearance of SN-38 lactone, CLSN-38L. Area under the plasma concentration–time curve from zero to infinity (AUC0-∞) for irinotecan and SN-38 lactone was estimated using the trapezoidal rule on the simulated concentration–time curve."[117]

Example 2. "Statistical analyses were conducted to assess the effect of coadministration of BMS-986142 on the PK [pharmacokinetics] of MTX [methotrexate]. For all treatment comparisons, a linear mixed-effect model was fitted to the log-transformed PK parameters C_{max}, $AUC_{(0\text{-}T)}$, and $AUC_{(inf)}$. Point estimates and 90% CIs [confidence intervals] for differences on the log-scale were exponentiated to obtain estimates for geometric mean ratios (GMRs) and respective 90% CIs on the original scale. Sample size determination is based on consideration of the precision of the estimate of the GMRs of AUCs [areas under the concentration curves] of MTX with and without BMS-986142. With 9 evaluable subjects, there will be an 80% probability that the 90% CI of AUC(INF) GMR will be within 89.9–111.2% of the point estimate. These precision estimates are based on an assumption that Cmax and AUC(INF) of MTX are log-normally distributed with intrasubject CV [coefficient of variation] of 14.67 and 10.38%, respectively, as calculated from Namour et al.[reference]. SAS® version 9.2 or greater (SAS Institute Inc., Cary, NC) was used for statistical analyses, tabulations and graphical presentations. R 3.0.1 or greater was used for the Bayesian Emax model."[53]

Explanation. The CONSORT statement[11] and E&E[15] document outline the reporting requirement for any subgroup and adjusted analyses and highlight the risk of spurious findings in subgroup analyses, particularly in analyses that are not prespecified. This is even more critical for EPDF trials, which typically have small sample sizes. As these analyses may inform decision-making and influence the subsequent clinical development of the intervention (e.g., in selecting the recommended dose(s) for further testing), pre-specification of the statistical methods to be used will aid interpretation and enhance the credibility of subsequent decisions.

Besides subgroup and adjusted analyses, statistical methods used for analysing other exploratory outcomes, such as pharmacokinetic/pharmacodynamic analyses (see both examples) and biomarker correlative analyses (e.g., correlating biomarker status with response), should also be provided. This information can be provided in an appendix but should be consistent with the associated objectives and reflect the planned analyses in the trial protocol. The authors should also specify if any sensitivity analyses were conducted for specific outcomes.

Item 12c [new] Analysis population(s) (e.g., evaluable population for dose-finding, safety population)

Example 1. "The primary safety population included patients who received at least 1 dose of any study drug. The DLT [dose-limiting toxicity] evaluable population (part 1) was defined as patients who experienced DLT in cycle 1, missed no more than four doses of CC-486 in cycle 1 and received the scheduled dose of carboplatin (arm A only) or, all scheduled doses of nab-paclitaxel in cycle 1 (arm B only). Patients who were not DLT evaluable were replaced so that dose escalation decisions could be based on a minimum of six DLT-evaluable patients. The efficacy-evaluable population included all patients who met eligibility criteria, completed at least two cycles of study treatment (i.e., received at least 70% of all assigned study treatment during the first two cycles), and had baseline and at least one post-baseline efficacy assessments."[125]

Example 2. "The safety analysis set included all the subjects who were randomized and received at least 1 dose of BIIB059 or placebo. The PD [pharmcodynamics] analysis set included all the subjects who were randomized and received at least 1 dose of BIIB059 or placebo and had at least 1 sample biomarker or other data collected after BIIB059 administration. The PK [pharmacokinetics] analysis set included all individuals in the safety analysis set for whom at least 1 primary PK parameter could be calculated."[126]

Explanation. A clear description of the analysis populations, also known as analysis sets, will allow the reader to assess whether they are directly relevant to, and guided by, the specific objectives of a given EPDF trial and, thus, whether the trial can address these objectives. The interim and final analysis populations

define the participants for whom the results of an EPDF trial will be generalisable. Criteria for participant replacement, which is common in EPDF trials, will help with interpretation and reproducibility, as well as assist readers in determining the credibility of the results.

Authors should clearly define trial-level participant (sub)populations or datasets used in statistical analysis (e.g., dose finding evaluable (see Example 1), response evaluable (see Example 1), safety (both examples)), detailing criteria for participants being evaluable for statistical analysis.[44] The minimum data set that was reviewed prior to making a dose decision should be specified. This should include the minimum number of participants who must have had data at the administered dose(s) and what data (e.g., safety, biomarker, or activity) were reviewed. For instance, escalation decisions could be based on an evaluable population defined as the set of participants who (i) received at least some predetermined amount of the planned doses (e.g., 70%, 85%, or 95%) during the assessment period or (ii) experienced a dose limiting toxicity[45] or dose limiting criteria (see Example 1).[127] For combination EPDF trials, it should be stated whether the predetermined amount for evaluability is based on each individual component in the combination or for the combination as a whole. Information on how unevaluable participants were treated in statistical analysis (e.g., using replacement or best/worst case analysis) and what happened to data collected from participants later found to be ineligible should also be provided (see Example 1). These definitions should also be provided for any interim analysis population(s).[44]

Item 12d [new] Strategies for handling intercurrent events occurring after treatment initiation (e.g., how dosing adjustments were handled) that can affect either the interpretation or the existence of the measurements associated with the clinical question of interest, and any methods to handle missing data

Example 1. "PFS [progression-free survival] was defined as the time from treatment initiation until the date of disease progression or death from any cause. For patients who had no disease progression or who did not die, the censoring date was defined as the last date at the nearest time of their last response evaluation. (…) Conversion surgery—defined as surgical treatment with a curative intent performed after tumors initially deemed technically or oncologically unresectable respond to therapy—was permitted, and PFS was censored at the time of conversion surgery."[128]

This example addresses handling of intercurrent events but lacks information on methods for handling missing data.

Example 2 (early phase statistical analysis plan guidance). "[26c] Variable of interest: Incidence of dose limiting toxicity (DLT) within the first 8 days of treatment. A DLT will be any adverse event (categorised as per CTCAE [common terminology criteria for adverse events]) which is graded as severe (grade 3) or higher and is deemed to be at least potentially related to treatment. Any patient who withdraws or dies due to treatment related reasons will be categorised as having experienced a DLT.

[26d] The following intercurrent events (IEs) of interest will be considered.

(1) Day 8 toxicity assessment not performed through patient related reasons.
(2) Day 8 toxicity assessment not performed due to site error.
(3) Day 8 toxicity assessment not being performed at the right time (performed either earlier or later than scheduled).

For IE (1), the reasons why the assessment was not performed will be investigated. Depending on the reasons for non-attendance a decision will be made regarding whether they are to be:

- Included in the analysis and assumed to have experienced a DLT;
- Included in the analysis and assumed to not have experienced a DLT; or
- Excluded from analysis and replaced with recruitment of additional patient."[44]

This example was extracted from a guidance document on the content of statistical analysis plans in early phase trials rather than from a published EPDF trial report.

Example 3 (early phase statistical analysis plan guidance). "The key intercurrent events pertains to blood samples not being analysed or returned from the central laboratory (e.g., due to samples haemolysing or being lost in transit). In order to mitigate against this further samples will be analysed locally. It is our intention to use the principal stratum strategy, and thus only analyse patients who have centrally analysed samples in the primary estimand."[44]

This example addresses handling of intercurrent events but lacks information on methods for handling missing data. It was extracted from a guidance document on the content of statistical analysis plans in early phase trials rather than from a published EPDF trial report.

Explanation. Intercurrent events are those events occurring after treatment initiation or randomisation (such as dosing delays, reductions, or interruptions), which may have affected either the interpretation or the existence of the measurements associated with the outcome of interest.[30,44] How missing data and intercurrent events were handled can impact the integrity and interpretability of study results. Transparent reporting of such information promotes methodological clarity, enhances the reader's ability to interpret the trial results and assess their robustness.

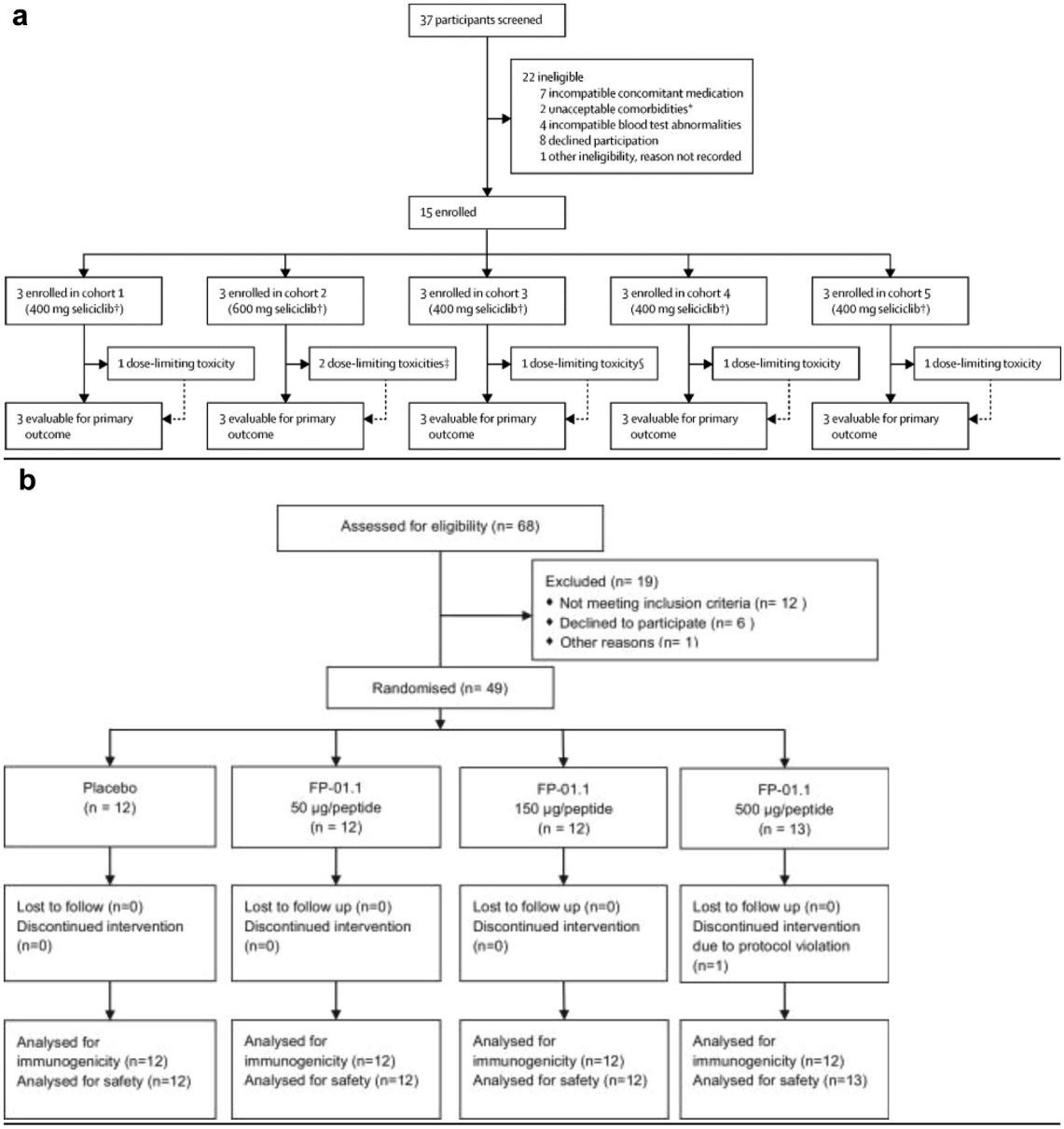


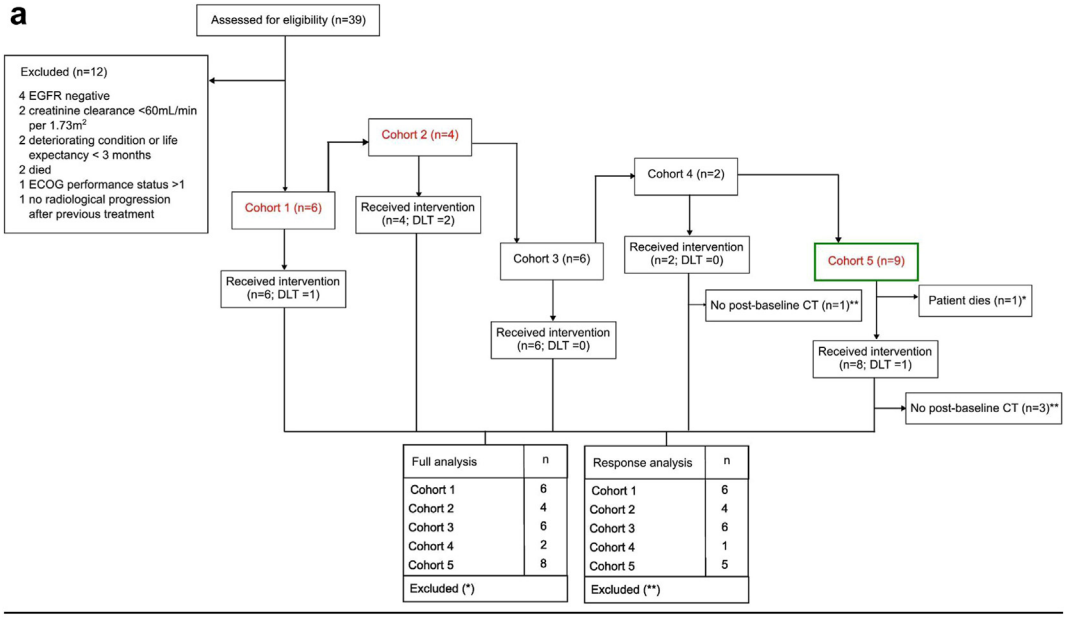
Fig. 3: **(a)** Item 13a, the number of participants who were assigned to each dose level at each interim analysis, received intended treatment, and were analysed, Example 1—obtained from Figure 1 in Pratt et al.,[31] used under CC BY 4.0; **(b)** Item 13a, the number of participants who were assigned to each dose level at each interim analysis, received intended treatment, and were analysed, Example 2—obtained from Figure 1 in Francis et al.,[129] used under CC BY-NC-ND 4.0.

