SPIRIT–DEFINE (DosE FIndiNG)

Development of a SPIRIT Extension for Early-Phase Dose-Finding Trials

Protocol
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Sponsor:	The Institute of Cancer Research
Funders:	National Institute for Health Research/Medical Research Council
Coordinating Trials Unit:	ICR Clinical Trials and Statistics Unit (ICR-CTSU) The Institute of Cancer Research

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Glossary

Basket Trial: Basket trials generally investigate the safety/efficacy/effect of an IMP or combination of IMPs across a variety of populations. A basket trial involves multiple diseases or histologic features (i.e., in cancer). After participants are screened for the presence of a target, target-positive participants are entered into the trial; as a result, the trial may involve many different diseases or histologic features [1, 2].

Cohen's kappa coefficient (κ): a statistic used to measure inter-rater reliability (and also intra-rater reliability) for qualitative (categorical) items

CONSORT: Consolidated Standards of Reporting Trials. It encompasses various initiatives developed by the CONSORT Group to alleviate the problems arising from inadequate reporting of randomised controlled trials.

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

Dose: Quantity of a medicine (e.g., drug or radiotherapy) to be administered or extent to which a patient may be exposed to a therapy.

Dose-finding trial: Early Phase trial where increasing doses/regimens of the investigated therapy are administered to sequential groups of patients, with interim assessments of the safety/tolerability and activity of the treatment.

Dose limiting toxicity: side effects of a drug or other treatment that are serious enough to prevent an increase in dose or level of that treatment.

E&E: Elaboration and Explanation

Expansion cohort: a phase in a clinical trial that aims to accrue additional patients, after an initial dose-escalation component, with different or targeted eligibility criteria in order to collect additional information on safety or activity.

FDA: Food and Drug Administration, the US regulatory authority for Clinical Trials

Maximum tolerated dose: The highest dose of a drug or treatment that does not cause unacceptable side effects.

MHRA: Medicine and Healthcare Products Regulatory Agency, the UK regulatory authority for Clinical Trials.

PD: Pharmacodynamics, described as what a drug does to the body, refers to how the drug works and how it affects the body.

Phase 0 trial: Phase 0 trials use only a few small doses of a new drug in a few people, without therapeutic intent. They aim at proving the drug behaves as expected in pre-clinical studies.

Platform trial: A type of clinical trial with an open master protocol, which allows for multiple treatments to enter or exit the trial over the course of the study.

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

Recommended Phase 2 Dose (RP2D): Dose of a drug or treatment recommended to be taken forward for phase II trials following a dose finding study.

Recommended Dose(s): Dose(s) of a drug or treatment recommended to be taken forward for further evaluation.

Schedule/Regimen: Definition of the dose, frequency, mode of administration and duration for a specific treatment.

SD: Standard Deviation - measure of how spread a set of values under consideration are.
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
Umbrella trial:
Umbrella trials investigate the safety/efficacy/effects of several drugs or other substances in a single population. Patients with the disease are screened for the presence of a biomarker or other characteristic and then assigned to a group on the basis of the results. Multiple drugs are studied in the various groups [2].
Window of opportunity trial: trial which allows a drug (or other intervention) of interest to be given to a patient over a short period of time, usually 2–-4 weeks, prior to the instigation of standard therapy.

1 Introduction

1.1 Background

A critical step in treatment development, early phase trials (Phase I or Phase I/II) are studies conducted in healthy volunteers or patients aiming at determining drug disposition (absorption, distribution, metabolism and excretion), adverse effects, drug exposure, pharmacodynamic (PD) biomarker activity, clinical activity and recommended dose(s) for further evaluation. As such, results from these trials directly influence decisions on further development and whether the selected doses and schedules are sufficiently safe and have promising results on activity.

