Enhancing Reporting Quality and Impact of Early Phase Dose-Finding Clinical Trials: The CONSORT Dose-Finding Extension (CONSORT-DEFINE) Guidance

The CONSORT-DEFINE Statement

CONSORT-DEFINE is a new reporting guideline that provides recommendations for essential items that should be reported in early phase dose-finding trials, by detailing extensions to existing CONSORT guidance with 21 new items and 19 modified items, to promote greater clarity, reproducibility, informativeness, and utility of results.

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Key messages

- Early phase dose-finding clinical trials are essential for clinical development as they lay the groundwork for further development and guide subsequent trials.
- The CONsolidated Standards Of Reporting Trials (CONSORT) 2010 statement focused on randomised trials and the new CONSORT-DEFINE guideline has been extended to broaden its applicability to early phase dose-finding trials with interim dose escalation/de-escalation strategies.
- Following an international consensus-driven guideline development process using the Enhancing QUAlity and Transparency Of health Research (EQUATOR) methodological framework, 40 early phase dose-finding-specific items were recommended for inclusion in clinical trial reports.
- Inclusion of these CONSORT-DEFINE items in clinical trial reports may enhance transparency, completeness, reproducibility of methods, and utility of results in early phase dose-finding trials.

Abstract

The CONsolidated Standards Of Reporting Trials (CONSORT) 2010 statement is the standard guideline for reporting completed randomised trials. CONSORT-DEFINE extends the guidance to early phase dose-finding trials with interim dose escalation/de-escalation strategies. These trials generally focus on safety, tolerability, activity, and recommending dosing and scheduling regimen(s) for further clinical development. Dose-finding trials are often inadequately reported, hampering their informativeness and making evidence-informed decisions difficult. The CONSORT-DEFINE guidance aims to develop an international, consensus-driven guideline for reporting early phase dose-finding trials to promote transparency, completeness, reproducibility, and facilitate the interpretation of the results.

Using the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) methodological framework for guideline development, CONSORT-DEFINE was developed through (1) a methodological review of published dose-finding trials to identify features and deficiencies in reporting and inform the initial generation of the candidate items; (2) further generation of candidate items through review of published and unpublished literature (e.g., regulatory and industry advice documents), analysis of examples from articles, citation and reference searches, and consultation with international experts; (3) a 2-round modified Delphi process (March–June 2022) involving 206 participants from 24 countries; (4) an international virtual consensus meeting (October 2022) attended by 34 participants from 7 countries; and (5) pilot-testing of the draft checklist (6 times).

Forty-four candidate items were included in the Delphi survey. The discussion during and after the consensus meeting yielded 40 CONSORT-DEFINE main checklist items: 21 new and 19 modified. New items focused on specific dose-finding issues such as range of planned dose levels, including starting dose(s) with rationale; dose escalation/de-escalation strategies and decision-making criteria; and reporting key outcomes by each dose. Five items were modified for the CONSORT-DEFINE abstract checklist. The final wording of the CONSORT-DEFINE checklists and explanations involved feedback from pilot-testing of the checklist and was agreed on by the DEFINE Executive Committee and consensus participants.

The CONSORT-DEFINE guidance provides recommendations for essential items that should be reported in early phase dose-finding trials to promote greater clarity, reproducibility, informativeness, and utility of results.

1. Introduction

Early phase dose-finding (EPDF) or dose (de-)escalation trials, commonly known as phase I or phase I/II, are an integral part of clinical development. EPDF trials typically evaluate new interventions that can be given in different doses and can be pharmacological (chemical or biological, e.g., drugs, vaccines, cell therapies, gene therapies), non-pharmacological (e.g., radiotherapy, rehabilitation, devices, digital therapies), or a combination thereof. These trials require the making of interim decisions on dosing changes of an intervention and generate data on safety and other information such as pharmacokinetics, pharmacodynamics, biomarker, or clinical activity to guide dosing selection and future clinical development (1, 2, 3, 4). In this article, a broad definition of dose is applied since terms like dose-finding, dose (de-)escalation/expansion, and dose level are widely used, referring not only to amount but also frequency, intensity, or duration of an intervention (5). Dose may therefore be regarded as synonymous and used interchangeably with dosage or dosing regimen, or as a unit dose, and applies to interventions given alone or in combination (see the Glossary [Box] for details).

Incomplete or unclear information on design, conduct, and analysis when reporting results of EPDF trials may hamper the assessment of their reliability and conclusions about safety and efficacy (6, 7), and undermine public confidence in research. Accurate evaluation of EPDF trial findings is crucial to prevent inadequate dose selection, which frequently results in subsequent failures in phase II and phase III trials, regulatory submission delays, additional post-marketing commitments, or dose changes after approval due to excessive toxicities or lack of efficacy (4, 8).

The use of more efficient but more complex dose (de-)escalation designs, such as model-assisted or model-based designs (9, 10), has risen from 1.6% (20/1235) in 1991–2006 (11) to 8.6% (68/788) of trials published in 2014–2019 (9). Recent findings based on a small sample of trials published in May-August 2022 showed a marked increase in the use of such designs, reaching 25.7% (9/35) (12). These designs require the specification of more study design features (3, 13, 14). To make informed judgments about potential biases and the reliability of EPDF study findings, more clarity is needed to help readers comprehend the design, understand how dose decisions were made, and ensure procedures and findings can be reproduced (7, 15).

