Enhancing Quality and Impact of Early Phase Dose-Finding Clinical Trial Protocols: The SPIRIT Dose-Finding Extension (SPIRIT-DEFINE) Guidance

The SPIRIT-DEFINE Statement

SPIRIT-DEFINE is a new guideline that provides recommendations for essential items that should be provided in protocols of early phase dose-finding clinical trials. It details extensions to the SPIRIT 2013 guidance, incorporating 17 new items and modifying 15 existing items. The purpose of this guideline is to promote transparency, completeness, reproducibility of methods, and interpretation of early phase dose-finding trial protocols.

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Key messages

- Early phase dose-finding clinical trials are essential for clinical development as they provide the groundwork for further development and guide subsequent trials.
- SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 focused on randomised trials and the new SPIRIT-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 guideline development process using the Enhancing QUAlity and Transparency Of health Research (EQUATOR) methodological framework, 32 early phase dose-finding specific items were recommended for inclusion in clinical trial protocols.
- Inclusion of these SPIRIT-DEFINE items in clinical trial protocols may enhance transparency, completeness, reproducibility of methods, and trial utility in early phase dose-finding trials.

ABSTRACT

SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 provides guidance for clinical trial protocol writing. However, neither the original guidance nor its extensions adequately cover the features of early phase dose-finding trials. The SPIRIT-DEFINE study aims to enhance transparency, completeness, reproducibility of methods, and interpretation of early phase dose-finding trial protocols by building on the checklist outlined in the SPIRIT 2013 statement.

SPIRIT-DEFINE was developed following the Enhancing QUAlity and Transparency Of health Research (EQUATOR) Network's methodological framework for guideline development. The initial SPIRIT-DEFINE candidate items were drawn from relevant items in the companion guidance project for trial reports of early phase dose-finding trials. The draft checklist was further enriched through the review of published and unpublished literature (e.g., regulatory and industry advice documents), real-world example analysis, citation and reference searches, and consultation with international experts, including regulators and journal editors. A two-round modified Delphi process (round one: 206 participants, March-May 2022; round two: 151 participants, May-June 2022) and a consensus meeting (34 participants, October 2022) were held. The SPIRIT-DEFINE checklist was piloted by eight multidisciplinary trialists, and the checklist final wording and explanation text were agreed on by the DEFINE Executive Committee and consensus meeting participants.

Thirty-six candidate items were considered in the Delphi survey. Twenty-six candidate items were recommended for inclusion; and ten items were discussed at the consensus meeting, where four items were recommended for inclusion. The discussion during and after the consensus meeting yielded 17 new and 15 modified SPIRIT-DEFINE checklist items. Newly included and modified items focused on dose-finding specific issues such as adaptive design features (e.g., interim adaptations, underlying statistical methods, operating characteristics), definition of analysis populations, and prevention of harms.

SPIRIT-DEFINE recommends essential items to be included in clinical trial protocols for early phase dose-finding trials, thus promoting transparency, comprehensiveness, and reproducibility of methods. We envision that the resulting improvements in early phase clinical trial design and conduct will ultimately reduce research inefficiencies, and inconsistencies, driving transformational advances in clinical care.

1. Introduction

Developing an intervention is a lengthy process pursued in stages where decisions are based on balances of benefits and risks or harms of the intervention under investigation. Lack of efficacy and/or evidence of harm due to adverse safety profiles are common reasons for phase II and phase III trials to be unsuccessful (1, 2). Phase III trial failures can reflect incorrect decisions made at earlier stages, including in early phase dose-finding (EPDF) trials (commonly known as phase I, phase I/II, or first-in-human trials). Reasons why interventions do not progress or succeed in later stages of clinical development include misleading preclinical studies, inadequate participant selection, inefficient trial design, suboptimal biomarker/outcome choices, and/or poor dose selection. The same reasons can also contribute to early discontinuation of promising interventions.

EPDF trials typically evaluate new interventions that can be administered in different doses, and can be pharmacological (chemical or biological, e.g., drugs, vaccines, cell therapies, gene therapies), non-pharmacological (e.g., radiotherapy, devices, rehabilitation, digital therapies) or a combination thereof. They usually include a small number of healthy volunteers or participants with the disease under investigation. Either based on safety outcomes alone or increasingly jointly with outcomes of activity, EPDF trials aim to recommend a tolerated dose range for further study. In this article, a broad definition of dose is used since terms like dose-finding, dose level, dose escalation, and dose expansion are widely understood. Here, dose may refer not only to the amount of dose but can, e.g., also comprise frequency, intensity, or duration of an intervention (3). It may therefore be regarded as synonymous to dosage or dosing regimen or as a unit dose, and it can apply to interventions given alone or in combination (see Glossary [Box] for details).