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Worldwide, there are considerably more phase I trials than phase III trials – 46% more (13,826 vs 9,501 of trials commencing in 2014-2018: clinicaltrials.gov). The attrition rate throughout the drug development process is high, and the success rate between phase I studies and marketing authorization has been reported as between 9.8% and 13.8% on the basis of several studies [3, 4]), with failure being primarily attributable to either poor tolerability or lack of biological activity (79% of failed studies over the period 2016–2018) [5]. Poor dose or schedule selection can contribute to this attrition rate, leading to later failures in phase II trials, unsuccessful regulatory submissions, or dose changes post-approval due to excessive toxicities or lack of efficacy [6].

Incomplete or unclear information on the design, conduct and analysis in dose-finding protocols hinder interpretability and reproducibility. This may impact on timely clinical development, lead to inadequate or biased reporting and erroneous conclusions on safety and efficacy. This wastes time and resources, but more importantly, may unethically expose participants to ineffective or even harmful interventions[7].

A clinical trial protocol is a vital document produced by study investigators specifying *a priori* the rationale, proposed methods and plans for how a clinical trial will be conducted. By providing the details to guide the conduct of a high-quality study, a well-written protocol is a shared central reference for the study teams [8, 9])and facilitates appraisal of its scientific, methodological, safety and ethical rigour by external reviewers (including funders, regulators, ethics committees/institutional review boards, journal editors and, increasingly, the wider public).

However, protocols can vary greatly in content and quality despite their importance [8, 9]. To address this, the SPIRIT 2013 (Standard Protocol Items: Recommendations for Interventional Trials) statement was established to provide evidence-based guidance for the minimum essential content of a clinical trial protocol and is an internationally recognised standard. The primary scope of SPIRIT 2013 relates to randomised trials and though the considerations are largely applicable across many types of trials, some circumstances require additional protocol items [8]. In particular, guidance on content specific to early phase trials (phase I or phase I/II), including dose and schedule determination based on safety/tolerability either alone or jointly with one or more pharmacokinetic or activity markers, is lacking. Examples of specific features unique to such trials include:

- starting dose and justification,
- how participants will be recruited and dosed (with pauses to assess safety),
- definition of dose-limiting toxicities, including length of assessment window,
- how interim dose decisions will be undertaken (including clearly defined outcome measures and analysis populations for interim adaptations, who will make the decisions and clear decision rules),
- how the recommended dose(s) to subsequent trials will be selected.

The use of proposedly more efficient but undoubtedly more complex dose escalation designs such as model-assisted or model-based designs is rising: **1.6%** (20/1,235 Phase I published cancer trials) used model-based designs in **1991-2006 [10]**, which increased to **6.4%** (11/172) by **2012–2014 [11]**. Such designs are technically more challenging to comprehend and more complex to implement than conventional designs[12-15]. Further transparency demands are needed in such protocols to facilitate understanding of the design and how dose decisions will be made [6].

No consensus-driven protocol guidance exists for dose-finding trials. It is therefore urgent to extend SPIRIT 2013 guidance for dose-finding trials to facilitate trial interpretability and reproducibility of methods and results and improve completeness and transparency.

The Principal Investigator (PI) and members of the Executive Committee are leading an MRC-NIHR-funded international effort to extend CONSORT guidance for dose-finding trials, CONSORT-DEFINE, which commenced in March 2021. Developing the protocol guidance (SPIRIT-DEFINE) in tandem with trial reporting guidance (CONSORT-DEFINE) will be an efficient use of resources and allow effective and efficient knowledge sharing as there is substantial overlap in the subject matter and stakeholders.

2 Aims and objectives:

The overall aim of this research is to develop and disseminate to stakeholders an extension to the SPIRIT 2013 statement tailored to the specific requirements of early phase dose-finding clinical trials across all disease areas.