Neither CONsolidated Standards Of Reporting Trials (CONSORT) 2010 (16, 17) nor its extensions to date fully cover the features of EPDF trials (7). The need for a CONSORT extension for EPDF trials was largely driven by the fact that such trials (1, 18, 19) have frequent reviews or analyses of interim data to make dosing decisions and other trial adaptations, may not be randomised (e.g., 99.2% of oncology trials and 25.1% of non-oncology trials are non-randomised (20)), and have requirements and statistical considerations that differ from later phase randomised trials (CONSORT 2010 (16), Adaptive designs CONSORT Extension (ACE) (18), and related extensions). Moreover, globally, there were more phase I trials (n = 18,716) than phase III trials (n = 10,451) registered on ClinicalTrials.gov, based on the number of trials first posted between 2018-2022. The number of phase I trials is most likely an underestimate, as it is not mandatory to register or report these trials on ClinicalTrials.gov (21).

Conference and journal abstracts of EPDF trials communicate important clinical development of a new intervention; since many EPDF trials remain unpublished (22), it is even more vital that they are well-reported to increase their informativeness, as critical decisions may often be based on them (23).

A methodological review to assess the reporting quality of 476 EPDF trial results publications from 2011 to 2020 (20) uncovered clear evidence of insufficient and inconsistent reporting of many aspects, including applicable CONSORT 2010 items. For instance, the rationale for starting dose and the specification of planned/maximum sample size were reported in less than 25% and 40% of EPDF trials, respectively. Furthermore, reporting quality has generally not improved over time (20).

The prevalence of EPDF trials, their direct influence on late-stage clinical development, and the urgent need to improve their reporting quality further highlight the importance of a tailored reporting guidance. The CONSORT-DEFINE study aimed to enhance the transparency, completeness, reproducibility, and interpretation of EPDF trial results by developing and disseminating an extension to the CONSORT 2010 statement that is specific to EPDF trials, investigating interventions across all disease areas (2, 7).

2. Methods

The CONSORT-DEFINE extension was developed following the EQUATOR methodological framework for guideline development (24); the DEFINE protocol (2) details how the project was developed. This project was approved for sponsorship by The Institute of Cancer Research's Committee for Clinical Research (CCR5460). The United Kingdom Health Research Authority confirmed that Research Ethics Approval was not required. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)-DEFINE (protocol guidance for EPDF trials) (25) was developed in parallel with CONSORT-DEFINE.

Informed consent was obtained from both the Delphi survey and consensus meeting participants.

2.1. Generation of candidate reporting items

A methodological review of published EPDF trials identified features and deficiencies in reporting to inform the initial generation of the candidate items for CONSORT-DEFINE (7, 20), based broadly on existing reporting guidelines or recommendations such as CONSORT 2010 (16, 17), SPIRIT 2013 (26), ACE (18), a checklist proposal for phase I dose-finding cancer trials (27), as well as consultation with experts. Further candidate items were generated through the analysis of peer-reviewed literature, unpublished sources (e.g., regulatory and industry advice documents), citation tracking, and expert opinion (28).

2.2. International Delphi process

Through a Delphi survey (Figure 1), the draft candidate items for the CONSORT-DEFINE checklist were presented for input and feedback from a large stakeholder group. The Delphi process was carried out following existing methodological guidance (29, 30, 31). Two hundred and six participants from 24 countries voted in round one (March-May 2022), and 151 participants voted in round two (May-June 2022) of the Delphi survey. Round two participants were shown the distribution of the item rating as well as their previous rating if they had completed round one (28).

Figure 1 The development process of the CONSORT-DEFINE checklist items.

According to the pre-specified decision criterion (2), items with at least 70% of respondents rating them as "critically important" were automatically included in the DEFINE checklist (Figure S1 in the **Web appendix 1**).

During the Delphi process, 34 of the 44 candidate items considered over two rounds of the Delphi survey met the criteria for inclusion in the checklist, leaving 10 items for consideration at the consensus meeting (Table S1 in the **Web appendix 1**). Further details, including the methods and results of the Delphi process and the qualitative and quantitative analyses, are reported within the DEFINE development process paper (28).

2.3. International consensus meeting

The online consensus meeting was held on October 11-12, 2022 and involved a total of 32 international delegates from the academic, commercial, and regulatory sectors, and two Patient and Public Involvement and Engagement (PPIE) partners (Table S2, Table S3 in the **Web appendix 1**). A series of slides was presented for each of the 10 candidate items: the Delphi voting results, alongside differences across stakeholder groups if they were present; supporting evidence of its importance; Delphi respondents' comments; and examples of the item reported in scientific publications.

After discussion of each candidate item, delegates voted anonymously on whether to keep the item. Out of ten candidate items, two were recommended for inclusion in the CONSORT-DEFINE checklist (meeting the threshold of 70% of votes), five were rejected (receiving less than 50% of votes), and three (with 50-70% votes) were left for further deliberation by the Executive Committee after the consensus meeting, of which two were recommended for inclusion in the checklist (Figure S1 in the **Web appendix 1**).

2.4. Final consultation and piloting of the checklist

Following the consensus meeting, participants and the DEFINE Executive Committee refined the wording of the checklist items and the corresponding explanatory text. The draft checklist was piloted six times using published and draft papers by international stakeholders (December 2022-February 2023) to evaluate its suitability and identify areas for improvement. The feedback gathered from the pilot testing further shaped the final version of the guideline, with the final wording agreed on by the DEFINE Executive Committee and consensus participants.