The strategies used for handling intercurrent events should be described. Different strategies may be used to handle different intercurrent events (see Example 2). Strategies used for handling missing data should also be specified with approaches to handle missing data being clearly distinguished from approaches to handle intercurrent events. Any sensitivity analyses that were performed to assess the robustness of the trial results should be reported.[44]

Results

Item 13a [modified] For each group, the number of participants who were assigned to each dose level at each interim analysis (e.g., for dosing decisions), received intended treatment, and were analysed for the primary outcome and, if applicable, any other outcomes used to inform prespecified adaptations

Example 1. *This example is from Figure 1 in Pratt et al.*[31]*, used under CC BY 4.0 (Fig. 3a).*



CT: computed tomography; DLT: dose-limiting toxicity; ECOG: Eastern Cooperative Oncology Group; EGFR: estimated glomerular filtration rate.

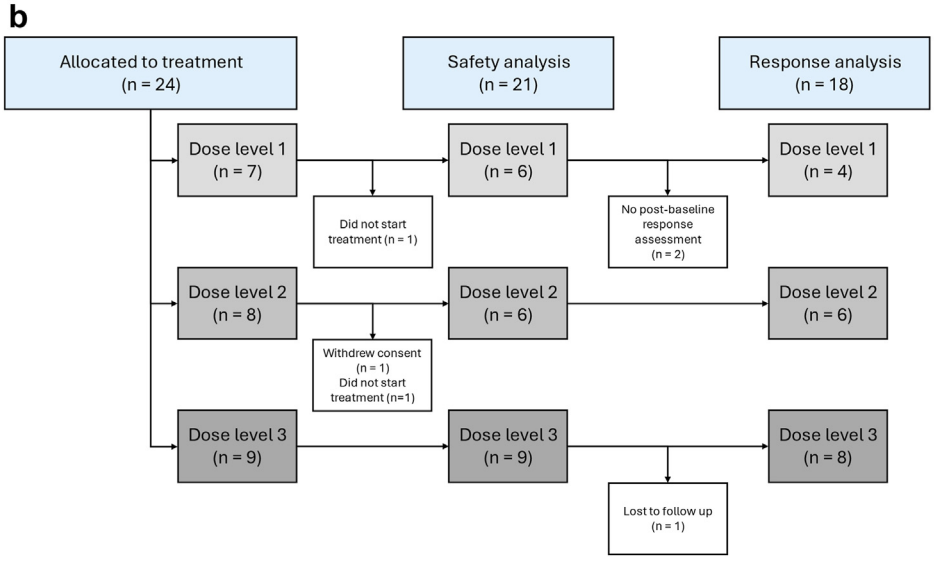


Fig. 4: **(a)** Item 13a, the number of participants who were assigned to each dose level at each interim analysis, received intended treatment, and were analysed, Example 3—obtained from Figure 3 in Alger et al.,[9] used under CC BY 4.0; **(b)** Item 13b, losses and exclusions after allocation to each dose level—a hypothetical example created by the authors of this article.

Example 2. *This example is from Figure 1 in Francis et al.,[129] used under CC BY-NC-ND 4.0 (Fig. 3b).*

Example 3. *This example is from Figure 3 in Alger et al.,[9] used under CC BY 4.0 (Fig. 4a).*

Explanation. The CONSORT E&E[15] discusses why it is necessary to describe the flow of participants adequately for final analyses, depending on the stage of reporting. The ACE statement[49] extends this necessity to interim analyses and highlights the importance of reporting the number of participants with outcome data used for adaptation for each group. EPDF trials are complex and typically have several interim data reviews to allow for dose or other trial adaptations. An informative participant flow communication tool that includes reporting per dose level at each interim data review will reduce the time it takes for readers to find essential information.[130,131]

Authors should specify the number of participants who were assigned to each dose level, received intended

treatment, and were analysed for the primary outcome(s)[11,15] and, if applicable, any other outcomes used to inform prespecified adaptations not only for each group[49] but also at each dose level for each interim analysis, particularly relating to dosing decisions.[130] Authors should ensure that the trial participant flow matches the key objectives as much as possible. There is no prescribed format for communicating the flow of participants; it can be presented as a flow diagram,[130] infographic, or flow table (see item 3a.6). The latter is feasible, particularly if the sample size is small.

Item 13b [modified] For each group, losses and exclusions after allocation to each dose level, together with reasons

Example (created). *A hypothetical example for item 13b was created by the authors of this article (Fig. 4b).*

Other examples. *Flow diagrams for item 13a, specifically examples 2 and 3, also include details on the number and reasons for exclusion at each dose or cohort level.*[9,129]

Explanation. Losses or exclusions of participants can impact interpretation depending on their nature, reasons, frequency, timing and how they are handled in the analysis (e.g., in dosing decisions). Transparently providing information on such losses and exclusions enhances scientific rigour, is necessary for results interpretation, and supports evidence-based decision making.

If participants were excluded after allocation to any dose level, the nature of the loss and reasons for exclusion should always be reported, including how or if they were replaced. Some participants may not have received the dose as allocated, may have been lost to follow-up, or may have been excluded for various reasons.[130,131] For example, they might be unevaluable for treatment tolerability or activity assessment if they did not receive at least a prespecified proportion of planned treatment. Such information can be presented in the flow diagram (item 13a).

Item 14a [elaborated] Dates defining the periods of recruitment and follow-up

Example (created). A phase I/II trial investigating the safety and activity of combination therapy <XYZ> in relapsed and refractory chronic myeloid leukaemia patients.

Phase I. Recruitment period: January 2016–December 2018.

Follow-up period: Until June 2019 (each patient was followed up for up to 6 months after intervention administration).

Phase II. Recruitment period: January 2019–December 2021.

Follow-up period: Until December 2022 (each patient was followed up for up to 12 months after intervention administration).

Note that this hypothetical example is for illustrative purposes on how authors can report different periods of recruitment and follow-up for different components of their trials.

Explanation. Reporting distinct recruitment and follow-up periods for a trial's major transition points, or group-specific stages, aids in understanding the trial's timeline and how different parts or groups evolve over time. Additionally, it provides context for understanding the impact of interventions within specific timeframes.

In the case of trials with different parts or major transition points (e.g., seamless trials, escalation/expansion, phase I/II, single ascending dose/multiple ascending dose), it is useful to provide separate periods of recruitment and follow-up. This also applies to platform EPDF trials that allow different groups (e.g., treatments, patient subgroups) to be added and removed at different times, resulting in different start and end dates of periods of recruitment and follow-up.

Item 14b [elaborated] Why the trial ended or was stopped

Example 1. "The study was prematurely terminated in March 2021 because of slow accrual."[132]

Example 2. "The study was terminated early because of CNS [central nervous system]-related toxicities noted in the single higher dose levels in a companion study, AHX-03-104."[133]

Example 3. "Due to regulatory issues which prevented from opening multiple centers, COVID-19 pandemic and withdrawal of Durvalumab from supporting company, the study was prematurely terminated in April 2021."[134]

Explanation. Providing explanations for early stopping, including the circumstances leading to the decision, assists readers to interpret the findings with appropriate considerations. This item addresses why the trial ended or was stopped outside the scope of prespecified adaptations (e.g., due to poor recruitment (see Example 1) or withdrawal of trial funding (see Example 3)). The standard CONSORT item does not differentiate between planned and unplanned criteria for stopping early. Stopping the trial early due to prespecified adaptations is covered in item 14c.

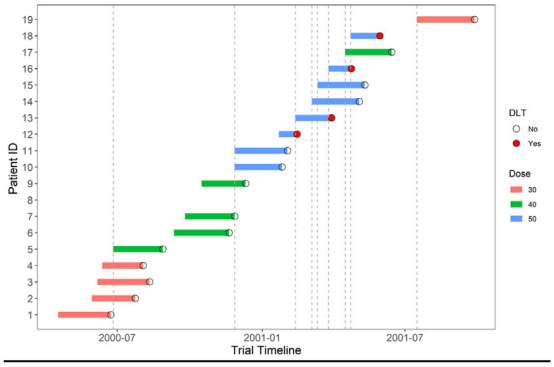
Thus, if the trial was stopped prematurely outside the scope of prespecified adaptations, the reasons and rationale should be clearly communicated.

a

Patient No.	Date on Study	Dose (mg/m²)	Date off Study	DLT
1	Apr 17, 2000	30	Jun 23, 2000	No
2	May 30, 2000	30	Jul 24, 2000	No
3	Jun 6, 2000	30	Aug 11, 2000	No
4	Jun 12, 2000	30	Aug 3, 2000	No
5	Jun 26, 2000	40	Aug 28, 2000	No
6	Sep 11, 2000	40	Nov 20, 2000	No
7	Sep 25, 2000	40	Nov 27, 2000	No
8	Oct 16, 2000	40	Oct 17, 2000	NA
9	Oct 16, 2000	40	Dec 11, 2000	No
10	Nov 27, 2000	50	Jan 26, 2001	No
11	Nov 27, 2000	50	Feb 2, 2001	No
12	Jan 22, 2001	50	Feb 14, 2001	Yes
13	Feb 12, 2001	50	Mar 30, 2001	Yes
14	Mar 5, 2001	50	May 4, 2001	No
15	Mar 12, 2001	50	May 11, 2001	No
16	Mar 26, 2001	50	Apr 24, 2001	Yes
17	Apr 16, 2001	40	Jun 14, 2001	No
18	Apr 23, 2001	50	May 30, 2001	Yes
19	Jul 16, 2001	30	Sep 27, 2001	No

DLT: dose-limiting toxicity; NA: not assessable.

b



DLT: dose-limiting toxicity.

Fig. 5: **(a)** Item 14c, trial adaptation decisions made in light of the prespecified decision making criteria and observed accrued data, Example 2—obtained from Table 2 in Muler et al.,[60] reprinted from *Journal of Clinical Oncology* with permission from Wolters Kluwer Health, Inc; **(b)** Item 14c, trial adaptation decisions made in light of the prespecified decision making criteria and observed accrued data, Example 3—obtained from Figure 3 in Yin et al.,[65] used under CC BY 4.0.

Item 14c [new] Trial adaptation decisions made (including on what basis they were made, and when) in light of the prespecified decision making criteria and observed accrued data

Example 1. "Since the toxicity profile of either PF [cisplatin and 5-fluorouracil] or cabazitaxel could account for these two DLTs [dose limiting toxicities], the decision was made to investigate the safety of cabazitaxel in cohorts –1, –2 and –3 (17.5, 20 and 22.5 mg/m^2) in conjunction with a lower dose of cisplatin (75 mg/m^2) and 5-FU [5-fluorouracil] at 800 mg/m^2/d × 4 days. No DLTs were observed in these cohorts. A total of nine patients were treated in the expansion cohort with cabazitaxel at 22.5 mg/m^2, cisplatin at 75 mg/m^2 and 5-FU at 800 mg/m^2/d × 4 days. No additional DLTs were reported in this cohort either. Due to the risk of increased toxicity with no benefit in efficacy observed at a cabazitaxel dose of 22.5 mg/m^2 in the TROPIC trial, dose escalation of our study did not progress beyond 22.5 mg/m^2, despite the lack of evidence of DLTs at this dose level, and remained in accordance with the original study design."[135]

Example 2. "The cisplatin dose was assigned using the TITE-CRM [time-to-event continual reassessment method] to establish the rate of DLT [dose limiting toxicity] (...). The assigned cisplatin dose levels of the 18 assessable patients are listed in Table 2. As a result of the cohort restriction, four patients were assigned at both the 30 mg/m^2 and 40 mg/m^2 dose levels, even though no DLTs [dose limiting toxicities] were observed and the estimated target dose was higher than the assigned dose. After Patient 12 (treated at 50 mg/m^2) experienced DLT, the estimate of α, and therefore the target dose, began to decrease, but not sufficiently to move the target dose to 40 mg/m^2. The DLT of patient 13 was dated March 30, 2001, but was not officially established until after Patients 17 and 18 were enrolled. At that time, based on two toxicities out of seven patients enrolled at 50 mg/m^2, the estimated target dose was still 50 mg/m^2. Patient 17 was enrolled at 40 mg/m^2, because of concerns about a potential DLT in Patient 16. Patient 18 was enrolled at the current estimated target dose of 50 mg/m^2, as additional time had passed and the DLT of patient 16 had not yet been established."[60]

This example is further supplemented by Table 2 in Muler et al.,[60] reprinted from Journal of Clinical Oncology with permission from Wolters Kluwer Health, Inc (Fig. 5a).