Specific core objectives for SPIRIT-DEFINE are as follows:

(a) Review CONSORT-DEFINE candidate Item generation list to identify relevant items to protocol content. (see the CONSORT-DEFINE protocol in annex 1 of this document)
(b) **Generate** further potential **protocol candidate items** through review of relevant literature (including published and grey literature, citations and reference search of key included articles), accessible protocol templates and recommendations by experts.
(c) Conduct an online **Delphi survey** to gather perceptions of key stakeholders on the importance of the drafted protocol candidate items and to suggest additional items. Results from earlier rounds will inform the design and modify the checklist of subsequent rounds
(d) Conduct a **consensus meeting**, independently chaired, which incorporates a broad range of key stakeholders to draw recommendations on essential protocol items that should be included in the SPIRIT-DEFINE checklist and other aspects that should be addressed in the explanation and elaboration (E&E) document.
(e) Finalise the **protocol checklist** and **E&E** paper explaining the items and what protocol writers are expected to include. We will pilot-test the near-final guidance with real-world examples (to identify any gaps and incorporate feedback to the final revision).
(f) Disseminate the SPIRIT-DEFINE statement and maximise engagement of stakeholders, including patient and public engagement through patient and public involvement (PPI) led activities, in particular the production of PPI lay summaries.

The SPIRIT guidance is not intended to dictate trial design or conduct. It is anticipated to serve as a useful resource for trialists, journal editors, peer reviewers, funders, regulators, and research ethics committees to promote best practice in designing protocols for early phase dose-finding trials and to facilitate protocol appraisal. To achieve these objectives, the SPIRIT-DEFINE guidance will be developed following gold standard methods for developing healthcare protocol guidelines

recommended by the EQUATOR [16] network. Additionally, the SPIRIT-DEFINE will be developed in parallel to the CONSORT-DEFINE, which is currently being worked-up by the team (see section 4 for study management and membership information). The intention is for SPIRIT-DEFINE to mirror applicable items from CONSORT-DEFINE, similar to how SPIRIT 2013 was developed to mirror CONSORT 2010 [17]. Consistent wording and structure used for items common to both checklists will facilitate the transition from a SPIRIT-based protocol to a CONSORT-based published report. Developing the protocol and reporting guidance in tandem will be an efficient use of resources as there is substantial overlap in the subject matter and stakeholders. This would allow effective and efficient knowledge-sharing, allowing the team to produce *long overdue* vital guidance.

It is anticipated that the SPIRIT-DEFINE guidance will result in:

- Facilitating effective protocol review and appraisal,
- Indirectly helping researchers in designing early phase dose-finding trials,
- Improving rigorous conduct of high-quality trials,
- Reducing the need for protocol amendments and associated costs,
- Improving the transparency of early phase dose-finding trials

Therefore, the generated guidance will ultimately benefit the overall clinical research community in contributing to reducing research waste, as well as patients.

3 Scope and General Principles

This SPIRIT-DEFINE statement is intended to be used across a range of disease and therapeutic areas, for trials aiming to determine the safety profile of the intervention and/or to identify a recommended dosing regimen(s) (including radiotherapy, e.g., chemo-radiation studies or studies to escalate dose and/or intensity of fractionation). As terms like “early phase”, “dose-escalation” and “dose-finding” are often used interchangeably, it is important to clarify the scope of the project, and the trials that it intends to cover as well as the general principles underpinning the project.

3.1 Scope

What it covers:

- Our focus is on early phase clinical trials (typically referred to as Phase I with or without dose expansion cohorts or Phase I/II), where interim dose-decisions are taken using accumulating trial data to either escalate, de-escalate, stay at the current level or stop a trial early. The dose assignment decisions could be based on safety, pharmacokinetic, pharmacodynamic or biological markers or a combination of these parameters.

- The guidance applies to all early phase dose-escalation (or de-escalation) clinical trials where more than one ascending (or descending) dosing regimens are investigated *sequentially*. This could be:
    - intra-participant escalation (where doses are increased sequentially over time *within* a participant),
    - inter-participant escalation (where each participant is allocated a specific dose and doses are increased sequentially over time for subsequent participants),
    - or both.

- Although this guidance does not specifically address the reporting needs of early phase trials that do not include interim dose decisions taken sequentially (e.g., trials with safety run-ins where only one dose is assessed for safety), some principles covered here may still apply to such trials.