2.5. Patient and Public Involvement and Engagement.

The DEFINE Study PPIE lead (AK) has contributed to the design of the study and the development of the protocol since the early stages. We also sought out additional PPIE representatives from both the oncology and non-oncology fields to review the checklists to ensure that the view of patients and participants was adequately represented. In collaboration with these representatives, we developed a toolkit for lay reporting of early phase trial results (28), and we plan to produce lay publications to chart the development of both the SPIRIT-DEFINE and CONSORT-DEFINE guidelines.

3. Results

Figure 1 presents the development journey of the CONSORT-DEFINE checklist items, from the Delphi survey to the consensus meeting, to the refinement of the checklist after final consultation and pilot testing. The final CONSORT-DEFINE guidance recommends that, in conjunction with the existing CONSORT 2010 items, 40 EPDF-specific items (21 new and 19 modified) be included in EPDF trial reports. **Table 1** presents the final CONSORT-DEFINE checklist for the main report of EPDF trials. It comprises the CONSORT 2010 checklist items and the recommended new or modified CONSORT-DEFINE items. **Table 2** presents the CONSORT-DEFINE checklist for the abstract of EPDF trials.

The CONSORT-DEFINE checklist includes several EPDF-specific design items to provide a detailed elaboration of the trial design (e.g., dosing strategies and adaptive features, dose allocation method,

and expansion cohort(s)) to help readers understand dose adaptation strategies and other trial design adaptations. The specification of planned design adaptations and their scope are critical for preserving the integrity of adaptive designs and for regulatory assessments, as well as ensuring that the procedures and findings can be replicated (18). These factors have an impact on statistical methods for design and analysis; thus, CONSORT-DEFINE recommends providing comprehensive information on statistical methods that cover these adaptive features, as well as requiring clear definitions of analysis populations and plans for dealing with intercurrent events that occur after treatment initiation. Both analysis populations and intercurrent events are related to the estimands framework, which provides guidance on defining the treatment effect under investigation in a clinical trial (see the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 (R1) addendum on estimands for further details (32)). As the results of key endpoints at each dose level are important findings of EPDF trials to understand the relationship between the dose of an intervention and its effects on participants, and to inform dose selection for subsequent trials, the CONSORT-DEFINE checklist also includes the additional requirement of reporting results by dose level to facilitate reproducibility, interpretation, utility of results, and evidence synthesis.

Key new CONSORT-DEFINE items and modified items of CONSORT 2010 tailored to EDPF trials include:

Title [1 modified item]

- Identification of features of EPDF trial in the title or abstract.

Background [2 new and 2 modified items]

- Coverage of nonclinical/preclinical research informing an EPDF trial (15) and biomarkers sub-study (33).

Methods [14 new and 10 modified items]

- Elaboration of the “Trial Design” section to include dosing strategies and adaptive features (18, 34), range of planned dose levels, including starting dose(s) with rationale, dose allocation method (whether participants are dosed continuously or in a staggered way), and expansion cohort(s) where applicable with rationale (7, 15, 19, 35, 36);
- Enhanced intervention details (5), including pre-specified criteria for dose discontinuation, dose modifications, or dose delays (15);
- Inclusion of clinical and statistical assumptions supporting the planned sample size and operating characteristics (37, 38);
- Specification of planned interim decision-making criteria/rules and stopping guidelines to reflect the dosing decision process and other trial adaptations (18, 34); progression criteria to move from one part of the trial to another where applicable (e.g., dose escalation to phase II) (15, 36).
- Increased details regarding statistical methods to cover adaptive features, analysis population(s), and intercurrent events that occur after treatment initiation (18, 37).

Results [2 new and 6 modified items]

- Update of the “Results” section to include reporting by dose level(s) (27).

Data Monitoring [2 new items]

- The addition of a new “Data Monitoring” section to cover decision-making or safety review committees, descriptions of interim data reviews (18).

Dissemination [1 new item]

- The addition of a new “Dissemination” section to cover external reporting of ongoing trials.

Minor wording changes were made to cover both randomised and non-randomised participant assignment; the term “where applicable” has been added to CONSORT 2010 items that may not apply to all EPDF trials. The wording of three CONSORT-DEFINE checklist items was elaborated to be consistent with the relevant items from the SPIRIT 2013 checklist.

Access to information addressing recommended items is what matters most, so if it is not possible to provide all the recommended information in the primary paper, authors can indicate where details can be found; for instance, in an accessible protocol, a statistical analysis plan, or a separate/supplementary file. Authors should provide explanations for items where details cannot be provided.

As variations in the terminology and definitions exist across disciplines and geographical areas in EPDF trials, key terms used throughout are provided in the Glossary [Box]. Henceforth, we use “CONSORT” to refer to CONSORT 2010.

For items that remain unchanged, we refer the user to the CONSORT 2010 explanation and elaboration document (16). The detailed explanation and rationale for the 40 new or modified CONSORT-DEFINE checklist items for the main report, along with examples from oncology and non-oncology settings, will be presented in a further publication by the authors. Here we provide general comments and a brief overview of the items that may be less self-explanatory.

The DEFINE-CONSORT checklist recommends detailed elaboration of the trial design and statistical methods covering its adaptive features, including (de-)escalation strategies. Several CONSORT items (13a, 13b, 15, 16, and 17a) were modified to add the requirement to report results by dose level and/or at each interim analysis for each intervention group/arm or specifically defined subgroups of interest, e.g., healthy volunteers and patients or young and elderly subjects. Authors are encouraged to provide an explanation if the level of reporting may not be appropriate in certain settings, such as easily identifiable participants.

