Enhancing quality and impact of early phase dose-finding clinical trial protocols: SPIRIT Dose-finding Extension (SPIRIT-DEFINE) guidance

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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 Dose-finding Extension (DEFINE) statement is a new guideline that provides recommendations for essential items that should be provided in the protocols of these 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. It is envisioned that the resulting improvements in the design and conduct of early phase clinical trials will ultimately reduce research inefficiencies and inconsistencies, driving transformational advances in clinical care.

SUMMARY POINTS

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 Dose-finding Extension (DEFINE) guideline has been extended to broaden its applicability to early phase dose-finding trials with interim strategies for dose escalation or de-escalation

After an international consensus guideline development process using the EQUATOR (Enhancing QUAlity and Transparency Of health Research) methodological framework, 32 items specific to early phase dose-finding were recommended for inclusion in clinical trial protocols

Inclusion of these SPIRIT-DEFINE items in clinical trial protocols could enhance transparency, completeness, reproducibility of methods, and trial usefulness in early phase dose-finding trials

Developing an intervention is a lengthy process pursued in stages where decisions are based on balance of benefits and risks or harms of the intervention under investigation. Lack of efficacy or evidence of harm due to adverse safety profiles are common reasons for phase 2 and phase 3 trials to be unsuccessful.[1 2] Phase 3 trial failures can reflect incorrect decisions made at earlier stages, including in early phase dose-finding (EPDF) trials (commonly known as phase 1, phase 1/2, 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 or outcome choices, and poor dose selection. The same reasons can also contribute to early discontinuation of promising interventions.

EPDF trials typically evaluate new interventions that can be used in different doses and can be pharmacological (chemical or biological—eg, drugs, vaccines, cell therapies, gene therapies), non-pharmacological (eg, radiotherapy, devices, rehabilitation, digital therapies), or a combination of both. 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 because terms such as “dose finding,” “dose level,” “dose escalation,” and “dose expansion” are widely understood. Here, dose might refer not only to the amount of dose but can also comprise frequency,

Box 1: 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 decision making process for dose escalation or de-escalation. Examples include traditional 3+3, accelerated titration, and pharmacologically guided dose escalation designs.[4 5]

Biomarker substudy

A part of a clinical trial that investigates biomarkers, which are "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 could include molecular, histological, radiographic, or physiological characteristics. A biomarker is not a measure of how an individual feels, functions, or survives."[6]

Clinical benefit

A favourable effect on a meaningful aspect of how a participant feels, functions, or survives as a result of an intervention.[7]

Delphi survey

A series of questionnaires used 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 can be considered synonymous with dosage or dosing regimen (dose or schedule), or a unit dose. The unit dose is the amount or intensity of an intervention (eg, drug quantity, radiotherapy, exercise level), or the extent to which a participant might 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 escalation or de-escalation

An incremental increase or decrease (or up-titration or down-titration) in the strength of any intervention (eg, a drug or exercise intensity level) to improve its tolerability or maximise its pharmacological or clinical effect.

Dose limiting criteria

Effects or markers that are presumably related to the intervention and that either are considered unacceptable or show the desired level of effect has been achieved and a further increase in dose is not required.[8]

Dose limiting toxicity

Side effects of an intervention that are serious enough to prevent an increase in the dose of that intervention.[5]

Dosing regimen or dosage

See dose.

Early phase dose-finding trial

An early phase trial where different doses of the investigated intervention are given 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.[9 10] They require to specify the treatment condition of interest, the population targeted by the clinical question, the variable of interest or endpoint used to answer that question, the handling strategies for intercurrent events (ie, events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question), and a population level summary of the variable or endpoint.

