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

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Summary

Transparent and accurate reporting in early phase dose-finding (EPDF) clinical trials is crucial for informing subsequent larger trials. The SPIRIT statement, designed for trial protocol content, does not adequately cover the distinctive features of EPDF trials. Recent findings indicate that the protocol contents in past EPDF trials frequently lacked completeness and clarity. To address this gap, the international consensus-driven SPIRIT-DEFINE checklist was developed through a robust methodological framework for guideline development, with the aim to improve completeness and clarity in EPDF trial protocols. The checklist builds on the SPIRIT statement, adding 17 new items and modifying 15 existing ones.

The SPIRIT-DEFINE explanation and elaboration (E&E) document provides comprehensive information to enhance understanding and usability of the SPIRIT-DEFINE checklist when writing an EPDF trial protocol. Each new or modified checklist item is accompanied by a detailed description, its rationale with supportive evidence, and examples of good reporting curated from EPDF trial protocols covering a range of therapeutic areas and interventions. We recommend utilising this paper alongside the SPIRIT statement, and any relevant extensions, to enhance the development and review of EPDF trial protocols.

By facilitating adoption of the SPIRIT-DEFINE statement for EPDF trials, this E&E document can promote enhancement of methodological rigour, patient safety, transparency, and facilitate the generation of high-quality, reproducible evidence that will strengthen the foundation of early phase research and ultimately improve patient outcomes.

Funding This work is a further extension of the SPIRIT-DEFINE study, which obtained no external funding. The principal investigator (CY) used internal staff resources, together with additional resources from external partners, to conduct this study. The SPIRIT-DEFINE study is a component of the DEFINE project, which also developed the MRC/NIHR funded CONSORT-DEFINE guidance. ICR-CTSU receives programmatic infrastructure funding from Cancer Research UK (C1491/A25351; CTUQQR-Dec22/100004), which has contributed to accelerating the advancement and successful completion of this work.

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

Research in context

Evidence before this study

The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement and its extensions offer evidence-based guidelines for the essential content of a clinical trial protocol. Notably, the recently published SPIRIT-DEFINE extension focuses on early phase dose-finding trials.

Added value of this study

This study provides a deeper understanding of the SPIRIT-DEFINE items and offers practical guidance on how to write a protocol that effectively addresses them. Examples of new and modified items in the SPIRIT-DEFINE guidelines were gathered from publicly available protocols on ClinicalTrials.gov or from published articles that included protocols in their supplementary materials.

Implications of all the available evidence

The examples provided will enable the trial community to develop more comprehensive, transparent, and high-quality early phase dose-finding trial protocols, leading to better implementation, fewer amendments, and improved appraisal for better patient care.

Introduction

Early phase clinical trials are a critical step in the clinical development process. The transparent and complete reporting of the design and execution of early phase dose-finding (EPDF) studies is paramount, as their findings are used to inform the design of subsequent larger clinical trials, maximising the potential for successful further development. For the scope of this manuscript, an EPDF trial is defined as an early phase trial in which 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 (Supplementary Box 1).[1,2] This definition encompasses dose-optimisation trials, which can include dose-escalation and dose de-escalation features aimed at determining the dosage(s) that maximise the benefit/risk profile or achieve the desired therapeutic effect while minimising toxicity.[3,4] A comprehensive and well-written trial protocol serves as the core document defining how a clinical trial will be conducted and how data from the study will be analysed. However, assessments of the quality of EPDF trial protocols have revealed significant shortfalls in documentation, with several key items being inadequately addressed. For instance, items such as informed consent materials, dissemination policy, dose transition pathways, definition of the dose-escalation analysis population, and operating characteristics of designs have been poorly reported, with fewer than 40% of trials including each item.[5]

Although the SPIRIT statement was established to provide evidence-based guidance for the essential content of a trial protocol, it does not fully cover all the specific features of EPDF trials. The SPIRIT-DEFINE (Standard Protocol Items: Recommendations for Interventional Trials Dose-finding Extension) checklist[6] was generated to improve reproducibility and clarity of EPDF trials by building on the core checklist outlined in SPIRIT, incorporating 17 new items and modifying 15 existing items.

The development of SPIRIT-DEFINE adhered to the methodological framework for guideline development[7] recommended by the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network. Further details regarding the scope and methods have been published elsewhere.[1,2,8] This SPIRIT-DEFINE explanation and elaboration (E&E) document aims to enhance the understanding and usability of the SPIRIT-DEFINE checklist when writing an EPDF protocol.

Methods

For almost all new or modified items in the SPIRIT-DEFINE checklist (Table 1), we include at least one example sourced from a comprehensive methodological review of 106 EPDF trials obtained from ClinicalTrials.gov by Villacampa et al. (2023).[5]

Search strategy and selection criteria

A working group was tasked primarily with reviewing these EPDF trial protocols to source examples across a variety of therapeutic areas that evaluated both pharmacological interventions (e.g., drugs, vaccines, cell therapies, gene therapies; in the oncology and non-oncology disease contexts) and non-pharmacological interventions (e.g., lifestyle or dietary interventions, digital therapeutics, rehabilitation, or radiotherapy) published between 2011 and 2023. We specifically sought protocols that adequately addressed the new or modified items in the SPIRIT-DEFINE checklist. This comprehensive approach allowed us to curate a list of high-quality examples from a wide range of disease contexts. In most cases, we provide at least two examples — one focused on oncology and the other on a non-oncology context. Additionally, the examples are often selected to illustrate alternative methods of presenting the required information, offering a broader perspective on how to approach these items effectively. For a few items, examples may be exclusively from oncology, depending on what was available. In instances where we could not locate suitable examples, we engaged the wider group of co-authors and external experts to recommend examples from protocols. If we remained unable to find relevant examples, we expanded our search to encompass published protocol papers, protocols that were not publicly accessible but willingly shared by the chief investigators, statistical analysis plans, and published trial reports; where required, we created and modified examples to illustrate good reporting practice.

Subsequently, the lead authors (GV, MU, CY) selected examples for each item, with a preference for examples from accessible protocols. A detailed description of each item and its rationale with supportive evidence is also provided, emphasising its importance and highlighting the main issues to consider.

Role of the funding source

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

Recommendations

Here, we present the 32 SPIRIT-DEFINE items, of which 17 are new and 15 are modified. Each item is accompanied by at least one example, explanations and elaborations, and rationale. Examples from published protocols are quoted verbatim. Any reference numbers cited in the original quoted text are denoted by superscript [reference] to distinguish them from the references cited in this E&E paper. For the sake of clarity, acronyms in examples are fully introduced at their first appearance. Additional comments are provided in italics below the example, where examples may lack some details or require further elaboration.

When drafting protocols for EPDF trials, authors are strongly encouraged to use this SPIRIT-DEFINE E&E

Category and section	Standard SPIRIT 2013 checklist item		SPIRIT-DEFINE checklist item for EPDF trials	
	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[b]	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 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[b]	Description of research question(s) and justification for undertaking the trial, including summary of relevant clinical studies (published and unpublished) examining benefits and harms for each intervention
			6a.2[a]	Summary of key findings from relevant non-clinical or preclinical research
			6a.3[a]	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[b]	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[b]	Description of trial design elements, such as dose escalation or de-escalation strategy, number of treatment groups, allocation ratio if relevant, and details of any prespecified trial adaptations
			8a.2[a]	Trial design schema to show the flow of major transition points (e.g., dose escalation to dose expansion, phase 1 to phase 2, single ascending dose to multiple ascending dose)
			8a.3[a]	Statistical methods or rationale underpinning the trial design
			8a.4[a]	Prespecified interim decision making criteria or rules to guide the trial adaptation process (e.g., 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[a]	Starting dose(s) with rationale
			8a.6[a]	Range of planned dose levels with rationale
			8a.7[a]	Presentation of planned dose levels (e.g., as a diagram, table, or infographic), where applicable
			8a.8[a]	Skipping of dose level(s), if applicable
			8a.9[a]	Planned cohort size(s) (e.g., fixed, flexible, adaptive)
			8a.10[a]	Dose allocation method within a dose level (including sequence and interval between dosing of participants, e.g., sentinel or staggered dosing)
			8a.11[a]	Dose expansion cohort(s), if applicable, with rationale

(Table 1 continues on next page)

Category and section	Standard SPIRIT 2013 checklist item		SPIRIT-DEFINE checklist item for EPDF trials	
	Item No	SPIRIT 2013	Item No	SPIRIT-DEFINE
(Continued from previous page)				
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 interventions (e.g., surgeons, psychotherapists)	10	
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11a[b]	Interventions for each dose level (within each group) with sufficient details to allow replication, including administration route and schedule showing how and when they 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[b]	Criteria for dose discontinuation, dose modifications, and dosing delays of allocated interventions for a given trial participant (e.g., dose change in response to harms, participant request, or improving or worsening disease)
	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, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12[b]	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[b]	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[b]	Estimated number of participants (minimum, maximum, or expected range) needed to address trial objectives and how it was determined, including clinical and statistical assumptions supporting any sample size and operating characteristics
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 document that is unavailable to those who enrol participants or assign interventions	16a.1	
			16a.2[a]	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 (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 intervention during the trial	17b	

(Table 1 continues on next page)

Category and section	Standard SPIRIT 2013 checklist item		SPIRIT-DEFINE checklist item for EPDF trials	
	Item No	SPIRIT 2013	Item No	SPIRIT-DEFINE
(Continued from previous page)				
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 found, if not in the protocol	19	
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[b]	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[a]	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[b]	Statistical methods for additional analyses (e.g., subgroup and adjusted analyses, pharmacokinetics or 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[b]	Analysis population(s) (e.g., evaluable population for dose-finding, safety population)
			20c.2[a]	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 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[b]	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[b]	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[b]	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported harms such as adverse events (e.g., 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 (e.g., 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 (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	

(Table 1 continues on next page)

Category and section	Standard SPIRIT 2013 checklist item		SPIRIT-DEFINE checklist item for EPDF trials	
	Item No	SPIRIT 2013	Item No	SPIRIT-DEFINE
(Continued from previous page)				
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 (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	31a.1	
			31a.2[a]	Plans for sharing results (e.g., 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	
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[a]	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

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. The SPIRIT checklist should be used in conjunction with the SPIRIT 2013 explanation and elaboration document[9] 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 CC BY-NC-ND 3.0 and was reproduced with permission. [a]New items that should only be applied in reference to SPIRIT-DEFINE. [b]Modified items that require reference to both SPIRIT 2013 and SPIRIT-DEFINE.

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

alongside the SPIRIT-DEFINE statement,[6] the SPIRIT statement, and E&E[9,10] (or any future updates) for unchanged items, and any other applicable SPIRIT extensions.[11]

As variations in the terminology and definitions exist across disciplines and geographical areas in EPDF trials, key terms used throughout are provided in the Glossary (Supplementary Box 1).[6]

Section: Administrative information

Item 1 [modified] 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

Example 1. "A First-in-Human, Open-Label, Multicenter, Dose-Escalation Phase I Clinical Study of Single-Agent RO7172508 in Patients with Locally Advanced and/or Metastatic CEA-Positive Solid Tumors."[12]

Example 2. "A Phase 1, Single-Blind, Randomized, Placebo Controlled, Parallel-Group, Multiple-Dose-Escalation Study to Investigate Safety, Tolerability, and Pharmacokinetics of Emodepside (BAY 44-4400) After Oral Dosing in Healthy Male Subjects."[13]

Example 3. "DOSE ranging in UPper limb rehabilitation post stroke (DOSE-UP): Phase I trial."[14]

Explanation. The SPIRIT statement highlighted the importance of indexing to identify a trial in literature or internet searches.[9] SPIRIT-DEFINE extends this requirement to help ensure that an EPDF trial is appropriately indexed and easily identified. Varying

terminology is used for EPDF trials in different disease areas. For protocols published in scientific journals, we encourage authors to provide the above information in the title and/or the abstract to enable such trial protocols to be easily indexed.

The title should identify the features of an EPDF trial (e.g., first-in-human, dose-finding, dose escalation/de-escalation, dose titration, single ascending dose, multiple ascending dose) and/or the phase of the trial (phase I, phase I/II), and, if applicable, authors should use "randomised" if any of the participants are planned to be randomly assigned treatment (see Example 2).

Section: Introduction

Item 6a.1 [modified] Description of research question(s) and justification for undertaking the trial, including summary of relevant clinical studies (published and unpublished) examining benefits and harms for each intervention

Example 1. "2.1 Study rationale

The purpose of the study is to rapidly describe the safety, tolerability, immunogenicity, and potential efficacy of 4 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19 in healthy adults. There are currently no vaccines to prevent infection with SARS-CoV-2 or antiviral drugs to treat COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is upmost importance.

[...]

2.3 Benefit/Risk assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic option available. While there are currently no data available from clinical trial on the use of BNT162 vaccines in humans, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, support a favorable risk/benefit profile. Anticipated adverse events (AEs) after vaccination are expected to be manageable using routine symptom-driven standard of care as determined by investigators and, as a result, the profile of these vaccine candidates support initiation of this Phase 1/2 clinical study.

[...]

2.3.1 Risk assessment

This example is represented in Fig. 1. The example has been adapted—only a portion of the original table is presented here, which has been reshaped into three columns with corresponding rewording."[15]

Example 2. "Low molecular-weight heparins have a long and well-established role in the prevention of venous thromboembolism (VTE) in subjects undergoing total knee replacement (TKR) surgery, and while very effective with an acceptable bleeding risk, subcutaneous (SQ) dosing once or twice a day is required. More recently, several direct-acting oral anticoagulants (DOACs) (e.g, apixaban, rivaroxaban, dabigatran, edoxaban) have been approved for use in TKR, based on comparisons with the low molecular-weight heparin (LMWH), enoxaparin, and their use has become more widespread in this patient population. Apixaban starting 12–24 h after TKR surgery demonstrated superior efficacy compared with enoxaparin 40 mg once daily and similar efficacy to enoxaparin 30 mg twice daily, with numerically less bleeding than both enoxaparin regimens. Apixaban was chosen as the active comparator for this study because it is orally administered and compares favorably with enoxaparin for both efficacy and bleeding endpoints.

JNJ-64179375 is a first-in-class, recombinant, fully human IgG4 monoclonal antibody that binds reversibly with high affinity and specificity to the exosite-1 region on thrombin. By only blocking exosite-1, the catalytic activity of the protease is maintained. Therefore, this unique mechanism of action of JNJ-64179375 may offer the potential for noninferior (or superior) efficacy

Risk Type	Details	Rationale/Evidence
Local reactions and systemic events following vaccination	Local reactions can include injection site redness, swelling, and injection site pain; systemic events can include fever, fatigue, headache, etc.	Common adverse reactions seen in other vaccines as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines.
Novel vaccine complications	Unknown adverse events and laboratory abnormalities due to the novelty of the vaccine.	One of the first two trials with the BNT162 vaccine, with no prior clinical data available.
COVID-19 disease enhancement	Potential for enhanced disease after vaccination.	Seen with vaccines for respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus.
Attendance during a pandemic	Attending healthcare facilities during the COVID-19 pandemic increases risk.	Risk of increased exposure to SARS-CoV-2, especially without social distancing and proper PPE.
Venipuncture	Bleeding, bruising, hematoma formation, and infection at the venipuncture site.	General risks associated with venipuncture procedures.

FDA: United States Food and Drug Administration; PPE: personal protective equipment.

Fig. 1: Item 6a.1, description of research question(s) and justification for undertaking the trial, Example 1—obtained from the study protocol of NCT04368728, which is available as supplementary material to Polak et al.[15] The example has been adapted—only a portion of the original table is presented here, which has been reshaped into three columns with corresponding rewording.

compared with currently available anticoagulant drugs (e.g, vitamin K antagonists, enoxaparin, and DOACs) with a reduced risk of bleeding. Given that TKR surgery carries a high risk of VTE combined with the hemostatic challenges of surgery, it provides a good setting to evaluate the relative efficacy and safety (bleeding) characteristics of novel anticoagulants. As a monoclonal antibody, JNJ-64179375 has an expected duration of action of approximately 4 weeks, thereby allowing for the postoperative administration of a single IV dose to be used for VTE prophylaxis after TKR surgery. Based on the preclinical and Phase 1 studies conducted to date, JNJ-64179375 is anticipated to have a favorable safety profile with respect to bleeding risk. Therefore, JNJ-64179375 offers the potential for an efficacious treatment that has limited bleeding, with a simpler dosing regimen compared with currently available oral or parenteral treatments."[16]

Explanation. Compared to subsequent trial phases, EPDF trials often involve a higher level of uncertainty around the balance of risk and benefit for participants due to limited previous evidence.[17] These trials may represent the first time a new intervention is being tested in healthy volunteers, patients, or specific participant subgroups. Thus, providing sufficient information for funders, ethics boards, regulatory authorities, and potential participants (and their family members, and/or their parent/legal guardian, in the case of paediatric studies) to understand the relevance and significance of the research question and to assess the ethical and scientific rationale for conducting the trial is crucial.[9] A clearly defined research question also helps the researchers to appropriately describe study objectives and to select a trial design and statistical analyses that address the trial objectives.