It is recommended that authors provide a detailed description of the applicable statistical methods used to set up and implement the adaptive design in EPDF trials (Item 3a.3*). For model-based designs (13), it is important to explain the model assumptions, parameters, and mathematical form of the model. For model-based and model-assisted dose-finding designs (13, 39), the rationale for choosing a target risk/toxicity rate or acceptable range (12), the dose transformation details (including the full skeleton and its elicitation), and Bayesian prior distributions should be provided, if applicable (37). For rule-based designs (such as 3+3, Rolling 6 (40), SAD/MAD (36)), the rationale for utilising them should be outlined. For other adaptations, such as early stopping for futility, the statistical methods (such as conditional power, predictive power, and posterior probability of treatment effect) used should be clearly described (18, 37).

Authors should explain how they will deal with missing data and intercurrent events (item 12d*), such as dosing delays, reductions, or interruptions, that occur after treatment initiation and could affect the interpretation or existence of measurements related to the clinical question (32, 37). These events may also include withdrawals of consent or unrelated deaths. Different strategies can

be used to handle different types of missing data and intercurrent events, and sensitivity analyses can be performed to assess the effect of the chosen strategies on trial results (37).

Glossary

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

Algorithm-based (rule-based) design: A trial design that uses a simple set of predefined algorithms or rules to guide the dose escalation or de-escalation decision-making process. Examples: traditional 3+3, accelerated titration, and pharmacologically guided dose escalation designs (9, 41).

Biomarker sub-study: A part of a clinical trial that investigates biomarker(s), "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions. Biomarkers may include molecular, histologic, radiographic, or physiologic characteristics. A biomarker is not a measure of how an individual feels, functions, or survives" (42).

Clinical benefit(s): A favourable effect on a meaningful aspect of how a participant feels, functions, or survives as a result of an intervention (43).

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

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

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

Dose-limiting criteria: Effects or markers that are presumably related to the intervention and are either considered unacceptable or show the desired level of effect has been achieved and further increase in dose is not required (44).

Dose-limiting toxicity (DLT): Side effects of an intervention that are serious enough to prevent an increase in the dose of that intervention (41).
Dosing Regimen / Dosage: See Dose.

Early phase dose-finding (EPDF) trial: An early phase trial where different doses/regimens of the investigated intervention are administered to groups of participants, with interim assessments of the safety/tolerability (and other markers such as activity) of the intervention.

Estimand framework: Estimands provide a structural framework to define the target of estimation for a particular clinical trial objective. They require to specify: (1) the treatment

condition of interest, (2) the population targeted by the clinical question, (3) the variable of interest or endpoint used to address that question, (4) handling strategies for intercurrent events (i.e., events that occur after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question), and (5) a population-level summary of the variable/endpoint.

Expansion cohort/Dose expansion: A part of a dose-escalation clinical trial that aims to accrue additional participants after an initial dose-escalation part with different or targeted eligibility criteria to collect additional information on safety or activity (45).

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

Harms: The totality of possible adverse consequences of an intervention or therapy; they are the direct opposite of benefits, against which they must be compared (46). They can comprise of adverse events, adverse (drug) reactions, toxicities, treatment-emergent adverse events, or those that are intolerable by participants (46, 47). They can also include tolerability assessment using patient-reported outcomes as complementary to investigators' reporting (48, 49).

Interim analysis/review: A statistical analysis or review of accumulating data from an ongoing trial (interim data) to inform trial adaptations (before the final analysis), which may or may not involve treatment group comparisons (18).

Model-assisted design: A trial design that combines a clearly predetermined algorithm to guide the dose (de-)escalation as in rule-based designs, and an underlying statistical model, as in model-based designs (50). Examples include the modified toxicity probability interval design (51) and the Bayesian optimal interval design (52).

Model-based design: A trial design that assumes a relationship between the dose of the intervention administered to the participant and the likelihood of the participant experiencing an effect (such as toxicity and/or activity) and uses a parametric model to estimate that relationship. Examples include the continual reassessment method (53), plus escalation with overdose control (54), and the efficacy-toxicity trade-off-based design (55).

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

Operating characteristics: Relate to the statistical behaviour or performance of the trial design in addressing research questions. These may include the probability of correctly selecting the correct dose(s), statistical power, false-positive error rate, bias in estimation of treatment effect(s), or probability of each adaptation taking place (18, 38).

Pharmacodynamics (PD): Described as "what a drug does to the body," PD refers to how the drug works and how it affects the body.

Pharmacokinetics (PK): Described as "what the body does to a drug," PK refers to the movement of the drug into, through, and out of the body. It includes the analysis of chemical metabolism and the measurement/modelling of a substance from the moment that it is administered up to the point at which it is completely eliminated from the body.

Pre-specified decision-making criteria: Planned or pre-specified rules to guide decisions, describing whether, how, and when the proposed trial adaptations will be used during the trial. It involves pre-specifying a set of actions guiding how decisions about implementing the trial adaptations are made given interim observed data (decision rules). It also involves pre-specifying limits or parameters to trigger trial adaptations (decision boundaries). For example, stopping boundaries that relate to pre-specified limits regarding decisions to stop the trial or treatment arm(s) early.

Pre-specified trial adaptations: 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, intra-participant dose-escalation); other adaptations considered (e.g., safety, futility, efficacy, enrichment) regardless of whether they were triggered (1, 18, 19).