Example 3. *This example is from Figure 3 in Yin et al.,[65] used under CC BY 4.0 (Fig. 5b). The swimmer plot illustrates "dosage received, presence of DLT [dose-limiting toxicity], the DLT follow-up period for evaluable participants. The vertical lines indicate the timing of interim analyses for dose assignments." The figure was created by Yin* et al.[65] *based on the information provided in Example 2.*[60]

Example 4. "Although enrolment of up to seven cohorts of three participants each (21 patients in total) was specified in the design, the primary analysis for the trial was event-driven, permitting early termination of enrolment under the prespecified stopping rules as described[reference]. After treatment of five cohorts, the trial steering committee, in consultation with the data monitoring committee, determined that a sufficient number of patients had been treated to define the maximum tolerated dose with confidence. Enrolment to the phase 1b component of the trial was therefore

a

	Stage 1			Stage 2					
Patients	20-mg cohort *n*=4	40-mg cohort *n*=4	60-mg cohort *n*=6	mCRC *n*=59	NSCLC *n*=20	Melanoma *n*=20	Biopsy *n*=16	mCRC biopsy *n*=21	All patients *N*=150
Age, years									
Median	48.0	49.0	62.5	57.0	61.0	53.5	49.5	57.0	57.0
Range	40–75	21–71	47–75	29–81	35–79	27–83	20–71	23–79	20–83
Sex, %									
Male/female	100/0	50/50	67/33	49/51	50/50	35/65	31/69	76/24	51/49
ECOG performance status, %									
0/1	50/50	100/0	17/83	48/52	55/45	75/25	44/56	38/62	51/49
Race, *n* (%)									
Asian	0	0	0	22 (37)	7 (35)	7 (35)	10 (63)	8 (38)	54 (36)
Black or African American	0	0	0	0	1 (5%)	0	0	0	1 (0%)
White	4 (100)	4 (100)	4 (67)	37 (63)	11 (55)	13 (65)	6 (38)	12 (57)	91 (61)
Other/Unknown	0	0	2 (33)	0	1 (5)	0	0	1 (5)	4 (3)

ECOG: Eastern Cooperative Oncology Group; mCRC: metastatic colorectal cancer; NSCLC: non-small cell lung cancer.

b

		Combination Dose of LEN with 75 mg/m² AZA			
Best Response	Overall	Dose 0 (5 mg LEN)	Dose 1 (10 mg LEN)	Dose 2 (15 mg LEN)	Dose 3 (25 mg LEN)
CR	3 (20)	1 (33.3)	0 (0)	0 (0)	2 (25)
CRi	3 (20)	0 (0)	1 (50)	2 (100)	0 (0)
PR	1 (6.7)	0 (0)	0 (0)	0 (0)	1 (12.5)
Resistant disease	7 (46.7)	1 (33.3)	1 (50)	0 (0)	5 (62.5)
Not evaluable	1 (6.7)	1 (33.3)	0 (0)	0 (0)	0 (0)

Data presented as No. (%). AZA: azacitidine; CR: complete remission; CRi: complete remission with incomplete blood count recovery; LEN: lenalidomide; PR: partial response.

Fig. 6: **(a)** Item 15, baseline demographic and clinical characteristics across each dose level within each group, Example 1—obtained from Table 1 in Hellmann et al.,[136] reprinted from *Annals of Oncology* with permission from Elsevier, cropped from original; **(b)** Item 16, the number of participants included in each analysis across each dose level, and whether the analysis was by original assigned interventions, Example 1—obtained from Table 4 in Craddock et al.,[115] used under CC BY 4.0.

concluded after 15 participants, emphasising the potential efficiency of such a Bayesian design."[31]

Explanation. The credibility of adaptive designs like EPDF trials requires strict adherence to preplanned adaptations and decision criteria. Thus, it is important for readers to be able to assess whether the prespecified adaptation rules were adhered to in the decision-making criteria (item 7b) given the observed accrued data at the interim analyses (item 17c). Failure to adhere to

prespecified decision rules (e.g., on dose (de-)escalation decisions or stopping early) can affect the operating characteristics of the design (item 7a), and can potentially have ethical and regulatory implications, undermining the integrity of the trial and validity of the trial results.[49]

For transparency and interpretation, an account of key adaptations that were made to the trial aspects, on what basis they were made, and when, should be provided.

Item 15 [modified] Baseline demographic and clinical characteristics across each dose level within each group, where appropriate

Example 1. *This example is from Table 1 in Hellmann et al.,[136] reprinted from Annals of Oncology with permission from Elsevier, cropped from original (Fig. 6a).*

Example 2. *This example is from Table 1 in Chandorkar et al.,[137] used under CC BY 4.0 (Supplementary Figure S3).*

Example 3. *This example is from a study in healthy volunteers and was taken from Table 1 in Dijkstra et al.,[105] reprinted from British Journal of Clinical Pharmacology with permission from John Wiley and Sons (Supplementary Figure S4).*

Explanation. This item enables readers to assess if participants across different dose levels within each group are comparable. It also helps to contextualise the relevance of results, such as dosing decisions, and assesses the extent of diversity among trial participants, thereby understanding the implications for subsequent trials.

In EPDF trials, it is useful to present baseline demographic and clinical characteristics (e.g., age, sex, ethnicity, socioeconomic data) for each group and each dose level. EPDF trials are often conducted with very small sample sizes, so when applying this item, authors should strike a balance between presenting clinically relevant information whilst avoiding de-anonymisation of participants if presentation of baseline characteristics render them easily identifiable, such as in studies of rare diseases.

Item 16 [modified] For each group, the number of participants (denominator) included in each analysis across each dose level, and whether the analysis was by original assigned interventions

Example 1. "Seven of 15 (47%) patients who received at least three cycles of treatment achieved a major clinical response to LEN/AZA [lenalidomide/azacitidine] salvage (CR [complete response], n = 3; CR with incomplete blood count recovery, n = 3; PR [partial response], n = 1)."[115]

This example is illustrated in Table 4 in Craddock et al.,[115] used under CC BY 4.0 (Fig. 6b).

The example states the number of participants included in each analysis across each dose level. The caption to a separate figure states that a patient who was incorrectly treated at a higher dose was included in the higher dose level for analyses, suggesting that patients were analysed based on treatment received, rather than original assignment. However, if the two were discrepant, this is not explicitly stated.

Other examples. *Flow diagrams of examples 1–3 for item 13a also provide the number of participants across each dose level (for each group) within their figures for analysis of their key objectives.*[9,129,138]

Explanation. Reporting the number of participants included in each analysis across each dose level within each group is important for transparent reporting and accurate interpretation of results.

The presentation of the numbers analysed should reflect the key objectives considered to address the research questions. Authors should clarify whether participants were analysed as per allocated dose level(s). The participant flow (item 13a) should provide the number of participants analysed at each dose within each group for both the interim and final analyses for the primary outcome and other outcomes used to inform prespecified adaptations. For other outcomes where a comparative assessment is performed, that information at interim and final analyses should also be reported.[49]

Item 17a [modified] For each primary and secondary outcome, results for each dose level within each group, and the estimated effect size and its precision, if applicable

Example 1. *This example is from Table 2 in Desai et al.,[139] reprinted from Journal of Clinical Oncology with permission from Wolters Kluwer Health, Inc (Fig. 7a).*

Example 2. *This example is from Figure 2 in Pearson et al.,[140] used under CC BY 4.0 (Fig. 7b).*

Example 3. *This example is from Table 3 in Rovner et al.,[141] used under CC BY-NC 4.0 (Fig. 7c).*

Example 4. *This example is from Figure 3 in Hutchings et al.,[54] reprinted from The Lancet with permission from Elsevier (Fig. 8).*

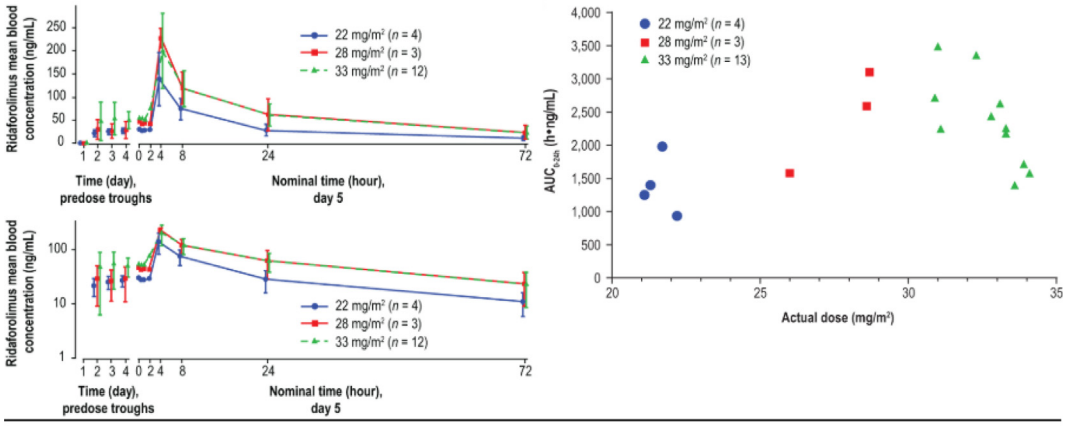
Explanation. Results from EPDF trials should be presented for each group and for each dose level(s) within each group to facilitate the assessment of safety, tolerability, and dose–response or dose–toxicity relationships. This will also aid in providing information on specific recommended doses being taken forward to subsequent phases of clinical development.

a

Level	No. Enrolled	No. of DLTs/No. Assessable	Final *P* (DLT)	90% Posterior Probability Interval
−1	0	—	.10	.05 to .18
1	6	0/5	.16	.08 to .26
2	5	1/5	.19	.10 to .30
3	12	3/12	.21	.12 to .33
4	14	2/12	.24	.14 to .36
5	7	3/6	.27	.16 to .39
6	0	—	.29	.19 to .42

DLT: dose-limiting toxicity; Final P (DLT): final posterior probability of experiencing a DLT.