To ensure the safety of trial participants in EPDF trials, decisions regarding dose escalation/de-escalation are made based on interim data. Different dose escalation approaches have been described in the literature, e.g., algorithm-based (also called rule-based), model-assisted, and model-based designs (4, 5). The use of model-assisted and model-based designs, which have been reported to be more efficient but also more complex than algorithm-based designs (6, 7), rose from 1.6% (20/1235 phase I published cancer trials) in 1991-2006 (8) to 8.6% (68/788) in 2014-2019 (6). Most recent data confirms this trend with the rate of advanced designs in cancer trials reported to be 19% (11/58) based on protocols posted on ClinicalTrials.gov in 2017-2023 (9). The complexity of these designs is reflected in a more multifaceted implementation and the requirement to specify more details on design features (10, 11, 12), which mandates more detailed protocols for EPDF trials to improve precision and transparency, and to facilitate understanding of trial design and decision-making processes.

A trial protocol is a crucial document that outlines how a clinical trial will be conducted, ensuring the safety of patients and the integrity of data. It provides details on objectives, design, methodology, statistical analyses, and trial implementation. The protocol serves as the shared central reference for a trial team and is evaluated by external reviewers. Despite the importance of trial protocols, their content and quality vary considerably (13). To address this, the SPIRIT 2013 (Standard Protocol Items: Recommendations for Interventional Trials) statement (14, 15) was established to provide evidence-based guidance for the essential content of a trial protocol. Protocols underpinning EPDF trials require more transparency to facilitate a better understanding of the trial design and how dose decisions would be made (16) Inadequate or unclear information on design, conduct, and analysis in EPDF protocols hinders interpretability and reproducibility. It may also lead to unnecessary amendments and associated costs, as well as inadequate or biased reporting resulting in erroneous conclusions on safety and efficacy. The overall quality of EPDF protocols from ClinicalTrials.gov in 2017-2023 was reported to be markedly variable and poor, with insufficient reporting in many

applicable SPIRIT 2013 items (9). For example, sections on ethics and dissemination strategy were frequently found to be addressed insufficiently. Although SPIRIT 2013 is largely applicable to many types of trial designs, trials that use specialised designs may require additional protocol considerations. Several SPIRIT extensions have been proposed to improve its utility for specialised topics (17, 18, 19, 20, 21, 22). Neither the SPIRIT 2013 statement nor any of its extensions, however, sufficiently cover the needs of EPDF trials – although, globally, there were more phase I trials (n = 18,716) than phase III trials (n = 10,451) registered on ClinicalTrials.gov and first posted between 2018 and 2022. The number of phase I trials may even be an underestimate as there is no requirement to register them on ClinicalTrials.gov (23). Since no consensus-driven protocol guidance exists for EPDF trials (24), there is an urgent need to extend the SPIRIT 2013 guidance to EPDF trials.

2. Methods

The SPIRIT-DEFINE extension was conceptualised, designed, and conducted between January 2022 and July 2023 in concordance with the Enhancing QUAlity and Transparency Of health Research (EQUATOR) network's methodological framework for guideline development (25). The study was led by the Principal Investigator (PI) and the DEFINE Executive Committee, who met online once or twice every three months before the international consensus meeting and once after. The DEFINE research team at the Institute of Cancer Research met weekly. Frequent email correspondences and one-to-one or small group meetings between the PI and key Executive Committee members were arranged for any discussions whenever needed. SPIRIT-DEFINE was approved for sponsorship by the Institute of Cancer Research's Committee for Clinical Research (reference number: CCR5460). The United Kingdom Health Research Authority confirmed that no approval for research ethics was necessary. All participants gave their informed consent to participate in the Delphi survey and consensus meeting.

2.1. Generation of candidate protocol items

An initial SPIRIT-DEFINE checklist was drafted based on SPIRIT 2013 (14), with additional protocol-related candidate items taken from the companion guidance for trial reports of EPDF trials, CONSORT-DEFINE, CONsolidated Standards Of Reporting Trials DosE FIndiNg Extension (16, 26). The multidisciplinary Executive Committee's expert opinions, and unpublished literature including regulatory and industry advice documents, were used to further refine the checklist as described (24, 26). Major international stakeholder groups were consulted, and their protocol or guidance templates included (when available) to inform the generation and wording of the candidate items, and the structuring of the eventual checklist. These groups included phase I units accredited by the Medicines and Healthcare products Regulatory Agency (MHRA), funders, pharmaceutical companies, contract research organisations and research ethics committees (24, 26).