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

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

Trial (design) adaptations: Pre-planned changes or modifications (specified in advance) that can be made to the aspects of a trial while it is ongoing without undermining its validity and integrity (56). These pre-planned modifications are driven by accruing interim data (57). Examples include adjusting the dose(s), changing the predetermined sample size, stopping the trial early for efficacy, futility, or safety, and switching the allocated treatment of participants due to lack of benefit or safety issues (18).

Table 1. Recommended checklist items to address in an early phase dose-finding (EPDF) clinical trial report from the CONSORT 2010 and the CONSORT-DEFINE checklist

Section/ Item No.	Standard CONSORT Statement	Item No.	CONSORT-DEFINE for EPDF Trials
Title and abstract			
1a	Identification as a randomised trial in the title	1a†	Identification as an early phase dose-finding (e.g., first-in-human, dose escalation/de-escalation, phase I, phase I/II, expansion, dose-titration) and, if applicable, randomised trial in the title or 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†	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*	Summary of key findings from relevant nonclinical/preclinical research
		2a.3*	Summary of findings from previously generated preclinical and translational studies to support any planned biomarker sub-studies (where applicable)
2b	Specific objectives or hypotheses	2b†	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†	Description of trial design elements, such as dose-escalation/de-escalation strategy, number of treatment groups, allocation ratio if relevant, and details of any pre-specified trial adaptations

Section/ Item No.	Standard CONSORT Statement	Item No.	CONSORT-DEFINE for EPDF Trials
		3a.2*	Trial design schema to show the flow of major transition points (e.g., dose escalation to dose expansion, phase I to phase II, single ascending dose to multiple ascending dose)
		3a.3*	Statistical methods or rationale underpinning the trial design
		3a.4*	Starting dose(s) with rationale
		3a.5*	Range of planned dose levels with rationale
		3a.6*	Presentation of planned dose levels (e.g., as a diagram, table, or infographic), where applicable
		3a.7*	Skipping of dose level(s), if applicable
		3a.8*	Planned cohort size(s) (e.g., fixed, flexible, adaptive)
		3a.9*	Dose allocation method within a dose level (including sequence and interval between dosing of participants, e.g., sentinel or staggered dosing)
		3a.10*	Dose expansion cohort(s), if applicable, with rationale
		3a.11*	Criteria for progression to the next part of the trial (e.g., phase I to phase II, single ascending dose to multiple ascending dose), where applicable
3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	3b†	Important changes to the design or methods after trial commencement (e.g., insertion of unplanned additional doses) outside the scope of the pre-specified adaptive design features, with reasons
Participants			
4a	Eligibility criteria for participants		
4b	Settings and locations where the data were collected		

Section/ Item No.	Standard CONSORT Statement	Item No.	CONSORT-DEFINE for EPDF Trials
Interventions			
5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5a†	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*	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/worsening disease)
Outcomes			
6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6a†	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 pre-specified adaptations should be described with the rationale
6b	Any changes to trial outcomes after the trial commenced, with reasons	6b†	Any unplanned changes to trial outcomes after the trial commenced, with reasons
Sample size			
7a	How sample size was determined	7a†	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†	Pre-specified interim decision-making criteria/rules that guided the trial adaptation process (e.g., dosing decision to (de-)escalate); pre-specified and actual timing and frequency of interim data reviews and the information to inform trial adaptations
Randomization (if applicable)			

Section/ Item No.	Standard CONSORT Statement	Item No.	CONSORT-DEFINE for EPDF Trials
Sequence generation			
8a	Method used to generate the random allocation sequence		
8b	Type of randomization; details of any restriction (such as blocking and block size)	8b†	Type of randomization; details of any restrictions (such as blocking and block size); any pre-specified 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		
Implementation			
10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions		
Blinding			
11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, and how		
11b	If relevant, description of the similarity of interventions		
Statistical methods			
12a	Statistical methods used to compare groups for primary and secondary outcomes	12a.1 †	Statistical methods for primary and secondary outcomes and any other outcomes used to make pre-specified adaptations

Section/ Item No.	Standard CONSORT Statement	Item No.	CONSORT-DEFINE for EPDF Trials
		12a.2 *	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†	Statistical methods for additional analyses (e.g., subgroup and adjusted analyses, pharmacokinetics/pharmacodynamics, biomarker correlative analyses)
		12c*	Analysis population(s) (e.g., evaluable population for dose-finding, safety population)
		12d*	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†	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 pre-specified adaptations
13b	For each group, losses and exclusions after randomization, together with reasons	13b†	For each group, losses and exclusions after allocation to each dose level, together with reasons
Recruitment			
14a§	Dates defining the periods of recruitment and follow-up		
14b§	Why the trial ended or was stopped		

Section/ Item No.	Standard CONSORT Statement	Item No.	CONSORT-DEFINE for EPDF Trials
		14c*	Trial adaptation decisions made (including on what basis they were made, and when) in light of the pre-specified decision-making criteria and observed accrued data
Baseline data			
15	A table showing baseline demographic and clinical characteristics for each group	15†	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†	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†	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§	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		
		17c*	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 pre-specified from exploratory		
Harms			

Section/ Item No.	Standard CONSORT Statement	Item No.	CONSORT-DEFINE for EPDF Trials
19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms (46))	19†	All important harms (e.g., adverse events/effects, toxicities) reported by dose level in each group
Discussion			
Limitations			
20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		
Generalizability			
21	Generalizability (external validity, applicability) of the trial findings		
Interpretation			
22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		
Other information			
Registration			
23	Registration number and name of trial registry		
Protocol			
24	Where the full trial protocol can be accessed, if available		
Funding			
25	Sources of funding and other support (such as supply of drugs), role of funders		
Data monitoring			

Section/ Item No.	Standard CONSORT Statement	Item No.	CONSORT-DEFINE for EPDF Trials
		26a*	Composition of any decision-making or safety review committee/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*	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*	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

^ This checklist should be used in conjunction with the CONSORT Explanation and Elaboration (16) 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 may also be relevant (58).