Authors should describe the importance of the research question(s), justify the need for the trial (see, e.g., Example 1, which provides a clear study rationale section), and detail what needs to be addressed before proceeding to further evaluation in later stage trials. It is helpful to include a reference to a systematic review of previous similar trials or an indication of the absence of such trials.[9] This item focuses on the justification of the need for the trial in the context of available evidence from relevant clinical trials examining potential benefits and harms,[9] whereas item 6a.2 addresses relevant non-clinical or preclinical research.

Item 6a.2 [new] Summary of key findings from relevant non-clinical or preclinical research

Example 1. "Our new optimised vector, AAV2/5-OPTIRPE65, provides 300-fold greater efficacy in animal models compared with that used in our previous trial.

The toxicity of a single dose of AAV2/5-OPTIRPE65 administered as a subretinal injection has been evaluated in mice and rabbits. Long-term (9-month) overexpression of RPE65 protein in the mouse RPE did not result in gross toxicity, as determined by clinical observations of health and behaviour or by increased mortality, or in ocular toxicity, as determined by functional and structural assessments of retinal health (Study RPE65-02/01). In 8-week single dose studies in mice (Study RPE65-02/02) and rabbits (Study RPE65-02/04), subretinal administration of AAV2/5-OPTIRPE65 did not result in local adverse effects on retinal structure or function. No overt systemic effects on health, as assessed by appearance or behaviour of the animals, or by macroscopic examination of the major organs post-mortem, were observed. Low level dissemination of vector to the liver, adrenal glands, and draining lymph nodes was detected in mice, and low level dissemination of vector to the liver and tissues of the optic tract was detected in rabbits. This low level dissemination of vector did not result in pathological changes. Subretinal administration of AAV2/-OPTIRPE65 in an Rpe65-deficient mouse strain did not result in adverse local or systemic effects (Study RPE65-02/03).

No immune responses against the RPE65 protein were detected in a 4-week, single dose study of bilateral subretinal injection in the Rpe65-deficient (Rpe65−/−) mouse Study (RPE65-02/03). There were some immune responses against the vector capsid in this study and in the 8-week single dose toxicity and biodistribution studies of AAV2/5-OPTIRPE65 in mice (Study RPE65-02/02) and rabbits (Study RPE65-02/04), as would be expected after administration of Adeno-Associated Virus (AAV) vector. These were only detectable using the neutralising antibody assay. Anti-AAV5 immune responses were not more pronounced in the Rpe65-deficient (Rpe65−/−) mouse compared with wild type (WT) mice, and did not correlate with any changes in any of the other assessments."[18]

Example 2. "The pharmacokinetics of GSK2857916 Antibody drug conjugate (ADC) and cys-mcMMAF has been investigated following IV (bolus) administration to the rat and cynomolgus monkey. Plasma concentrations were quantifiable over the entire sampling period (144 h in rat and 504 h in cynomolgus monkey) at doses of 10, 30 and 100 mg/kg for the rat and 3, 10, and 30 mg/kg for the cynomolgus monkey. The maximum concentrations were observed at 0.25 h (first sampling occasion) in the rat and between 0.25 and 6 h in the cynomolgus monkey. Systemic exposure (maximum plasma drug concentration, Cmax, and area under the concentration time curve over the dosing interval, AUC(0-t)) for ADC and total increased approximately proportionally with increasing dose and there was no notable sex difference. Similar concentrations between ADC and total antibody suggest that GSK2857916 remains largely intact in circulation. This is further confirmed with the relatively low levels of cys Monomethyl auristatin F (cys-mcMMAF) observed in both plasma and urine. GSK2857916 was

cleared slowly (total plasma clearance; rat 0.333 mL/h/kg and cynomolgus monkey 1.07 mL/h/kg). The mean steady state volume of distribution (Vss) was low in both the rat and monkey being 97.6 mL/kg and 105 mL/kg, respectively; suggesting GSK2857916 is mainly confined to the systemic circulation."[19]

Explanation. Information on non-clinical or preclinical data (e.g., in-vitro, in-vivo, or in-silico studies[20,21]), pharmacokinetics, pharmacodynamics, and toxicology and their translation to humans is an important basis for planning and conducting EPDF trials, particularly when clinical evidence has not yet been acquired. Indeed, in initial human trials, this data is commonly utilised to establish the starting dose and dose increments and to pinpoint potential safety concerns.

The protocol should include a summary of available key non-clinical data and results, focusing on, where applicable: the relevance of animal models (e.g., which species are considered most relevant for human translation); information uncertainty (given the sample size of previous studies); non-clinical pharmacokinetic and toxicokinetic data; safety; pharmacology; toxicology; genotoxicity; the nature of the target; and pharmacodynamics.[22] If not provided, an explanation why this information is not relevant for planning the trial should be provided, e.g., if previous trials in other settings, such as diseases or participant populations, were already performed and the planned trial is based on this clinical evidence. In these cases, supporting evidence of these trials should be provided (c.f. item 6a.1).

Item 6a.3 [new] Summary of findings from previously generated preclinical and translational studies to support any planned biomarker substudies (where applicable)

Example 1. "Based on preclinical studies targeting B cell maturation antigen (BCMA), JNJ-64007957 has shown efficacy in vitro in multiple myeloma cells and prolonged overall survival in xenograft rodent models (mice) in vivo. These results indicate that JNJ-64007957 may have a potential therapeutic relevance for patients with relapsed or refractory multiple myeloma for whom only limited treatment options are available and no known curative therapy exists."[23]

Example 2. "Preclinical xenograft data confirms the activity of SRA737 as a single-agent in diverse genetically-aberrant tumor settings including models of pediatric neuroblastoma, acute myeloid leukemia (AML), double-hit lymphoma and triple negative breast cancer. A number of genetic alterations are thought to predict sensitivity to SRA737 therapy including (i) activating mutations or amplification of growth promoting oncogenes; (ii) loss-of-function mutations or deletions in tumor suppressor pathways controlling the G1/S checkpoint; (iii) defects in DNA damage response (DDR) signaling and DNA repair genes; and (iv) gain of function mutations of replication stress genes. Tumor indications of high unmet medical need with high prevalence of these genetic aberrations include metastatic colorectal, ovarian, prostate, head and neck, and non-small cell lung cancer."[24]

Explanation. There is growing interest in the use of biomarkers to aid the evaluation of new treatments in EPDF trials.[25] Biomarkers may help trialists decide on recommended dose(s) for subsequent testing or confirm mechanisms of action. They may indicate biological activity of the intervention (e.g., drug), indicate the likelihood, presence, or extent of harm (e.g., toxicity of a drug), identify participant subgroups more likely to benefit or experience harm, or serve as an early or surrogate endpoint for clinical benefit. However, many EPDF trials are designed based on limited preliminary information obtained from non-clinical/preclinical testing.[26] To optimise success in biomarker studies, researchers need to have a clear rationale and scientific hypothesis supported by existing findings from previous studies on the planned biomarkers, even if limited.

Where applicable, authors should provide background information to support each planned biomarker substudy, including the biological rationale and research question(s) and objective(s), as well as details on any relevant non-clinical/preclinical, translational, and clinical data (if available). Correlative studies, which are research activities that investigate the relationships between biological markers and clinical outcomes, should align with exploratory or correlative objectives.[27] For further information, see definitions and recommendations from a regulatory standpoint for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data, and sample coding categories[28–30] and related guidelines for correlative studies in clinical trials.[31]

Item 7 [modified] Specific objectives (e.g., relating to safety, activity, pharmacokinetics, pharmacodynamics, recommended dose(s))

Example 1. "Primary objective.

- To assess the safety, tolerability and toxicities of intravesical and intravenous pembrolizumab after transurethral resection of bladder tumour (TURBT) in patients with intermediate risk non-muscle invasive bladder cancer (NMIBC)

Secondary objectives.

- To provide a preliminary assessment of efficacy of treatment with intravesical pembrolizumab in patients with intermediate risk NMIBC
- To provide a preliminary assessment of efficacy of treatment with intravenous pembrolizumab in patients with intermediate risk NMIBC

Tertiary/Exploratory objectives.

- Determine correlation between expression of PD-L1 and PD-1+ infiltrating lymphocytes and efficacy of pembrolizumab therapy after TURBT in intermediate risk NMIBC patients.
- Definition of gene expression signatures and genetic profiles capable of predicting efficacy of pembrolizumab treatment in NMIBC patients.
- To evaluate the effects of pembrolizumab treatment on immunological profile and tumour specific immune responses in patients and intermediate risk NMIBC.
- Identification of myeloid or T cell responses in the tumour microenvironment associated with response to treatment
- To investigate the pharmacokinetics of intravesical pembrolizumab."[32]

This example has been adapted—only a portion of the original list is reported here.

Example 2. "Primary study objective.

- Assess the safety and reactogenicity of the Andes Virus (ANDV) DNA vaccine by dosage cohort and treatment arm when administered using the PharmaJet Stratis® Needle-Free Injection system in normal, healthy adults.

Secondary study objectives.

- Assess the immunogenicity of the ANDV DNA vaccine by dosage cohort and treatment arm.

Exploratory study objectives.

- Assess cellular immune response to ANDV DNA vaccine by dosage cohort and treatment arm.
- Assess immunogenicity of the ANDV DNA vaccine by dosage cohort and treatment arm at additional time points."[33]

Explanation. In addition to the need to precisely describe the trial objectives, which inform the trial design (e.g., outcomes) and analysis methods and facilitate the subsequent interpretation of trial findings, as outlined in the SPIRIT statement,[9] this modified SPIRIT-DEFINE item additionally highlights that participant well-being is usually the primary consideration in EPDF trials.

Every trial should clearly describe its research objectives, i.e., the specific scientific questions the trial is intended to answer. The objectives should encompass safety, toxicity, activity (e.g., preliminary measures of efficacy), pharmacokinetics, pharmacodynamics, feasibility assessment, recommended dose(s), or some combination thereof. Primary objectives should be distinguished from secondary and exploratory objectives to emphasise the main aims of the trial (see both examples). Although formal statistical hypothesis testing is not typically the centrepiece of an EPDF trial, any such hypotheses should be stated.

Item 8a.1 [modified] Description of trial design elements, such as dose escalation or de-escalation strategy, number of treatment groups, allocation ratio if relevant, and details of any prespecified trial adaptations

Example 1. "This study is a two-arm, open-label Phase Ib dose escalation and dose expansion cohort study with oral administration of GSK525762 in combination with either abiraterone (Arm A) or enzalutamide (Arm B) in male subjects with metastatic castration-resistant prostate cancer (mCRPC) in whom at least one line of treatment with abiraterone or enzalutamide has failed. [...] During dose escalation, both treatment arms will follow a modified Toxicity Probability Interval (mTPI) design. The design assumes (i) approximately 3–6 subjects per dose cohort will complete the dose limiting toxicity (DLT) evaluation period and (ii) the true underlying toxicity rate for GSK525762 in combination with either abiraterone or enzalutamide falls within the range from 25% to 35% and centered at 30%. [...] Because of the concern for potential drug–drug interactions (DDI) between GSK525762 and both abiraterone and enzalutamide, there will be extensive pharmacokinetics (PK) sampling as noted in Section 7.1, to specifically address the DDI effects with these drugs. Specifically, enzalutamide is a known CYP3A4 inducer, and DDI could potentially lower the exposure to GSK525762. Also, GSK525762 is a moderate CYP3A inducer and could potentially lower the exposure of abiraterone, which is a substrate of CYP3A. Therefore, emerging PK data will be used to assist with dose decisions for the maximum tolerated dose (MTD) and Recommended Phase 2 Dose (RP2D). During dose expansion, the study will employ a Bayesian predictive adaptive design that allows the trial to be monitored more frequently at multiple stages based on the utility score of the dose.

In the Arm A, eligible subjects with mCRPC will be enrolled into two dosing level cohorts to determine the MTDs (and RP2D) of GSK525762 when administered in combination with abiraterone [...] During dose escalation, eligible subjects will be dosed in at least two dose levels to identify the two dose level cohorts to explore in dose expansion [...] To further explore and identify the MTDs (and RP2Ds), the two most tolerable dose levels may be initiated and randomized by prior lines of therapy (L2 and Lx). A total of 30 subjects each may be enrolled into both cohorts, and approximately 10 enrolled subjects will be L2 and 20 subjects will be Lx. If only one dose level is tolerable for dose expansion, subjects will be enrolled and not randomized.

In the Arm B, eligible subjects with mCRPC will be enrolled into dosing level cohorts to determine the MTDs (and RP2D) of GSK525762 when administered in

combination with enzalutamide. During dose escalation, eligible subjects will be dosed in at least two dose levels to identify the two dose level cohorts to explore in dose expansion [...] To further explore and identify the MTDs (and RP2Ds), the two most tolerable dose levels may be initiated and randomized by prior lines of therapy (L2 or Lx). A total of 30 subjects each may be enrolled into both cohorts, and approximately 10 enrolled subjects will be L2 and 20 subjects will be Lx. If only one dose level is tolerable for dose expansion, subjects will be enrolled and not randomized."[34]

Example 2. "Dose-escalation rules.

Guidelines recommend an initial intensity of cardiorespiratory fitness [...] training of 40%–45% heart rate reserve/peak volume of oxygen uptake (HRR/VO_{2peak}) or 50%–55% heart rate peak (HR_{peak})[reference]. The decision to escalate the target training intensity by 5% or repeat the same target training intensity in the next cohort or stop the trials is based on the occurrence of dose limiting events (DLEs) and pre-defined rules.

A dose-intensity will be assessed as safe and tolerable if ≥ 3 of 5 participants in a cohort complete the training without experiencing one of the pre-defined DLEs. The dose escalation rules [..] are as follows:

- If a dose-intensity is determined to be safe and tolerable, another cohort of 5 participants will be enrolled and will receive a pre-defined increased exercise dose (i.e., +5% HRR/VO_{2peak}).
- If 3 of the 5 participants in a cohort experience at least one DLE, the following cohort of 5 participants will receive the same dose as the previous cohort.
- If ≥ 4 of 5 participants (or ≥ 6 of 10 participants over 2 consecutive cohorts receiving the same dose) experience at least one DLE, the study will be terminated, and the previous dose will be considered the maximum safe dose."[35]

Explanation. The SPIRIT statement and its related extensions reflected on trial design features for randomised clinical trials and their close relation to the trial objectives, as well as their influence on the choice of statistical method, conduct, and costs.[36] EPDF trials may or may not be randomised,[37] use intra-participant or inter-participant dose escalation/de-escalation strategies, and incorporate trial adaptations (e.g., dose levels can be escalated, de-escalated, retained, or dropped based on observed interim toxicity and efficacy data).[38,39] All of these aspects influence the statistical methods for design and analysis. Specification of planned opportunities for adaptations and their scope is essential to preserve trial integrity and for regulatory assessments.[40] It is important to describe these important features of the trial design adequately to enable readers to gain a broad understanding of the trial.

Authors should provide a description of the adaptive dose-finding design utilised, with underlying rationale and design concepts, and details on any planned trial adaptations. These aspects include, but may not be limited to:

- Phase of clinical research (e.g., I, I/II, first-in-human, first-in-child — see Example 1);
- Specific features such as open-label, double-blinded, placebo-controlled, dose escalation or de-escalation, expansion cohort(s), or intra-participant dose escalation;
- The number of groups (which could be treatment groups or specifically defined [targeted] subgroups, e.g., according to age or disease type — see Example 1);
- any planned trial adaptations: (i) dose adaptations based on type of escalation/de-escalation design strategies (e.g., algorithm-based, model-assisted, model-based designs, single ascending dose, multiple ascending dose, intra-participant dose escalation); (ii) other adaptations relating to, e.g., enrichment strategies, early stopping for safety, futility, or efficacy.[38–40]

Specific details of design features are addressed in items 8a.3–8a.11.