b



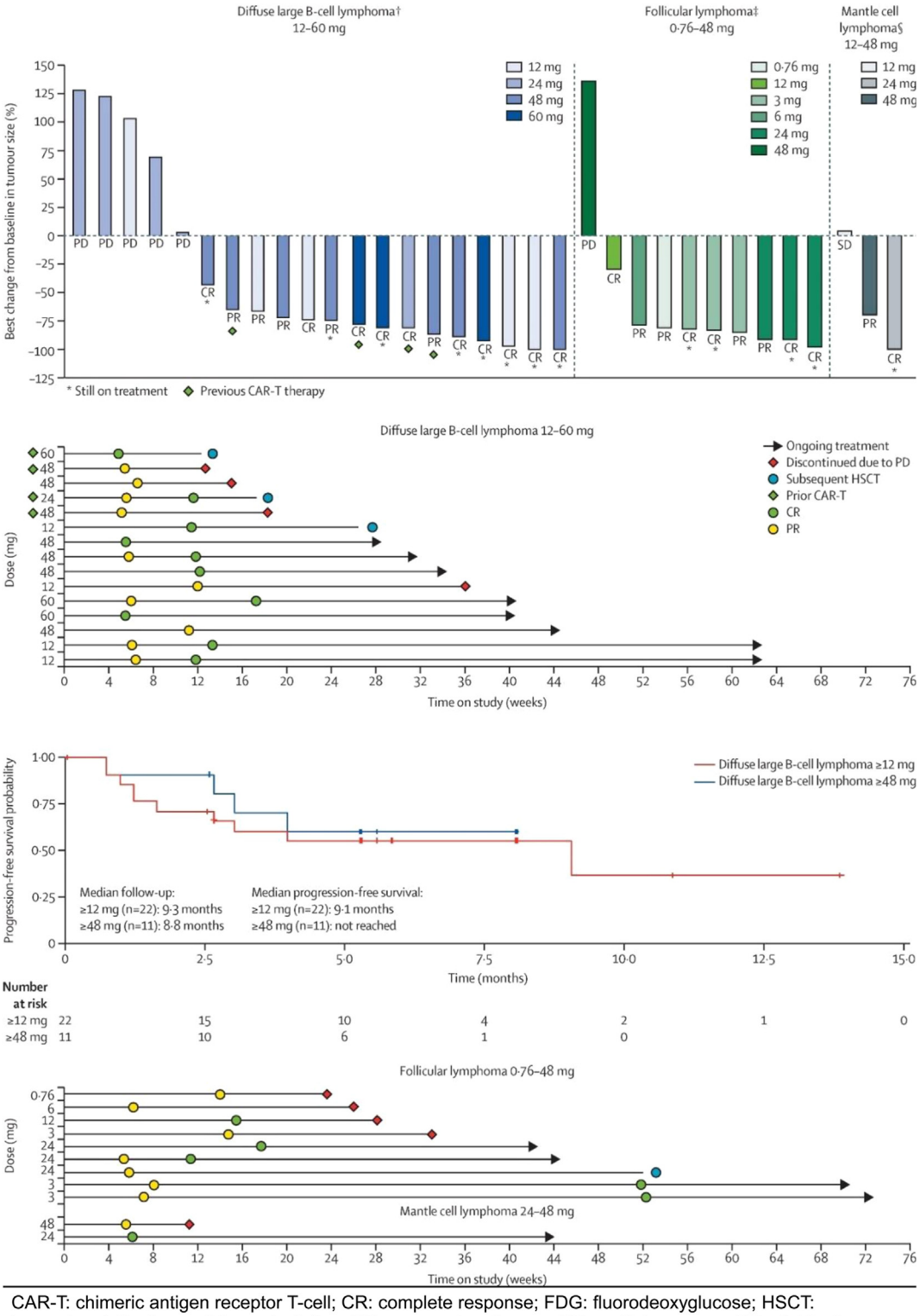
c

		Placebo (n = 4)	URO-902 16 000 µg (n = 6)	URO-902 24 000 µg (n = 3)	Both active doses (n = 9)
Week 4	Mean change from baseline (SD)	8.33 (21.52)	−33.33 (33.33)	−38.89 (19.25)	−35.19 (28.19)
	P value change from BL	.675	.004	.015	<.001
	P value change from BL vs placebo		.030	.035	.015
Week 8	Mean change from baseline (SD)	8.33 (28.87)	−25.00 (22.97)	−38.89 (19.25)	−29.63 (21.70)
	P value change from BL	.476	.023	.014	.001
	P value change from BL vs placebo		.047	.020	.014
Week 12	Mean change from baseline (SD)	4.17 (28.46)	−27.78 (29.19)	−38.89 (19.25)	−31.48 (25.61)
	P value change from BL	.694	.012	.014	<.001
	P value change from BL vs placebo		.056	.032	.021
Week 24	Mean change from baseline (SD)	16.67 (23.57)	−16.67 (27.89)	−38.89 (9.62)	−24.07 (25.15)
	P value change from BL	.181	.118	.014	.005
	P value change from BL vs placebo		.047	.007	.007

BL: baseline; SD: standard deviation.

Fig. 7: **(a)** Item 17a, results for each dose level within each group, Example 1—obtained from Table 2 in Desai et al.,[139] reprinted from *Journal of Clinical Oncology* with permission from Wolters Kluwer Health, Inc; **(b)** Item 17a, results for each dose level within each group, Example 2—obtained from Figure 2 in Pearson et al.,[140] used under CC BY 4.0; **(c)** Item 17a, results for each dose level within each group, Example 3—obtained from Table 3 in Rovner et al.,[141] used under CC BY-NC 4.0.

It is important that the reported results of an EPDF trial reflect the research objectives. Results might include, for example, the number and percentage of people who experienced adverse events or activity rates at each dose level, or the estimated toxicity rate(s) at the recommended dose(s), within each group. As the number of participants at each dose level is typically small, the results will likely be imprecise. For proportions, authors can report both the numerator and the denominator or provide expressions of uncertainty (such as confidence intervals or credible intervals) so that readers can be made aware of their precision. If the objectives include evaluating differences, for instance, across dose levels or treatment groups, those



CAR-T: chimeric antigen receptor T-cell; CR: complete response; FDG: fluorodeoxyglucose; HSCT: haematopoietic stem-cell transplantation; PD: progressive disease; PR: partial response; SD: stable disease.

Fig. 8: Item 17a, results for each dose level within each group, Example 4—obtained from Figure 3 in Hutchings et al.,[54] reprinted from *The Lancet* with permission from Elsevier.

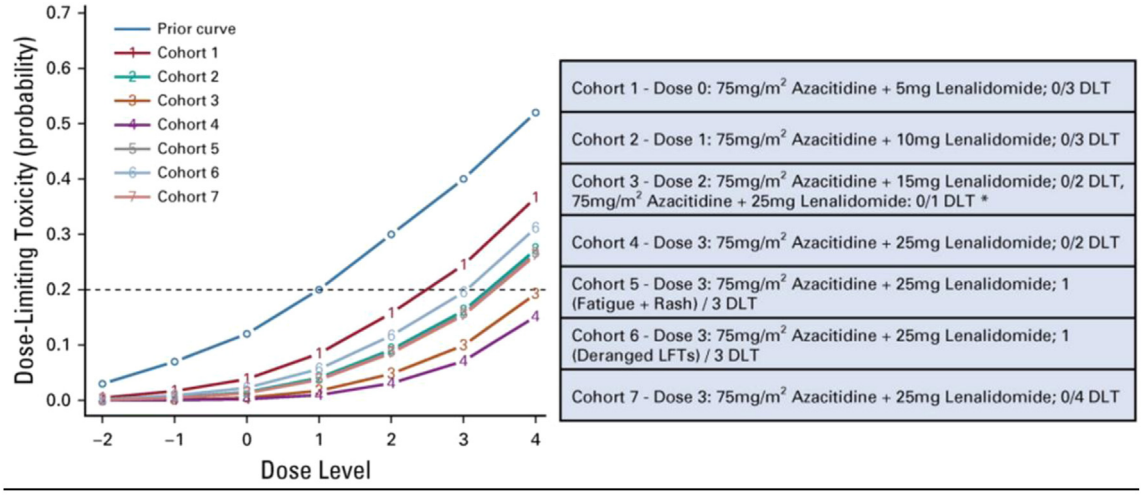


Fig. 9: Item 17c, interim results used to inform interim decision making such as dose escalation, de-escalation, or staying at the same dose, Example 2—obtained from Figure A1 in the online appendix of Craddock et al.,[115] used under CC BY 4.0.

can be reported with measures of uncertainty where applicable.

Item 17b [elaborated] For binary outcomes, presentation of both absolute and relative effect sizes is recommended
This item might only apply in specific circumstances, for instance, in trials with larger sample sizes. For details, see the CONSORT E&E document.[15]

Item 17c [new] Report interim results used to inform interim decision making such as dose escalation, de-escalation, or staying at the same dose
Example 1. "The first patient experienced a DLT [dose-limiting toxicity] of diarrhea and posterior reversible encephalopathy syndrome. Hence, another 3 patients were enrolled at this dosage level, without additional DLTs [dose-limiting toxicities] observed. Three patients were enrolled at each of the next dosing levels, 1.3 mg/m^2 and 1.6 mg/m^2, without a DLT occurring. This led to the phase II portion of the study, in which an additional 20 patients were recruited to receive 1.6 mg/m^2 of bortezomib on days −4 and −1."[142]

Example 2. *This example is from Figure A1 in the online appendix of Craddock et al.,[115] used under CC BY 4.0 (Fig. 9).*

Explanation. Reporting interim results ensures full transparency, methodological clarity and understanding of the trial's evolution and outcomes. Additionally, it enhances trial integrity by assuring reviewers and regulators that the trial was conducted transparently, adhering to adaptive design principles.

Relevant interim analysis results that were used to make interim decisions, such as dose escalation, de-escalation, or staying at the same dose, should be reported. This will most likely include data on toxicity and harms, but it could also include results of (preliminary) activity, pharmacokinetics/pharmacodynamics, or biomarker analyses. Authors should also report interim results for dose levels or subpopulations (a subgroup of participants with certain characteristics) that were discontinued due to a lack of activity or poor safety. In terms of trial integrity, these details will allow readers to judge whether trial modifications (item 14c) were in accordance with what was planned at the design stage.

Item 19 [modified] All important harms (e.g., adverse events or effects, toxicities) reported by dose level in each group
For specific guidance see CONSORT for Harms 2022.[14]

Example 1. *This example is from Table 3 in Lee et al.,[143] reprinted from Clinical Cancer Research with permission from AACR (Fig. 10a).*

Example 2. *This example is from Table 1 in McBride et al.,[144] reprinted from Arthritis & Rheumatology with permission from John Wiley and Sons (Fig. 10b).*

Example 3. *This example is from a study in healthy volunteers and was taken from Table 3 in Dijkstra* et al.,[105] *reprinted from British Journal of Clinical Pharmacology with permission from John Wiley and Sons (Supplementary Figure S5).*

Explanation. Detailed reporting of important harms by dose level in EPDF trials helps the readers to identify the types of events that occurred at different dose levels and, hence, to evaluate the safety and tolerability at those dose levels of a new intervention to inform dose selection in

a

	DL 1 (*N* = 6)		DL −1 (*N* = 3)		DL −1G (*N* = 7)		DL 1G (*N* = 6)		All (*N* = 22)	
Grade	**≥3**	**All**	**≥3**	**All**	**≥3**	**All**	**≥3**	**All**	**≥3**	**All**
Hematologic										
Leukopenia	6 (100)	6 (100)	1 (33)	1 (33)	3 (43)	5 (72)	1 (17)	4 (67)	11 (50)	16 (73)
Neutropenia	6 (100)	6 (100)	3 (100)	3 (100)	5 (72)	5 (72)	3 (50)	4 (67)	17 (77)	18 (82)
Lymphopenia	2 (33)	5 (83)	0 (0)	1 (33)	2 (29)	4 (57)	0 (0)	3 (50)	4 (18)	13 (59)
Anemia	0 (0)	4 (67)	0 (0)	2 (67)	3 (43)	5 (72)	0 (0)	2 (33)	3 (14)	13 (59)
Thrombocytopenia	1 (17)	3 (50)	0 (0)	1 (33)	0 (0)	3 (43)	1 (17)	2 (33)	2 (9)	9 (41)
Gastrointestinal										
Abdominal pain	0 (0)	2 (33)	0 (0)	0 (0)	0 (0)	2 (29)	0 (0)	2 (33)	0 (0)	6 (27)
Anorexia	0 (0)	4 (67)	0 (0)	0 (0)	1 (14)	3 (43)	0 (0)	3 (50)	1 (5)	10 (45)
Constipation	0 (0)	3 (50)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	4 (18)
Diarrhea	0 (0)	2 (33)	2 (67)	2 (67)	1 (14)	4 (57)	1 (17)	3 (50)	4 (18)	11 (50)
Dysgeusia	0 (0)	3 (50)	0 (0)	0 (0)	0 (0)	1 (14)	0 (0)	0 (0)	0 (0)	4 (18)
Nausea	0 (0)	5 (83)	0 (0)	1 (33)	0 (0)	6 (86)	1 (17)	4 (67)	1 (5)	16 (73)
Vomiting	0 (0)	1 (17)	0 (0)	3 (100)	0 (0)	4 (57)	0 (0)	2 (33)	0 (0)	10 (45)
Infections and fevers										
Infections	0 (0)	2 (33)	0 (0)	1 (33)	0 (0)	1 (14)	0 (0)	0 (0)	0 (0)	4 (18)
Neutropenic fever	1 (17)	1 (17)	2 (67)	2 (67)	2 (29)	2 (29)	0 (0)	0 (0)	5 (23)	5 (23)
Fever	1 (17)	5 (83)	0 (0)	1 (33)	0 (0)	2 (29)	0 (0)	0 (0)	1 (5)	8 (36)
Renal and hepatobiliary										
Acute kidney injury	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (17)	1 (5)	1 (5)
Increased Alk phos	1 (17)	3 (50)	0 (0)	1 (33)	0 (0)	5 (72)	0 (0)	2 (33)	1 (5)	11 (50)
Increased AST	0 (0)	2 (33)	0 (0)	0 (0)	1 (14)	4 (57)	0 (0)	1 (17)	1 (5)	7 (32)
Skin										
Alopecia	0 (0)	3 (50)	0 (0)	1 (33)	0 (0)	2 (29)	0 (0)	2 (33)	0 (0)	8 (36)
Other										
Injection site reactions	0 (0)	4 (67)	0 (0)	1 (33)	0 (0)	5 (72)	0 (0)	4 (67)	0 (0)	14 (64)
Fatigue or malaise	0 (0)	3 (50)	0 (0)	2 (67)	1 (14)	4 (57)	1 (17)	5 (87)	2 (9)	14 (64)
Generalized muscle weakness	1 (17)	1 (17)	0 (0)	0 (0)	0 (0)	1 (14)	0 (0)	0 (0)	1 (17)	2 (9)
Lower extremity edema	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	4 (57)	0 (0)	1 (17)	0 (0)	6 (27)
Myalgia	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	2 (29)	0 (0)	0 (0)	0 (0)	3 (14)
Dehydration	0 (0)	0 (0)	1 (33)	1 (33)	0 (0)	3 (43)	1 (17)	1 (17)	2 (9)	5 (23)
Dizziness and lightheadedness	0 (0)	1 (17)	0 (0)	1 (33)	0 (0)	2 (29)	0 (0)	0 (0)	0 (0)	4 (18)
Headaches	0 (0)	3 (50)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (14)

DL: dose level.

b

		Rontalizumab						
	Placebo (n = 12)	0.3 mg/kg IV (n = 8)	1 mg/kg IV (n = 8)	1 mg/kg SC (n = 8)	3 mg/kg IV (n = 8)	3 mg/kg SC (n = 8)	10 mg/kg IV (n = 8)	Total (n = 48)
≥1 AE	11 (91.7)	8 (100)	8 (100)	8 (100)	8 (100)	7 (87.5)	8 (100)	47 (97.9)
Grade 2 or higher	6 (50)	8 (100)	5 (62.5)	6 (75)	6 (75)	5 (62.5)	5 (62.5)	35 (72.9)
Grade 3 or higher	1 (8.3)	2 (25)	1 (12.5)	3 (37.5)	2 (25)	2 (25)	2 (25)	12 (25)
≥1 SAE	1 (8.3)	1 (12.5)	0	2 (25)	2 (25)	2 (25)	0	7 (14.6)
Drug-related AE								
≥1 drug-related AE within 24 hours	1 (8.3)	0	1 (12.5)	3 (37.5)	1 (12.5)	3 (37.5)	2 (25)	10 (20.8)
≥1 drug-related AE	2 (16.7)	1 (12.5)	5 (62.5)	4 (50)	4 (50)	3 (37.5)	3 (37.5)	20 (41.7)
Infection								
≥1 infection AE	9 (75)	7 (87.5)	7 (87.5)	7 (87.5)	7 (87.5)	5 (62.5)	6 (75)	39 (81.3)
Rate of infections per patient-year (95% CI)	1.25 (0.9–1.8)	0.73 (0.4–1.3)	0.96 (0.6–1.6)	1.45 (0.9–2.3)	1.91 (1.3–2.8)	1.15 (0.7–2.0)	1.72 (1.1–2.6)	1.28 (1.1–1.5)
≥1 infection SAE	0	0	0	0	1 (12.5)	0	0	1 (2.1)

Except where indicated otherwise, values are the number (%) of patients. AE: adverse event; CI: confidence interval; IV: intravenous; SAE: serious adverse event; SC: subcutaneous.