* New items that should only be applied in reference to CONSORT-DEFINE;
† Modified items that require reference to both CONSORT and CONSORT-DEFINE;
§ Item wording remains unchanged in reference to CONSORT, but additional CONSORT-DEFINE explanatory text has been provided to clarify additional considerations for early phase dose-finding trials.
Note that the term “dose” in the checklist may be considered synonymous and used interchangeably with dosage, or dosing regimen (dose/schedule), or a unit dose.

The suggested abstract structure for EPDF trials, CONSORT-DEFINE for abstracts, follows a similar format as the 2008 CONSORT extension for journal and conference abstracts (23). The modifications are to tailor them to the objectives of EPDF trials (**Table 2**). We outlined the recommended items that should be included in abstracts where possible, as the level of information 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 the CONSORT for journal and conference abstracts (23) and other applicable extensions where relevant.
There are five modifications to the abstract guideline for EPDF trials, comprising of:

Title:

i. Identification of key features of EPDF trial in the title to facilitate electronic searching

Trial Design:

ii. Description of EPDF trial design

Methods:

iii. Specification of dose(s) used

iv. Specification of objectives of EPDF trials (such as safety and recommended dose(s))

Results:

v. Added the provision of the results of the primary outcome(s) at each dose (where possible) in each group.

Other minor refinements include: (1) the term "randomised" has been replaced with "allocated," as EPDF trials can be randomised or non-randomised; (2) allowance of one or joint primary outcomes, which is not an uncommon feature in EPDF trials.

Table 2. CONSORT Extension for Abstracts and CONSORT-DEFINE for Abstract Extension Checklists: Items to Include when Reporting an Early Phase Dose-Finding (EPDF) Trial in a Journal or Conference Abstract

Section/ item	**CONSORT Extension for Abstracts**	**CONSORT-DEFINE for Abstracts of EPDF trials**
Title†	Identification as a randomised trial in the title	Identification as an early phase dose-finding (e.g., dose escalation/de-escalation, phase I, phase I/II or dose-titration) trial in the title or abstract, and, if applicable, randomisation and/or trial acronym
Authors *	Contact details for the corresponding author	
Trial design†	Description of the trial design (e.g. parallel, cluster, non-inferiority)	Description of trial design elements, such as dose-escalation/de-escalation strategy, number of treatment groups, allocation ratio if relevant, and details of any pre-specified trial adaptations
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	
Interventions †	Interventions intended for each group	Interventions for each dose level within each group
Objective†	Specific objective or hypothesis	Specific objectives (e.g., relating to safety, pharmacokinetics, pharmacodynamics, recommended dose(s))

Section/ item	CONSORT Extension for Abstracts	CONSORT-DEFINE for Abstracts of EPDF trials
Outcome	Clearly defined primary outcome for this report	Clearly defined primary outcome(s) for this report
Allocation	How participants were allocated to interventions	
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers allocated	Number of participants randomised to each group	Number of participants allocated to each group
Recruitment	Trial status	
Numbers analysed	Number of participants analysed in each group	
Outcome†	For the primary outcome, a result for each group and the estimated effect size and its precision	For the primary outcome(s), results for each dose within each group, and the estimated effect size and its precision, if applicable
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

*this item is specific to conference abstracts

† Modified items

4. Discussion

This CONSORT-DEFINE provides international evidence- and consensus-based guidance for reporting EPDF trials in main reports and journal/conference abstracts. CONSORT-DEFINE extends the CONSORT checklist for the main trial report with 40 items. These include 21 new items and 19 modifications to existing CONSORT items to tailor them to EPDF trials to be used alongside the latest CONSORT guidance. CONSORT-DEFINE for abstracts includes five modifications to the existing CONSORT-Abstract recommendation (23).

CONSORT-DEFINE, like other CONSORT extensions, is developed through an international consensus-driven process using the Enhancing QUAlity and Transparency Of Health Research (EQUATOR) methodological framework. The key difference is that CONSORT-DEFINE addresses the distinctive features of EPDF trials.

In addition, we developed a dose-finding extension for SPIRIT 2013 (26), SPIRIT-DEFINE, which has been reported elsewhere (25). CONSORT-DEFINE and SPIRIT-DEFINE form an interconnected continuum to facilitate the writing of the trial protocol and report, as well as assess the adherence of the final report to the protocol (59).

Application of CONSORT-DEFINE

The CONSORT-DEFINE guidance is anticipated to serve as a useful resource to trialists, journal editors, peer reviewers, funders, regulators, and research ethics committees to promote best practice in reporting EPDF trials. We also envision that it will enable both trial participants and the public to be more confident in EPDF trial design and results. CONSORT-DEFINE presents the minimum essential items that should be reported for EPDF trials to maximise their transparency, replication, and utility and limit selective reporting of their results. There will, however, be settings where it may be useful to report additional items viewed as important, especially for complex trial designs. Like CONSORT, CONSORT-DEFINE guidance is not prescriptive regarding the structure or location of the required information; authors are encouraged to "address checklist items somewhere in the article, with ample detail and lucidity" (17), or to indicate where details can be found (e.g., in an accessible protocol, a statistical analysis plan, or supplementary documents).