Item 8a.2 [new] Trial design schema to show the flow of major transition points (e.g., dose escalation to dose expansion, phase 1 to phase 2, single ascending dose to multiple ascending dose)

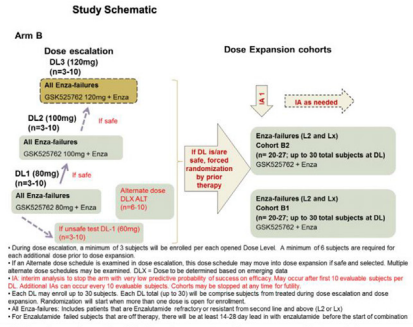
Example 1. This example is represented in Fig. 2a.[34]

Example 2. This example is represented in Fig. 2b.[41]

Explanation. Planning dosing strategies in EPDF trials can be complex depending on the research context, adaptive trial design features, and methods considered. EPDF trials are increasingly designed to seamlessly address multiple objectives spanning across multiple transition points of clinical research (e.g., dose escalation to (multiple) expansion cohort(s), phase I to phase II, single ascending dose to multiple ascending dose).[22] The increasing complexity of trial design and dosing strategies can be challenging for readers to comprehend. A graphical representation of the overall trial schema can help show the timing of major reviews and decision points, highlighting any overlap between trial cohorts and stages to aid interpretation and assess logical stages of the process.[22]

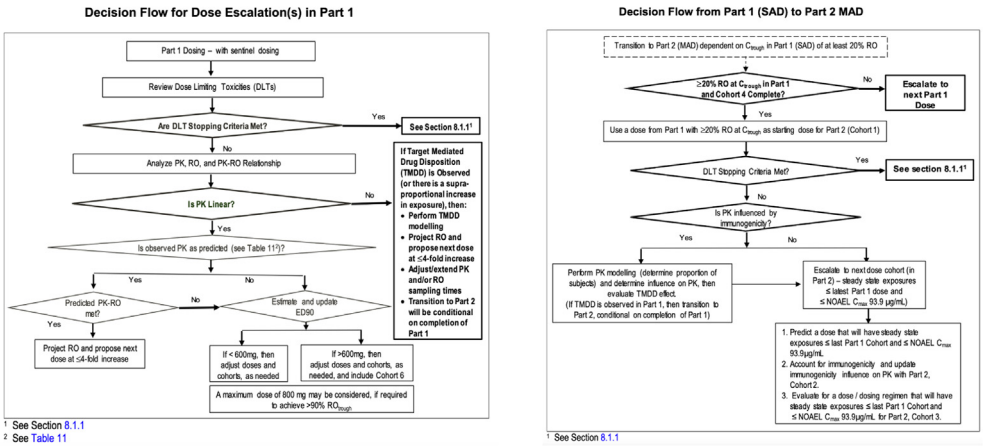
It is recommended that authors provide a trial design schema to display the different parts and/or phases. This schema should demonstrate the timing and criteria for major transition or progression points (e.g., dose escalation to expansion (see Example 1), dose escalation to dose optimisation (particularly as outlined in projects like the FDA Optimus project, which focuses on

a



DL: dose level; ALT: alternate; Enza: enzalutamide.

b



DLTs: dose liming toxicities; C_{max}: maximum observed concentration; $C_{through}$: trough concentration; ED90: effective dose 90; MAD: multiple ascending doses; NOAEL: no observed adverse effect level; PK: pharmacokinetic; RO: receptor occupancy; TMDD: target-mediated drug disposition; SAD: single ascending doses.

Fig. 2: Item 8a.2, trial design schema to show the flow of major transition points, **(a)** Example 1—obtained from study NCT03150056 on ClinicalTrials.gov (https://clinicaltrials.gov), a database of privately and publicly funded clinical studies conducted around the world,[34] **(b)** Example 2—obtained from study NCT03984812 on ClinicalTrials.gov (https://clinicaltrials.gov), a database of privately and publicly funded clinical studies conducted around the world.[41]

selected tolerable doses to ensure they are active and tolerable),[3,4] phase I to phase II, single ascending dose to multiple ascending dose (Example 2), or stage 1 to stage 2, with a formal interim analysis for futility or activity, monotherapy to combination regimen, or exploration of an alternative administration schedule or route).[42]

Item 8a.3 [new] Statistical methods or rationale underpinning the trial design

Example 1. "We will employ the Bayesian Optimal Interval (BOIN) design[Reference] to find the maximum tolerated dose (MTD). The BOIN design is a novel Bayesian dose-finding method that optimizes patient ethics by minimizing the chance of exposing patients to sub-therapeutic and overly toxic doses. The BOIN design yields an average performance comparable to that of the Continual Reassessment Method (CRM) in terms of selecting the MTD, but has a lower risk of assigning patients to subtherapeutic or overly toxic doses (i.e., better patient ethics). The target toxicity rate for the MTD is 0.3 and the maximum sample size is 30. We will enroll and treat patients in cohorts of size 3. But in this study, there are two early stopping rules: (1) when the lowest dose level is eliminated due to toxicity and (2) when the new patient number at certain dose level reaches 15."[43]

Example 2. "A modified Continual Reassessment Method (mCRM) design will be implemented for dose escalation in this study to allow for dose escalation decisions based on all available data including, but not limited to, safety, pharmacodynamic, RO, pharmacokinetic, and other biomarker(s). In Part 1, the mCRM will be carried out in 2 phases: (1) accelerated titration phase and (2) standard titration phase.

[...]

Statistical Model for Probability of Dose limiting Toxicity: The probability of DLTs by a two-parameter Bayesian logistic regression model (BLRM) with the escalation with overdose control will guide the dose escalation and RP2D(s) recommendation, which is at or

lower than estimated MTD. The incidence of DLTs, e.g, DLT occurred or not during the DLT evaluation period, is the primary variable for dose escalation. These accumulated DLT data from the eligible subjects for the DLT evaluable analysis set will be used to model the relationship between the dose and DLT of JNJ-64007957. The two parameter BLRM will be used to calculate the probability of DLTs at dose d.

$$\text{logit}(\pi(d)) = \log(\alpha) + \beta \cdot \log(d/d^*) \quad \alpha>0,\ \beta>0$$

where, $\pi(d)$ be the probability of DLTs when JNJ-64007957 is given as a single agent at dose = d, d is the planned dose during the DLT evaluation period, and $\text{logit}(\pi(d)) = \log[\pi(d)/\{1-\pi(d)\}]$ and d* is the reference dose. The details of the statistical model including specifications for the prior data used, prior distributions, posterior distributions, and hypothetical data scenarios of the BLRM can be found in Attachment 12.

The probability of the true DLT rate for each dose level will be summarized as follows:

- [0%, 20%) Under-dosing interval
- [20%, 33%) Targeted toxicity interval
- [33%, 100%] Excessive toxicity interval

The probability of DLT will be calculated by BLRM, as described above, when all subjects in a dose cohort finish the DLT evaluation period. The highest dose level for the next dose cohort will be recommended using the probability of DLTs at all dose levels of study drug. The highest dose will need to satisfy EWOC principle, ie, less than 25% probability that the estimated DLT rate is in the excessive toxicity interval, and also to have the highest probability that the estimated DLT rate is in the target toxicity interval."[44]

This example lacks a more explicit explanation regarding the rationale behind selecting a target risk/toxicity rate.

Explanation. The statistical methods that underpin the trial design are central to achieving the research objectives of EPDF trials, which are often adaptive in response to accumulating data. Pre-specifying how the statistical information will be gathered and used to direct planned adaptations at interim analyses, which are guided by pre-specified decision-making criteria or rules (item 8a.4), is vital in EPDF trials. Such information enhances transparency and reproducibility and enables readers to assess the appropriateness of the statistical methods used to evaluate the operating characteristics of the adaptive design (item 14), which will be used for performing statistical inference (item 20a.2).[40]

Authors should present the rationale or logical basis for selection of the trial design. This includes not only model-based/assisted designs but also rule-based designs, such as 3 + 3, rolling 6, single ascending dose, and multiple ascending dose. A description of the underlying statistical methods or algorithms/rules used to set up and implement the EPDF trial design should be presented. Analytical derivations of statistical models or formulae should be provided to facilitate reproducibility[40] and subsequent interpretation of results.[40] For dose adaptations utilising model-based and model-assisted dose-finding designs,[45,46] comprehensive details and explanations of the statistical methods should be provided. This includes, where applicable, model assumptions, mathematical form of the model, choice of model parameters, Bayesian prior distribution and its elicitation, and the rationale for choosing a target risk/toxicity rate or acceptable range for the recommended dose(s).[47] 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 specified.[40,48] Details of statistical software and packages (with versions) used for design and parameter choices (e.g., via simulation) should be provided.[40,49]

Item 8a.4 [new] Prespecified interim decision-making criteria or rules to guide the trial adaptation process (e.g., 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

Example 1. "In Bayesian Optimal Interval (BOIN) design, the decision to escalate or de-escalate is based on the probability of toxicities from updated information on pre-defined toxicity rate, which is set at 30% in this study. When the probability of dose limiting toxicity (DLT) is lower than 21% (70% of target rate), the dose in the next cohort escalates to the next level. By contrast, when the probability of DLT is higher than 39% (130% of target rate), the dose in the next cohort de-escalate to the next lower level. The enrollment continues until the maximum of 30 patients is reached. The rule of dose escalation and de-escalation is tabulated in Table 1. There are two early stopping rules set in this study. Stop the trial if the lowest dose (dose level 1, i.e., 250 mg) is eliminated due to overt toxicities. Stop the trial and estimate the maximum tolerated dose (MTD) if the number of new patients treated at the current dose level reaches 15. The detailed statistical methods for dose escalation and de-escalation and determination of MTD are described in Section 11.

Dose modification is based on the toxicities from previous infusions. Patients who experience reversible DLTs are allowed to receive additional infusions at the next lower dose level, provided that the toxicities have reverted to grade ≤1 in 28 days after last infusion, and that the patients still meet the inclusion criteria for adequate organ functions. For patients who experience

DLTs, re-escalation to the dose level that causes DLT is not permitted. Up to two dose-level reductions per patient are allowed in this study."[43]

Example 2. "Each dose group will have hzVSF-v13 and the placebo randomized at a 3:1 ratio to conduct the clinical study. The study will be proceeded sequentially from the lowest dose, and whether to proceed with the next dose will be determined based on the tolerability and safety results of the previous dose. Each subject in Group 1 and Group 2 will be administered, and if no significant dose limiting toxicity (DLT) occurs within 72 h, then the next subject will be administered. In the case of all dose groups except for Group 1 and Group 2 (Group 3–Group 8), 3 out of 8 subjects in each dose group (2 subjects for the study drug and 1 subject for the placebo) will receive the investigational product (hzVSF-v13 or placebo) at least 72 h earlier than the remaining subjects in the same dose group. If no significant dose limiting toxicity occurs within 72 h, the remaining subjects in the relevant dose group will receive the investigational product (hzVSF-v13 or placebo) depending on the randomization. In the case that at least 3 subjects experience a Grade 3 adverse event or at least 1 subject in certain dose groups experience a Grade 4 adverse event based on the Common Terminology Criteria for Adverse Events (CTCAE) published by the United States National Cancer Institute (NCI), the principal investigator shall consult the independent Safety Monitoring Committee (SMC), established separately from this study, and discuss discontinuation of the relevant dose group and dose escalation with the sponsor. [...] Accordingly, after all subjects complete all scheduled tests up to 15 d for each dose group, the SMC will evaluate the safety-related data. With reference to the evaluation result of the SMC, the principal investigator and the sponsor will decide by mutual consent whether to continue the clinical study and to proceed with the next step."[50]

Example 3. "In this exercise trial, DLEs are based on symptoms related to cardiorespiratory fitness (CRF) training exercise related adverse events, such as pain and exhaustion above and beyond that normally expected after CRF training, or to underlying cardiovascular risks, adverse events related to the intervention. In the proposed dose ranging trial study, the DLEs will be defined as [...]

A dose-intensity will be assessed as safe and tolerable if ≥ 3 of 5 participants in a cohort complete the training without experiencing one of the pre-defined DLEs. The dose escalation rules are outlined in Figure 2 and are as follows:

- If a dose-intensity is determined to be safe and tolerable, another cohort of 5 participants will be enrolled and will receive a pre-defined increased exercise dose (i.e., +5% heart rate reserve/peak volume of oxygen uptake (HRR/VO_{2peak})).
- If 3 of the 5 participants in a cohort experience at least one DLE, the following cohort of 5 participants will receive the same dose as the previous cohort.
- If 4 of 5 participants (or ≥ 6 of 10 participants over 2 consecutive cohorts receiving the same dose) experience at least one DLE, the study will be terminated, and the previous dose will be considered the maximum safe dose."[35]

Explanation. The importance of transparency and a complete description of pre-specified decision-making criteria in adaptive designs is highlighted in the Adaptive designs CONSORT Extension (ACE) to the CONSORT reporting guidance.[40] As EPDF trials are highly adaptive in response to accruing outcome data, complete descriptions of the interim decision-making criteria as well as timing, frequency, and information used to inform the adaptations are vital as they directly affect the operating characteristics of the design (item 14) and the clinical interpretation of the findings. In addition, knowing the basis for decisions on the early stopping of a trial is key to the credibility of these decisions. A rationale for such stopping rules should be provided where possible. Similarly, criteria for stopping the trial early influence the operating characteristics of a design. For example, early stopping for futility would result in fewer participants being treated with an ineffective treatment.

For EPDF trials, authors should specify:

- Pre-specified guidance or rules for trial adaptations (item 8a.1), including:
  - o Dose adaptations such as dosing decision to escalate or de-escalate, e.g., based on observing fewer than a pre-specified number of toxicities in a cohort or less than a given toxicity probability or toxicity probability interval;
  - o Early stopping due to safety, futility, or efficacy;
  - o Other trial adaptations, such as criteria for progression to the next part of the trial, e.g., from phase I to phase II in a seamless phase I/II trial or guidance for switching from a single ascending dose to a multiple ascending dose.
- Planned timing and frequency of interim data looks, e.g., at set time intervals or after a certain number of participants have been observed for a specified period;
- Observed data (such as toxicity, activity, pharmacokinetics, or pharmacodynamics data, either singularly or in combination) or statistical information that will inform the trial adaptations (item 8a.3).

Whether futility-stopping rules are binding or non-binding should be indicated to facilitate assessment of the implications in the case when they cannot be adhered to.[40] An explanation should be provided if the

interim decision-making criteria/rules are not pre-specified.

Item 8a.5 [new] Starting dose(s) with rationale

Example 1. "The starting dose for PF-06463922 in the first-in-patient trial in cancer patients has been determined to be 10 mg daily, based on information derived from the 1-month repeat dose toxicology studies in rats and dogs. According to DeGeorge et al.[reference], the currently accepted algorithm for calculating a starting dose in clinical trials for cytotoxic agents is to use one-tenth of the dose that causes severe toxicity (or death) in 10% of the rodents (STD10, severely toxic dose) on a mg/m^2 basis, provided this starting dose does not cause serious, irreversible toxicity in a non-rodent species. If irreversible toxicities are produced at the proposed starting dose in non-rodents or if the non-rodent is known to be the more appropriate animal model, then the starting dose would generally be one-sixth of the highest dose tested in the non-rodent that does not cause severe, irreversible toxicity (HNSTD, highest non severely toxic dose). The doses tested in the 1-month toxicology study in the male/female rats were 2/1, 8/4, and 30/15 mg/kg/day orally, and in the 1-month dog study were 2, 7, and 25 mg/kg/day orally. The STD10 in male/female rats was determined to be 8/15 mg/kg/day respectively (free AUC24 5760/24660 ng h/mL) and HNSTD following 1 month of dosing was 25 mg/kg/day in dogs (free AUC24 40000 ng h/mL).

The human equivalent starting dose was calculated to be 8.6 mg based on the rat STD10 of 8 mg/kg/day, and 150 mg based on the HNSTD of 25 mg/kg/day in the dog (assuming a body surface area of 1.8 m^2 for humans). Because the rat was determined to be the more sensitive species and provides a lower starting dose, the dose of PF-06463922 will be rounded to 10 mg and used as the starting dose for the FIP study. At the starting dose of 10 mg dose once daily, the projected unbound exposure (AUC24, 249 ng/mL) is ~23-fold lower than the unbound exposure observed (AUC24, 5760 ng/mL) at rat STD10 dose and provides a good safety margin."[51]

Example 2. "In the 42-day repeat oral dose toxicology studies, no observed adverse effect levels (NOAELs) in the mouse and the dog were 500 mg/kg/day and 50 mg/kg, respectively, corresponding to human equivalent doses (HEDs) of 40 and 27 mg/kg, respectively. Therefore applying a 10-fold safety margin the maximum recommended starting dose (MRSD) is 2.7 mg/kg, approximately 162 mg for a 60 kg subject. In vitro data in human cells suggests an IC50 of GB1211 of 0.1 μM (0.5 μg/mL) supporting the chosen MRSD.

In the pharmacodynamic (PD) study[reference] evaluating the effect of GB1211 in carbon tetrachloride-induced liver fibrosis in mice there was no pharmacological activity observed at 2 mg/kg but there was activity at 10 mg/kg. Therefore the MRSD that is not considered to be pharmacologically active, based on the 2 mg/kg dose level, is 0.16 mg/kg, equivalent to approximately 9.6 mg in a 60 kg subject. The lowest pharmacologically active dose has been defined as 10 mg/kg, representing a HED of 48 mg for a 60 kg subject.

The proposed starting dose of 5 mg is 1.9-fold lower than the MRSD of 9.6 mg (based on the PD study6) and therefore is not expected to have any pharmacological activity."[52]

Explanation. Reporting the starting dose and its rationale is crucial for understanding the basis of dose selection, which enhances scientific rigour and reproducibility, aids regulatory evaluations, and enhances transparency, allowing evaluation of whether a given method was useful in a particular setting.[53] Additionally, this information is essential for contextualising and assessing safety and supporting clinical decision-making, such as final dose adjustments, in response to accumulating observed outcomes.