Expansion cohort or 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.[11]

Group

Can refer to an intervention group or 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 treatment; they are the direct opposite of benefits, against which they must be compared.[12] Harms can comprise of adverse events, adverse (drug) reactions, toxicities, treatment emergent adverse events, or those that are intolerable by participants.[12 13] They can also include tolerability assessment using patient reported outcomes as complementary to investigators' reporting.[14 15]

Interim analysis or review

A statistical analysis or review of accumulating data from an ongoing trial (interim data) to inform trial adaptations (before the final analysis), which might or might not involve treatment group comparisons.[16]

(*Continued*)

Model assisted design

A trial design that combines a clearly predetermined algorithm to guide the dose escalation or de-escalation as in rule based designs, and an underlying statistical model, as in model based designs.[17] Examples include the modified toxicity probability interval design[18] and the bayesian optimal interval design.[19]

Model based design

A trial design that assumes a relation between the dose of the intervention given to the participant and the likelihood of the participant experiencing an effect (such as toxicity or activity) and uses a parametric model to estimate that association. Examples include the continual reassessment method,[20] escalation with overdose control,[21] and the efficacy-toxicity trade-off based design.[22]

Multiple ascending dose

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

Operating characteristics

Characteristics that relate to the statistical behaviour or performance of the trial design in answering research questions. These might include the probability of correctly selecting the correct dose, statistical power, false positive error rate, bias in estimation of treatment effect, or probability of each adaptation taking place.[16 23]

Pharmacodynamics

Described as what a drug does to the body; pharmacodynamics refer to how the drug works and how it affects the body.

Pharmacokinetics

Described as what the body does to a drug; pharmacokinetics refer to the movement of the drug into, through, and out of the body. It includes the analysis of chemical metabolism and the measurement or modelling of a substance from the moment that it is used up to the point when it is completely eliminated from the body.

Prespecified decision making criteria

Planned or prespecified rules to guide decisions, describing whether, how, and when the proposed trial adaptations will be used during the trial. The criteria involve prespecifying a set of actions guiding how decisions about implementing the trial adaptations are made given interim observed data (decision rules). They also involve prespecifying limits or parameters to trigger trial adaptations (decision boundaries), for example, stopping boundaries that relate to prespecified limits regarding decisions to stop the trial or any treatment arms early.

Single ascending dose

A trial design in which a small number of participants receive one dose of a therapeutic intervention at a given dose level to assess safety or 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 that strict safety, effect, or pharmacokinetic criteria are met.

Transition points

The points or 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 1 to phase 2, or from a single ascending dose to multiple ascending dose.

Trial (design) adaptations

Prespecified changes or modifications (defined in advance) that can be made to various aspects of a trial while it is ongoing without undermining the trial's validity and integrity.[24] These prespecified modifications are driven by accruing interim data.[25] Examples include adjusting the doses; changing the predetermined sample size; stopping the trial early for efficacy, futility, or safety; and switching the allocated treatment of participants owing to a lack of benefit or safety issues.[16]

intensity, or duration of an intervention, for example.[3] The term could therefore be regarded as synonymous to dosage, or dosing regimen, or unit dose, and it can apply to interventions given alone or in combination (see the glossary in box 1 for details).

To ensure the safety of trial participants in EPDF trials, decisions regarding dose escalation or de-escalation are made based on interim data. Different dose escalation approaches have been described in the literature, for example, algorithm based (also called rule based), model assisted, and model based designs.[26 27] 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,[4 28] rose from 1.6% (20/1235) of phase 1 cancer trials published in 1991-2006[29] to 8.6% (68/788) in 2014-19.[4] Most recent data confirm 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 2017-23.[30] The complexity of these designs is reflected in a more multifaceted implementation and the requirement to specify more details on design features,[31-33] 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