Fig. 10: **(a)** Item 19, all important harms reported by dose level in each group, Example 1—obtained from Table 3 in Lee et al.,[143] reprinted from *Clinical Cancer Research* with permission from AACR; **(b)** Item 19, all important reported by dose level in each group, Example 2—obtained from Table 1 in McBride et al.,[144] reprinted from *Arthritis & Rheumatology* with permission from John Wiley and Sons.

subsequent trials. It is also essential in EPDF trials for interpreting the balance between the likelihood of benefits and risks of harms, and for evidence synthesis.

Authors should present all important harms for each group as aggregated data and also by dose level. Harms, as possible adverse consequences of an intervention, can comprise adverse events, adverse (drug) reactions, toxicities, treatment-emergent adverse events, or those that are intolerable by participants.[13,145] They may also include tolerability assessment using patient-reported outcomes to complement investigators' reporting.[145–147]

Other information: Data monitoring

Data monitoring is a new section added to the CONSORT-DEFINE checklist due to its critical role in EPDF trials. Monitoring of accruing data for safety as well as for making dose decisions are key features of EPDF trials.

Item 26a [new] Composition of any decision making or safety review committee or group; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details can be found (such as in a charter or protocol)

Example 1. "We started with a once a day schedule and allowed for exploration of other dosing schedules according to the decision of the Safety Monitoring Committee (consisting of all principal investigators, the sponsor's medical and safety officers, and an independent expert, who made all decisions regarding patient safety, dose-limiting toxicity (DLT) qualification, dose escalation, and recommended dose definition)."[148]

This example addresses the composition of the decision making or safety review committee or group but lacks the reporting structure.

Example 2. "Prior to dosing of the next cohort, the Data Monitoring Committee (DMC), which included two independent clinicians with expertise in immunology/rheumatology and coagulopathies, reviewed blinded safety data from dosing to 14 days and PK [pharmacokinetics] data from at least seven days after the last administered dose within the previous dose cohort."[149]

This example addresses the composition of the decision making or safety review committee or group but lacks the reporting structure.

Example 3. "The Data Monitoring Committee reviewed all available data and evaluated newly emergent safety data including dose-limiting toxicity and provided the Sponsor Safety Committee with recommendations for the next dose level."[54]

This example addresses the reporting structure but lacks the composition of the decision making or safety review committee or group.

Explanation. EPDF trials typically include frequent interim reviews of accumulated key outcome data and analyses to inform interim decisions, particularly on safety and dose adaptations. The decision-making committee/group typically involves members with relevant specialist expertise to assess an EPDF trial, including clinical (and pharmacological and toxicological, depending on the intervention) experience,[150] who may not necessarily be independent from the sponsor.[151] It is helpful to specify the composition of people who make decisions in EPDF trials, as their expertise and perspectives can influence the conduct and interpretation of results. Moreover, as the type and composition of decision-making groups vary across different trials, the provision of detailed information may increase transparency, enhance the trial's data credibility, and help readers assess potential biases.

Details on the composition of any decision-making committee/group that reviewed key outcomes, such as safety and treatment tolerability, and made or recommended decisions (including dose (de-)escalation, dose expansion, or progression to another phase); summary of its role and reporting structure (see Example 3); and a statement on whether it is independent from the sponsor, funder, or trials team (see Example 1 and Example 2) and competing interests should be provided. It can be helpful to provide a reference to where further details, such as a charter, can be found if they are not in the report. Such an oversight committee/group in EPDF trials could be an individual or a group of members and is sometimes referred to as the safety review committee/group, the dose escalation committee/group, or the data (safety) monitoring committee or board.

Item 26b [new] Description of who had access to interim results and made the interim and final decision to terminate the trial (or part(s) of the trial, e.g., end of dose escalation), and measures to safeguard the confidentiality of interim information

Example 1 (protocol). "Each cohort will recruit a minimum of 4 subjects to a dose level. After the final participant has completed dosing within a given cohort and data are available, a dose escalation meeting will take place. If additional participants are added to a particular dose level, a further meeting may be held to review the additional data.

The study review team may include the following (or delegates as appropriate): Clinical Statistics, CPMS [Clinical Pharmacology Modelling and Simulation], GCSP [Global Clinical Safety and Pharmacovigilance], CIL [Clinical Investigative Lead], OSL [Operational Study Lead], Medical Monitor and DQL [Data Quality Lead]. Other functions may be invited as required. The data will be used to support the decision to move to the next dose level as planned. Decisions made at each meeting in relation to a given dose, will be documented in the CPSR [Clinical Pharmacology Study Report]. (...)

Prior to each dose escalation meeting, unblinded safety data for this open-label study will be made available to the study team via listings from Inform and Q2 Results Viewer. In addition, CPMS will obtain the interim unblinded PK [pharmacokinetic] concentration data from SMS2000 via HARP [Harmonisation of Analysis & Reporting Program] according to current working practices. If any process changes occur which affect the way in which SMS2000 data is obtained during the study, then the applicable process at the time will be followed and any changes in processes between dose escalations will be documented."[152]

This example lacks details on measures to safeguard the confidentiality of interim information. It was extracted from the trial protocol.

Example 2 (protocol). "Cumulative AE [adverse event] data will be provided to the SMC [safety monitoring committee] after all subjects in cohorts 1 and 2 have

completed Day 8 and again after all subjects have completed Day 36. Documentation of review and any concerns noted will be solicited electronically. The SMC does not need to meet for dose escalation to 250 mcg (cohort 3). The SMC will meet when trial halting criteria are met, or as requested by the sponsor or PI [principal investigator]. The SMC will have a final review meeting at the end of the study. Procedures for SMC reviews/meetings will be defined in the SMC charter. The SMC will review applicable data, including, but not limited to, enrollment, demographics, dosing data, clinical laboratory data, and safety data, at scheduled timepoints during this trial as defined in the SMC charter. The SMC will review blinded aggregate data in the open session of the SMC meetings. Additional data may be requested by the SMC, and interim statistical reports may be generated as deemed necessary and appropriate by DMID [Division of Microbiology and Infectious Diseases; the sponsor]. As an outcome of each review/meeting, the SMC will make a recommendation as to the advisability of proceeding with study product administration, and to continue, modify, or terminate this trial (...). Data may be disseminated to public health officials and partners as needed and included in scientific publications and presentations to inform the global scientific community."[153]

This example was extracted from the trial protocol, which is available as an online supplement to the published paper. It lacks details on measures to safeguard the confidentiality of interim information.

Example 3 (created). Access to interim results and the authority to make interim and final decisions about dose adaptations rested with an independent Data Monitoring Committee (DMC). The DMC consisted of experts with no direct involvement in the trial. The interim analysis was conducted by an independent biostatistician, and the results were shared exclusively with the DMC. All data were kept confidential through encrypted communication channels. Decisions about what information would be shared for dose assignments were collectively determined by the DMC to maintain an unbiased and confidential data handling.

This hypothetical example was created by the authors of this article.

Explanation. In contrast to late phase trials, it is not uncommon that clinical investigators who recruit participants for open-label EPDF trials are unblinded to interim data and aware of the next dose(s). Investigators being aware of the interim results may lead to operational bias during the trial. Providing details on who had access to interim results and made the interim and final decision to terminate the trial helps the reader in understanding the measures taken to minimise operational and selection bias, during interim analysis and decision-making for adaptations.[49] It promotes accountability and facilitates understanding of the decision-making process, enabling assessment of the validity and interpretation of trial results.

There should be a description of who: 1) had access to the interim data, 2) performed the interim analysis, 3) made decisions on dose adaptations and other trial adaptations, and 4) made the final decision to terminate the trial or any of its parts. It should be clear what measures were taken to minimise potential operational biases during the trial (e.g., which interim results were communicated, how, and to whom and when) and, if applicable, what measures were used to safeguard the confidentiality of interim information (see Example 3).

Other information: Dissemination

Item 27 [new] Specify, if applicable, whether and when results (such as safety and/or activity) were reported externally (e.g., through scientific presentations, journal publication, or the trial website) while the trial (or part(s) of the trial) was still ongoing

Example. "[Prior presentation:] Presented at the American Society of Hematology 59th Annual Meeting, Atlanta, GA, December 9–12, 2017; the ASCO 54th Annual Meeting, Chicago, IL, June 1–5, 2018; the 23rd Congress of the European Hematology Association, Stockholm, Sweden, June 14–17, 2018; the Sociedad Espanola de Hematologia y Hemoterapia–LX Reunion Nacional, Granada, Spain, October 11–13, 2018; the Acute Leukemias XVII Biology and Treatment Strategies, Munich, Germany, February 24–27, 2019; the ASCO 55th Annual Meeting, Chicago, IL, May 31-June 4, 2019; the 24th Congress of the European Hematology Association, Amsterdam, the Netherlands, June 13–16, 2019; the 7th Annual Meeting of the Society of Hematologic Oncology, Houston, TX, September 11–14, 2019; and the American Society of Hematology 61st Annual Meeting, Orlando, FL, December 7–10, 2019."[154]

Explanation. In EPDF trials (e.g., in open-label studies), it is not uncommon for some interim results relating to key outcomes (such as adverse events or activity) to be reported at scientific meetings or conferences while the trial is still ongoing.[43] Depending on the circumstances, such dissemination of interim data may introduce biases.[49] For example, dissemination of preliminary findings may lead to selection bias depending on how the findings are interpreted by investigators and patients. The purpose of having disclosure is to allow readers to assess the risk of potential sources of bias and, as a result, judge how robust the results can be expected to be.[49]

When results are reported while a trial is still ongoing (e.g., through scientific presentations, journal publication, or the trial website), whether prespecified or

unplanned, authors must disclose this and explain the process and timeframe for sharing trial results. In seamless phase I/II EPDF trials or those with multiple parts (e.g., phase Ia/Ib/II), it should also be specified whether results were shared at major transition points (such as at the end of the dose escalation phase).

Discussion

Well-designed and executed EPDF trials are a critical step in the development of novel therapies as they inform every aspect of subsequent phases of clinical development and provide valuable insights for reverse translation. The landscape of these studies is evolving,[79] adapting to advances in understanding diseases and therapeutic modalities, rising cost of clinical development, regulatory changes, and the demand for greater efficiency.[155–157] In addition to improving the conduct of EPDF trials, optimising their reporting is also critical. Well-reported EPDF trials enhance transparency and clarity in the interpretation, dissemination, and validation of the research findings. Inadequate reporting of EPDF trials could negatively affect or delay clinical development, and lead to patient harm or loss of trust in the healthcare and research professions.[10,158]

The overarching goal of the CONSORT-DEFINE statement and the E&E document is to enhance the completeness, quality, and transparency of the reporting of EPDF trials. This E&E document was developed to serve as an implementation guide, with a comprehensive rationale, explanations, and published and hypothetical examples, to improve the interpretability and assist authors in applying the CONSORT-DEFINE statement.

Similar to the positive impact of the CONSORT statement on the reporting quality of parallel group randomised trials,[11] the CONSORT-DEFINE statement has the potential to enhance the transparency and reproducibility of the reporting of EPDF trials. The CONSORT-DEFINE statement can help EPDF trial authors, journal editors, and reviewers to align expectations during the appraisal of trial reports. Sustained improvement in the reporting quality of EPDF trials would benefit from the endorsement and implementation of the CONSORT-DEFINE statement by scientific journals when considering manuscripts on EPDF trial results. To this end, an implementation strategy is currently being developed.