Published and recommended approaches exist for determining the appropriate starting dose(s) for first-in-human and early phase clinical trials.[22,54–56] Regardless of the approach used, authors should state the starting dose(s) and provide a scientific justification for their choice (for each investigated intervention and participant population — see Example 2). The rationale should include, but is not limited to, key findings from relevant non-clinical/preclinical studies (for first-in-human trials) and clinical experience with the intervention(s) or, if applicable, with similar interventions in other disease areas or populations.[57,58]

Item 8a.6 [new] Range of planned dose levels with rationale

Example 1. "The projected dose levels (DLs) of GSK525762 are 60 mg and 80 mg administered orally once daily. DL2 (80 mg) has been discontinued. If unacceptable toxicity is observed at the 60 mg DL, then 40 mg once daily may be explored (DL-1). The projected DL of fulvestrant is the approved dose regimen of 500 mg intramuscularly (IM) on Days 1, 15, and 29 of cycle 1, and monthly thereafter. Additional doses and schedules may be explored based on emerging safety, pharmacokinetics (PK), and pharmacodynamics (PD) data. No doses will be explored beyond 100 mg GSK525762 or 500 mg (IM) fulvestrant, these doses that are considered to be the Maximum Feasible Dose (MFD), unless emerging PK data demonstrate reduced exposure of either drug in combination compared to single agent."[59]

Example 2. "Rationale for Dose and Schedule Selection

There will be 2 dose cohorts in this study:

- Low-dose cohort: Approximately 8 subjects will receive a single intravenous (IV) dose of Advate 25 IU/kg followed by a single IV dose of BIVV001 25 IU/kg

- High-dose cohort: Approximately 10 subjects will receive a single IV dose of Advate 65 IU/kg followed by a single IV dose of BIVV001 65 IU/kg

The low-dose level for this study is based on nonclinical study results for BIVV001 and clinical and nonclinical results for marketed factor VIII (FVIII) products, including rFVIIIFc (Eloctate). The high-dose level is determined by the upper limit of the physiological plasma FVIII activity level of 150 IU/dL in healthy subjects and taking into account an anticipated incremental recovery (IR) of 2 IU/dL per IU/kg (based on values typically observed for FVIII products, including rFVIIIFc). Data from nonclinical studies have shown a BIVV001 procoagulation capacity per IU similar to those of other FVIII products. The 2 dose levels considered for this study are expected to approximately bracket the therapeutic dose range. The physiological plasma FVIII activity level in healthy subjects is between 50 and 150 IU/dL. The low dose (25 IU/kg) for this study is expected to provide a peak activity level close to the lower limit of this range and the high dose (65 IU/kg) to achieve a peak activity level under the upper limit, taking into account an anticipated IR of 2 IU/dL per IU/kg, as described above. Four-week, repeated-dose toxicity studies of BIVV001 in rats and monkeys revealed a no observed adverse effect level (NOAEL) of 750 IU/kg (Section 4.3.1), which is a dose level that is 30 times (30 ×) higher than the low dose for this study, and approximately 11.5 × higher than the high dose. As this is the first study of BIVV001 in humans, a step-wise dosing and data review/monitoring procedure (described in Section 7.1) will be followed in both the low-dose and high-dose cohorts to minimize the potential of adverse reactions occurring in several subjects. Additionally, following completion of dosing and data collection for the low-dose cohort, the Sponsor and an independent Data Safety Monitoring Committee (DSMC) will review all available data to determine the appropriateness of escalation to the higher BIVV001 dose; refer to Section 7.1 and Figure 1 for details."[60]

Explanation. Careful selection and justification of doses of an intervention is needed in EPDF trials to safeguard the participants and should be clearly described for regulatory assessment and for readers to understand how those were chosen. Whether the doses and the number of dose levels are pre-specified or are adjusted based on accrued data can impact dosing decisions and trial findings. Hence, it is important to provide such information in order to enhance reproducibility and interpretation of findings, regardless of the research context.

Authors should specify the planned dose levels (whether single or combination therapies) together with their rationale (see Example 2) and provide details on associated boundaries of maximum dose, maximum expected exposure, desired pharmacological activity, and/or intra-participant dose adaptations, where applicable. The dose escalation/de-escalation schedule (whether for single or combination therapies) and range of dose levels should be provided. Authors should indicate whether the doses and the number of dose levels are pre-specified or may be adapted in accordance with safety, tolerability, and pharmacokinetic/pharmacodynamic data, as applicable.[42,54] The maximum allowed increment between dose levels should also be defined.[22,42] For interventions given in combination,[61,62] authors should clarify whether interventions are planned to be given in parallel or in a pre-specified sequence and the maximum allowed increases in each component of the combination. The specific ways an intervention will be administered are covered in item 11a.

Item 8a.7 [new] Presentation of planned dose levels (e.g., as a diagram, table, or infographic), where applicable

Example 1. "There will be no intra-patient escalation of venetoclax. The first cohort of patients will start venetoclax at Dose Level 0 (400 mg), administered PO (per os) daily (QD), days 1–10 of each 21-day cycle, except for cycle 1 when venetoclax will be administered days 3–12. The dose limiting toxicity (DLT) assessment period will be cycle 1. Dose escalation will proceed according to Table 1.

A cohort expansion will be accrued at the recommended phase 2 dose (RP2D) on a 5 day instead of a 10 day schedule. If no more than 1 patient experiences a DLT, we will enroll an additional 9 patients at the RP2D."[63]

Fig. 3a represents the dose levels. The table was reprinted from the supplementary material of Rutherford et al.[63] from The Lancet Haematology with permission from Elsevier.

Example 2. "To minimize the risk of severe cytokine release syndrome (CRS), an intra-patient dose escalation in Cycle 1 is proposed, as shown in Table 1. Lead-in doses include the first 2 doses in Dose Level (DL) 1 and DL2 (ie, Week 1 and Week 2 administered doses), the first 3 doses in DL3 to DL5, and the first 4 doses in DL6 to DL8. After the lead-in doses, each patient will receive a fixed dose until the end of treatment, unless the dose needs to be decreased for safety reasons. DL1 to DL8 will achieve a range of lead-in doses from [...] and a range of final doses from [...]. During Cycle 1 and Cycle 2, pharmacokinetic and pharmacodynamic data will be collected that will be used, together with acute safety monitoring, to inform the choice of subsequent dose levels for both the Dose Escalation Part and the Expansion Part.

For subsequent cycles, patients will maintain the maximum weekly dose [...]."

a

Dose level	Venetoclax dose	Cycle 1 Schedules	Cycle 2-6 Schedules
-1	400mg PO QD	Days 3-7	Days 1-5
0	400mg PO QD	Days 3-12	Days 1-10
1	600mg PO QD	Days 3-12	Days 1-10
2	800mg PO QD	Days 3-12	Days 1-10

b

Table 1

Dose Level	Cycle 1 (doses in ng/kg)						
	W1		W2	W3	W4	W5	W6
	D1	D4	D8	D15	D22	D29	D36
DL1							
DL2							
DL3							
DL4							
DL5							
DL6							
DL7							
DL8							

DL: dose level; D: days; W: weeks.

Fig. 3: Item 8a.7, presentation of planned dose levels, **(a)** Example 1—obtained from the supplementary material of Rutherford et al.[63] from *The Lancet Haematology*, reprinted with permission from Elsevier, **(b)** Example 2—obtained from study NCT03594955 on ClinicalTrials.gov (https://clinicaltrials.gov), a database of privately and publicly funded clinical studies conducted around the world,[64] The example was masked as displayed in the original protocol.

Fig. 3b represents this example, which was masked as displayed in the original protocol.[64]

Explanation. Most EPDF trials use multiple dose levels (in monotherapy or in combination with other therapies) and complex dosing strategies. Hence, using a visual aid to present the information provided in item 8a.6 (where applicable) can aid trial comprehension and facilitate comparisons across different studies.

Presentation of the dose levels, or their combinations in case of two or more agents, as described in item 8a.6, can be provided with a visual aid, such as a diagram, table, or infographic (see both examples).[31,48,49,65] A graphical or tabular presentation may not be necessary when dose levels are not pre-defined or the dose range is very simple (e.g., the details can be presented in the text for two dose levels).

Item 8a.8 [new] Skipping of dose level(s), if applicable

Example 1. "Dose escalation is also conducted according to a set of rules that govern entry into the study and assignment of dose level. These rules allow skipping untried dose levels provided they are estimated to be safe. The trial is continuously monitored for safety and for early stopping for successfully identifying the maximum tolerated dose (MTD)."[66]

Example 2. "For both groups, dosing starts at level 0 and allows for possible escalation to two higher levels, or deescalation to a lower dose, as recommended by the time-to-event continual reassessment method (TITE-CRM), without skipping untried doses in escalation. [...] Restriction is applied to avoid skipping of untried doses in escalation."[67]

Explanation. EPDF trial designs may allow skipping of dose level(s).[45] Because this feature affects the design's performance, reproducibility, and interpretation, it is important that this be precisely described. For example, in terms of operating characteristics and design performance, allowing for skipping in escalation will result in faster attainment of pharmacologically and/or clinically active dose levels, the maximum allowed dose, or treatment exposure if the true target dose is at the upper end of the investigated dose range, but it may introduce a risk of overdosing.

In settings with pre-defined dose levels, it is useful to specify whether the planned design allows for skipping predefined dose levels in escalation or de-escalation (e.g., from level 2 to level 4). This may apply to skipping any dose level in escalation/de-escalation or only untried dose levels. It may not be applicable in settings where dose levels are not predefined, such as when the next dose level is determined after observing the tolerability data from previous dose levels.

Item 8a.9 [new] Planned cohort size(s) (e.g., fixed, flexible, adaptive)

Example 1. "Evaluation of a cohort of at least 3 evaluable subjects is required prior to determining the dose for the next cohort. To proactively ensure at least 3 subjects are considered evaluable, a 4th subject may be enrolled and treated. No dose escalation decisions will be made until all subjects enrolled at a given dose level have completed the dose limiting toxicity (DLT) evaluation period. If one subject experiences a DLT, the cohort will expand to 6 evaluable subjects."[68]

Example 2. "Each cohort will comprise 8 healthy Caucasian male subjects, 6 of whom will be allocated to receive emodepside, and 2 of whom will be allocated to receive placebo. 3 cohorts will be recruited, to test 3 multiple dose levels of emodepside Liquid Service Formulation (LSF) oral solution."[13]

Explanation. In EPDF trials, safety assessments and dose-decision reviews are usually performed after each cohort of participants.[49] Cohort sizes in EPDF trials often differ greatly and are subjectively chosen based on precedence and preference.[54,69] In placebo-controlled EPDF trials, there is also great variability in the number and ratio of active and placebo-treated participants in each cohort.[69] As accruing data are reviewed after each cohort, the cohort size directly affects the timing of interim analysis and any trial adaptations, and hence the performance of the design and interpretation of the results.

Authors should specify whether the planned cohort size is fixed (e.g., cohorts of three or six participants) or variable. For cohort sizes that are not fixed, any criteria for determining the cohort size during the trial should be pre-specified. For randomised EPDF trials, whether involving a control/placebo group or active doses only, it is important to provide details regarding the allocation of participants to their respective groups in each cohort (see items 16 and 17 in SPIRIT[9]).

Item 8a.10 [new] Dose allocation method within a dose level (including sequence and interval between dosing of participants, e.g., sentinel or staggered dosing)

Example 1. "The first three patients in each trial arm are treated at the starting dose level. Thereafter, patients are assigned to a dose level using time-to-event continual reassessment method (TITE-CRM) and dose escalation rules. Upon enrolment of a new patient, TITE-CRM estimates the current maximum tolerated. New patients are assigned to the dose level that is closest to but not exceeding this current estimated maximum tolerated dose (MTD) after applying two restrictive dose-escalation rules: 1) at least three patients have completed a minimal follow-up time of three months after end of treatment at the dose level below the assigned dose level, and 2) the assigned dose level may not increase more than one dose level between two consecutive patients. There is no restriction on the decrease in number of levels between consecutive patients."[70]

Example 2. "This is a randomized, double-blind, placebo-controlled trial designed to evaluate the safety, pharmacokinetics, and pharmacodynamic effects of multiple doses of COR-001 or placebo administered to sequential cohorts of haemodialysis patients.

Ten haemodialysis patients will be randomized to COR-001 or placebo within each dosing cohort. When a higher dose than studied in a prior cohort is being initiated, the first 2 (sentinel) patients in that cohort will be randomized in 1:1 to COR-001 or placebo; the remaining patients will be randomized at least 48 h later in a 7:1 ratio of COR-001 to placebo."[71]

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

Authors should describe how participants will be allocated to each dose level (see Example 2). They should specify whether sentinel or staggered dosing will be implemented. A sentinel participant is the first to be dosed in a study or a cohort of participants,[72] with allowance for a minimum time to elapse for review prior to dosing subsequent participants at the same dose level. Staggered dosing describes an approach in which all participants dosed are separated by a minimum time interval.[22]

Item 8a.11 [new] Dose expansion cohort(s), if applicable, with rationale

Example 1. "The expansion stage will include approximately 60 patients aged ≥ 18 years old at the time of study registration who have previously untreated diffuse large B-cell lymphoma (DLBCL) and with high-intermediate to high risk as defined by International Prognostic Index (IPI) score of 2–5. Forty patients will receive R–CHP in combination with polatuzumab vedotin at a dose less than or equal to the maximum

tolerated dose (MTD) identified during escalation and an additional 17 patients will receive G-CHP in combination with polatuzumab vedotin at a dose less than or equal to the MTD identified during escalation.

The purpose of the expansion stage is to evaluate the safety and preliminary efficacy of the selected dose and schedule for the combination therapy, determined from the dose-escalation portion of the study. In the event that the observed toxicities during the expansion stage are different from what was predicted on the basis of the escalation portion of the study, additional expansion cohorts of approximately 40 patients may be enrolled to evaluate lower doses of polatuzumab vedotin. Additional patients may be enrolled in the expansion cohort in order to obtain additional safety, tolerability, and pharmacokinetic (PK) data, as well as data in specific biologic risk groups."[73]

Example 2 (adapted). "To further characterise the tolerability, safety, pharmacokinetic (PK) and activity of the combination of drug A and drug B in NSCLC (non-small cell lung cancer), LGSOC (low-grade serous ovarian cancer), colorectal cancer, pancreatic cancer, endometroid ovarian cancer … [,] the dose expansion phase will treat 20 NSCLC patients, 20 LGSOC patients, 10 colorectal cancer patients, 10 pancreatic patients, … [,] at the dose level selected during the dose escalation phase.

If the true response rate is 20%, there is <0.1% probability of observing 0 responses and a 99.9% probability of observing 2 or more responses. The 80% confidence interval for a 10% response rate is (6.4%, 16.0%); the 80% confidence interval for a 20% response rate is (14.3%, 26.4%) and the 80% confidence interval for 30% response rate is (23.7%, 37.5%). An additional 6 patients with advanced solid tumours will also be recruited to characterise pharmacodynamics combination."

This example has been adapted to reduce its identifiability.

Explanation. Expansion cohorts can enhance understanding of the toxicity profile, pharmacology, or effects on other biomarkers.[17,74] They may also be used to obtain preliminary evidence of activity to justify progression to future studies (e.g., from phase I to phase II). Expansion cohorts may allocate more participants to either selected doses or subgroup-specific cohorts.[4,75] Clear objectives of any expansion cohorts, as well as providing information on whether their sample sizes are statistically justified (item 14) and whether pre-defined criteria to inform go/no-go decisions (item 8a.4) about the clinical development of the intervention exist, will help the reader understand the questions that any expansion cohort is designed to answer.[76]

The criteria used to determine which dose(s) to expand should be specified, along with the number of participants to be treated with the selected dose(s) in each expansion cohort, as well as the objectives of the expansion cohort(s). If backfilling (defined as allocating additional participants to doses deemed safe to collect additional information on safety profile, pharmacokinetics/pharmacodynamics, or activity) is allowed,[77] an indication of whether these backfill cohorts can be opened in parallel to the dose-finding part and how their data will be used to inform subsequent trial adaptations and the final recommended dose(s) should be provided.