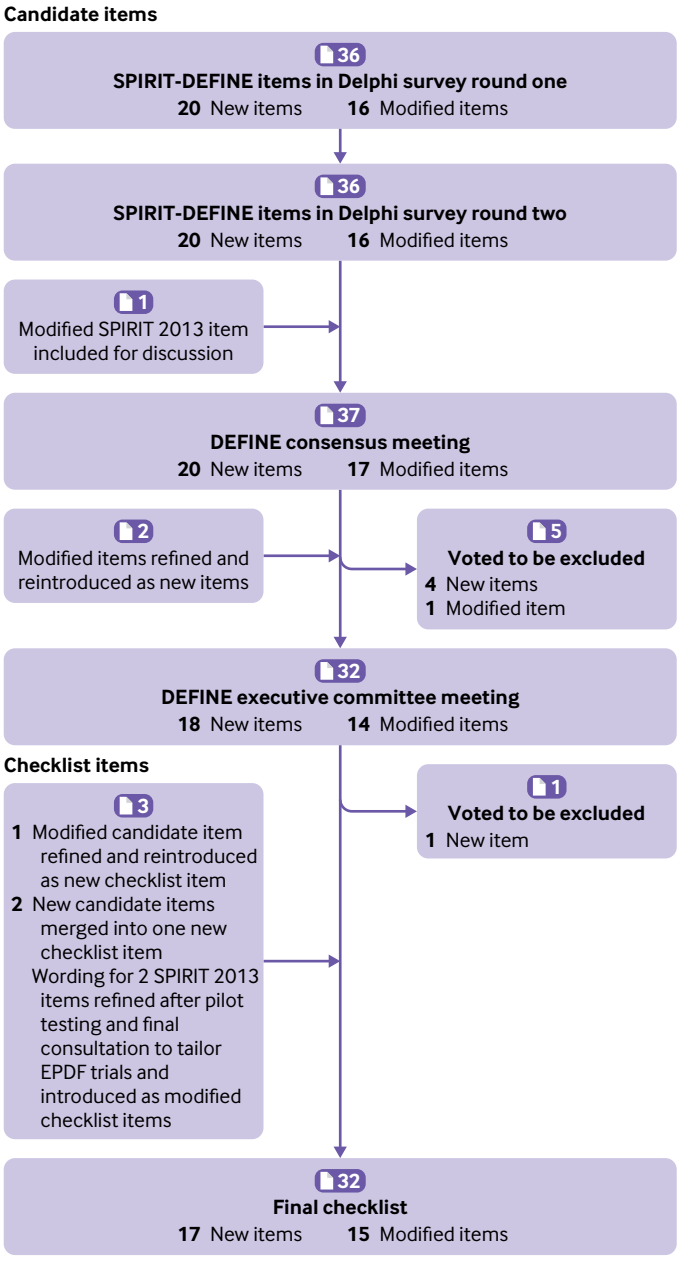

Fig 1 | Development process of items in the SPIRIT-DEFINE (Standard Protocol Items: Recommendations for Interventional Trials Dose-finding Extension) checklist

and is evaluated by external reviewers. Despite the importance of trial protocols, their content and quality vary considerably.[34] To resolve this problem, the SPIRIT 2013 (Standard Protocol Items: Recommendations for Interventional Trials) statement[35 36] 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.[37] Inadequate or unclear information on design, conduct, and analysis in EPDF protocols hinders interpretability and reproducibility. It might 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 2017-23 was reported to be substantially variable and poor, with insufficient reporting in many applicable SPIRIT 2013 items.[30] For example, sections on ethics and dissemination strategy were frequently found to be dealt with insufficiently. Although SPIRIT 2013 largely applies to many types of trial designs, trials that use specialised designs might require additional protocol considerations. Several SPIRIT extensions have been proposed to improve its usefulness for specialised topics.[38-43] Neither the SPIRIT 2013 statement nor any of its extensions, however, sufficiently cover the needs of EPDF trials—although, globally, more phase 1 trials (n=18 716) than phase 3 trials (n=10 451) were registered on ClinicalTrials.gov and first posted between 2018 and 2022. The number of phase 1 trials might even be an underestimate, because researchers are not required to register them on ClinicalTrials.gov.[44] Because no consensus driven protocol guidance exists for EPDF trials,[45] extension of the SPIRIT 2013 guidance to EPDF trials is urgently needed.

Methods

The SPIRIT Dose-finding Extension (DEFINE) was conceptualised, designed, and conducted between January 2022 and July 2023 in concordance with the EQUATOR (Enhancing QUAlity and Transparency Of health Research) network's methodological framework for guideline development.[46] The study was led by the principal investigator (CY) 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 principal investigator and key members of the executive committee 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 No CCR5460). The UK 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.