The CONSORT-DEFINE E&E document inherits all strengths and limitations of the CONSORT-DEFINE statement, as previously discussed.[10] Briefly, in the CONSORT-DEFINE statement, 19 items from CONSORT were modified and 21 items were added to tailor it to EPDF trials. The introduction of the CONSORT-DEFINE E&E document as a companion to the statement now offers significantly greater detail to facilitate implementation of the CONSORT-DEFINE statement. First, it provides an extensive description of each item, giving authors of EPDF trial reports a more precise idea of what aspects they should consider when addressing an item. These item descriptions have undergone the same scrutiny as the main CONSORT-DEFINE statement and gained consensus among CONSORT-DEFINE co-authors. Second, it enriches the understanding of these items by presenting published examples from diverse therapeutic settings. The availability of these examples from publications for almost all items underscores the feasibility of comprehensively addressing each item in the CONSORT-DEFINE statement within trial manuscripts. Third, our approach to identifying and curating these high-quality examples has been systematic, drawing from over 500 published trials identified in a previous methodological review.[7] Fourth, we have included exemplars of different EPDF trial designs to further assist authors and to broaden the scope of their implementation. We believe that the CONSORT-DEFINE statement and this E&E document are sufficiently robust to accommodate changes in the landscape of EPDF trials. They provide the flexibility to address rule-based, model-assisted, and model-based dose-finding designs. Notably, they also cover dose optimisation trials, which are expected to cause a shift from traditional dose-finding methods to a more comprehensive evaluation of non-clinical and clinical data, including pharmacokinetics, safety, tolerability, and activity—following the recommendations outlined in the FDA Project Optimus.[4]

A limitation of this E&E document is the inability to identify suitable published examples for a small number of items in the CONSORT-DEFINE checklist. To address this gap, we extended our search to trial design publications, trial protocols and statistical analysis plans, and drafted hypothetical exemplars of good reporting for item 13b, item 14a, and item 26b. Item 13b focuses on losses and exclusions after allocation to each dose level. We chose to provide a simple hypothetical example for illustrative purposes, but the published examples for item 13a also address item 13b. For item 14a, which relates to the dates defining the periods of recruitment and follow-up, we drafted a hypothetical example as we were not able to identify any suitable example in the literature. Information on access to interim results, responsibility for terminating the trial, and measures to safeguard the confidentiality of interim information (item 26b) is often provided in the protocol. However, we found that the identified published examples, even those from trial protocols, addressed only part of this item and opted for drafting an additional hypothetical example. Item 3a.7 addresses whether skipping of dose levels was allowed. We were able to identify one suitable example in a trial publication but identified additional examples in trial design and protocol publications that the publication on the trial results could refer to. For item 12d, which pertains to intercurrent events and where the

handling of such events is closely connected to the estimand framework, we found one example in the literature and sourced two further examples from a recently published guideline for the content of statistical analysis plans of EPDF trials. The scarcity of published examples in the context of EPDF trials may be attributed to the relative novelty of the estimand framework.[30] This framework is gaining traction in the statistical and scientific communities, especially in later phase trials,[159,160] but it is still emerging in the context of EPDF trials.[44,161,162]

Outstanding questions

The main question with any guidance document is whether the target community will implement the recommendations. The CONSORT-DEFINE statement aims for broad adoption, but challenges remain, such as lack of awareness and limited editorial buy-in. Even though many journals endorse the main CONSORT guidelines, and their extensions, editors and peer reviewers might not be fully aware of this specific extension for EPDF trials. Additionally, time and budget constraints in journals may hinder the implementation of checking compliance with reporting guidelines. Investigating these potential barriers could inform strategies to increase uptake. Closely related is the question what impact the CONSORT-DEFINE statement will have, which systematic reviews could measure by comparing the reporting quality of EPDF trials before and after the statement's dissemination.

As EPDF trials and the utilised trial designs evolve, further modifications to the CONSORT-DEFINE statement may be necessary. Research could explore whether specific aspects of new designs require additional reporting features. Since the guidelines draw from diverse therapeutic settings, it would be useful to understand if certain areas require targeted adaptations. Generally, updating and improving the CONSORT-DEFINE checklist will rely on identifying effective ways to incorporate feedback—whether from journal editors, trial authors, readers or reviewers. Relating to the examples in this document, it would be desirable to replace hypothetical examples with real world ones as this guidance is increasingly adhered to. Understanding whether methodological gaps or evolving practices contributed to the scarcity of published examples for some items could identify barriers to comprehensive reporting in these areas and provide insight into overcoming these limitations.

Conclusions

The CONSORT website (https://www.equator-network.org/reporting-guidelines/consort/) offers the latest updates. We value feedback on CONSORT-DEFINE in shaping future improvements. Through collective commitment to widespread adoption and support, we can enhance the completeness, quality, and review efficiency of EPDF trial reports.

In conclusion, EPDF trials are the backbone of early clinical research. High-quality reporting ensures the availability of crucial evidence regarding the safety, tolerability, and activity of interventions, serving as the cornerstone for informed and successful future investigations.

Contributors

JR and CG contributed equally. JR, CG, OS, MD, CJW, and CY conceived the study. JR, CG, OS, MD, MR, DP, EA, CHG, RG, KSH, IM, RP, MU, and CY collected examples and curated the data. MD, JdB, TRJE, SH, TJ, AK, SL, AM, CJW, and CY acquired the funding. JR, CG, OS, MD, MU, CJW, and CY contributed to the methodology. JR, CG, OS, DP, and CY conducted the project administration. CY supervised the project. JR and CG were responsible for data validation. JR, CG, OS, and CY handled data visualisation. JR, CG, OS, MD, CJW, and CY wrote the original draft. All authors were involved in the investigation and in the reviewing and editing of the manuscript. CY is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Data was viewed and verified by JR, CG, and CY. All authors read and approved the final version of the manuscript.

Data sharing statement

This study compiled examples from previously published articles, each referenced individually in the manuscript. As this study did not generate new data, no additional dataset is provided. Permissions for re-using previously published material can be viewed upon reasonable request.

Declaration of interests

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102987.

References
1 Araujo D, Greystoke A, Bates S, et al. Oncology phase I trial design and conduct: time for a change - MDICT Guidelines 2022. *Ann Oncol*. 2023;34(1):48–60.
2 Espinasse A, Solovyeva O, Dimairo M, et al. SPIRIT and CONSORT extensions for early phase dose-finding clinical trials: the DEFINE (DosE-FIndiNg Extensions) study protocol. *BMJ Open*. 2023;13(3):e068173.
3 Solovyeva O, Dimairo M, Weir CJ, et al. Development of consensus-driven SPIRIT and CONSORT extensions for early phase dose-finding trials: the DEFINE study. *BMC Med*. 2023;21(1):246.
4 US Food and Drug Administration. Optimizing the dosage of human prescription drugs and biological products for the treatment of oncologic diseases guidance for Industry. https://www.fda.gov/media/164555/download; 2023. Accessed June 21, 2024.
5 Alger E, Minchom A, Lee Aiyegbusi O, Schipper M, Yap C. Statistical methods and data visualisation of patient-reported outcomes in early phase dose-finding oncology trials: a methodological review. *eClinicalMedicine*. 2023;64:102228.
6 Bulsara S, Wu M, Wang T. Phase I CAR-T clinical trials review. *Anticancer Res*. 2022;42(12):5673–5684.
7 Yap C, Solovyeva O, Yin Z, et al. 53P Assessing the reporting quality of early phase dose-finding trials. *Ann Oncol*. 2022;33:S24.
8 European Medicines Agency. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf; 2017. Accessed June 21, 2024.
9 Alger E, Zhang Y, Yap C. Reporting quality of CONSORT flow diagrams in published early phase dose-finding clinical trial reports: improvement is needed. *Contemp Clin Trials*. 2023;131:107277.
10 Yap C, Solovyeva O, de Bono J, et al. Enhancing reporting quality and impact of early phase dose-finding clinical trials: CONSORT Dose-finding Extension (CONSORT-DEFINE) guidance. *BMJ*. 2023;383:e076387.
11 Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMC Med*. 2010;8:18.
12 Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. *PLoS Med*. 2010;7(2):e1000217.
13 Ioannidis JPA. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med*. 2004;141(10):781.
14 Junqueira DR, Zorzela L, Golder S, et al. CONSORT Harms 2022 statement, explanation, and elaboration: updated guideline for the reporting of harms in randomised trials. *BMJ*. 2023;381:e073725.
15 Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c869–c.
16 Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT statement for randomized trials of nonpharmacologic treatments: a 2017 update and a CONSORT extension for nonpharmacologic trial abstracts. *Ann Intern Med*. 2017;167(1):40.
17 Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis*. 2021;21(2):181–192.
18 Dite W, Langford ZN, Cumming TB, Churilov L, Blennerhassett JM, Bernhardt J. A Phase 1 exercise dose escalation study for stroke survivors with impaired walking. *Int J Stroke*. 2015;10(7):1051–1056.
19 Schram AM, Gandhi L, Mita MM, et al. A phase Ib dose-escalation and expansion study of the oral MEK inhibitor pimasertib and PI3K/MTOR inhibitor voxtalisib in patients with advanced solid tumours. *Br J Cancer*. 2018;119(12):1471–1476.
20 Danto SI, Shojaee N, Singh RSP, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of PF-06650833, a selective interleukin-1 receptor-associated kinase 4 (IRAK4) inhibitor, in single and multiple ascending dose randomized phase 1 studies in healthy subjects. *Arthritis Res Ther*. 2019;21(1):269.
21 Banerji U, van Herpen CML, Saura C, et al. Trastuzumab duocarmazine in locally advanced and metastatic solid tumours and HER2-expressing breast cancer: a phase 1 dose-escalation and dose-expansion study. *Lancet Oncol*. 2019;20(8):1124–1135.
22 Zhu F-C, Li Y-H, Guan X-H, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. *Lancet*. 2020;395(10240):1845–1854.
23 Hopewell S, Clarke M, Moher D, et al. CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med*. 2008;5(1):e20.
24 Shepshelovich D, Goldvaser H, Wang L, Abdul Razak AR. Comparison of published and unpublished phase I clinical cancer trials: an analysis of the ClinicITrials.gov database. *Invest N Drugs*. 2017;36(5):933–938.
25 Strevel EL, Chau NG, Pond GR, Murgo AJ, Ivy PS, Siu LL. Improving the quality of abstract reporting for phase I cancer trials. *Clin Cancer Res*. 2008;14(6):1782–1787.
26 Guo C, Chenard-Poirier M, Roda D, et al. Intermittent schedules of the oral RAF-MEK inhibitor CH5126766/VS-6766 in patients with RAS/RAF-mutant solid tumours and multiple myeloma: a single-centre, open-label, phase 1 dose-escalation and basket dose-expansion study. *Lancet Oncol*. 2020;21(11):1478–1488.
27 Julg B, Stephenson KE, Wagh K, et al. Safety and antiviral activity of triple combination broadly neutralizing monoclonal antibody therapy against HIV-1: a phase 1 clinical trial. *Nat Med*. 2022;28(6):1288–1296.
28 Bittlinger M, Bicer S, Peppercorn J, Kimmelman J. Ethical considerations for phase I trials in oncology. *J Clin Oncol*. 2022;40(30):3474–3488.
29 Schnarr A, Mertz M. States of uncertainty, risk-benefit assessment and early clinical research: a Conceptual investigation. *Sci Eng Ethics*. 2022;28(6):68.
30 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). https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf; 2019. Accessed June 21, 2024.