Section: Methods: participants, interventions, and outcomes

Item 11a [modified] Interventions for each dose level (within each group) with sufficient details to allow replication, including administration route and schedule showing how and when they will be administered

Example 1. "All cohorts will consist of therapy with a fixed dose of azacitidine (75 mg/m^2) to be administered by subcutaneous injection on 7 consecutive days (excluding weekends). Therapy should be commenced on day 1 of the treatment cycle and should be administered on a 5-2-2 schedule (i.e., days 1–5 (Monday-Friday) and then days 8–9 (Monday and Tuesday) of each cycle. In the event of holiday closures, treatment may be scheduled to start ± 2 days. Patients will then receive an allocated dose of oral lenalidomide (once daily) to be commenced sequentially after azacitidine. […] Lenalidomide will be supplied in 2.5, 5, 10, 15 and 25 mg capsules to be taken orally. The investigational medicinal product (IMP) will be packaged and labelled in accordance with local regulations and good manufacturing practice (GMP), stating that the drug is for clinical trial use only. […] Patients should receive 21 days (day 10–day 30) of lenalidomide and compliance should be documented in a medication diary. Following this, patients will undergo a rest period of 12 days (day 31–day 42) during which no further trial therapy should be administered. The proposed duration of treatment with study drugs will be 6 cycles (each cycle being 42 days) subject to tolerability and toxicity. If there is evidence of a clinical response with the treatment, patients will have the option of continuing with trial drugs (azacitidine monotherapy or azacitidine in combination with lenalidomide) at the patient's and Investigator's discretion, until loss of response, toxicity or death."[78]

Example 2. "SBI-087 Dose Administration Six intravenous (IV) dosing cohorts were planned for the first-inhuman rheumatoid arthritis (RA) study: 0.015, 0.05, 0.15, 0.5, 1.5, and 2.0 mg/kg. In the systemic lupus erythematosus (SLE) study, only one 0.5-mg/kg IV dose was investigated. Infusion rates were 25 mL/h in the 0.015- to 0.15-mg/kg cohorts. In the 0.5- and 1.5-mg/kg cohorts in the RA study, infusion was started at 25 mL/h

for 30 min, and if no adverse events (AEs) occurred, infusion was increased by 25 mL/h every 30 min to a maximum of 250 mL/h, as tolerated. In the 2.0-mg/kg cohort in the RA study and in the 0.5-mg/kg cohort in the SLE study, infusion was started at 25 mL/h for 1 h, and if no AEs occurred, was increased by 25 mL/h every hour to a maximum of 100 mL/h, as tolerated. The mean duration of infusion ranged between 0.16 h (0.015-mg/kg cohort) and 4.4 h (2-mg/kg IV cohort). Four subcutaneous (SC) doses also were planned in the RA study: 50, 100, 200, and 300 mg; and 4 SC cohorts were planned in the SLE study: 25, 75, 200, and 300 mg. SC injections were administered in the abdomen, arm, or thigh.

Because infusion reactions have been observed in patients with RA receiving rituximab, an anti-CD20 agent with a mechanism of action similar to that of SBI-087, a pretreatment regimen similar to that recommended for use with rituximab was initiated in the IV cohorts.[24,25] Approximately 1 h before IV administration, each patient was premedicated with methylprednisolone 100 mg IV, acetaminophen 1000 mg per os (PO), and an antihistamine 25 mg PO."[79]

Example 3. "All participants will perform 30 min of cardiorespiratory fitness [...] interval training three times per week for four weeks (excluding 5 min of warm up and cool down). The interval training will consist of 60 s bouts with a work-to-rest ratio of 1:1 (i.e., 15 bouts of 60 s work and 15 bouts of 60 s of active rest). The mode of training will be treadmill walking or cycling on a upright or recumbent stationary bike depending on patient preference. To ensure participant work at the target intensity treadmill speed and incline will be adjusted and for cycling the resistance will be adjusted to increase or decrease heart rate as needed. The participants will also complete strength training two times per week, which will be added on to the 1st and 3rd training session during each week of the intervention.

One important consideration in the design of a dose ranging study for an exercise intervention in stroke is a familiarisation and adaptation stage before testing the intervention at the target dose. [...] In the first two weeks, stage-one, the participants will be familiarised with the exercise equipment and the session procedures. The training sessions in this stage-one do not have a set target intensity but will be used to work up to the target intensity set in stage-two of the intervention.

In stage-two the participant will work at the predefined intensity which is set as a target heart rate (HR) based on a percentage of heart rate reserve (HRR). For example, the first cohort of participant will start training at 45% of HRR, which is calculated by the following formula: [220-age(years)-resting HR] * 0.45 + resting HR. Resting heart rate will be measured before training started after 10 min of sitting.

Only during the work-bouts of the interval training will the participant need to train at the set target intensity. The strength component of the training sessions will not have a specific target intensity or workload., however participants will be encouraged to work between a rating of perceived exertion (RPE) of 11–14 on the Borg scale[reference], which correlates with a moderate intensity of exercise training[reference]."[35]

Explanation. There is generally a high level of uncertainty about EPDF trial interventions due to their early exploratory nature in clinical development associated with limited knowledge of the dose–toxicity profile and concerns about participant safety. Thus, how and when an intervention will be administered needs to be prespecified precisely to enhance standardised processes across different sites or investigators and to ensure reproducibility of methods outside of the trial. It will also facilitate the interpretation of the results and guide decision-making on the selection of dose(s) and mode of delivery to carry forward to subsequent trials.

Items 8a.5 and 8a.6, which cover the specification and rationale of the range of dose levels and the starting dose, overlap with item 11a. As dose levels are a key feature of EPDF trial designs, items 8a.5 and 8a.6 are intentionally placed separately in the trial design section. In contrast, item 11a focuses on a complete description of the interventions based on the Template for Intervention Description and Replication (TIDieR) checklist and guide,[80] which is an extension of the SPIRIT statement (item 11) and the CONSORT statement (item 5a)[81] addressing the description of trial interventions. Particularly for the trial planning stage, the TIDieR checklist requires specifying how (mode of delivery), where (location), and when the intervention will be administered. It also requires descriptions of how much (number of times, over what period of time, including number of sessions, schedule, duration, and intensity or dose) of the intervention will be delivered, as well as whether and what tailoring techniques (personalised to each individual or groups of participants, e.g., titration or intra-participant dose escalation/de-escalation) will be considered.

Item 11b [modified] Criteria for dose discontinuation, dose modifications, and dosing delays of allocated interventions for a given trial participant (e.g., dose change in response to harms, participant request, or improving or worsening disease)

Example 1. "Dose modifications are not permitted in this trial unless agreed previously with the chief investigator. In the event of a dose limiting toxicity (DLT), that patient's therapy should be temporarily halted. Further management of this patient should be discussed with the chief investigator. The dose of Azacitidine should not be altered from 75 mg/m^2 without

consultation with the chief investigator. Patients experiencing grade 1 or 2 acute graft-versus-host disease (GvHD) should temporarily discontinue lenalidomide therapy until complete resolution of symptoms of GvHD. Patients should re-start at the same dose of lenalidomide upon resolution of symptoms. Recurrent grade 1 GvHD should be managed by temporary discontinuation of lenalidomide and re-started once all symptoms have resolved. Recurrent grade 2 GvHD occurring within the first 2 cycles of treatment is defined as a DLT and the patient should be discontinued. If grade 2 GvHD persists for ≥42 days, patients should discontinue lenalidomide. In the event of an increase in the grade of GvHD (e.g., grade 1 to 2), patients should discontinue lenalidomide. Patients may continue therapy with azacitidine during episodes of GvHD. Patients who discontinue treatment due to GvHD may continue to receive azacitidine off trial at the discretion of the chief investigator. Delays to therapy for reasons other than GvHD may be considered if clinically indicated and must be discussed and agreed previously with the chief investigator.

In the event of discontinuation of study treatment, e.g., unacceptable toxicity or patient choice, full details of the reason/s for discontinuation should be recorded on the appropriate pages on the case report form (CRF). All patients, including non-compliant subjects, should be followed up according to the protocol unless they withdraw specific consent."[78]

Example 2. "Dosing of USL311 may be interrupted to allow for recovery from toxicity, with dosing held for up to 14 days. Thereafter, treatment at the same or a reduced USL311 dose can be considered, based upon discussions between Sponsor or designee and Investigator, if the subject has not developed progressive disease. Subjects with toxicities that require interruptions of greater than 14 days should be discontinued from the study. [....] Dose modifications should be made based on observed toxicity as follows:

Grade 1 or 2 toxicity: No requirement for dose interruption or dose reduction. If the toxicity persists at grade 2, a dose reduction to the next lower dose level may be implemented at the discretion of the Investigator.

Grade 3 toxicity: Dosing should be stopped. USL311 dosing may resume at the next lower dose level when toxicity resolves to grade 1 or returns to baseline.

Grade 4 toxicity: Dosing should be stopped. USL311 may resume at a lower dose level (1–2 dose level decrease) with the approval of the medical monitor when toxicity resolves to grade 1 or returns to baseline."[66]

Explanation. In EPDF trials, discontinuation, modification, or delay of allocated interventions for a given trial participant may occur for different reasons. Examples include dose changes in response to adverse events, participant requests, or improving or worsening disease. Addressing the primary focus of EPDF trials on participant wellbeing, options, and criteria for adapting the dose will help to protect trial participants from potential harm. While important for any EPDF trial, this item is particularly crucial for first-in-human trials, where information about the dose–toxicity profile is often limited. Clearly and transparently outlining these criteria is essential, not only for ensuring adherence but also for allowing readers to understand the trial's process. Clarity in these criteria is key for evaluating adherence and impacts both the interpretation and credibility of the trial's findings.

Authors should describe the pre-defined criteria to guide these decisions for individual participants (see Example 2). It should also be specified if these criteria vary across different periods, such as between the acute tolerability assessment period and any subsequent longer-term follow-up. In contrast to item 8a.4, which addresses stopping rules for the entire trial or a given cohort, this item 11b focuses on the individual participant.[82]

Item 12 [modified] 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

Example 1. Fig. 4 represents this example, which has been adapted; only a portion of the original table is reported here.[83]

Example 2. "Primary endpoints:

(a) Phase I part: dose limiting toxicity (DLT). The number of DLT cases noted within the period between the start of treatment and Day 28 and their incidence will be calculated by the level. DLT is defined as an event that falls under any of the following items among the adverse events that develop during the above DLT evaluation period and is possibly related to the AM80 and GEM/nabPTX combination therapy: i) Grade 4 haematotoxicity persisting for more than 7 days, ii) non-haematological toxicity ≥ Grade 3 persisting for more than 7 days, even if symptomatically treated, iii) an adverse event that impedes the administration of GEM or nab-PTX on Days 8 and 15 and iv) an adverse event that impedes the administration of GEM or nab-PTX on Day 8, leading to dose reduction on Day 15.

(b) Phase II part: Response rate defined as the rate calculated with the number of cases analysed as the denominator and the number of patients with the best overall response assessed as complete response (CR) or partial response (PR) as the numerator based on RECIST version 1.1.

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
Primary Objective To evaluate the safety and immunogenicity of ChAdOx1 85A – MVA85A prime-boost vaccination in Ugandan adolescents	Actively and passively collected data on adverse events	All Adverse Events (AEs) from day 0-28 post vaccination Serious Adverse Events (SAEs) throughout follow up
	T-cell Interferon-γ ELISpot response to antigen 85A	ELISpot spot-forming counts per $1x10^6$ peripheral blood mononuclear cells (PBMCs) at day 14 for groups 1-4 ELISpot spot-forming counts per $1x10^6$ peripheral blood mononuclear cells (PBMCs) at day 63 for groups 5 and 6 Area under the curve (AUC) analysis of immunogenicity (days 0-168 for groups 1-4; days 0-168 for groups 5 and 6)
Secondary Objective To further characterise immunogenicity of ChAdOx1 85A – MVA85A prime-boost vaccination in Ugandan adolescents	Antibody response to antigen 85A Exploratory immunology including ELISpot response to BCG, flow cytometry, gene expression, and mycobacterial killing assays	Screening and follow up visits as shown in Schedule of Visits, section 3

Fig. 4: Item 12, primary, secondary, and other outcomes, Example 1—obtained from study NCT03681860 on ClinicalTrials.gov (https://clinicaltrials.gov), a database of privately and publicly funded clinical studies conducted around the world.[83] The example has been adapted; only a portion of the original table is reported.

Secondary endpoints:

(a) Overall survival is defined as the period from the date of the start of investigational dosing to the date of death for any reason, defining the date of completion of the post-observation period in all cases as the cut-off.
(b) Progression-free survival is defined as the period from the date of the start of investigational dosing to the date when progression is identified or date of death if the subject dies without identifying progression (regardless of cause), defining the date of completion of the post-observation period in all cases as the cut-of.
(c) Blood MIKE-1 concentration Plasma MIKE-1 concentration will be confirmed at each time point."[84]

Both examples would be improved by including the clinical relevance of the chosen outcomes, even if it seems straightforward.

Explanation. A clear and complete description of trial outcomes, including those used for trial adaptations, is essential in the protocol across all trial contexts.[9,40,81,85] Like the ACE statement,[40] this modified SPIRIT-DEFINE item addresses the need to pre-specify outcomes that are planned to inform pre-specified adaptations. These outcomes, together with the primary outcome, influence the adaptation process and the performance of the statistical design.[40]

Authors should describe pre-specified outcomes that relate to assessing the research objectives (item 7), including the method and time points of assessment. This guidance also applies to outcomes informing planned trial adaptations. The clinical relevance of such outcomes should be explained. In some situations, trial adaptations may rely on early observed outcomes considered informative for the primary outcome or a combination of an early outcome and the primary outcome.[86–89] In such cases, authors should provide a clinical rationale supporting the use of a trial adaptation outcome different from the primary outcome(s) to aid in the clinical interpretation of results.[40] For example, tolerability and activity outcomes may both be used to inform dose adaptations or early stopping (for safety and/or futility), and activity data from an earlier assessment point may be used as an early indicator of efficacy.[89]

Item 13 [modified] 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

Example 1. Fig. 5a represents this example with the schedule of events.[90]

Example 2. Fig. 5b represents this example.[91]

Explanation. Information about interventional run-ins and washouts is particularly important in EPDF trials, where little is known about the dose–toxicity profile of

a

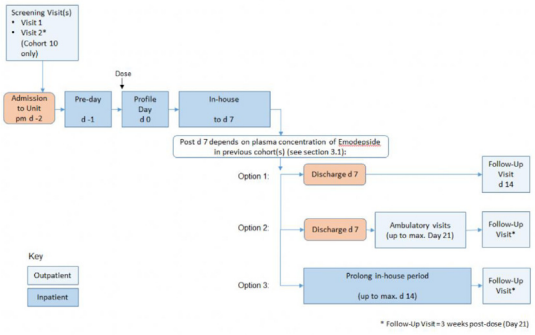
Schedule of Events Table 1: Treatment Group A: 28 Days

Timepoint/Study Visit	Screening (14 days)	Baseline	Treatment			Follow up	
	Visit 1 (Days -13 to Day 0)	Day 1 / Visit 2	Day 8 / Visit 3 (+/- 1 d)	Day 15 / Visit 4 (+/- 1 d)	Day 29 / Visit 15 (+/- 2 d)	Day 43 / Visit 6 (+/- 2 d)	Day 59 / Visit 3 (+/- 2 d)
Informed Consent	X						
History and Demographics[footnote]	X						
Inclusion/Exclusion	X	X[2]					
Height and Weight	X						
Physical Examination[footnote]	X	X	X	X	X	X	
Vital Signs[footnote]	X	X	X	X	X	X	
ECOG Performance Status	X						
Hematology and Chemistry	X		X	X	X	X	
Urinalysis	X					X	
Pregnancy Test	X						
Pharmacokinetic (PK) Assays[footnote]		X	X	X	X	X	
Pain Assessment	X	X	X	X	X	X	
Tumor Measurements[footnote]	X	X					
Tumor Assessment[footnote]			X	X	X	X	
Photography		X	X	X	X	X	
Distribute SOR007 Tube(s)		X	X	X			
Collect SOR007 Tube(s)			X	X	X		
SOR007 Application Training[footnote]		X	X	X			
SOR007 Application[footnote]		X	X	X			
Adverse Events[footnote]	X	X	X	X	X	X	X[10]

The footnotes were removed from this table for reasons of brevity.

b

Figure 2- Parts 1 and 2: Study Flow Chart – Subject Level



*If eligible for study entry based on Screening Visit 1, subjects to be included in Part 2 Cohort 10 will have a second Screening Visit in order to undergo an ophthalmology assessment (within 7 days prior to Profile-Day [Day 0]) or on Pre Day at the latest.
D: day

Fig. 5: Item 13, time schedule of enrolment, interventions, assessments, and visits for participants, **(a)** Example 1—obtained from study NCT03101358 on ClinicalTrials.gov (https://clinicaltrials.gov), a database of privately and publicly funded clinical studies conducted around the world,[90] **(b)** Example 2—obtained from study NCT02661178 on ClinicalTrials.gov (https://clinicaltrials.gov), a database of privately and publicly funded clinical studies conducted around the world.[91]

the intervention and any intervention–intervention interactions. Details on the intervention, its delivery, assessments, and monitoring are particularly important in first-in-human trials to assess the tolerability and acceptability of the intervention. In addition to giving an indication of the perceived risk of the intervention and the supportive care available to protect participants, these details provide the reader with an idea of the complexity of the trial and the intervention, the expected burden on participants and trial sites, and the feasibility of the trial, which may inform subsequent phases of treatment development and deliverability of the intervention in clinical practice. With the growing complexity of all clinical trials[92] this information will be important to sites interested in participating in the trial (e.g., expansion cohorts) or in any subsequent phases of treatment development. It also provides the sponsor with criteria to benchmark sites against their facilities (e.g., overnight observed monitoring ward or other post-dosing monitoring requirements) and for their risk assessments, to select them for this or subsequent trials.

Protocol authors should provide a description of the trial schedule in order of occurrence. They should specify the minimum/maximum inpatient stay or follow-up periods for specific safety and/or tolerability outcomes. If applicable, the degree of flexibility in prolonging or shortening the in-house stay or outpatient follow-up period should be described. A diagram is suggested to help in simplifying and improving understanding of complex designs (see Example 2).