- The guidance covers trials where the dose-finding element is only a part of the whole trial in one or more experimental arms/disease groups (e.g., in basket, umbrella, platform trials or master protocols) are included.

What it does not cover:

- It excludes clinical trials which randomise patients simultaneously to several dosing regimens, without any initial sequential dose-decision evaluation, sometimes referred to as dose-ranging trials.

- The guideline does not primarily address specific reporting needs for Phase 0/window of opportunity trials, phase II/III, food-effect [18, 19] or feasibility trials or animal studies, which incorporate interim dose-decisions, but some principles covered here may still apply to such trials.

3.2 Principles

- SPIRIT-DEFINE covers general reporting principles to make it applicable to a wide range of current and future dose-finding trials in all disease settings and participant population (encompassing both adults and paediatric), which evaluate sequential dosing regimens in one or more interventional treatments.

- It presents the *minimum* essential requirements that should be reported but we also encourage authors to report additional information that may enhance the interpretation of trial protocols.

- It intends to provide generic protocol guidelines relevant to all dose-finding designs, not to legitimise or discourage any dose-finding design, trial adaptation, underpinning methods (model or rule-based) or statistical framework used (frequentist or Bayesian methods).

- It aims to promote transparent and adequate reporting of dose-finding trial protocols to maximise their potential benefits and improve the interpretability of their results and their reproducibility, without impeding their appropriate use or stifling design innovation. Therefore, the guideline does not specifically address the appropriateness of statistical methods.

- access to information regardless of the source and form of publication. For example, use of appendices and citation of accessible materials (such as protocols, statistical analysis plans (SAPs), or related publications) is sufficient.

- The order in which researchers report information does not necessarily need to follow the order of the checklist.

4 Study Management and membership

4.1 Establishment of an International Executive Committee and Independent Expert Panel

To support the development of the guidance, and increase impact and uptake, an international SPIRIT-DEFINE Executive Committee has been formed, comprising of a multi-disciplinary team of international statistical methodologists and trialists (clinicians and statisticians conducting trials) in early phase trials in both academia and pharmaceutical industry, SPIRIT and CONSORT group representatives, a patient and public representative and two expert advisors with regulatory expertise. The SPIRIT-DEFINE Executive Committee will meet around every 2 months to discuss progress and specific aspects of the project as required. The members of the Executive Committee are:

- Professor Christina Yap, Institute of Cancer Research
- Dr Munyaradzi Dimairo, University of Sheffield
- Professor Christopher Weir, University of Edinburgh
- Professor Adrian Mander, Cardiff University
- Professor Thomas Jaki, Lancaster University / University of Cambridge
- Professor Jeff Evans, University of Glasgow
- Dr Rong Liu, Bristol-Myers Squibb
- Dr Shing Lee, Columbia University
- Mr Andrew Kightley, Patient and Public Involvement lead
- Professor Sally Hopewell, University of Oxford
- Professor Johann de Bono, Institute of Cancer Research
- Dr John Kirkpatrick, Roche.
- Dr An-Wen Chan, University of Toronto
- Dr Siew Wan Hee, Institute of Cancer Research
- Dr Olga Solovyeva, Institute of Cancer Research
- Ms Aude Espinasse, Institute of Cancer Research

And including expert advisors:

Dr Stephen Hann, Flagship Pioneering

Dr Khadija Rantell, MHRA

A small Project Team, which comprises of the Principal Investigator, the Senior Trial Methodologist, the Trial Methodologist and the Clinical Trials Programme manager, will be tasked with the day-to-day management of the project and will meet weekly via video platform.