31 Pratt AG, Siebert S, Cole M, et al. Targeting synovial fibroblast proliferation in rheumatoid arthritis (TRAFIC): an open-label, dose-finding, phase 1b trial. *Lancet Rheumatol*. 2021;3(5):e337–e346.
32 Yap TA, LoRusso PM, Wong DJ, et al. A phase 1 first-in-human study of FS118, a tetravalent bispecific antibody targeting LAG-3 and PD-L1 in patients with advanced cancer and PD-L1 resistance. *Clin Cancer Res*. 2023;29(5):888–898.
33 European Medicines Agency. Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation_en.pdf; 2018. Accessed June 21, 2024.
34 Viceconti M, Pappalardo F, Rodriguez B, Horner M, Bischoff J, Musuamba Tshinanu F. In silico trials: verification, validation and uncertainty quantification of predictive models used in the regulatory evaluation of biomedical products. *Methods*. 2021;185:120–127.
35 Garon EB, Rizvi NA, Hui RN, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *New Engl J Med*. 2015;372(21):2018–2028.
36 Yap TA, Fontana E, Lee E, et al. Camonsertib in DNA damage response-deficient advanced solid tumors: phase 1 trial results. *Nat Med*. 2023;29(6):1400–+.
37 Goulart BHL, Clark JW, Pien HH, Roberts TG, Finkelstein SN, Chabner BA. Trends in the use and role of biomarkers in phase I oncology trials. *Clin Cancer Res*. 2007;13(22):6719–6726.
38 Yee LM, Lively TG, McShane LM. Biomarkers in early-phase trials: fundamental issues. *Bioanalysis*. 2018;10(12):933–944.
39 UCSF Helen Diller Family Comprehensive Cancer Center. Phase I protocol template. https://cancer.ucsf.edu/sites/cancer.ucsf.edu/files/itr/sm_files/HDFCCC_Phase1_Protocol_Template_current.docx; 2019. Accessed June 21, 2024.
40 Rugo HS, Herbst RS, Liu G, et al. Phase I trial of the oral antiangiogenesis agent AG-013736 in patients with advanced solid tumors: pharmacokinetic and clinical results. *J Clin Oncol*. 2005;23(24):5474–5483.
41 Boof M-L, Géhin M, Voors-Pette C, et al. Pharmacokinetics, pharmacodynamics and safety of the novel C-X-C chemokine receptor 3 antagonist ACT-777991: results from the first-in-human study in healthy adults. *Br J Clin Pharmacol*. 2024;90(2):588–599.
42 Kankam Martin K, Burns Jennifer M, Collett Marc S, Corrado Michael L, Hincks Jeffrey R. A phase 1 study of the safety, tolerability, and pharmacokinetics of single and multiple oral doses of V-7404 in healthy adult volunteers. *Antimicrob Agents Chemother*. 2021;65(10). https://doi.org/10.1128/aac.01029-21.
43 Dahlberg SE, Gray RJ. Pragmatic approaches to address expansion cohort design. *Cancer*. 2018;124(16):3290–3292.
44 Homer V, Yap C, Bond S, et al. Early phase clinical trials extension to guidelines for the content of statistical analysis plans. *BMJ*. 2022;376:e068177.
45 Petroni GR, Wages NA, Paux G, Dubois F. Implementation of adaptive methods in early-phase clinical trials. *Stat Med*. 2017;36(2):215–224.
46 Iyer SP, Beck JT, Stewart AK, et al. A Phase IB multicentre dose-determination study of BHQ880 in combination with anti-myeloma therapy and zoledronic acid in patients with relapsed or refractory multiple myeloma and prior skeletal-related events. *Br J Haematol*. 2014;167(3):366–375.
47 Staton TL, Peng K, Owen R, et al. A phase I, randomized, observer-blinded, single and multiple ascending-dose study to investigate the safety, pharmacokinetics, and immunogenicity of BITS7201A, a bispecific antibody targeting IL-13 and IL-17, in healthy volunteers. *BMC Pulm Med*. 2019;19(1):5.
48 Italiano A, Miller WH, Blay J-Y, et al. Phase I study of daily and weekly regimens of the orally administered MDM2 antagonist idasanutlin in patients with advanced tumors. *Invest N Drugs*. 2021;39(6):1587–1597.
49 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.
50 Saxena A, Rubens M, Ramamoorthy V, et al. A brief overview of adaptive designs for phase I cancer trials. *Cancers*. 2022;14(6):1566.
51 The Association of the British Pharmaceutical Industry. Guidelines for Phase I clinical trials. https://www.abpi.org.uk/media/tnnpj2lb/guidelines-for-phase-i-clinical-trials-2018-edition-20180626.pdf; 2018. Accessed June 21, 2024.
52 Zhang P, Xu B, Gui L, et al. A phase 1 study of dalpiciclib, a cyclin-dependent kinase 4/6 inhibitor in Chinese patients with advanced breast cancer. *Biomark Res*. 2021;9(1):24.
53 Lee SK, Xing J, Catlett IM, et al. Safety, pharmacokinetics, and pharmacodynamics of BMS-986142, a novel reversible BTK inhibitor, in healthy participants. *Eur J Clin Pharmacol*. 2017;73(6):689–698.
54 Hutchings M, Mous R, Clausen MR, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. *Lancet*. 2021;398(10306):1157–1169.
55 Shen J, Swift B, Mamelok R, Pine S, Sinclair J, Attar M. Design and conduct considerations for first-in-human trials. *Clin Transl Sci*. 2019;12(1):6–19.
56 US Food and Drug Administration. Expansion cohorts: use in first-in-human clinical trials to expedite development of oncology drugs and biologics guidance for industry. https://www.fda.gov/media/115172/download; 2022. Accessed June 21, 2024.
57 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.
58 Copland M, Slade D, McIlroy G, et al. Ponatinib with fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor chemotherapy for patients with blast-phase chronic myeloid leukaemia (MATCHPOINT): a single-arm, multicentre, phase 1/2 trial. *Lancet Haematol*. 2022;9(2):e121–e132.
59 Mossé YP, Lipsitz E, Fox E, et al. Pediatric phase I trial and pharmacokinetic study of MLN8237, an investigational oral selective small-molecule inhibitor of Aurora kinase A: a Children's Oncology Group Phase I Consortium study. *Clin Cancer Res*. 2012;18(21):6058–6064.
60 Muler JH, McGinn CJ, Normolle D, et al. Phase I trial using a time-to-event continual reassessment strategy for dose escalation of cisplatin combined with gemcitabine and radiation therapy in pancreatic cancer. *J Clin Oncol*. 2004;22(2):238–243.
61 Skolnik JM, Barrett JS, Jayaraman B, Patel D, Adamson PC. Shortening the timeline of pediatric phase I trials: the rolling six design. *J Clin Oncol*. 2008;26(2):190–195.
62 Wheeler GM, Mander AP, Bedding A, et al. How to design a dose-finding study using the continual reassessment method. *BMC Med Res Methodol*. 2019;19(1):18.
63 Yuan Y, Lee JJ, Hilsenbeck SG. Model-assisted designs for early-phase clinical trials: simplicity meets superiority. *JCO Precis Oncol*. 2019;3. PO.19.00032.
64 Frankel PH, Groshen S, Beumer JH, Cleveland L, Kim ES, Karp JE. Ethics and clinical research: improving transparency and informed consent in phase I oncology trials. *J Clin Oncol*. 2023;41(12):2155–2158.
65 Yin Z, Mander AP, de Bono JS, Zheng H, Yap C. Handling incomplete or late-onset toxicities in early-phase dose-finding clinical trials: current practice and future prospects. *JCO Precis Oncol*. 2024;(8):e2300441.
66 Sjöberg F, Waters S, Löfberg B, Sonesson C, Waters N, Tedroff J. A first-in-human oral dose study of mesdopetam (IRL790) to assess its safety, tolerability, and pharmacokinetics in healthy male volunteers. *Pharm Res Perspect*. 2021;9(3):e00792.
67 Recourt K, van der Aart J, Jacobs G, et al. Characterisation of the pharmacodynamic effects of the P2X7 receptor antagonist JNJ-54175446 using an oral dexamphetamine challenge model in healthy males in a randomised, double-blind, placebo-controlled, multiple ascending dose trial. *J Psychopharmacol*. 2020;34(9):1030–1042.
68 Suh HY, Peck CC, Yu K-S, Lee H. Determination of the starting dose in the first-in-human clinical trials with monoclonal antibodies: a systematic review of papers published between 1990 and 2013. *Drug Des Devel Ther*. 2016;10:4005–4016.
69 European Medicines Agency. Note for guidance on dose response information to support drug registration (ICH E4). https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-4-dose-response-information-support-drug-registration-step-5_en.pdf; 1994. Accessed June 21, 2024.
70 Tibbitts J, Cavagnaro JA, Haller CA, Marafino B, Andrews PA, Sullivan JT. Practical approaches to dose selection for first-in-human clinical trials with novel biopharmaceuticals. *Regul Toxicol Pharmacol*. 2010;58(2):243–251.
71 US Food and Drug Administration. Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers guidance for industry. https://www.fda.gov/media/72309/download; 2005. Accessed June 21, 2024.
72 Ali S, Kjeken R, Niederlaender C, et al. The European medicines agency review of kymriah (tisagenlecleucel) for the treatment of

acute lymphoblastic leukemia and diffuse large B-cell lymphoma. *Oncol*. 2020;25(2):e321–e327.
73 Exley AR, Rantell K, McBlane J. Clinical development of cell therapies for cancer: the regulators' perspective. *Eur J Cancer*. 2020;138:41–53.
74 Harrington JA, Wheeler GM, Sweeting MJ, Mander AP, Jodrell DI. Adaptive designs for dual-agent phase I dose-escalation studies. *Nat Rev Clin Oncol*. 2013;10(5):277–288.
75 Riviere MK, Le Tourneau C, Paoletti X, Dubois F, Zohar S. Designs of drug-combination phase I trials in oncology: a systematic review of the literature. *Ann Oncol*. 2015;26(4):669–674.
76 Gadgeel SM, Gandhi L, Riely GJ, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. *Lancet Oncol*. 2014;15(10):1119–1128.
77 Yang H, Merica E, Chen Y, et al. Phase 1 single- and multiple-ascending-dose randomized studies of the safety, pharmacokinetics, and pharmacodynamics of AG-348, a first-in-class allosteric activator of pyruvate kinase R, in healthy volunteers. *Clin Pharmacol Drug Dev*. 2019;8(2):246–259.
78 Han K, Cremer J, Elston R, et al. A randomized, double-blind, placebo-controlled, first-time-in-human study to assess the safety, tolerability, and pharmacokinetics of single and multiple ascending doses of GSK3389404 in healthy subjects. *Clin Pharmacol Drug Dev*. 2019;8(6):790–801.
79 Wong KM, Capasso A, Eckhardt SG. The changing landscape of phase I trials in oncology. *Nat Rev Clin Oncol*. 2016;13(2):106–117.
80 Bird SM, Bailey RA, Grieve AP, Senn S. Statistical issues in first-in-human studies on BIA 10-2474: neglected comparison of protocol against practice. *Pharm Stat*. 2017;16(2):100–106.
81 Cancer Therapy Evaluation Program. Generic protocol template. https://ctep.cancer.gov/protocoldevelopment/docs/CTEP_Generic_Protocol_Template_for_Cancer_Treatment_Trial.docx; 2022. Accessed June 21, 2024.
82 Kong A, Good J, Kirkham A, et al. Phase I trial of WEE1 inhibition with chemotherapy and radiotherapy as adjuvant treatment, and a window of opportunity trial with cisplatin in patients with head and neck cancer: the WISTERIA trial protocol. *BMJ Open*. 2020;10(3):e033009.
83 Kong A, Kirkham AJ, Savage JS, et al. Results and lessons learnt from the WISTERIA phase I trial combining AZD1775 with cisplatin pre- or post-operatively in head and neck cancer. *BJC Reports*. 2024;2(1):6.
84 Cole M, Yap C, Buckley C, et al. TRAFIC: statistical design and analysis plan for a pragmatic early phase 1/2 Bayesian adaptive dose escalation trial in rheumatoid arthritis. *Trials*. 2021;22(1):433.
85 Wrangle JM, Velcheti V, Patel MR, et al. ALT-803, an IL-15 superagonist, in combination with nivolumab in patients with metastatic non-small cell lung cancer: a non-randomised, open-label, phase 1b trial. *Lancet Oncol*. 2018;19(5):694–704.
86 Koyama T, Shimizu T, Iwasa S, et al. First-in-human phase I study of E7090, a novel selective fibroblast growth factor receptor inhibitor, in patients with advanced solid tumors. *Cancer Sci*. 2020;111(2):571–579.
87 Oldfield EH, Loomba JJ, Monteith SJ, et al. Safety and pharmacokinetics of sodium nitrite in patients with subarachnoid hemorrhage: a phase IIa study. *J Neurosurg*. 2013;119(3):634–641.
88 Buöen C, Holm S, Thomsen MS. Evaluation of the cohort size in phase I dose escalation trials based on laboratory data. *J Clin Pharmacol*. 2003;43(5):470–476.
89 Yap C, Billingham LJ, Cheung YK, Craddock C, O'Quigley J. Dose transition pathways: the missing link between complex dose-finding designs and simple decision-making. *Clin Cancer Res*. 2017;23(24):7440–7447.
90 Smit MJ, Sander AF, Ariaans MBPA, et al. First-in-human use of a modular capsid virus-like vaccine platform: an open-label, non-randomised, phase 1 clinical trial of the SARS-CoV-2 vaccine ABNCoV2. *Lancet Microbe*. 2023;4(3):e140–e148.
91 Aliprantis AO, Shaw CA, Griffin P, et al. A phase 1, randomized, placebo-controlled study to evaluate the safety and immunogenicity of an mRNA-based RSV prefusion F protein vaccine in healthy younger and older adults. *Hum Vaccin Immunother*. 2021;17(5):1248–1261.
92 Dumez H, Awada A, Piccart M, et al. A phase I dose-finding clinical pharmacokinetic study of an oral formulation of irinotecan (CPT-11) administered for 5 days every 3 weeks in patients with advanced solid tumours. *Ann Oncol*. 2006;17(7):1158–1165.
93 Hong DS, Van Tine BA, Biswas S, et al. Autologous T cell therapy for MAGE-A4+ solid cancers in HLA-A*02+ patients: a phase 1 trial. *Nat Med*. 2023;29(1):104–114.
94 Infante JR, Fecher LA, Falchook GS, et al. Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: a phase 1 dose-escalation trial. *Lancet Oncol*. 2012;13(8):773–781.
95 Iasonos A, O'Quigley J. Sequential monitoring of Phase I dose expansion cohorts. *Stat Med*. 2017;36(2):204–214.
96 Dehbi H-M, O'Quigley J, Iasonos A. Controlled backfill in oncology dose-finding trials. *Contemp Clin Trials*. 2021;111:106605.
97 Iasonos A, O'Quigley J. Dose expansion cohorts in Phase I trials. *Stat Biopharm Res*. 2016;8(2):161–170.
98 Nogova L, Sequist LV, Perez Garcia JM, et al. Evaluation of BGJ398, a fibroblast growth factor receptor 1-3 kinase inhibitor, in patients with advanced solid tumors harboring genetic alterations in fibroblast growth factor receptors: results of a global phase I, dose-escalation and dose-expansion study. *J Clin Oncol*. 2017;35(2):157–165.
99 Turley CB, Rupp RE, Johnson C, et al. Safety and immunogenicity of a recombinant M2e–flagellin influenza vaccine (STF2.4xM2e) in healthy adults. *Vaccine*. 2011;29(32):5145–5152.
100 Rutherford SC, Abramson JS, Bartlett NL, et al. Venetoclax with dose-adjusted EPOCH-R as initial therapy for patients with aggressive B-cell lymphoma: a single-arm, multicentre, phase 1 study. *Lancet Haematol*. 2021;8(11):e818–e827.
101 Kimmelman J. A theoretical framework for early human studies: uncertainty, intervention ensembles, and boundaries. *Trials*. 2012;13(1):173.
102 Orkin AM, Gill PJ, Ghersi D, et al. Guidelines for reporting trial protocols and completed trials modified due to the COVID-19 pandemic and other extenuating circumstances: the CONSERVE 2021 statement. *JAMA*. 2021;326(3):257–265.
103 Pallmann P, Bedding AW, Choodari-Oskooei B, et al. Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med*. 2018;16(1):29.
104 Faivre S, Delbaldo C, Vera K, et al. Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol*. 2006;24(1):25–35.
105 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):321–335.
106 Banfield C, Rudin D, Bhattacharya I, et al. First-in-human, randomized dose-escalation study of the safety, tolerability, pharmacokinetics, pharmacodynamics and immunogenicity of PF-06480605 in healthy subjects. *Br J Clin Pharmacol*. 2020;86(4):812–824.
107 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.
108 Kato T, Kudo T, Kagawa Y, et al. Phase II dose titration study of regorafenib in progressive unresectable metastatic colorectal cancer. *Sci Rep*. 2023;13(1):2331.
109 Breithaupt-Groegler K, Coch C, Coenen M, et al. Who is a 'healthy subject'?-consensus results on pivotal eligibility criteria for clinical trials. *Eur J Clin Pharmacol*. 2017;73(4):409–416.
110 Butcher NJ, Monsour A, Mew EJ, et al. Guidelines for reporting outcomes in trial reports. *JAMA*. 2022;328(22):2252.
111 Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *Br Med J*. 2013;346:e7586.
112 Cheung YK, Chappell R. Sequential designs for phase I clinical trials with late-onset toxicities. *Biometrics*. 2000;56(4):1177–1182.
113 Zhou Y, Lee JJ, Yuan Y. A utility-based Bayesian optimal interval (U-BOIN) phase I/II design to identify the optimal biological dose for targeted and immune therapies. *Stat Med*. 2019;38(28):5299–5316.
114 Bhattacharya I, Pawlak S, Marraffino S, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of domagrozumab (PF-06252616), an antimyostatin monoclonal antibody, in healthy subjects. *Clin Pharmacol Drug Dev*. 2018;7(5):484–497.
115 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. *J Clin Oncol*. 2019;37(7):580–588.