Generation of candidate protocol items

An initial SPIRIT-DEFINE checklist was drafted based on SPIRIT 2013,[35] 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).[37 47] We used the multidisciplinary executive committee's expert opinions and unpublished or grey literature including regulatory and industry advice documents to further refine the checklist as described.[45 47] Major international stakeholder groups were consulted, and their protocol or guidance templates included (when available), to inform the generation and wording of the candidate

Table 1 | Recommended checklist items to consider in EPDF clinical trial protocols from SPIRIT 2013 and SPIRIT-DEFINE checklists

	Standard SPIRIT 2013 checklist item		SPIRIT-DEFINE checklist item for EPDF trials	
Category and 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 (eg, 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 Organization Trial Registration Data Set	2b	
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 or preclinical research
			6a.3*	Summary of findings from previously generated preclinical and translational studies to support any planned biomarker substudies (where applicable)
	6b	Explanation for choice of comparators	6b	
Objectives	7	Specific objectives or hypotheses	7†	Specific objectives (eg, relating to safety, activity, pharmacokinetics, pharmacodynamics, recommended dose(s))
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8a.1†	Description of trial design elements, such as dose escalation or de-escalation strategy, number of treatment groups, allocation ratio if relevant, and details of any prespecified trial adaptations
			8a.2*	Trial design schema to show the flow of major transition points (eg, dose escalation to dose expansion, phase 1 to phase 2, single ascending dose to multiple ascending dose)
			8a.3*	Statistical methods or rationale underpinning the trial design
			8a.4*	Prespecified interim decision making criteria or rules to guide the trial adaptation process (eg, dose escalation or 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 prespecified
			8a.5*	Starting dose(s) with rationale
			8a.6*	Range of planned dose levels with rationale
			8a.7*	Presentation of planned dose levels (eg, as a diagram, table, or infographic), where applicable
			8a.8*	Skipping of dose level(s), if applicable
			8a.9*	Planned cohort size(s) (eg, fixed, flexible, adaptive)
			8a.10*	Dose allocation method within a dose level (including sequence and interval between dosing of participants, eg, 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 (eg, 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 interventions (eg, surgeons, psychotherapists)	10	

(*Continued*)

Table 1 | Continued

	Standard SPIRIT 2013 checklist item		SPIRIT-DEFINE checklist item for EPDF trials	
Category and section	Item No	SPIRIT 2013	Item No	SPIRIT-DEFINE
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 (eg, 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 (eg, dose change in response to harms, participant request, or improving or worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, 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 (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12†	Primary, secondary, and other outcomes (which include those intended for prespecified adaptations), 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.
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 (eg, computer generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16a.1	
			16a.2*	Any prespecified rule or algorithm to update allocation with timing and frequency of updates, if applicable
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, 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 (eg, 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 intervention during the trial	17b	
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 (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, 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 (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	19	

(*Continued*)

Table 1 | Continued

	Standard SPIRIT 2013 checklist item		SPIRIT-DEFINE checklist item for EPDF trials	
Category and section	**Item No**	**SPIRIT 2013**	**Item No**	**SPIRIT-DEFINE**
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 prespecified 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 (eg, safety, dose(s), treatment effects) and to make inferences
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	20b†	Statistical methods for additional analyses (eg, subgroup and adjusted analyses, pharmacokinetics or pharmacodynamics, biomarker correlative analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	20c.1†	Analysis population(s) (eg, evaluable population for dose-finding, safety population)
			20c.2*	Strategies for handling intercurrent events occurring after treatment initiation (eg, 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 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 or group; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details, 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, eg, 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 harms such as adverse events (eg, toxicities) and other unintended effects of trial interventions or trial conduct, including time frames of reporting these events or effects to allow informed interim decision making (eg, before 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 dissemination				
Research ethics approval	24	Plans for seeking REC/IRB approval	24	
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, 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 experience 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 (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	31a.1	
			31a.2*	Plans for sharing results (eg, safety, activity) externally while 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	

(*Continued*)

Table 1 | Continued

	Standard SPIRIT 2013 checklist item		SPIRIT-DEFINE checklist item for EPDF trials	
Category and section	Item No	SPIRIT 2013	Item No	SPIRIT-DEFINE
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, eg, a flow diagram or table) projecting in advance how a proposed dose-finding design will recommend doses based on participants' key outcomes