To provide independent oversight of the project, in particular the development of the Delphi survey and the SPIRIT-DEFINE guidance prior to submission, an Independent Expert Panel has also been formed. Members include:

- Professor Elizabeth Garrett-Mayer [chair], American Society of Clinical Oncology, expert methodologist/trialist in dose-finding oncology trials.
- Professor Deborah Ashby OBE, Imperial College London, expert methodologist/trialist in various diseases and independent chair of the ACE (Adaptive Designs) CONSORT extension.
- Professor John Isaacs, Newcastle University, expert clinician scientist in Rheumatology.
- Professor Melanie Calvert, University of Birmingham, expert in outcome methodology and was the lead of the SPIRIT-PRO (Patient Reported outcomes) extension.
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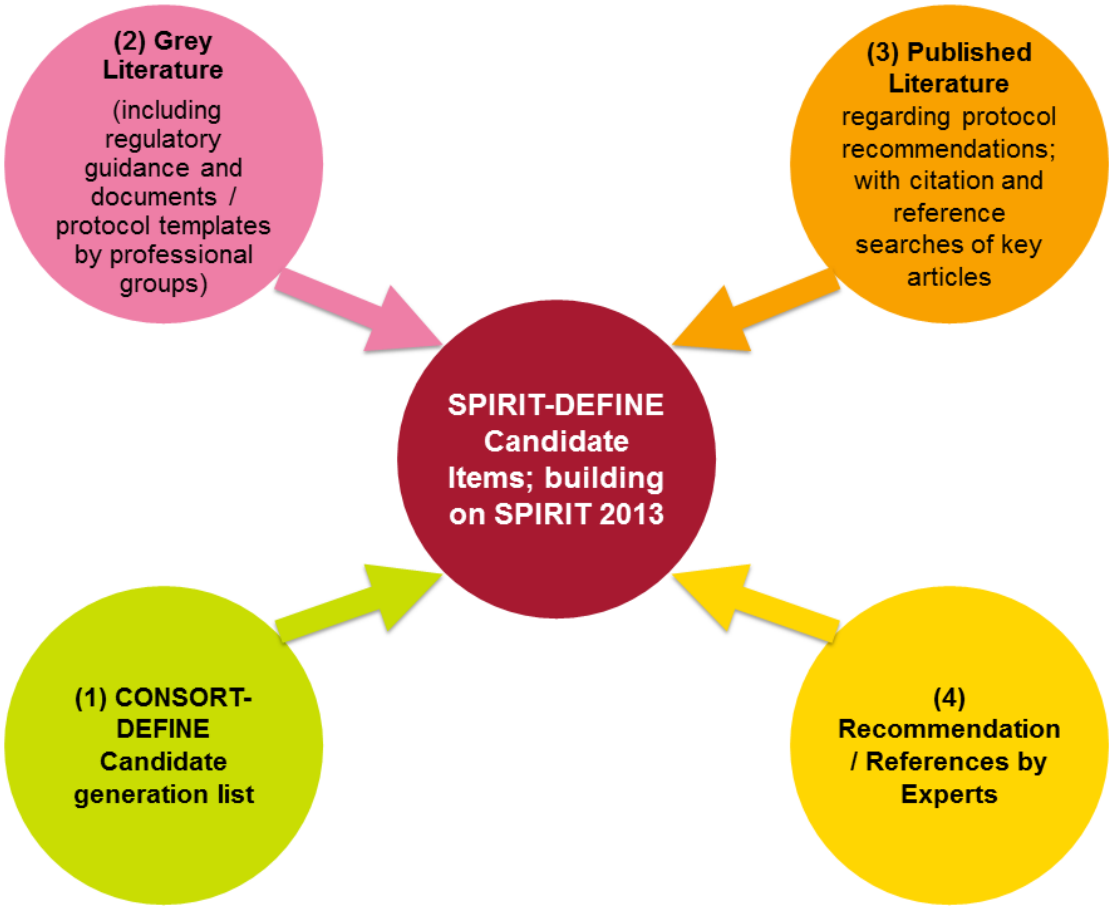
5 Methodology

To achieve these objectives, the SPIRIT-DEFINE development group will follow gold standard methods for developing healthcare guidelines recommended by the EQUATOR network. The SPIRIT-DEFINE development process will build on the development work already undertaken for the CONSORT-DEFINE guidance (its development protocol in the appendix to this document).

5.1 Stage one: Draft checklist generation

The SPIRIT-DEFINE Candidate Generation team will produce a draft of the SPIRIT candidate items, with support from members of the SPIRIT-DEFINE Executive Committee. The process is described below and presented in Figure 1.