2.2. International Delphi process

We solicited feedback on the draft candidate items for the SPIRIT-DEFINE checklist from a broad stakeholder group using a Delphi survey (**Figure 1**). A comprehensive outline of the recruitment procedure for the Delphi survey is provided in the section titled 'The Delphi process' within the DEFINE development process paper (26). The Delphi process adhered to established methodological guidance (27, 28, 29). A total of 206 participants from 24 countries voted in round one (March to May 2022), and 151 participants voted in round two (May to June 2022). Before voting for round two, participants were presented with the distribution of round one ratings for each item as well as their own prior ratings.

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

According to a predetermined rule, items voted "not important" (scores 1 to 3) by at least 80% of respondents in round one were eliminated between rounds subject to approval by the Executive Committee. Items voted "critically important" (scores 7 to 9) by at least 70% of respondents in round one were considered to have reached consensus and were automatically included in the SPIRIT-DEFINE checklist (24) (Figure S1 in the **Web appendix 1**).

In these two rounds of the Delphi poll, 36 SPIRIT-DEFINE candidate items were reviewed, 26 items satisfied the criterion to be included in the checklist, and ten items qualified to be discussed at the consensus meeting. The process, decision criterion, and voting results of the SPIRIT-DEFINE candidate items are described in Figure S1 and Table S1 in the **Web appendix 1**. Additional information on the Delphi method, including qualitative and quantitative analyses and the outcomes of rounds one and two, is provided elsewhere (26).

2.3. International consensus meeting

A total of 32 international delegates from academic, commercial, and regulatory sectors and two patient and public involvement and engagement partners attended the online consensus meeting on October 11-12, 2022 (see Table S2 and Table S3 in the **Web appendix 1** for affiliations/roles of participants). The Delphi survey findings were presented alongside supporting evidence, written comments from participants, and examples from published protocols for each candidate item to be reviewed at the consensus meeting. Following the presentation, members were invited to discuss each item, before voting anonymously. Voting options for the candidate items were to include or discard the item in the checklist, with the threshold for inclusion being ≥70% and exclusion being <50%, with the rest left for further deliberation by the DEFINE Executive Committee (Figure S1 in the **Web appendix 1**).

Out of ten candidate items, four were recommended for inclusion in the SPIRIT-DEFINE checklist and five were rejected. One item was left for further deliberation at the subsequent Executive Committee meeting, at which it was rejected (Figure 1; Table S1 in the **Web appendix 1**).

2.4. Final consultation and piloting of the checklist

After the consensus meeting, participants and the DEFINE Executive Committee refined the language of the items and their related explanations. During the checklist pilot-testing phase (December 2022 to January 2023), eight multidisciplinary trialists evaluated the SPIRIT-DEFINE checklist by applying it to actual trial protocols of planned or existing trials and noting areas for improvement. The feedback gathered further shaped the final version of the guideline, with the DEFINE Executive Committee and consensus meeting participants agreeing on the final wording.

2.5. Patient and Public Involvement and Engagement

The DEFINE Study patient and public involvement and engagement (PPIE) lead (AK) was closely involved in the development of the project, and actively contributed to the development of the protocol and each of the development stages. We also engaged with several PPIE partners from both oncology and non-oncology fields for them to feed back on the checklists and to ensure patient voices were heard. As part of our dissemination plan, we will be producing PPIE-led 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 SPIRIT-DEFINE checklist items from the Delphi survey to the consensus meeting, to refinement of the checklist after the final consultation and pilot-testing. The final SPIRIT-DEFINE guidance recommends that, in conjunction with the existing SPIRIT 2013 items, 32 EPDF-specific items (17 new and 15 modified) should be included