When applying the CONSORT-DEFINE guidance, authors can indicate why any recommended item may not apply to their trial. For instance, providing key findings from relevant non-clinical or preclinical research (item 2a.2) may be unnecessary for paediatric trials of drugs for which there is ample evidence of usage in adults where the disease is the same or very similar in adults and children (60) (covered in item 2a.1).

CONSORT-DEFINE is a reporting guideline and is thus not intended to advocate for any specific trial design. Its focus is to provide the minimum essential contents for transparent and complete reporting of the design, conduct, analyses, and interpretation of the conducted early phase dose-finding clinical trials (including what was planned and what was actually implemented), regardless of the trial design used, to enable readers to critically and comprehensively assess the validity and reliability of the trial results.

Key strengths and limitations

There are noteworthy strengths and limitations.

We were successful in engaging and involving more than 200 multidisciplinary stakeholders from 24 countries to participate in the Delphi survey to develop these guidelines and increase awareness and usability internationally. However, the survey results are not immune to non-response bias. Participants were self-selecting, as only those interested would sign up to participate in the Delphi survey, and we were unable to determine the experiences or characteristics of those who did not sign up to participate.

Moreover, throughout the development process, we have successfully engaged with patients and public partners. Besides the participation of two patient representatives at the DEFINE consensus

meeting, who played a significant part in shaping the eventual checklist, our PPIE work has also resulted in the co-production of a lay summary toolkit for reporting EPDF trials (28). Such engagement in the development of reporting guidance has been rare to date and should be greatly encouraged to ensure that patients' voices are taken into account.

Around 16% of registered participants did not complete their round one survey despite at least three reminders. This could be due to the length of the survey (80 questions for both SPIRIT-DEFINE and CONSORT-DEFINE), which would have taken around 30 minutes to complete. We tried to reduce the time taken by displaying each new or modified item that is relevant to both the SPIRIT-DEFINE and CONSORT-DEFINE candidate items at the same time in the survey to reduce participant fatigue; the save functionality also permitted the survey to be completed in multiple sessions.

The consensus participants were purposefully chosen from commercial and non-commercial organisations, including PPIE representatives, to reflect different expertise and job roles relevant to trial design, conduct, and reporting. However, some groups that were less well represented in the consensus meeting panel (for example, those outside Europe, North America, and Asia) may have different views. Nonetheless, the systematic and evidence-based approach used to develop this guideline, including a review of reporting practices on EPDF trials and the widespread engagement in the Delphi survey, may have mitigated the potential effect of these limitations (2, 24).

Of note, CONSORT-DFEINE is generic to cover diverse trial designs that are applicable in EPDF trials. The design of an EPDF trial is generally more multifaceted than that of a two-arm parallel-group trial. A major strength of the CONSORT-DEFINE guidance is that, while based on the original CONSORT, it has also been refined to address the distinctive purposes and characteristics of EPDF clinical trials through a specific extension. These characteristics may include diverse populations (healthy volunteers or patients), interventions (pharmacological, non-pharmacological, or a combination thereof), and trial designs that may range from pharmacokinetic modelling in healthy volunteers to complex Bayesian modelling of joint outcomes such as toxicity and activity. Consequently, there are some new or modified items in this extension that some researchers may perceive as difficult to adhere to. We, therefore, intentionally kept some items separate as individual items rather than combining them as a composite item to ensure they would not be missed in reporting. For instance, CONSORT-DEFINE 2a.1, 2a.2, and 2a.3 were kept separate rather than combined as one modified item of CONSORT 2a. Similarly, for the trial design, CONSORT-DEFINE 3a.1-3a.11 were kept separate as 11 individual items rather than as a composite modified item of CONSORT item 3a.

Enhancing the uptake and relevance of CONSORT-DEFINE

Wide dissemination of the CONSORT-DEFINE guidance is essential to increasing its appropriate uptake, and this will be done as previously outlined (2, 7), including to journals currently known to endorse CONSORT through the EQUATOR Network.

We are preparing an explanation and elaboration document to provide in-depth details and exemplars from published papers in different settings, to assist reviewers, editors, and readers who require additional information or clarity about specific items.

The design of EPDF trials is rapidly evolving, with an increasing use of seamless phases as well as innovative and efficient approaches to address multiple objectives with faster go/no-go decisions.

Additional considerations may be needed as newer trial designs emerge. The DEFINE Executive Committee will monitor the literature and assess the need to update the CONSORT-DEFINE guidance. Users are encouraged to provide any feedback on the content, usability, and clarity of the guidance and how it can be further refined, which will be used to shape future updates.

5. Conclusions

This robust, consensus-driven CONSORT-DEFINE guidance will allow researchers to effectively address the essential items that should be included in EPDF trial reports. It will promote greater transparency, reproducibility, informativeness, and utility of results, which in turn will increase the trustworthiness of EPDF trial with patients and the public.

6. Abbreviations

ACE	Adaptive designs CONSORT Extension
CONSORT	CONsolidated Standards of Reporting Trials
DEFINE	Dose-Finding Extension
EPDF trials	Early Phase Dose-Finding trials
EQUATOR	Enhancing the QUAlity and Transparency Of health Research
ICH E9 (R1)	Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials by International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MAD	Multiple ascending dose
PPIE	Patient and Public Involvement and Engagement
SAD	Single ascending dose
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials

7. Article information

7.1. Author Contributions

Conceptualisation: CY, OS, JDB, TJ, AM, TRJE, SH, KRR, MC, SL, AK, AWC, AE, MD, CJW. Data curation: CY, OS, JR, DP. Formal analysis: JR and DP. Funding acquisition: CY, JDB, TJ, AM, TRJE, SH, SL, AK, MD, CJW. Methodology: CY, OS, JDB, TJ, AM, TRJE, SH, MU, KRR, MC, SL, AK, AE, MD, CJW. Project administration: CY, OS, DP, and AE. Investigation: All. Supervision: CY, SH, MC, AK, DA, AWC, EGM, JDI, MD, and CJW. Writing of the original draft: CY, OS, JDB, JR, TJ, RP, KH, MU, MC, MD, and CJW. Writing – reviewing and editing: All.