Figure 1: SPIRIT-DEFINE Candidate Generation development process



5.1.1 CONSORT-DEFINE items review

An initial draft of the SPIRIT-DEFINE checklist will be prepared, building on the original SPIRIT 2013 and enriched by the draft items identified as specific to dose finding trials identified through the CONDORT-DEFINE development work. The list will be further refined through expert opinions of the SPIRIT-DEFINE Executive Committee.

5.1.2 Grey literature review

Regulatory and industry guidance documents (e.g., EMA guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products [20], FDA and MHRA guidance [21, 22] ABPI guidelines for Phase I clinical trials [23] will be reviewed to identify protocol content recommendations and extract requirements specific to early phase dose finding trials. Additionally, key stakeholder groups identified in the CONSORT-DEFINE development protocol (clinical trials units, including MHRA accredited Phase I units, funders, and ethics committees) and experts from other protocol-standards initiatives relevant to dose-finding trials (e.g., trial registries) will be consulted and their protocol templates (if available) included in the review process.

5.1.3 Published literature review

Building on the methodological review conducted for the CONSORT-DEFINE, the search strategy will be updated to identify protocol recommendations in peer-reviewed literature. Relevant literature that are not picked up by the search strategy but recommended by members of Executive

Committee will be included. Backward and forward search of key articles identified through the above that have contributed to protocol candidate items will also be reviewed.

Keywords used in the literature review search strategy will be presented in a table with the number of hits. A flow diagram will be used to summarise the number of papers found, duplicated, excluded and included to inform the checklist generation.

5.1.4 Expert recommendations

Throughout the stage one (draft checklist generation) process, the Executive Committee will review and refine the candidate items through expert discussion. Other working groups may also be consulted as appropriate.

5.2 Stage two: Delphi survey

Once the draft checklist of potentially important protocol items has been developed, it will be submitted for feedback by a wider stakeholder group through a Delphi survey. A single Delphi survey will be used to gather stakeholders' opinions on the importance of both the draft protocol items (SPIRIT-DEFINE) and the reporting items (CONSORT-DEFINE).

Particular attention will be paid to piloting the Delphi survey to ensure patient and public engagement and representation can be optimised. Selected patient representative with extensive experience in the field of dose-finding trials will be approached to take part in the pilot, and their feedback will be sought to ensure the survey is accessible to this particular stakeholder category. Should the Delphi survey not allow lay participants to fully contribute, due to the complexity, technicality or number of items to be assessed, a focus group will be organised with PPI experts in order to identify a core set of SPIRIT-DEFINE items relevant to PPI contributors. This core set will then be submitted for feedback to a wider PPI audience through a separate process.

The full methodology for the Delphi survey can be found in the CONSORT-DEFINE protocol (appendix 1).

5.3 Stage three: Consensus meeting

Following the Delphi Survey, an independently chaired consensus meeting will take place, incorporating a broad range of key stakeholders to finalise the standards and wording for inclusion in SPIRIT-DEFINE. The outputs will be two-fold: the protocol checklist and an E&E paper. The consensus meeting will be held over two days alongside that for CONSORT-DEFINE and will:

- Review the findings from the Delphi surveys and advise on which protocol items to retain or exclude in the final checklist via a confidential voting system
- Discuss the structure of what to include in the supporting E&E of the checklist.

See appendix 1 (CONSORT-DEFINE protocol) for full consensus meeting methodology.

5.4 Stage four: Development of a protocol guidance and explanatory support document

5.4.1 Guideline development process

After the consensus meeting, the Executive Committee will continue working on refining the content and wording of the guidance, as well as preparing a detailed explanation and elaboration document.

The guidance will be piloted by a small selection of key stakeholders with expertise in developing protocols of early phase dose-finding trials to test its usability and provide insight into issues that should be addressed in detail in the Explanation & Elaboration statement.