prospectively in EPDF trial protocols. **Table 1** presents the items of the SPIRIT 2013 checklist as well as new and modified items for the SPIRIT-DEFINE extension. To enable readers to comprehend the dose escalation/de-escalation strategies and trial design adaptations and to ensure that the procedures and findings can be reproduced, aspects of the SPIRIT-DEFINE checklist specific to EPDF trials include a detailed elaboration of the trial design (e.g., adaptive features, timing of interim analyses, planned dose range with starting dose(s), dose allocation method, interim decision-making criteria, expansion cohort(s), operating characteristics, and dose transition pathways). Specification of planned opportunities for adaptations and their scope is essential to preserve the integrity of adaptive designs and for regulatory assessments (30). All these aspects influence the statistical methods for design and analysis; hence this extension recommends providing comprehensive information on statistical methods covering these adaptive features and requiring clear definitions of analysis populations and plans for handling intercurrent events that occur after treatment initiation (31). Both, analysis populations and intercurrent events, relate to the estimands framework, which provides guidance on defining the treatment effect under investigation in a clinical trial (for details, see the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 (R1) addendum on estimands (32, 33)). In more detail, the new and modified items specific to EPDF trials are as follows:

Administrative information [1 modified item]

- Identifying the early phase dose-finding design in the title of the protocol.

Introduction [12 new items, 3 modified items]

- Coverage of non-clinical/preclinical research informing an EPDF trial (34) and any planned biomarker sub-studies in the background and rationale section (35).
- Highlighting key objectives for EPDF trials in the objectives section.
- Elaboration of the trial design section to include adaptive features (30, 36), starting dose(s) and range of dose levels with rationale, skipping of doses, planned cohort size, dose allocation method, and expansion cohort(s) (16, 34, 37, 38, 39).

Methods: Participants, interventions, and outcomes [5 modified items]

- Enhanced intervention details (3) including reporting them for each dose level and describing pre-specified criteria for dose discontinuations, modifications, or delays (34).
- Extending the description of outcomes to any outcomes that will be used to inform planned adaptations (30).
- Inclusion of clinical and statistical assumptions supporting the planned sample size and operating characteristics, which relate to the statistical behaviour or performance of the trial design (31, 40) (see Glossary [Box] for details).

Methods: Assignment of interventions (for controlled trials) [1 new item]

- Details on any rule or algorithm to update the allocation strategy (30).

Methods: Data collection, management, and analysis [2 new items, 3 modified items]

- Increased details regarding statistical methods to cover adaptive features, analysis population(s) as well as handling of missing data and intercurrent events that occur after treatment initiation (30, 31).

Methods: Data monitoring [3 modified items]

- Increased details regarding interim decision-making process (30) and reporting of harms (e.g., toxicities, adverse events).

Dissemination policy [1 new item]

- Details on any plans for sharing results while the trial is still ongoing.

Appendices [1 new item]

- A new section to cover dose transition pathways or dose decision paths (12, 41, 42).

Authors should state where information on recommended items can be accessed if not in the protocol (e.g., in a data management plan, statistical analysis plan, or other trial-specific documents). Authors should provide explanations for items where details cannot be provided.

There is variation in terminology and definitions associated with EPDF trials, for instance, for different interventions and disease areas. Key terms used throughout this article are provided in the Glossary [Box].

For items that remained unchanged, we refer the user to the SPIRIT 2013 statement paper (14) and its explanation and elaboration document (15). The detailed explanation of new (*) and modified (**†**) SPIRIT-DEFINE items in **Table 1**, 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.

For item 8a.3, the protocol should include a description of the underlying statistical methods used to set up and implement the adaptive trial design. For dose adaptations based on model-based designs (43), authors should provide details and explanations of the statistical methods, including model assumptions, the choice of model parameters, and the mathematical form of the model, if applicable. For model-based and model-assisted dose-finding designs (5, 43), the rationale for choosing a target risk/toxicity rate or acceptable range should be provided (44), the details on the dose transformation (including the full skeleton and its elicitation) and Bayesian prior distributions chosen, should be provided, if applicable (31). For rule-based designs such as 3+3 or Rolling 6 (45), the rationale for using them should be outlined. For other adaptations, such as early stopping for futility, the underlying statistical methods (such as conditional power, predictive power, or posterior probability of treatment effect) should be clearly specified (30, 31).

For item 20c.2, authors should describe methods to be utilised to handle missing data, and detail strategies for handling intercurrent events, i.e., events (such as dosing delays, reductions, or interruptions) occurring after treatment initiation that may affect either the interpretation or the existence of the measurements associated with the clinical question of interest. Such events are not limited to those connected to treatment but may also include withdrawal of consent or deaths unrelated to treatment or disease. Different strategies may be used for different types of intercurrent events (31), and sensitivity analyses may be planned to assess the effect of the chosen strategies on the trial results.