7.2. Conflict of Interest Disclosures

Professor Johann de Bono has served on advisory boards and received fees from companies including Amgen, Astra Zeneca, Astellas, Bayer, Bioxcel Therapeutics, Daiichi, Genentech/Roche, GSK, Harpoon, ImCheck Therapeutics, Janssen, Merck Serono, Merck Sharp & Dohme, Pfizer, Sanofi Aventis. Additionally, Professor de Bono is an employee of The Institute of Cancer Research, which have received funding or other support for his research work from AZ, Astellas, Bayer, Cellcentric, Daiichi, Genentech, Genmab, GSK, Janssen, Merck Serono, MSD, Menarini/Silicon Biosystems, Orion, Sanofi Aventis, Sierra Oncology, Taiho, Pfizer, Vertex. The ICR has a commercial interest in abiraterone and PARP inhibition in DNA repair defective cancers and PI3K/AKT pathway inhibitors (no personal income). Furthermore, Professor Johann de Bono was named as an inventor, with no financial interest for patent 8,822,438, submitted by Janssen that covers the use of abiraterone acetate with corticosteroids. He has been the CI/PI of many industry sponsored clinical trials. Professor Johann de Bono is a National Institute for Health Research (NIHR) Senior Investigator. The

views expressed in this article are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

Dr Adrian Mander is employed by GSK.

Professor Thomas R. Jeffry Evans has received honoraria for consultancies (payable to the employing institution) from Ascelia, Astra Zeneca, Bayer, Bicycle Therapeutics, Bristol-Myers Squibb, Celgene Eisai, Karus Therapeutics, Medivir, MSD, Otsuka, Roche, Seagen and honoraria for speaker's fees (payable to employing institution) from Astra Zeneca, Ascelia, Bayer, Bicycle therapeutics, Bristol Myers Squibb, Celgene, Eisai, Nucana, Otsuka, MSD, Roche, Medivir, Seagen, United Medical. In addition, support of costs of commercial clinical trials (payable to employing institution) was received from Astra Zeneca, Basilea, Bayer, Celgene, MiNa Therapeutics, Roche, Pfizer, Sierra, Lilly, Eisai, Glaxo Smith Kline, Novartis, Bicycle Therapeutics, Johnson & Johnson, CytomX, Vertex, Plexxikon, Boehringer, Athinex, Adaptimmune, Bristol-Myers Squibb, MSD, Medivir, Versatem, Nucana, Immnuocore, Berg, Beigene, Iovance, Modulate, BiolinerX, Merck Serono, Nurix Therapeutics, T3P, Janssen Clovis, Sanofi – Aventis, Halozyme, Starpharma, UCB, Sapience, Seagen, Avacta, Codiak. Furthermore, funding was received from Cancer Research UK, Chief Scientist's Office Scotland, and the Medical Research Council UK. In addition, Professor Evans is also the editor-in-chief of the British Journal of Cancer and has an honorary clinical contract with the NHS Greater Glasgow & Clyde Health Board.

Professor Richard Peck is an employee and a stockholder in F Hoffmann la Roche, and a family member is also an employee and a stockholder of F Hoffmann la Roche.

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Dr Dawn P. Richards is the volunteer Vice President of the Canadian Arthritis Patient Alliance, a patient-led and -run organization that derives the majority of its funding from independent grants from pharmaceutical companies.

Mr. Oliver Boix is an employee of Bayer AG.

Mr. James Matcham is an employee of Cytel (Australia) Pty Ltd.

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Dr Lynley Marshall received honorarium for speaker fees from Bayer and co-organizer, chair, and speaker at two Educational Preceptorships (online webinars) and advisory board/consultancy honoraria from Tesaro, BMS, and Illumina. Dr Marshall is also a member of External Data Monitoring Committees for early phase clinical trials run between Eisai and Merck.

Dr Rong Liu is an employee and stockholder of Bristol Myers Squibb.

Dr Jordan Berlin declares consultancy fees from Mirati, Insmed, Oxford biotherapeutics, Biosapien, EMD servon, Ipsen, Merck Sharp & Dohme, Perus, BMS, Bexion and grant funding from Abbvie, Astellas, Atreca, Bayer, Dragonfly, I-Mab, Lilly, Incyte, EMD Serono, Pfizer, BMS, Transcenta Therapeutics, Tyra, Totus, Sumitomo Dainippon Pharma Oncology, 23 and me, Parthenon, Hibercell. Dr Berlin also sits on Data Safety Monitoring Committees for Astra Zeneca, Novocure, Boehringer-Ingelheim.

All other authors declare no conflict of interest.

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7.5. Disclaimer

This article reflects personal the views of the authors, the Delphi participants, and the Consensus Meeting participants, and may not represent the views of the broader stakeholder groups, the

authors' institutions, or other affiliations. The personal views may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties, or to any organization with which the author(s) are affiliated.

7.6. Additional Contributions

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