Item 14 [modified] Estimated number of participants (minimum, maximum, or expected range) needed to address trial objectives and how it was determined, including clinical and statistical assumptions supporting any sample size and operating characteristics

Example 1. "The table below shows the operating characteristics of the proposed design for this trial with 5 scenarios defined by different dose limiting toxicity (DLT) rates for 4 doses. These operating characteristics are based on 1000 simulations of the trial. The operating characteristics show that the design selects the true maximum tolerated dose (MTD) with high probabilities and allocates more patients to the dose levels with the DLT rate closest to the target of 0.25.[63]

Fig. 6a represents this example that was reprinted from the supplementary material of Rutherford et al.[63] from The Lancet Haematology with permission from Elsevier. This example has been adapted—only a portion of the original table is reported here.

Example 2. "The dose escalation portion of this study is a modified 3 + 3 design with no dose de-escalation. The sequential cohort enrollment characteristics of this design do not allow a fixed computation of sample size. The parameters of the design that can be calculated are shown in Table 4. Based on an assumed vector of probabilities of any pharmacologic activity or an adverse drug reaction (ADR) for a subject, the probability of each dose being the maximum tolerated dose (MTD) is shown in the table. The average sample size of the dose escalation phase of the study is n = 26.3 patients for the assumed vector of probabilities of any pharmacologic activity or an ADR.[93]" (Fig. 6b).

Explanation. Details of the sample size and the statistical performance of the trial design are important to assess its ability to address the research objectives and summarise any limitations to aid interpretation. For example, operating characteristics can indicate poor statistical performance of the design when it exposes a high proportion of participants to overly toxic doses, has a low probability of correctly identifying the maximum tolerable dose or recommended dose(s), or results in inappropriate early termination of the trial or dose levels.[94] The total sample size may be challenging to specify in advance in EPDF trials as it may depend on trial adaptations in the design.[49] However, it is possible to decide upon a maximum sample size or approximate the possible range of participant numbers required. Such estimates can be informed by design operating characteristics, often determined by statistical simulation results, but may also be constrained by feasibility and costs (e.g., the number of participants that may realistically contribute to the trial in the planned time frame).

Authors should provide sample size determination or justification, including, for example, simulations of outcomes (such as toxicity or activity) to generate operating characteristics to assess the performance of the EPDF design. The assumptions and details of methods used should be specified [item 8a], e.g., relating to parameter choice, simulated scenarios, and decision

a **Operating Characteristics of the BOIN design [adapted]**

	Dose level				Number of pts	% early stopping
	-1	0	1	2		
True DLT rate	0.05	0.10	**0.25**	0.45		
Selection %	0.9	27.4	**56.2**	15.5	18.0	0.0
# pts treated	1.4	7.1	**6.9**	2.6		
True DLT rate	0.12	**0.25**	0.46	0.60		
Selection %	22.3	**62.0**	14.9	0.6	18.0	0.2
# pts treated	5.0	**8.9**	3.6	0.4		
True DLT rate	0.01	0.05	0.08	**0.25**		
Selection %	3.6	26.4	70.0	**0.0**	18.0	0.0
# pts treated	0.5	4.5	6.2	**6.8**		
True DLT rate	**0.20**	0.65	0.75			
Selection %	**77.2**	19.0	3.5	0.1	17.7	3.7
# pts treated	**10.6**					
True DLT rate	0.02	0.06	0.12	**0.18**		
Selection %	0.1	6.3	22.8	**70.8**	18.0	0.0
# pts treated	0.7	5.0	5.5	**6.8**		

pts: patients; BOIN: Bayesian optimal interval design; The results related to the dose levels with the DLT rate closest to the target of 0.25 are shown in bold.

b **Design Characteristics for the Study Design**

Dose Group	1	2	3	4	5	6	7	8	9	Total
Assumed Probability of any pharmacologic activity or a ADR for a subject	.01	.02	.05	.08	.10	.13	.16	.19	.22	---
Probability of the Dose Being the MTD	.002	.012	.039	.071	.103	.136	.152	.148	.065	---
Average Sample Size for Each Dose and Total	3.1	3.2	3.4	3.5	3.3	3.2	2.8	2.2	1.6	26.3

MTD: maximum tolerated dose; ADR: adverse drug reaction.

Fig. 6: Item 14, estimated number of participants, **(a)** Example 1—obtained from the supplementary material of Rutherford et al.[63] from *The Lancet Haematology*, reprinted with permission from Elsevier. The example has been adapted—only a portion of the original table is reported here, **(b)** Example 2—obtained from study NCT02865434 on ClinicalTrials.gov (https://clinicaltrials.gov), a database of privately and publicly funded clinical studies conducted around the world.[93]

thresholds.[48] If applicable, plans for managing the sample size to ensure there are sufficient evaluable participants should be outlined (e.g., through the replacement of participants who are not evaluable for the primary endpoint [item 20c]). Authors should provide a summary of the trial design's statistical performance, regardless of whether the design used has a statistical basis (e.g., algorithm-based 3 + 3 design), as this enhances the interpretation of results and highlights key limitations.

Section: Methods: assignment of interventions

16a.2 [new] Any prespecified rule or algorithm to update allocation with timing and frequency of updates, if applicable

Example. "The second stage allocated eligible participants based on a continual reassessment method (CRM) modeling approach that accounts for both toxicity and immune response in combinations of agents. Toxicity assessment was based on the occurrence of dose limiting toxicities (DLTs), and immune response assessment was based on achievement of durable immune response (dRsp). The estimated DLT probabilities at each arm were used to adaptively define an 'acceptable' set of safe arms, based on which arms had estimated DLT rates below the 25% DLT threshold with high confidence. Once the set of acceptable arms was determined after each new accrual, the recommended arm for the next accrual was chosen at random from the safe set, with each acceptable arm weighted by its estimated dRsp probability. This weighted randomization scheme was employed for the first one-third of the trial. In the latter portion of the trial, the recommended arm for the next accrual was the acceptable arm with the maximum estimated dRsp probability. Additional details regarding the modeling approach have been summarized in a prior report[reference]."[95]

Explanation. Changes in the allocation ratio influence the efficiency and operating characteristics of the trial design. For instance, the performance of a design with 1:1:1 allocation throughout is different from a trial with 1:1:1 allocation followed by 1:3:2 allocation after an adaptation. Thus, it is important that any opportunities to adapt the allocation ratio or update the randomisation rule are prespecified.

In EPDF trials, the allocation ratio(s) may remain the same throughout the trial or may be updated during the trial as a consequence of planned trial adaptations, e.g., when modifying randomisation to favour treatments more likely to show benefits, after treatment selection, or upon introduction of a new arm to an ongoing trial.[40] In cases of a modifiable allocation ratio, authors should describe the nature and the criteria for updating the allocation rule, including when and how often changes can be made.

Section: Methods: data collection, management, and analysis

Item 20a.1 [modified] 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

Example 1. "Efficacy Endpoints Analysis:

Efficacy will be evaluated in both phase 1 and phase 2 components. In phase 1, preliminary efficacy parameters such as 6-month progression-free survival rate (PFS-6m), objective response rate (ORR%), disease control rate (DCR) and overall survival (OS) will be determined using Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 or Response Assessment in Neuro-Oncology (RANO) criteria as appropriate. The phase 2 analyses will characterize efficacy in subjects in the dose expansion cohorts treated at the RP2D for USL311 as a single agent and in combination with lomustine as determined by % PFS-6m, progression free survival (PFS), OS, ORR%, DCR, and as defined by RANO criteria. There is no formal hypothesis testing in this trial for efficacy endpoints. Approximately 20 evaluable subjects will be studied in each of the two phase 2 dose-expansion groups to provide a preliminary estimate of efficacy in relapsed/recurrent glioblastoma multiforme (GBM). The primary objective, PFS-6m, will be calculated with two-sided 90% confidence interval (CI) using Kaplan–Meier (K-M) product-limit estimate of PFS. This will be performed based on both the full analysis set and response-evaluable set. Median PFS will be calculated using K-M product-limit estimates and presented with two-sided 90% CIs. [...]

Safety Endpoints Analysis:

Adverse event (AE) data will be descriptively evaluated. Descriptive statistics (e.g., number of observations, means, standard deviations, medians, maximum and minimum values) will be used to summarize continuous variables. Frequencies, proportions, and the exact 95% confidence intervals (CI), when appropriate, will be used to summarize categorical variables. Subject listings will also be provided. In both phase 1 and phase 2, the incidence and duration of toxicities will be tabulated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. All laboratory results and vital sign measurements will be summarized using appropriate descriptive statistics. The schedule of assessments tables describes the timing of required evaluations.

Safety and tolerability will be evaluated in both phase 1 and phase 2 components. The Phase 1 primary analyses will include determination of the maximum tolerated dose (MTD) and ecommended phase 2 dose (RP2D) for USL311 as a single agent and in combination with lomustine. All available safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) data

will be considered by Sponsor in dose escalation decisions. Additional safety analyses other than those described in this section may be performed if deemed appropriate and will be described in detail in a separate analysis plan."[66]

In this example, the distinction between primary, secondary, and exploratory outcomes could have been stated more explicitly.

Example 2. "All analyses are predefined and documented in the statistical analysis plan approved by the chief investigator. The statistical design will be reported in detail in a separate manuscript. Briefly, part 1 will report the recommended maximum tolerated dose (MTD), the Bayesian posterior probability of dose limiting toxicity (DLT) at each dose level (with 90% probability interval) and the posterior probability that the DLT rate at dose level 1 (200 mg) is greater than the target level of 35%. The number of participants experiencing DLT at each dose level, together with the proportion of participants with DLT at that dose level, will be reported. Secondary outcome measures including the relationship of pharmacodynamic (PD) biomarkers and pharmacokinetic (PK) parameters will be presented graphically.

Part 2 will assess potential efficacy of treatment based on a composite outcome of response following 12 cycles of treatment. Individual components of the composite response outcome and all adverse events (AEs) will also be reported descriptively. Secondary outcome measures including PK parameters and PD biomarkers will be presented graphically.

[…]

The MTD was established using a restricted 1-stage Bayesian Continual Reassessment Method (CRM)[reference] based on a target dose limiting toxicity (DLT) probability of 35% (similar to what is observed with methotrexate, the "anchor" drug in rheumatoid arthritis (RA) clinical practice[reference]), or determination of unacceptable toxicity leading to cessation of the trial. It is planned that up to 7 cohorts of 3 participants each will be treated, with each cohort receiving 1 of 5 possible doses of the investigational medicinal product (IMP). The trial design allows for early stopping if sufficient evidence of MTD has been achieved or if the lowest IMP dose is too toxic."[96]

Explanation. The SPIRIT statement[9] addresses the importance of pre-specifying statistical methods to analyse primary and secondary outcomes. This SPIRIT-DEFINE modified item extends this requirement to a similar description for statistical methods used for interim analyses for dose escalation/de-escalation decisions or other trial adaptations (e.g., for determining the next participant's dose or stopping the trial early due to safety concerns or futility). Details of statistical methods used to analyse any other trial adaptation outcomes enhance the transparency and reproducibility of the adaptation process. Stating statistical software and packages with version (if applicable) to be used for analyses (e.g., dose escalation/de-escalation decisions and biomarker analyses) is recommended as good practice.

There should be a detailed description of the statistical methods used to address the objectives (item 7) of an EPDF trial, along with their pre-specified adaptations (item 8a.1). These statistical methods may be based on descriptive statistics such as frequencies, percentages, means, and narrative descriptions (e.g., descriptions of adverse events experienced), deterministic approaches/algorithms, statistical models, or a combination of these. Furthermore, planned statistical methods for analysing any outcomes used for trial adaptation should be detailed. This may include statistical methods for safety monitoring and data-driven pharmacokinetics or pharmacodynamics modelling if either is used to inform trial adaptations. Authors should specify whether a frequentist or Bayesian framework was used and report indications of uncertainty (e.g., using confidence intervals or credible intervals) as appropriate.[48] For Bayesian methods, it is recommended that details on the description of the prior distributions of model parameters be provided in accordance with item 8a.3.

Item 20a.2 [new] For the proposed adaptive design features, statistical methods used for estimation (e.g., safety, dose(s), treatment effects) and to make inferences

Example 1. "The dose escalation will employ a modified continual reassessment method (mCRM) with overdose control design in order to define the maximum tolerated dose (MTD) and/or the recommended dose for subsequent cohorts. The design is based on the primary safety variable, that is, the occurrence of a dose limiting toxicity (DLT).

The maximum tolerated dose (MTD) is defined as the dose that maximizes the probability of achieving a DLT rate of 16%–33% (target toxicity interval) and results in a 35% probability of having a DLT rate of 33% (overdose control) […].

A detailed algorithm for the selection of the next recommended combination of doses in the dose-escalation procedure is described in Appendix 6. As stated above, only combinations of doses with a <35% probability of having a DLT rate of >33% will be allowed.

Dose escalation will stop when the maximum allowed sample size, 60 patients, has been reached or there is enough confidence in the prediction of the MTD (e.g., at least 6 patients have been recruited at the MTD doses and there is a >40% probability of having a DLT rate of 16%–33%).

The following two marginal models (two-parameter logistic regression), which describe the relationship between DLT and idasanutlin dose in the absence of venetoclax, and conversely, the relationship between

DLT and venetoclax dose in the absence of idasanutlin, were considered:

...

In order to define the prior distributions (priors) for the parameters of the two marginal models, the Sponsor's clinical team went through a process of prior elicitation, based on expert knowledge and previous data (i.e., Study GO27878 for venetoclax and Study NP27872 for idasanutlin), to reach a consensus on the questions listed in Table 3.

...

Based on the answers from Table 3, the following priors were defined:

$$\begin{bmatrix} \alpha_1 \\ log(\beta_1) \end{bmatrix} \sim N\left[\begin{pmatrix} -2.0 \\ 0.916 \end{pmatrix}, \begin{pmatrix} 1.665 & 0.037 \\ 0.037 & 0.002 \end{pmatrix} \right]$$

$$\begin{bmatrix} \alpha_2 \\ log(\beta_2) \end{bmatrix} \sim N\left[\begin{pmatrix} -3.905 \\ 1.685 \end{pmatrix}, \begin{pmatrix} 1.47 & 0.0299 \\ 0.0299 & 0.003 \end{pmatrix} \right]$$

[...]

During the expansion phase, predictive probabilities may be used to guide early stopping for futility by comparing the observed proportion of patients who achieve a positron emission tomography (PET)-computed tomography (CT) defined Complete response (CR) at end of induction (EOI) with that in historical controls. The design is based on Lee and Liu[reference] with the modification that the uncertainty in historical control data is fully taken into account by utilizing a distribution on the control response rate. Interim analysis decision rules will be based on the predictive probability that this trial will a positive outcome if carried out to completion and will use the historical control data available at the time of analysis."[97]

Example 2. "We will employ the Bayesian Optimal Interval (BOIN) design[reference] to find the maximum tolerated dose (MTD). The BOIN design is a novel Bayesian dose-finding method that optimizes patient ethics by minimizing the chance of exposing patients to sub-therapeutic and overly toxic doses.

...

The BOIN trial design is described as follows:

1. Patients in the first cohort are treated at dose level 0.
2. To assign a dose to the next cohort of patients, we conduct dose escalation/de-escalation according to the rule displayed in Table 13.

When using Table 13, please note the following:

(a) "Eliminate" means that we eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.
(b) When we eliminate a dose, we automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, we stop the trial for safety. In this case, no dose should be selected as the MTD.
(c) If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, we treat the new patients at the current dose.
(d) If the current dose is the lowest dose and the rule indicates dose de-escalation, we will treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point we will terminate the trial for safety.
(e) If the current dose is the highest dose and the rule indicates dose escalation, we will treat the new patients at the highest dose.
(f) If the number of patients treated at the current (or any) dose reaches 12, we will stop the trial early and select the MTD as described below.

3. Repeat step 2 until the maximum sample size of 24 is reached or the trial is stopped.

After the trial is completed, we select the MTD based on isotonic regression as specified previously[reference]. Specifically, we select as the MTD the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, we select the higher dose level when the isotonic estimate is lower than the target toxicity rate; and we select the lower dose level when the isotonic estimate is greater than the target toxicity rate."[98]

The table 13 mentioned in this example is represented in Fig. 7.

Explanation. In EPDF trials, a common key objective is the estimation of the recommended dose(s), which can be informed by statistical methods estimating toxicity, activity, a combination of both, or other parameters of interest. There is also an increasing use of seamless phase I/II designs with initial dose (de-)escalation, which may then be followed by dose expansion or a randomised dose-ranging part to explore potential promising dose(s) that are tolerable and active.[4] For the dose-ranging part, see the ACE statement,[40] which discusses several statistical issues that may arise when using an adaptive randomised design to estimate treatment effects for key outcomes. Such issues include estimation bias that may result if conventional estimates of treatment effect based on fixed design methods are used. Similar issues arise for single-arm multi-stage designs.[99] Results and conclusions may differ when different analysis methods are used. Hence, authors should pre-specify the statistical methods for estimating measures of treatment effects, with associated measures of uncertainty and a p-value (where appropriate). This

Table 13: Dose escalation/de-escalation rules

	The number of patients treated at the current dose					
Action	3	6	9	12	15	18
Escalate if # of patients who experienced DLT <=	0	1	2	3	4	4
De-escalate if # of patients who experienced DLT >=	2	3	4	6	7	8
Eliminate if # of patients who experienced DLT >=	3	5	6	7	9	10

DLT: dose-limiting toxicity.