6 Stage five: Dissemination plan

The Executive Committee will devise a detailed dissemination strategy to maximise guideline awareness and uptake, building on that detailed in the CONSORT-DEFINE protocol (see appendix 1)

7 Ethics approval

This project has been formally assessed for risk and approved by the Sponsor's Committee for Clinical Research. The Health Research Authority has been consulted and confirmed Research Ethics Approval is not required.

8 Funding and any additional support

SPIRIT-DEFINE does not receive any external funding.

9 Declaration of Conflict of Interest

All Protocol Development Group members declare that they have no conflict of interest to disclose.

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CONSORT-DEFINE (DosE FIndiNG Extensions):

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Dose: Quantity of a medicine (e.g. drug or radiotherapy) to be administered or extent to which a patient may be exposed to a therapy.

Dose-finding trial: Early Phase trial where increasing doses/regimens of the investigated therapy are administered to sequential groups of patients, with interim assessments of the safety/tolerability and activity of the treatment.

Dose limiting toxicity: side effects of a drug or other treatment that are serious enough to prevent an increase in dose or level of that treatment.

E&E: Elaboration and Explanation

Expansion cohort: a phase in a clinical trial that aims to accrue additional patients, after an initial dose-escalation component, with different or targeted eligibility criteria in order to collect additional information on safety or activity.

FDA: Food and Drug Administration, the US regulatory authority for Clinical Trials

Maximum tolerated dose: The highest dose of a drug or treatment that does not cause unacceptable side effects.

MHRA: Medicine and Healthcare Products Regulatory Agency, the UK regulatory authority for Clinical Trials.

PD: Pharmacodynamics, described as what a drug does to the body, refers to how the drug works and how it affects the body.

Phase 0 trial: Phase 0 trials use only a few small doses of a new drug in a few people, without therapeutic intent. They aim at proving the drug behaves as expected in pre-clinical studies.

Platform trial: A type of clinical trial with an open master protocol, which allows for multiple treatments to enter or exit the trial over the course of the study.

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

Recommended Phase 2 Dose (RP2D): Dose of a drug or treatment recommended to be taken forward for phase II trials following a dose finding study.

Schedule/Regimen: Definition of the dose, frequency, mode of administration and duration for a specific treatment.**SD**: Standard Deviation - measure of how spread a set of values under consideration are.

Umbrella trial: Umbrella trials investigate the safety/efficacy/effects of several drugs or other substances in a single population. Patients with the disease are screened for the presence of a biomarker or other characteristic and then assigned to a group on the basis of the results. Multiple drugs are studied in the various groups [2].

Window of opportunity trial: trial which allows a drug (or other intervention) of interest to be given to a patient over a short period of time, usually 2–4 weeks, prior to the instigation of standard therapy.

11 Introduction

11.1 Background

Often termed “Dose-finding” or “Dose escalation” studies, early phase trials (Phase I or Phase I/II) conducted in healthy volunteers or patients and including interim dose decisions are a critical step in therapy development. Results from dose-finding trials, such as drug disposition (absorption, distribution, metabolism and excretion), adverse effects, exposure, Pharmacodynamics (PD) biomarker activity, clinical activity and recommended dose(s) for further evaluation. As such, results from these trials directly influence decisions on further development and whether the selected doses and schedules are sufficiently safe and have promising results on activity.

Poorly reported dose-finding trials with inadequate rigour may lead to bias in reporting and lack of reproducibility. This runs the risk of progressing study treatments (e.g. pharmacotherapies or radiotherapy) to subsequent later phase studies with a false sense of their proven safety and activity, and with inappropriate dosing regimens that may become fixed for the duration of the life cycle of that treatment. The converse may also occur – the inappropriate discontinuation of a potentially safe or efficacious treatment. This wastes time and resources, but more importantly, may unethically expose participants to ineffective or even harmful interventions [3].