DEFINE=Dose-finding Extension; DMC=data monitoring committee; EPDF=early phase dose-finding IRB=institutional review board; REC=research ethics committee; SPIRIT=Standard Protocol Items: Recommendations for Interventional Trials.
A downloadable version of the SPIRIT-DEFINE checklist is available in web appendix 2. The checklist should be read in conjunction with the SPIRIT 2013 explanation and elaboration document[36] 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. The term "dose" in the checklist might be considered synonymous and used interchangeably with dosage or dosing regimen (dose and schedule) or a unit dose. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license and reproduced with permission.
*New items that should only be applied in reference to SPIRIT-DEFINE.
†Modified items that require reference to both SPIRIT 2013 and SPIRIT-DEFINE.

items and the structuring of the eventual checklist. These groups included phase 1 units accredited by the Medicines and Healthcare products Regulatory Agency, funders, pharmaceutical companies, contract research organisations, and research ethics committees.[45 47]

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 (fig 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.[47] The Delphi process adhered to established methodological guidance.[48-50] 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

Box 2: Overview of new and modified items in the SPIRIT-DEFINE checklist

Administrative information (one modified item)
- Identifying the early phase dose-finding design in the title of the protocol.

Introduction (12 new items, three modified items)
- Incorporating non-clinical or preclinical research informing an EPDF trial[52] and any planned biomarker substudies in the background and rationale section.[53]
- Highlighting key objectives for early phase dose-finding trials in the objectives section.
- Expanding the trial design section to include adaptive features,[16 54] starting doses, and range of dose levels with rationale, skipping of doses, planned cohort size, dose allocation method, and any expansion cohorts.[37 52 55-57]

Methods: participants, interventions, and outcomes (five modified items)
- Providing enhanced intervention details[3] including reporting them for each dose level and describing prespecified criteria for dose discontinuations, modifications, or delays.[52]
- Extending the description of outcomes to any outcomes that will be used to inform planned adaptations.[16]
- Including clinical and statistical assumptions supporting the planned sample size and operating characteristics, which relate to the statistical behaviour or performance of the trial design[23 51] (see box 1 for details).

Methods: assignment of interventions (for controlled trials) (one new item)
- Detailing any rule or algorithm to update the allocation strategy.[16]

Methods: data collection, management, and analysis (two new items, three modified items)
- Providing increased details regarding statistical methods to cover adaptive features, analysis populations, as well as handling of missing data and intercurrent events that occur after treatment initiation.[16 51]

Methods: data monitoring (three modified items)
- Providing increased details regarding the interim decision making process[16] and reporting of harms (eg, toxicities, adverse events).

Dissemination policy (one new item)
- Including plans for sharing results while the trial is still ongoing.

Appendices (one new item)
- Adding a new section to cover dose transition pathways or dose decision paths.[18 33 58]

SPIRIT=Standard Protocol Items: Recommendations for Interventional Trials; DEFINE=Dose-finding Extension.

two, participants were presented with the distribution of round one ratings for each item as well as their own prior ratings.

According to a predetermined rule, items voted as not important (scores 1-3) by at least 80% of respondents in round one were eliminated between rounds subject to confirmation by the executive committee. Items voted as critically important (scores 7-9) by at least 70% of respondents in round one were considered to have reached consensus and were automatically included in the SPIRIT-DEFINE checklist[45] (fig S1 in 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 10 items qualified to be discussed at the consensus meeting. The process, decision criteria, and voting results of the SPIRIT-DEFINE candidate items are described in figure S1 and table S1 in 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.[47]

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 11-12 October 2022 (tables S2 and S3 in web appendix 1 list the affiliations or roles of participants). The Delphi survey findings were presented alongside supporting evidence, written comments from participants, and examples from protocols for each candidate item to be reviewed at the consensus meeting. After 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 (fig S1 in web appendix 1).

Of 10 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 (fig 1; table S1 in web appendix 1).