Fig. 7: Item 20a.2, for the proposed adaptive design features, statistical methods used for estimation and to make inferences, Example 2—obtained from study NCT02942264 on ClinicalTrials.gov (https://clinicaltrials.gov), a database of privately and publicly funded clinical studies conducted around the world.[98]

can aid interpretation and reproducibility and may also increase the credibility of the results if statistical analysis methods are described before accessing any trial data.[100]

Authors should detail statistical methods for estimating key parameters (which include estimation of parameters for primary, secondary, and other important outcomes). Typical key parameters in EPDF trials include toxicity rates, treatment effects, or recommended dose(s). For instance, the statistical methods and criteria used to select the recommended dose (such as a dose with dose limiting toxicity closest to a prespecified threshold) should be described. Authors should specify whether a frequentist or Bayesian framework (see Example 1) will be used to make inferences and what indications of uncertainty (e.g., confidence intervals or credible intervals) and a p-value (where appropriate) will be reported. If different statistical methods are used for interim and final analyses, it is important to explicitly state that in the protocol. For rule-based designs, where no statistical methods are utilised for estimation or to make inferences, this item is not applicable.

Item 20b [modified] Statistical methods for additional analyses (e.g., subgroup and adjusted analyses, pharmacokinetics or pharmacodynamics, biomarker correlative analyses)

Example 1. "Pharmacokinetic/Pharmacodynamic Analyses.

Pharmacokinetic (PK) parameters will be assessed by non-compartmental analysis, including maximum concentration observed (Cmax), area under the concentration time curve (AUC) to the end of the dosing interval (AUC0-tau), to infinite time (AUC0-inf), clearance, elimination half-life (t 1/2) and volume of distribution will be calculated, if data allow.

PK-PD modeling and simulation will be performed and may be used in support of dose escalation decisions and determination of the recommended phase 2 dose (RP2D) and dosing schedule; it will however be reported separately.

An explorative analysis of the relationship between exposure and body weight, if data allow, will be conducted, either graphically or as part of the PK-PD modeling activities.

Further exploratory analysis of PK data may be performed, such as the potential relationship with other covariates. These analyses will be described in a separate document outside of the SAP.

Exploratory biomarker analyses will be performed using descriptive biostatistics."[68]

Example 2. "Exploratory Aim Analysis.

There are a number of patient subgroups that could be of interest and might be expected to respond differently to Dodecafluoropentane emulsion (DDFPe) as evaluated by National Institutes of Health Stroke Scale (NIHSS) scores:

- In those early patients who get some successful therapy and get DDFPe early at less than 3 h from last known well (LKWT), the values should drop with the DDFPe and stay down with reperfusion. Late DDFPe uncertain.
- In those that get Rx and it fails, scores may perhaps go down with early DDFPe and come back up when it wears off. With late DDFPe little change is expected.
- In those that do not get reperfusion therapy and do get DDFPe in the first 3 h, scores should go down but come back up when it wears off.
- In those that do not get reperfusion therapy and get DDFPe late, scores should not change much.
- In those that get placebo, should see little change, early or late, unless they have successful reperfusion therapy or spontaneous reperfusion.

Fewer than 20% are likely to get intravenous (IV) tissue plasminogen activator (tPA) or Intra-arteria (IA) reperfusion therapy of the total 24 patients; the patient numbers in any of these groups will be quite small, obviating the ability to make formal statistical comparisons or to draw conclusions about the impact of DDFPe therapy on outcome. This is a phase I safety trial, and not designed to test treatment outcomes. As an exploratory analysis, we will compare the patients without reperfusion therapy, IV or IA, who got early DDFPe under 3 h from LKWT, to placebo patients of similar characteristics. Due to the small sample sizes and because each of the proposed doses were effective in animal studies, we will ignore dose in this comparison."[101]

Explanation. Due to their usually small sample size, spurious findings in any unplanned analyses could be a more critical issue for EPDF trials than for late-phase trials. Beyond the SPIRIT statement,[9] this modified SPIRIT-DEFINE item highlights the role of statistical methods for pharmacokinetic, pharmacodynamic, and biomarker correlative analyses. As these analyses may inform the target population of any expansion cohort(s) of participants or later trials, pre-specification of the statistical methods to be used will aid interpretation and enhance the credibility of subsequent decisions.

Besides subgroup and adjusted analyses, EPDF trial protocols should give particular attention to statistical methods used for analysing other exploratory outcomes, such as pharmacokinetic/pharmacodynamic analyses and biomarker correlative analyses, unless they are already covered as secondary outcomes. The information can be provided in an appendix but should be consistent with associated objectives.[27] Authors should also specify if any sensitivity analyses will be conducted for specific outcomes.

Item 20c.1 [modified] Analysis population(s) (e.g., evaluable population for dose-finding, safety population)

Example 1. This example of analysis populations is represented in Fig. 8.[12]

Example 2. "13.3.1.2. Full Analysis Set

As the sample size was small, immunogenicity data will be analyzed on the population of injected volunteers in an "intent to treat" analysis. This population will be identified as the Full analysis set. Volunteers' data will be analyzed in the treatment group allocated by randomization. No per protocol analysis will be performed. A complete description of protocol violations will be performed in order to investigate the possible impact of protocol violations on the immunogenicity evaluation. Volunteers included and not injected

Analysis Populations

Population	Description
Efficacy	All participants who received at least one dose of RO7172508.
Safety	All participants enrolled in the study who received at least one dose of study treatment (RO7172508 and/or obinutuzumabif applicable) will be included in the safety population. Unless otherwise specified, the safety population will be the default analysis set used for all analyses.
Dose-limiting toxicity (DLT) evaluable	DLT–evaluable participants are those who have completed the DLT window without a DLT, or participants who reported with a DLT. This population will be used in the determination of the maximum tolerated dose (MTD) *[and during the dose-escalation process]*.
Pharmacokinetic (PK)	All participants who have received at least one dose of study treatment and who have data from at least one post-dose sample will be included in the PK analysis population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.
Immunogenicity	Participants who had at least one pre-dose and one post-dose anti-drug antibodies (ADA) assessment will be included and analyzed according to the treatment they actually received. The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

DLT: dose-liming toxicity; PK: pharmacokinetics.

Fig. 8: Item 20c.1, analysis population(s), Example 1—obtained from study NCT03539484 on ClinicalTrials.gov (https://clinicaltrials.gov), a database of privately and publicly funded clinical studies conducted around the world.[12]

(i.e., not in the full analysis set) will not be taken into account.

13.3.1.3. Safety analysis sets

The safety data will be analyzed for all volunteers who receive at least one injection (= Full analysis set). Only safety information collected after at least one injection will be taken into account. Adverse events which occur between V0 and the first injection will be listed. In case of randomization error, a volunteer will be analyzed according to the treatment he/she actually received. For safety evaluation "after any injection" all the volunteers injected and evaluated at least once will be considered as assessable. In case of withdrawal, it may lead to an underestimation of the occurrence rate. Exploratory analyses will be performed (e.g., examination of frequency distributions, modality of distributions, kurtosis and skewness, etc.) for all variables collected before subjecting the values to statistical analysis.

13.3.1.4. Immunogenicity analysis sets

The immunogenicity data will be analyzed for all volunteers who receive at least one injection (= Full analysis set). Only safety information collected after at least one injection will be taken into account. In case of randomization error, a volunteer will be analyzed according to the treatment he/she actually received. Exploratory analyses will be performed (e.g., examination of frequency distributions, modality of distributions, kurtosis and skewness, etc.) for all variables collected before subjecting the values to statistical analysis."[102]

Explanation. A comprehensive description of the analysis populations, also known as analysis sets, will allow the reader to assess whether they are directly relevant to, and guided by, the specific objectives of a given EPDF trial, and thus, whether the trial can address these objectives. Analysis populations for interim and final analyses also define the participants to whom the results of an EPDF trial will be generalizable. Criteria for participant replacement, which is common in EPDF trials, will aid interpretation and reproducibility.

Authors should define trial-level participant analysis sets for statistical analyses (e.g., those evaluable for dose-finding, response, safety), specifying the criteria for participants to be considered in statistical analysis.[48] For instance, setting a pre-specified lower threshold for the proportion of the planned dose actually delivered (e.g., 85%) will only consider participants in escalation/de-escalation decisions who will have had adequate exposure to the intervention or experienced a dose limiting toxicity[49] or dose-limiting criteria.[103] For combination EPDF trials, it should be stated whether the predetermined amount for evaluability is based on each individual component in the combination or for the combination as a whole. Information on how unevaluable participants will be treated in statistical analysis (e.g., using participant replacement or best/worst case analysis) and what happens to data collected from participants later found to be ineligible should also be stated. These definitions should also be provided for any interim analysis population.[48]

Item 20c.2 [new] 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

Example. "The following intercurrent events (IEs) of interest will be considered:

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

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

- Included in the analysis and assumed to have experienced a dose limiting toxicity (DLT);
- Included in the analysis and assumed to not have experienced a DLT; or
- Excluded from analysis and replaced with recruitment of additional patient.

For intercurrent event (2) data from subsequent visit(s) will be used to ascertain if a suspected DLT occurred during the DLT reporting window. The main estimand will use all patients who had their day 8 assessment and those who it can be definitely ascertained to have experienced a DLT within the report window (using data from subsequent visits). Any patient who did not have the day 8 assessment and who either did not experience a DLT or experienced a DLT outside of the reporting window will be excluded from the analysis. The sensitivity estimand will then include the entire population as defined above, therefore covering all those as in the population who both did and did not have their day 8 assessment performed. For patients who missed the day 8 the following will hold: any patient who experiences an event which fulfils the criteria of a DLT at any point up until their safety visit will be assumed to experience a DLT; any patient who does not experience an event fulfilling the criteria of a DLT at any point up until their safety visit will be assumed to not experience a DLT at any point.

For IE (3) an analogous approach to the strategy defined to handle IE (2) will hold. Where it is the case that the safety assessment occurs prior to completion of the DLT reporting window, then data will also be ascertained from the first safety visit occurring after the completion of the DLT reporting window."[48]

Explanation. Intercurrent events are those events occurring after treatment initiation or randomisation (such as dosing delays, reductions, or interruptions), which may affect either the interpretation or the existence of the measurements associated with the outcome of interest.[48,104,105] How missing data and intercurrent events are handled can impact the integrity and interpretability of study results. Transparent pre-specification of such information promotes methodological clarity and subsequently enhances the reader's ability to interpret the trial results and assess their robustness.

The strategies to handle intercurrent events and missing data should be discussed and pre-specified in the protocol. Different strategies may be used for different types of intercurrent events.[48] Strategies used for handling missing data should also be specified, with approaches to handle missing data being clearly distinguished from approaches to handle intercurrent events. Any sensitivity analyses that are planned to assess the effect of the chosen strategies on the trial results should be included in the protocol.[48]

Section: Methods: data monitoring

Item 21a [modified] 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

Example 1. "An internal monitoring committee (IMC) will monitor patient safety throughout the study. The IMC will include Sponsor representatives from Clinical Science, Drug Safety, Biostatistics, and Statistical Programming and Analysis. In addition to the ongoing assessment of the incidence and nature of adverse events (particularly Grade 3 events), SAEs, deaths, and laboratory abnormalities performed by the investigator and the Medical Monitor, the IMC will review data supporting the determination of the recommended phase 2 dose (RP2D) and then, at regular intervals during the expansion phase. At the time of each review, the IMC will make appropriate recommendations (e.g., the study should continue as planned, additional analyses should be performed, enrollment should be held pending further safety evaluations). Decisions will be made in consideration of the totality of the available data. Ad hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any potential new safety signals."[106]

Example 2. "For Part A, the safety review committee (SRC) will be comprised by a sponsor medical representative, the Medical Monitor, a sponsor-independent investigator, and a site representative. For the decision to progress to Part B, an independent statistical consultant and a third party expert will also be included.

Key roles of the SRC are as follows:

- Before progression to the next cohort, assess the data, decide whether to approve initiation of the next cohort/dose level and to confirm the planned dose or define another dose for use. The data assessed by the SRC is defined in Section 1.1.
- After completing its evaluation of the 48 h data for the first 6 subjects per group in cohort, the SRC may request a prolongation of the observation period to up to Day 7 data for later cohorts or other similar adaptions to protect subject wellbeing.
- Throughout the trial, assess whether to replace trial subjects permanently discontinued due to safety issues.
- Throughout the trial, approval from the SRC will be required prior to resuming any dosing in a "stopped" cohort (see Section 6.6.1). The SRC may call for the opening of a lower dose level cohort.
- SRC may make recommendations on increasing the length of the observation periods and additional subject wellbeing calls may be included at the discretion of the SRC.

The SRC will act according to its own written procedures described in a charter, and will prepare written minutes of its meetings."[107]

Example 3. "The SMC [Safety Monitoring Committee] is an independent group of at least 3 experts that monitors subject safety and advises DMID [Sponsor]. SMC members will be separate and independent of study staff participating in this trial and should not have scientific, financial, or other conflicts of interest related to this trial. The SMC will consist of members with appropriate expertise to contribute to the interpretation of data from this trial. A quorum will consist of a simple majority.

The SMC will hold an organizational meeting prior to enrollment. At this meeting, the SMC will review the charter, protocol, ICF, and safety report template. [...]

Procedures for SMC reviews/meetings will be defined in the SMC charter. The SMC will review applicable data, including, but not limited to, enrollment, demographics, dosing data, clinical laboratory data, and safety data, at scheduled timepoints during this trial as defined in the SMC charter. The SMC will

review blinded aggregate data in the open session of the SMC meetings."[108]

Explanation. For EPDF trials, with their focus on risk of harm, their characteristically adaptive nature, and a high number of possible interim analyses, it is key to be transparent in describing who will be involved in decision-making and, if possible, detail how decisions are made. The decision-making committee/group typically involves members with relevant specialist expertise to assess an EPDF trial, including clinical (and pharmacological and toxicological, depending on the intervention) experience,[109] who may not necessarily be independent from the sponsor.[110] Extensive information on the backgrounds of the committee/group members will increase the trial's credibility and reassure that the decision-making committee/group acts in the best interest of the trial participants.

Authors should specify the composition of any decision-making committee/group who will review key outcomes, including safety and treatment tolerability, and make or recommend decisions (e.g., dose escalation/de-escalation, dose expansion, progression to another phase, stopping the trial early for futility). Such groups are sometimes referred to as a safety review committee/group, dose escalation committee/group, data (safety) monitoring committee or board, or similar. Details should include a summary of the role and reporting structure of the decision-making committee/group. A statement should be included addressing whether the decision-making committee/group is independent from the sponsor, funder, or trial team, and any competing interests should be described. Reference should be given to where further details, such as a decision-making committee charter, can be found, if not in the protocol.

Item 21b [modified] 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

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

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

Prior to each dose escalation meeting, unblinded safety data for this open-label study will be made available to the study team via listings from Inform and Q2 Results Viewer. In addition, CPMS will obtain the interim unblinded pharmacokinetic (PK) concentration data from SMS2000 via Harmonisation of Analysis & Reporting Program (HARP) according to current working practices. If any process changes occur which affect the way in which SMS2000 data is obtained during the study, then the applicable process at the time will be followed and any changes in processes between dose escalations will be documented."[111]

Example 2. "Once the third subject of a cohort has attended their final visit, the chief investigator, principal investigators from each site, trial manager and trial statistician discuss any adverse events/reactions (AEs/ARs) and dose limiting toxicities (DLTs) and make the decision whether or not to open the subsequent cohort, according to the Continual Reassessment Methods (CRM) algorithm, with sponsor and Data Monitoring Committee (DMC) approval. An independent DMC undertakes independent review with the purpose of monitoring safety and efficacy endpoints."[96]

Example 3. "Cumulative adverse event (AE) data will be provided to the Safety Monitoring Committee (SMC) after all subjects in cohorts 1 and 2 have completed Day 8 and again after all subjects have completed Day 36. Documentation of review and any concerns noted will be solicited electronically. The SMC does not need to meet for dose escalation to 250 mcg (cohort 3). The SMC will meet when trial halting criteria are met, or as requested by the sponsor or Principal Investigator (PI). The SMC will have a final review meeting at the end of the study. Procedures for SMC reviews/meetings will be defined in the SMC charter. The SMC will review applicable data, including, but not limited to, enrollment, demographics, dosing data, clinical laboratory data, and safety data, at scheduled timepoints during this trial as defined in the SMC charter. The SMC will review blinded aggregate data in the open session of the SMC meetings. Additional data may be requested by the SMC, and interim statistical reports may be generated as deemed necessary and appropriate by the Division of Microbiology and Infectious Diseases (DMID). As an outcome of each review/meeting, the SMC will make a recommendation as to the advisability of proceeding with study product administration, and to continue, modify, or terminate this trial [...]. Data may be disseminated to public health officials and partners as needed and included in scientific publications and presentations to inform the global scientific community."[108]

None of the examples have provided information on measures to safeguard the confidentiality of interim information.