The rationale for the starting dose and choice of the method, for example according to current regulatory guidelines (34, 46) (item 8a.5), as well as trial adaptation process and stopping rules should be clearly specified (item 8a.4). Dose Transition Pathways (DTPs) or dose decision paths can take the form of a decision table or a flow diagram (item 34) to map out in advance how a proposed design would recommend doses (escalate, de-escalate, stay, or stop) based on participants' key outcomes, e.g., what the next dose would be if a certain number of participants in a cohort experience a significant adverse event. For instance, if there are no significant adverse events in two participants, a design may recommend escalating to the next higher dose, but if both participants experience significant adverse events, the same design may recommend de-escalating to a lower dose. The exact content and form of DTPs can vary depending on the specific features of the trial design, and there is no standard format.

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 (6, 47).

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" (48).

Clinical benefit(s): A favourable effect on a meaningful aspect of how a participant feels, functions, or survives as a result of an intervention (49).

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 (3).

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 (50).

Dose-limiting toxicity (DLT): Side effects of an intervention that are serious enough to prevent an increase in the dose of that intervention (47).
Dosing regimen/dosage: See Dose.

Early phase dose-finding (EPDF) trial: An early phase trial where different doses 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 (51).

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 (52). They can comprise of adverse events, adverse (drug) reactions, toxicities, treatment-emergent adverse events, or those that are intolerable by participants (52, 53). They can also include tolerability assessment using patient-reported outcomes as complementary to investigators' reporting (54, 55).

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 (30).

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 (56). Examples include the modified toxicity probability interval design (41) and the Bayesian optimal interval design (57).

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 (58), escalation with overdose control (59), and the efficacy-toxicity trade-off-based design (60).

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 (30, 40).

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.

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 (61). These pre-planned modifications are driven by accruing interim data (62). 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 (30).

Table 1 Recommended checklist items to address in an early phase dose-finding (EPDF) clinical trial protocol from the SPIRIT 2013 and the SPIRIT-DEFINE checklist^

Category	Standard SPIRIT 2013 checklist item			SPIRIT-DEFINE checklist item for EPDF trials	
	Section	**Item No**	**SPIRIT 2013**	**Item No**	**SPIRIT-DEFINE**
Administrative information	**Title**	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1†	Descriptive title identifying the early phase dose-finding trial design (e.g., dose escalation or de-escalation, placebo-controlled, multiple ascending dose), population, interventions, and whether the trial was randomised, and, if applicable, trial acronym
	Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2a	
		2b	All items from the World Health	2b	

			Organization Trial Registration Data Set		
	Protocol version	3	Date and version identifier	3	
	Funding	4	Sources and types of financial, material, and other support	4	
	Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	5a	
		5b	Name and contact information for the trial sponsor	5b	
		5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	5c	
		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5d	

Introduction	**Background and rationale**	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6a.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
				6a.2*	Summary of key findings from relevant non-clinical/preclinical research
				6a.3*	Summary of findings from previously generated preclinical and translational studies to support any planned biomarker sub-studies (where applicable)
		6b	Explanation for choice of comparators	6b	
	Objectives	7	Specific objectives or hypotheses	7†	Specific objectives (e.g., relating to safety, activity, pharmacokinetics, pharmacodynamics, recommended dose(s))
	Trial design	8	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)	8a.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
				8a.2*	Trial design schema to show flow of major transition points (e.g., dose escalation to dose expansion, phase I to phase II, single ascending dose to multiple ascending dose)
				8a.3*	Statistical methods or rationale underpinning the trial design

				8a.4*	Pre-specified interim decision-making criteria/rules to guide the trial adaptation process (e.g., dose escalation/de-escalation, early stopping, progression to the next part of the trial); planned timing and frequency of interim data looks and the information to inform the adaptations; alternatively, an explanation of why they are not pre-specified
				8a.5*	Starting dose(s) with rationale
				8a.6*	Range of planned dose levels with rationale
				8a.7*	Presentation of planned dose levels (e.g., as a diagram, table, or infographic), where applicable
				8a.8*	Skipping of dose level(s), if applicable
				8a.9*	Planned cohort size(s) (e.g., fixed, flexible, adaptive)
				8a.10*	Dose allocation method within a dose level (including sequence and interval between dosing of participants, e.g., sentinel or staggered dosing)
				8a.11*	Dose expansion cohort(s), if applicable, with rationale
Methods: Participants, interventions, and outcomes	**Study settings**	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9	
	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the	10	