Final consultation and piloting of the checklist

After the consensus meeting, the DEFINE executive committee and consensus participants refined the language of the items and their related explanations. During the pilot testing phase of the checklist (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.

Box 3: Advantages of the SPIRIT-DEFINE checklist

The SPIRIT-DEFINE checklist can improve:

Transparency

The impact of the guidance will vary depending on its adoption across different channels (journals, regulators, and ethics committees 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 using 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 checklist enhances clarity, aids understanding of the planned approaches, and could reduce delays, for example, owing 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 improve data collection and analysis for the remainder of the trial. Any changes to the protocol should be noted as amendments, and 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), readers 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 what was prespecified in the protocol is fully reported.

SPIRIT=Standard Protocol Items: Recommendations for Interventional Trials; DEFINE=Dose-finding Extension.

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. The downloadable version of the SPIRIT-DEFINE checklist is available in web appendix 2.

It is useful to note that terminology and definitions associated with EPDF trials can vary, for instance, for different interventions and disease areas. Key terms used throughout this article are provided in the glossary (box 1).

To enable readers to comprehend the strategies for dose escalation or de-escalation 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 (eg, adaptive features, timing of interim analyses, planned dose range with starting dose, dose allocation method, interim decision making criteria, any expansion cohorts, 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.[16] 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.[51] 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[9 10]).

In more detail, the new and modified items specific to EPDF trials are listed in box 2.

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

For items that remained unchanged, we refer users to the SPIRIT 2013 statement paper[35] and its explanation and elaboration document.[36] Detailed explanations 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,[59] 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,[27 59] researchers should provide the rationale for choosing a target risk or toxicity rate or acceptable range,[60] the details on the dose transformation (including the full skeleton and its elicitation), and bayesian prior distributions chosen, if applicable.[51] For rule based designs, such as 3+3 or Rolling 6,[61] the rationale for their use should be outlined. For other adaptations, such as early stopping for futility, the underlying statistical methods (eg, conditional power, predictive power, or posterior probability of treatment effect) should be clearly specified.[16 51]

For item 20c.2, authors should describe methods to be used to handle missing data, and detail strategies for handling intercurrent events—that is, events (such as dosing delays, reductions, or interruptions) occurring after treatment initiation that might 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 might also include withdrawal of consent or deaths unrelated to treatment or disease. Different strategies might be used for different types of intercurrent events,[51] and sensitivity analyses can be planned to assess the effect of the chosen strategies on the trial results.

Researchers should clearly specify the rationale for the starting dose and choice of the method, for example, according to current regulatory guidelines[52 62] (item 8a.5), as well as the trial adaptation process and stopping rules (item 8a.4). Dose transition pathways 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 (eg, what the next dose would be if a certain number of participants in a cohort experience a clinically significant adverse event).[18 33 58] For instance, if two participants experienced no clinically significant adverse events, a design might recommend escalating to the next higher dose, but if both participants experienced clinically significant adverse events, the same design might recommend de-escalating to a lower dose. The exact content and form of dose transition pathways can vary depending on the specific features of the trial design, and no standard format exists.

Discussion

Owing 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 2 and phase

3 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 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 EQUATOR methodological framework. The key difference is that SPIRIT-DEFINE focuses on 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 or non-oncology) or participant population (eg, adults or paediatric groups, patients or 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 might apply 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. Box 3 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.[47 63] 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 (table S2 in web appendix 1 shows the roles and 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 (eg, groups outside Europe, North America, and Asia) holding different views were potentially under-represented 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 with randomised parallel group trials. The SPIRIT-DEFINE extension contains several new or modified items that might 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 SPIRIT-DEFINE

Wide dissemination of the SPIRIT-DEFINE guidance is essential to increasing its appropriate uptake, and this will be done as previously outlined,[45] 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 might 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[63] guidelines.

Conclusions

The SPIRIT-DEFINE guideline provides recommendations for essential items to be considered 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.

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Web appendix 1: Supplementary materials
Web appendix 2: SPIRIT-DEFINE downloadable checklist
Web appendix 3: Acknowledgements of contributors to the development of SPIRIT-DEFINE guidance