Explanation. In contrast to late-phase trials, it is not uncommon that clinical investigators who recruit participants for open-label EPDF trials are unblinded to interim data and aware of the next dose(s). Investigators being aware of the interim results may lead to operational bias during the trial. Providing details on who had access to interim results and made the interim and final decision to terminate the trial helps the reader understand the measures taken to minimise operational and selection bias during interim analysis and decision-making for adaptations.[40] It promotes accountability and facilitates understanding of the decision-making process, enabling assessment of the validity and interpretation of trial results.

Authors should describe who will 1) have access to the interim data, 2) perform the interim analyses, 3) make decisions on dose and other trial adaptations, and 4) make the final decision to terminate the trial or any of its parts. It should be clear what measures are taken to minimise potential operational biases during the trial (e.g., which interim results will be communicated and how, to whom, and when) and, if applicable, what measures will be used to safeguard the confidentiality of interim information.

Item 22 [modified] Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported harms such as adverse events (e.g., 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 (e.g., before any planned next dosing)

Example 1. "Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Safety events of interest on a sponsor study drug that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, e.g, name confusion)
- Exposure to a sponsor study drug from breastfeeding

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated informed consent form (ICF) is obtained until 100 days after the last dose of study drug or until the start of subsequent systemic anticancer therapy, if earlier, and may include contact for follow-up of safety [...] The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions.

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 h of their knowledge of the event. Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 h. The initial and follow-up reports of a serious adverse event should be made by facsimile."[23]

Example 2. "During Part 1 of the study, Study Team Safety Update Meetings will be held every three weeks to review relevant data with the Principal Investigators (or delegates) and site staff. These meetings will be held on an "as needed" basis (but no less frequent than once a month) during Part 2 (e.g, to share safety experience and to communicate results of scheduled futility analyses). Safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical outcome data available for all subjects at the time of the scheduled Safety Update Meeting will be reviewed and summarized. In addition, Dose Escalation Meetings will be scheduled at the conclusion of the DLT assessment period for subjects enrolled in each cohort to review safety PK, and PD data and determine the next dose level appropriate for study. Dose escalation decisions will be made with team and investigator agreement after review of available safety data from at least one cycle of therapy with GSK2867916 (i.e., 21 days for the once every 3 weeks schedule and 28 days for weekly schedule). All dose escalation or safety decisions will be documented in writing with copies maintained at each site and the Master Study Files at GSK. Available data will be provided to participants prior to each scheduled Safety or Dose Escalation Meeting.

Attendees of Safety Update and Dose Escalation Meetings will include but not limited to all clinical investigators (or designees) and site staff, the GSK Medical Monitor, Clinical Investigation Lead, Clinical Operations Study Lead (USA and Local Operating Company designees), Data Quality Leader, Global Clinical Safety and Pharmacovigilance Representative,

Statistician, Clinical Pharmacology Modeling and Simulation (CPMS) representative, and Translational Medicine Lead."[112]

Explanation. To better fit EPDF trials, "adverse events and other unintended effects" from the SPIRIT statement[9] were substituted for "toxicities and adverse events." Complete reporting of safety data is essential in EPDF trials for benefit-risk interpretation and to inform subsequent trials. Safety data often include toxicities and adverse events (with their grading). To address the first-in-human nature of many EPDF trials, this SPIRIT-DEFINE modification of the original SPIRIT statement[9] item also highlights the importance of processes to report toxicities and adverse events of a trial intervention rapidly so that information is available before dosing the next participant and before making the next dose escalation decision. In the case of emerging safety issues such as severe or serious adverse events, plans should include the time frame within which the sponsor should inform investigators and participants (at any site). Such time frames may be considerably shorter than in late-phase trials, given the limited information on the dose–toxicity profile of the intervention available before and during an EPDF trial.

Authors should outline plans for presenting all safety data, e.g., unfavourable changes in symptoms, vital signs, laboratory values, or health conditions, whether they can be attributed to the trial treatment or not, including data beyond those used for dose escalation/de-escalation decisions. It is important that safety data be presented by dose.

Section: Ethics and dissemination

Item 31a.2 [new] Plans for sharing results (e.g., safety, activity) externally while the trial is still ongoing, if applicable

Example 1. "Cumulative safety information, study status, and primary endpoint results may be presented at a public forum in a blinded manner or presented as summaries aggregated by study arm at the discretion of the sponsor while the primary study is ongoing. Any ad-hoc analyses, jointly developed by the Statistical and Data Coordinating Center (SDCC) and/or the Vaccine Research Center (VRC) and ModernaTX, Inc., will be executed by the SDCC as needed. None of the interim analyses will include any formal statistical hypothesis testing; therefore, p-value adjustment will not be made to any analyses."[108]

Example 2 (created). "At the conclusion of the dose-escalation phase, an abstract detailing the safety outcomes and key secondary outcomes (including the overall response rate) of the explored dose levels will be prepared for submission to relevant conferences, and if accepted, will be presented. At the conclusion of the dose-expansion phase, a second abstract summarising the efficacy and safety results of all patients included in the study will be submitted and presented at relevant conferences. The Trial Management Group has the discretion to decide whether to publish separate manuscripts for the dose escalation and dose expansion components, or to combine both components into a single manuscript."

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

Explanation. In contrast to later phase trials, where it is often prohibited, it is not uncommon for results of open-label EPDF trials (e.g., on adverse events or activity outcomes) to be reported at scientific meetings whilst the trial is still ongoing, with these results being updated over time.[57] This can lead to different challenges if it is not properly planned. For example, interim results may affect the actions of key decision-makers involved in the trial and thus pose a risk to trial validity and integrity. Moreover, investigators may tend to present chance results that favour the intervention. Outlining detailed strategies in the protocol on how and when to externally share interim results may reduce such risks, minimise the potential for operational bias, and lend credence to the reported results.[40]

Authors should state the process and timeframe for sharing trial results while the trial is still ongoing (for example, results for completed phase I may be reported via scientific presentations, journal publications, regulatory submission, or on the trial website, whilst phase II is still ongoing for a seamless phase I/II trial). If it is not planned to share results while the trial is still ongoing, this should be stated.

Section: Appendices

Item 34 [new] 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

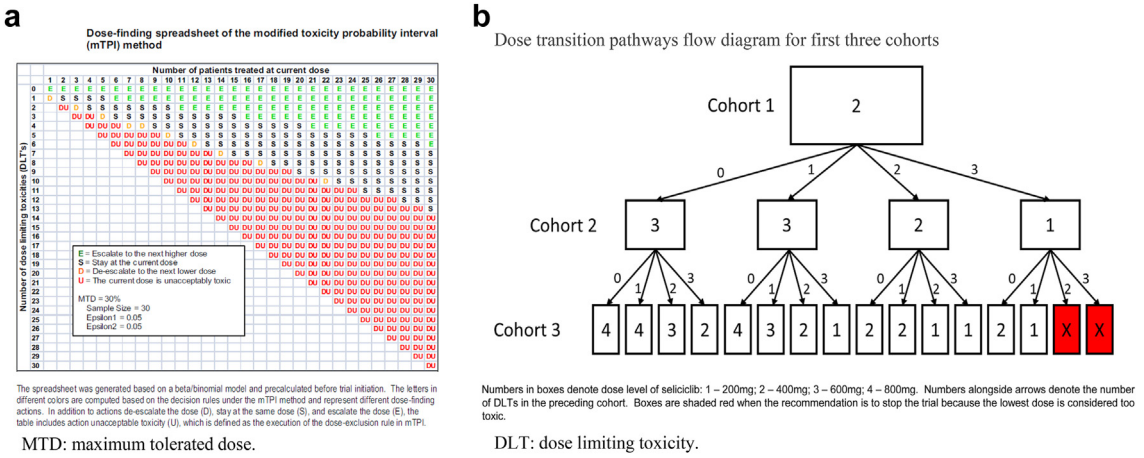
Example 1. This example is represented in Fig. 9a.[59]

Example 2. This example is represented in Fig. 9b, from Cole et al,[113] used under the terms of the Creative Commons CC BY licence.

Example 3. This example is represented in Fig. 10a.[114]

Example 4. This example is represented in Fig. 10b, originally Figure 2 of Kramer et al,[35] reprinted from the Journal of Stroke and Cerebrovascular Diseases with permission from Elsevier.

Explanation. Dose Transition Pathways (DTPs) or dose decision paths can take the form of a decision table or a flow diagram to map out in advance how a proposed design would recommend doses (escalate, de-escalate, stay, or stop) based on previous participants' key outcomes, e.g., what the next dose would be if a certain



MTD: maximum tolerated dose.

DLT: dose limiting toxicity.

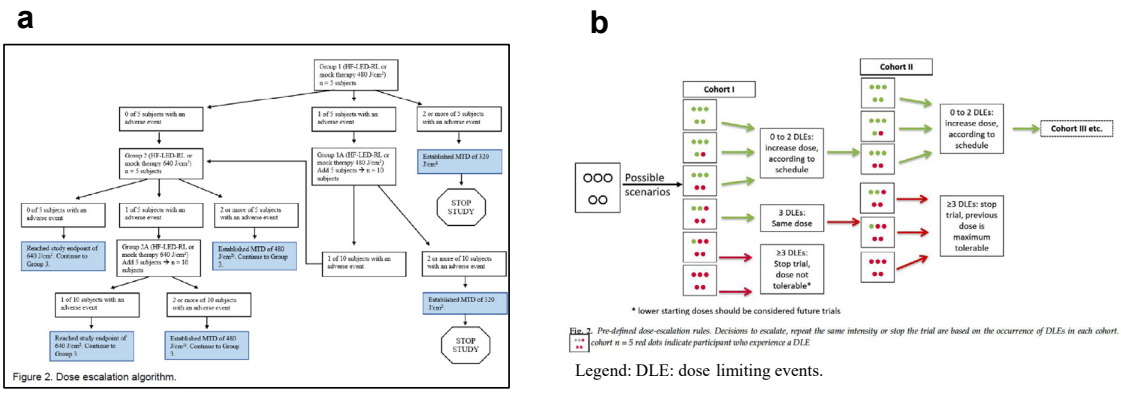
Fig. 9: Item 34, dose transition pathways or dose decision paths, **(a)** Example 1—obtained from study NCT02964507 on ClinicalTrials.gov (https://clinicaltrials.gov), a database of privately and publicly funded clinical studies conducted around the world,[59] **(b)** Example 2—obtained from Cole et al,[113] used under the terms of the Creative Commons CC BY licence.

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. DTPs also help in communicating complex designs to the clinical team or review committees more clearly, accelerating review processes, and facilitating trial conduct.[48,115–117]

Authors should discuss or develop possible ways of mapping out DTPs or dose decision paths not only for simple but also for more complex adaptive designs. The exact content and form of DTPs can vary depending on the specific features of the trial design, and there is no standard format. It may sometimes only be feasible to project the first few participants or cohorts in advance. For simple rule-based (e.g., 3 + 3 design) and model-assisted designs (e.g., modified toxicity probability interval design,[118] Bayesian optimal interval design[119]), DTPs can be fully pre-enumerated via a flow diagram or decision table and included in the protocol before the onset of the trial.

Discussion

EPDF trials are critically positioned at the beginning of the clinical development process and significantly affect all subsequent clinical development stages. Therefore, they should be conducted following as rigorous



HF-LED-RL: high fluence light emitting diode-red light; MTD: maximum tolerated dose.

Legend: DLE: dose limiting events.

Fig. 10: Item 34, dose transition pathways or dose decision paths, **(a)** Example 3—obtained from study NCT03433222 on ClinicalTrials.gov (https://clinicaltrials.gov), a database of privately and publicly funded clinical studies conducted around the world,[114] **(b)** Example 4—obtained from Figure 2 in Kramer et al,[35] reprinted from the *Journal of Stroke and Cerebrovascular Diseases* with permission from Elsevier.

standards as their later phase counterparts, i.e., phase II and phase III randomised clinical trials. To enhance the development of a comprehensive and transparent EPDF protocol that can help ensure the quality and rigorous conduct of EPDF trials, the SPIRIT-DEFINE guidance was proposed via the SPIRIT-DEFINE Statement[6] and this Explanation and Elaboration (E&E) paper. As with other SPIRIT initiatives, the strength of SPIRIT-DEFINE lies in its systematic and transparent development methods[2]; the involvement of international multidisciplinary stakeholders (including trialists, clinicians, statisticians, regulators, ethics committee members, journal editors, patient advocates, and funders); recommendations supported by literature and practical use evidence; and detailed guidance with examples from published protocols.

SPIRIT-DEFINE is not intended to prescribe rules on how researchers should conduct a clinical trial but to promote best practice in protocol writing for EPDF trials and to facilitate protocol appraisal. Moreover, its application is intended to ensure that the protocol provides a comprehensive and accurate reference point for the critical appraisal of the trial conduct and reporting of the final trial results. With this in mind, several SPIRIT-DEFINE items match those on the CONSORT-DEFINE checklist.[8]

In addition to the limitations inherited from the SPIRIT-DEFINE Statement,[6] this E&E text may also be affected by the limited quantity of publicly available protocols. While not many EPDF trial protocols are currently made public, due to factors such as commercial confidentiality agreements, there is a growing trend among journals to request the inclusion of protocol versions as supplementary materials when publishing trial results. It is strongly encouraged to provide, at the minimum, access to redacted versions, omitting commercially sensitive details.[120] To address the constraint of limited protocol accessibility, we expanded our search for examples by including published protocol papers (including those attached as supplementary materials in trial results publications) and statistical analysis plans, in addition to registries (e.g., ClinicalTrials.gov) and other sources.

We encourage users, including authors, reviewers, and editors, to utilise the SPIRIT-DEFINE Statement and E&E documents, in conjunction with SPIRIT statement[9] and related extensions, when drafting or reviewing EPDF trial protocols. Furthermore, we invite users to consistently apply the guidelines for various types of EPDF trials in different research settings and to provide feedback to guideline authors for informing future revisions. EPDF trials are continuously evolving, but we anticipate that the SPIRIT-DEFINE Statement and this E&E document are sufficiently robust to accommodate most changes. For instance, the FDA Project Optimus, launched in 2021, released their final guidance in August 2024 on dosage optimisation in the development of oncologic drugs and biological products.[4] This guidance moves away from conventional dose-finding methods for cytotoxic chemotherapeutics, advocating and promoting a comprehensive evaluation of non-clinical and clinical data, and exploring a range of dose(s) early in development to optimise the benefit/risk profile or provide the desired therapeutic effect while minimising toxicity. This initiative promotes model-informed or model-based approaches, as well as advanced adaptive trial designs, to improve patient outcomes. Such designs could involve multiple integrated outcomes (beyond toxicity only) for interim and final dose decisions. They could also involve an initial dose-escalation phase, followed by randomisation to a few candidate doses to ultimately determine the RP2D based on the overall available data. With increasing support from the FDA and other regulatory bodies, these approaches are expected to become more prevalent in future trials. Importantly, the SPIRIT-DEFINE guidance applies to trials aiming at dose optimisation, and its best practices are to be adhered to for this purpose.

Outstanding questions

The central question with any guidance document is whether the intended community will adopt the recommended practices. The SPIRIT-DEFINE statement seeks broad adoption, yet barriers such as limited awareness, lack of institutional endorsement, or resource limitations within the community may affect its implementation. Identifying these potential obstacles could help develop strategies to increase uptake. A related question is what impact the SPIRIT-DEFINE statement will have, which systematic reviews could assess by examining the completeness of EPDF trial protocols before and after the statement's adoption. As EPDF trial designs evolve, further adjustments to the SPIRIT-DEFINE statement may be necessary, and research could examine whether new design elements require additional considerations. Given the guidelines' broad application across therapeutic areas, it would be useful to determine if specific fields require further attention or tailored adaptations. Generally, refining and updating the SPIRIT-DEFINE checklist will depend on identifying effective ways to incorporate feedback—from trial authors, protocol reviewers, regulators or ethics committee members. Where this document currently provides hypothetical examples, replacing them with future real-world cases would be beneficial. Understanding whether methodological gaps or evolving practices have led to a shortage of examples for certain items could help identify barriers to comprehensive reporting and suggest ways to address these challenges.

Conclusions

This work aligns with other initiatives advocating for transparency, clarity and completeness of trial protocols,

including those from various regulatory bodies for medicinal products.[22,74] Widespread uptake and support of the SPIRIT-DEFINE guidelines should enhance trial protocol completeness and quality while streamlining protocol review and improving ultimate trial quality. Such improvements have the potential to reduce research inefficiencies and inconsistencies, driving transformational advances in clinical care through more effective early phase clinical trials.

Contributors

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

Data sharing statement

This study compiled examples from previously published articles and material openly available on ClinicalTrials.gov (https://clinicaltrials.gov), a database of privately and publicly funded clinical studies conducted around the world. As this study did not generate new data, no additional dataset is provided. Permissions for re-using previously published material can be viewed upon reasonable request.

Declaration of interests

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Appendix A. Supplementary data

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