116 Wages NA, Horton BJ, Conaway MR, Petroni GR. Operating characteristics are needed to properly evaluate the scientific validity of phase I protocols. *Contemp Clin Trials*. 2021;108:106517.
117 Brennan RC, Furman W, Mao S, et al. Phase I dose escalation and pharmacokinetic study of oral gefitinib and irinotecan in children with refractory solid tumors. *Cancer Chemother Pharmacol*. 2014;74(6):1191–1198.
118 Green FH, Leigh R, Fadayomi M, et al. A phase I, placebo-controlled, randomized, double-blind, single ascending dose-ranging study to evaluate the safety and tolerability of a novel biophysical bronchodilator (S-1226) administered by nebulization in healthy volunteers. *Trials*. 2016;17:361.
119 Slingluff JCL, Petroni GR, Chianese-Bullock KA, et al. Trial to evaluate the immunogenicity and safety of a melanoma helper peptide vaccine plus incomplete Freund's adjuvant, cyclophosphamide, and polyICLC (Mel63). *J Immunother Cancer*. 2021;9(1):e000934.
120 Muenzer J, Hendriksz CJ, Fan Z, et al. A phase I/II study of intrathecal idursulfase-IT in children with severe mucopolysaccharidosis II. *Genet Med*. 2016;18(1):73–81.
121 Patel SP, Petroni GR, Roszik J, et al. Phase I/II trial of a long peptide vaccine (LPV7) plus toll-like receptor (TLR) agonists with or without incomplete Freund's adjuvant (IFA) for resected high-risk melanoma. *J Immunother Cancer*. 2021;9(8).
122 Glue P, Lockhart M, Lam F, Hung N, Hung C-T, Friedhoff L. Ascending-dose study of noribogaine in healthy volunteers: pharmacokinetics, pharmacodynamics, safety, and tolerability. *J Clin Pharmacol*. 2015;55(2):189–194.
123 Wu J, Yuan Y, Long Priel DA, et al. Phase I study of zotiraciclib in combination with temozolomide for patients with recurrent high-grade astrocytomas. *Clin Cancer Res*. 2021;27(12):3298–3306.
124 Grayling MJ, Mander AP. Two-stage single-arm trials are rarely analyzed effectively or reported adequately. *JCO Precis Oncol*. 2021;5. PO.21.00276.
125 Von Hoff DD, Rasco DW, Heath EI, et al. Phase I study of CC-486 alone and in combination with carboplatin or nab-paclitaxel in patients with relapsed or refractory solid tumors. *Clin Cancer Res*. 2018;24(17):4072–4080.
126 Furie R, Werth VP, Merola JF, et al. Monoclonal antibody targeting BDCA2 ameliorates skin lesions in systemic lupus erythematosus. *J Clin Invest*. 2019;129(3):1359–1371.
127 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 Neural Repair*. 2021;35(8):663–679.
128 Lee C-k, Rha SY, Kim HS, et al. A single arm phase Ib/II trial of first-line pembrolizumab, trastuzumab and chemotherapy for advanced HER2-positive gastric cancer. *Nat Commun*. 2022;13(1):6002.
129 Francis JN, Bunce CJ, Horlock C, et al. A novel peptide-based pan-influenza A vaccine: a double blind, randomised clinical trial of immunogenicity and safety. *Vaccine*. 2015;33(2):396–402.
130 Alger E, Zhang Y, Yap C. 80MO Optimising participant flow diagrams for phase I clinical trials. *ESMO Open*. 2023;8(1):100938.
131 Hopewell S, Hirst A, Collins GS, Mallett S, Yu L-M, Altman DG. Reporting of participant flow diagrams in published reports of randomized trials. *Trials*. 2011;12:253.
132 Li J, Tian Y, Zheng M, et al. Anlotinib plus chemotherapy for T790M-negative EGFR-mutant non-sqNSCLC resistant to TKIs: a multicenter phase 1b/2 trial. *Thorac Cancer*. 2022;13(24):3496–3503.
133 de Lima Lopes G Jr, Dicksey JS, Peters WP, Palalay M, Chang AY. Final results of a prematurely discontinued Phase 1/2 study of eniluracil with escalating doses of 5-fluorouracil administered orally in patients with advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol*. 2011;68(4):1067–1073.
134 Bonomo P, Desideri I, Mangoni M, et al. Durvalumab with cetuximab and radiotherapy for locally advanced squamous cell carcinoma of the head and neck: a phase 1/2 trial. *Radiother Oncol*. 2022;169:64–70.
135 Camille N, Rozehnal J, Roy E, et al. A phase I study of cabazitaxel in combination with platinum and 5-fluorouracil (PF) in locally advanced squamous cell carcinoma of head and neck (LA-SCCHN). *Oral Oncol*. 2017;71:99–104.
136 Hellmann MD, Kim TW, Lee CB, et al. Phase Ib study of atezolizumab combined with cobimetinib in patients with solid tumors. *Ann Oncol*. 2019;30(7):1134–1142.
137 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.
138 Herold KC, Bucktrout SL, Wang X, et al. Immunomodulatory activity of humanized anti-IL-7R monoclonal antibody RN168 in subjects with type 1 diabetes. *JCI Insight*. 2019;4(24).
139 Desai SP, Ben-Josef E, Normolle DP, et al. Phase I study of oxaliplatin, full-dose gemcitabine, and concurrent radiation therapy in pancreatic cancer. *J Clin Oncol*. 2007;25(29):4587–4592.
140 Pearson AD, Federico SM, Aerts I, et al. A phase 1 study of oral ridaforolimus in pediatric patients with advanced solid tumors. *Oncotarget*. 2016;7(51):84736–84747.
141 Rovner E, Chai TC, Jacobs S, et al. Evaluating the safety and potential activity of URO-902 (hMaxi-K) gene transfer by intravesical instillation or direct injection into the bladder wall in female participants with idiopathic (non-neurogenic) overactive bladder syndrome and detrusor overactivity from two double-blind, imbalanced, placebo-controlled randomized phase 1 trials. *Neurourol Urodyn*. 2020;39(2):744–753.
142 Biran N, Rowley SD, Vesole DH, et al. A phase I/II study of escalating doses of bortezomib in conjunction with high-dose melphalan as a conditioning regimen for salvage autologous peripheral blood stem cell transplantation in patients with multiple myeloma. *Biol Blood Marrow Transplant*. 2016;22(12):2165–2171.
143 Lee V, Wang J, Zahurak M, et al. A phase I trial of a guadecitabine (SGI-110) and irinotecan in metastatic colorectal cancer patients previously exposed to irinotecan. *Clin Cancer Res*. 2018;24(24):6160–6167.
144 McBride JM, Jiang J, Abbas AR, et al. Safety and pharmacodynamics of rontalizumab in patients with systemic lupus erythematosus: results of a phase I, placebo-controlled, double-blind, dose-escalation study. *Arthritis Rheum*. 2012;64(11):3666–3676.
145 European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf; 2017. Accessed June 21, 2024.
146 Basch E, Yap C. Patient-reported outcomes for tolerability assessment in phase I cancer clinical trials. *J Natl Cancer Inst*. 2021;113(8):943–944.
147 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.
148 Amorim S, Stathis A, Gleeson M, et al. Bromodomain inhibitor OTX015 in patients with lymphoma or multiple myeloma: a dose-escalation, open-label, pharmacokinetic, phase 1 study. *Lancet Haematol*. 2016;3(4):e196–e204.
149 Tocoian A, Buchan P, Kirby H, et al. First-in-human trial of the safety, pharmacokinetics and immunogenicity of a PEGylated anti-CD40L antibody fragment (CDP7657) in healthy individuals and patients with systemic lupus erythematosus. *Lupus*. 2015;24(10):1045–1056.
150 Medicines and Healthcare products Regulatory Agency. Phase I accreditation scheme guidance. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1102630/2._MHRA_Phase_I_Accreditation_Scheme_Guidance_v4.1_12_August_2022.pdf; 2022. Accessed June 21, 2024.
151 European Medicines Agency. Questions and answers on data monitoring committees issues2018. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-questions-and-answers-data-monitoring-committees-issues_en.pdf. Accessed June 3, 2024.
152 GlaxoSmithKline A. Dose-escalation study in subjects with pulmonary arterial hypertension (PAH)[protocol]. https://cdn.clinicaltrials.gov/large-docs/03/NCT03177603/Prot_000.pdf; 2018. Accessed June 10, 2024.
153 Anderson EJ, Rouphael NG, Widge AT, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. *N Engl J Med*. 2020;383(25):2427–2438.
154 DiNardo CD, Stein AS, Stein EM, et al. Mutant isocitrate dehydrogenase 1 inhibitor ivosidenib in combination with azacitidine for newly diagnosed acute myeloid leukemia. *J Clin Oncol*. 2020;39(1):57–65.
155 Getz KA, Campo RA. Trial watch: trends in clinical trial design complexity. *Nat Rev Drug Discov*. 2017;16(5):307.
156 Oncology Center of Excellence. Project optimus: reforming the dose optimization and dose selection paradigm in oncology.

https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus; 2024. Accessed June 10, 2024.
157 Smietana K, Siatkowski M, Møller M. Trends in clinical success rates. *Nat Rev Drug Discov*. 2016;15(6):379–380.
158 Yap C, Bedding A, de Bono J, et al. The need for reporting guidelines for early phase dose-finding trials: dose-finding CONSORT Extension. *Nat Med*. 2022;28(1):6–7.
159 Ratitch B, Bell J, Mallinckrodt C, et al. Choosing estimands in clinical trials: putting the ICH E9(R1) into practice. *Ther Innov Regul Sci*. 2020;54(2):324–341.
160 Ratitch B, Goel N, Mallinckrodt C, et al. Defining efficacy estimands in clinical trials: examples illustrating ICH E9(R1) guidelines. *Ther Innov Regul Sci*. 2020;54(2):370–384.
161 Englert S, Mercier F, Pilling EA, et al. Defining estimands for efficacy assessment in single arm phase 1b or phase 2 clinical trials in oncology early development. *Pharm Stat*. 2023;22(5):921–937.
162 Mercier F, Homer V, Geng J, et al. Estimands in oncology early clinical development: assessing the impact of intercurrent events on the dose-toxicity relationship. *Stat Biopharm Res*. 2024:1–9.