			interventions (e.g., surgeons, psychotherapists)		
	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11a†	Interventions for each dose level (within each group) with sufficient details to allow replication, including administration, route, and schedule showing how and when they will be administered
		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	11b†	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)
		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	11c	
		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11d	
	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median,	12†	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

			proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended		
	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended	13†	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants (including in-house stay or out-patient follow-up period, if applicable); a schematic diagram is highly recommended
	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14†	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
	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15	
Methods: Assignment of interventions (for controlled trials)	**Allocation: Sequence generation**	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate	16a.1	

			document that is unavailable to those who enrol participants or assign interventions		
				16a.2*	Any pre-specified rule or algorithm to update allocation with timing and frequency of updates, if applicable
	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16b	
	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16c	
	Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	17a	
		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated	17b	

			intervention during the trial		
Methods: Data collection, management, and analysis	**Data collection methods**	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18a	
		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	18b	
	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be	19	

			found, if not in the protocol		
	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	20a.1†	Statistical methods for primary and secondary outcomes, and any other outcomes used to make pre-specified adaptations; reference to where other details of the statistical analysis plan can be accessed, if not in the protocol
				20a.2*	For the proposed adaptive design features, statistical methods used for estimation (e.g., safety, dose(s), treatment effects) and to make inferences
		20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	20b†	Statistical methods for additional analyses (e.g., subgroup and adjusted analyses, pharmacokinetics/pharmacodynamics, biomarker correlative analyses)
		20c	Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	20c.1†	Analysis population(s) (e.g., evaluable population for dose-finding, safety population)
				20c.2*	Strategies for handling intercurrent events occurring after treatment initiation (e.g., how dosing adjustments will be 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

Methods: Data monitoring	**Data monitoring – formal committee**	21a	Composition of data monitoring committee (DMC); 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 about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	21a†	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, such as a charter, can be found, if not in the protocol; alternatively, an explanation of why such a committee is not needed
	Data monitoring – interim analyses	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	21b†	Description of who will have access to interim results and make 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
	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	22†	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported toxicities and adverse events of trial interventions or trial conduct including time frames of reporting toxicities and adverse events to allow informed interim decision-making (e.g., prior to any planned next dosing)
	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	23	
Ethics and dissem ination	**Research ethics approval**	24	Plans for seeking research ethics committee/institutiona	24	

			l review board (REC/IRB) approval		
	Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	25	
	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	26a	
		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	26b	
	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	27	
	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	28	

	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	29	
	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	30	
	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	31a.1	
				31a.2*	Plans for sharing results (such as safety and/or activity) externally whilst the trial is still ongoing, if applicable
		31b	Authorship eligibility guidelines and any intended use of professional writers	31b	
		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	31c	
	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	32	

	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	33	
Appendices	**Dose transition pathways**			34*	Dose transition pathways or dose decision paths (using, e.g., a flow diagram or table) projecting in advance how a proposed dose-finding design will recommend doses based on participants' key outcomes

Abbreviations: DEFINE, Dose-Finding Extension; DMC, Data Monitoring Committee; IRB, Institutional Review Board; REC, Research Ethics Committee; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

^ This checklist should be read in conjunction with the SPIRIT 2013 Explanation & Elaboration (15) for important clarification on the items. Amendments to the protocol should be tracked and dated. Empty items in the SPIRIT-DEFINE column indicate no modification from the SPIRIT 2013 items.

* New items that should only be applied in reference to SPIRIT-DEFINE.

† Modified items that require reference to both SPIRIT 2013 and SPIRIT-DEFINE.

Note that the term "dose" in the checklist may be considered synonymous and used interchangeably with dosage or dosing regimen (dose and schedule) or a unit dose.

4. Discussion

Due to their importance and impact on later clinical development, EPDF trials should always be conducted to the same rigorous standards as their late phase counterparts including phase II and phase III randomised clinical trials. Moreover, although there are more EPDF trials than late phase trials, insufficient guidance has been available to date on the essential information that an EPDF protocol should provide to ensure accurate, reproducible, and transparent trial conduct.

SPIRIT-DEFINE is aimed at extending the SPIRIT 2013 statement, proposing and/or modifying items tailored to the specific features of EPDF trials across all disease areas. A total of 17 new items have been proposed, and 15 SPIRIT 2013 items have been modified or refined to fit EPDF settings.

SPIRIT-DEFINE, like other SPIRIT 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 SPIRIT-DEFINE addresses the distinctive features of EPDF trial protocols.

Application of SPIRIT-DEFINE

Like SPIRIT 2013, the SPIRIT-DEFINE guidance is not intended to dictate trial design or conduct. It 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 designing protocols for EPDF trials and to facilitate protocol appraisal. We also envision that it will enable both trial participants and the public to be more confident in EPDF trial design. It proposes minimum requirements that EPDF trial protocols should address, not necessarily in the order as presented in the checklist, with authors reporting additional information to enhance the quality of trial protocols. SPIRIT-DEFINE covers general trial protocol principles applicable to a wide range of EPDF trials, regardless of disease setting (oncology/non-oncology) or participant population (e.g., adults/paediatric, patients/healthy volunteers, populations with impaired hepatic or renal function). Its primary focus is on early phase clinical trials, in which interim dosing adaptations are taken using accumulating trial data to either escalate, de-escalate, stay at the current dose, or stop the trial early. Nonetheless, some aspects of this guidance may be applicable and benefit the reporting quality of other types of trial protocols including early phase trials with only one dose or later phase dose-finding trials with dose escalation or de-escalation parts.

Key strengths and limitations

There are noteworthy strengths and limitations.

A special Box describes how using the SPIRIT-DEFINE guideline can improve transparency, completeness, reproducibility of methods, and interpretation of EPDF protocols.

The SPIRIT-DEFINE guidance was shaped by experts in different fields including trialists, clinicians, statisticians, regulators, ethics committee members, journal editors, and funders. Throughout the development process, we collaborated effectively with stakeholders and the public, including two patient partners who brought their perspectives to the consensus meeting and made important contributions to the guidance document. This SPIRIT-DEFINE effort also benefited from the contemporaneous CONSORT-DEFINE development. Aligning CONSORT-DEFINE and SPIRIT-DEFINE involved continuous exchange of information and evaluation of the pertinence of proposed items resulting in items being shared by both statements, with these being rephrased to fit the purposes of each guideline.

To increase the accuracy and usability of the SPIRIT-DEFINE guidance, we engaged and involved an international group of multidisciplinary stakeholders (see Table S2 in the **Web appendix 1** for role/affiliations of consensus meeting participants). However, as with any survey, our results are subject to non-response bias. Respondents were self-selected, as only interested individuals participated in the Delphi survey, and the demographics of those who did not participate could not be determined. Consensus participants were specifically approached to reflect the multidisciplinary expertise and professional roles relevant to the design, conduct, and reporting of EPDF trials. Nevertheless, smaller groups (e.g., groups outside Europe, North America, and Asia) holding different views were potentially underrepresented during the Delphi process, at the consensus meeting, and on the DEFINE Executive Committee. However, the utilised systematic, evidence-based approach to

develop these guidelines, including rigorous review of reporting practices in EPDF trials by stakeholders will have helped mitigate this potential bias.

Another limitation reflects the complexity of EPDF trials compared to randomised parallel group trials. The SPIRIT-DEFINE extension contains several new or modified items that may challenge adherence to the checklist. To guarantee the visibility of certain components, we intentionally kept them separate as independent items rather than combining them. For example, SPIRIT item 8 (trial design for a randomised parallel group trial) was modified to become SPIRIT-DEFINE item 8a.1, and 10 new items (8a.2–8a.11) corresponding to different features of EPDF trial designs (and can be considered as sub-items of item 8) were added to the checklist as separate items rather than combining them into one composite item.

Enhancing the uptake and relevance of CONSORT-DEFINE

Wide dissemination of the SPIRIT-DEFINE guidance is essential to increasing its appropriate uptake, and this will be done as previously outlined (24), including but not limited to journals currently known to endorse SPIRIT through the EQUATOR Network.

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

Finally, the design of EPDF trials is a rapidly evolving field, particularly with the increasing use of seamless phases as well as innovative approaches such as basket, umbrella, and platform trials that all pursue multiple objectives in increasingly efficient ways with faster go or no-go decisions. As newer trial designs emerge, additional considerations may be needed to facilitate transparency, reproducibility, minimise potential biases, and ensure the veracity of the findings of EPDF trials. Thus, the DEFINE Executive Committee will continue to monitor and assess the need for updates to both the SPIRIT-DEFINE and CONSORT-DEFINE guidelines.

SPIRIT-DEFINE can improve:	
Transparency	The impact of the guidance will vary depending on its adoption across different channels (journals, regulators, and ethics are the expected routes). By promoting full reporting of relevant protocol details in regulatory submissions, ethics applications, and protocol publications, the guidance will significantly enhance transparency.
Completeness	By addressing the checklist of recommended SPRIIT-DEFINE items in an EPDF protocol, it enables researchers to develop comprehensive, robust, detailed, and well-structured protocols, providing essential contents on the trial design, conduct, and analytical approaches. This enhances clarity, aids understanding of the planned approaches, and can potentially reduce delays, e.g., due to protocol amendments. SPIRIT-DEFINE is primarily intended to guide the planning and writing of a trial protocol before a trial begins. However, this guidance can also be useful in reviewing and enhancing the completeness of protocols for ongoing trials. For instance, researchers can clarify outcome measures or how missing data will be handled if they have not been clearly defined. The SPIRIT-DEFINE guidelines can guide revision of these definitions to

SPIRIT-DEFINE can improve:	
	improve data collection and analysis for the remainder of the trial. It is important to note that any changes to the protocol should be noted as amendments, and those should be reported to maintain the scientific integrity of the trial.
Reproducibility of methods	Reproducibility is a cornerstone of scientific research. By using the SPIRIT-DEFINE guidelines, researchers can increase the reproducibility of their trials, enhancing the reliability and trustworthiness of their findings. For instance, by requiring a clear and explicit description of the trial design with escalation and de-escalation strategies and any other adaptive features (including providing essential information on model specifications for a model-based dose-escalation design), the reader can better understand how the design would work and replicate the assessment of the design's performance and analytical methods.
Interpretation	With a full description of relevant features in the protocol guided by the checklist, a proper critical appraisal of the protocol's strengths, limitations, and any potential sources of bias is possible, assisting in the interpretation of the trial's results. Also, the subsequent trial conduct can be better interpreted if full reporting of what was pre-specified in the protocol has taken place.

5. Conclusions

The SPIRIT-DEFINE guideline provides recommendations for essential items to be addressed and included in clinical trial protocols to improve completeness and reporting quality for EPDF trials. We strongly recommend that stakeholders and reviewers adopt the SPIRIT-DEFINE checklist to enable the delivery of high quality, transformative, EPDF trials that impact clinical care.

6. Article information

6.1. Author Contributions

Professor Christina Yap, Dr Olga Solovyeva, and Dr Jan Rekowski had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Yap, Solovyeva, Ursino, Mander, Kightley, Chan, Evans, de Bono, Seymour, Rantell, Hope, Ivy, Lee, Jaki, Dimairo, Weir, Calvert. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Yap, Rekowski, Ursino, Solovyeva. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Rekowski. Administrative, technical, or material support: Patel, Solovyeva, Espinasse. All authors contributed to the DEFINE Consensus Meeting. Supervision: Yap

6.2. 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, Seagenand honoraria for speaker's fees (payable to employing institution) from Astra Zeneca, Ascelia, Bayer, Bicycle therapeutics, Bristol Myers Squibb, Celgene, Eisai, Nucana, Otsuka, Medivir, 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 Moreno Ursino acted as consultant for eXYSTAT, Saryga, PTC Therapeutics International Ltd., ImCheck Therapeutics.

Professor Melanie Calvert is Director of the Birmingham Health Partners Centre for Regulatory Science and Innovation, Director of the Centre for Patient Reported Outcomes Research, and is a National Institute for Health and Care Research (NIHR) Senior Investigator. MJC receives funding from the NIHR, UK Research and Innovation (UKRI), NIHR Birmingham Biomedical Research Centre, the NIHR Surgical Reconstruction and Microbiology Research Centre, NIHR, Applied Research Collaboration (ARC) West Midlands, UK SPINE, Research England, European Regional Development Fund DEMAND Hub at the University of Birmingham and University Hospitals Birmingham NHS

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Dr Dawn P. Richards is the volunteer Vice President of the Canadian Arthritis Patient Alliance, a patient-led and -run organisation 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.

Professor Lesley Seymour declares grant funding from AstraZeneca, Bayer, Pfizer, Merck, Roche, REPARE, Treadwell, Janssen and has provided expert testimony for CADTH. Health Canada. Professor Seymour also declares AstraZeneca stock/options ownership.

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.

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6.5. Disclaimer

This article reflects 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.

6.6. Additional Information

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