This is particularly relevant as a considerable number of early phase trials are sponsored and run by academic institutions or publicly funded National Health Service (NHS) Trusts, with funding from non-commercial sources including Research Councils and medical charities (e.g. Cancer Research UK). In the UK, 159 out of 1157 (14%) Phase I clinical trials, which started in 2014-2018, had non-industry sponsors (data from ClinicalTrials.gov). This emphasises the importance of this research to public research institutions and industry alike.

Based on results from ClinicalTrials.gov of trials in all countries, there are substantially more Phase I trials than Phase III trials – 46% more (13826 versus 9501 of trials, which started in 2014-2018). Data from pharmaceutical trials in the US in 2004-2012 show that the estimated average cost of a Phase I trial across all therapeutic areas ranged from US $1.4 to 6.6 million [4]; such high costs reinforces the importance of managing resources efficiently. The attrition rate throughout the drug development process is high, and the success rate between phase I studies and marketing authorization has been reported as between 9.8% and 13.8% on the basis of several studies [5, 6], with failure being primarily attributable to either poor tolerability or lack of biological activity (79% of failed studies over the period 2016–2018) [7]. Poor dose selection can lead to failed trials in Phase II (> 80% attrition from Phase I) or Phase III (around 50% attrition from Phase II); or unsuccessful regulatory submissions or dose changes post-approval due to excessive toxicities or lack of efficacy [8].

11.2 Reporting quality in early phase dose-finding trials

More than 580 biomedical journals now require that trial reports conform to the CONSORT 2010 reporting guidelines for randomised parallel group clinical trials or an appropriate CONSORT extension to improve transparency, reproducibility, consistency and accuracy in reporting [9, 10]. Endorsement of the CONSORT guidelines is usually demonstrated by a statement in a journal’s “Instructions to Authors” indicating support or a recommendation or requirement for authors to adhere to the CONSORT checklist when submitting a manuscript of a randomised trial for publication consideration [11]. A systematic review, based on more than 16,000 trials, published in 2012 showed that journal endorsement of the CONSORT guidelines was associated with more completely reported randomised trials [12].

A consensus-driven CONSORT guideline does not exist for the reporting of early phase dose-finding trials (as defined in Section 3.1). Hence, reporting standards are often poor, given the challenges in reporting the findings of potentially complex early phase trial designs. Incomplete, unclear, or inaccurate reporting of the design, conduct and analysis of trials can hinder interpretability, reproducibility and impact on timely clinical development, and lead to erroneous conclusions on safety and efficacy. For example, vital information such as trial design, key outcomes and analysis populations used for dosing decisions and pre-planned dosing decision criteria should be included, to allow readers to interpret the trial findings accurately.

Most early phase dose-findings trials are non-randomised, and therefore it is likely that many have not used the CONSORT 2010 guidance though many of its reporting items would be applicable. There is a need to extend the CONSORT guidance for dose-finding trials, to produce a robust and comprehensive consensus-driven guidance, incorporating their unique features, that is applicable across all early phase dose-finding trials (regardless of the specific trial design that has been implemented or disease area).

12 Aims and objectives:

The overall aim of this research is to develop and disseminate to stakeholders an extension to the CONSORT 2010 statement tailored to the specific requirements of early phase dose-finding clinical trials across all disease areas.

Specific core objectives are as follows:

(g) Identify the gaps in reporting of dose-finding trials and to inform objective (b) through a rapid scoping review of the literature.
(h) Generate potential reporting items through review of existing dose-finding trials guidance, the results of the rapid scoping review in (a), and expert opinions.
(i) Conduct Delphi surveys to gather perceptions of key stakeholders on the importance of the drafted reporting items and to suggest additional items.
(j) Conduct consensus exercise to review Delphi survey findings and draw recommendations on essential reporting items that should be included in the final CONSORT extension checklist and other aspects that should be addressed in the explanation and elaboration (E&E) document.
(k) Finalise the reporting statement and supporting documentation including the E&E document. We will pilot-test the near-final guidelines with real-world examples (to identify any gaps, and incorporate feedback to the final revision.
(l) Disseminate the CONSORT extension statement and maximise engagement of stakeholders, including patient and public engagement through patient and public involvement (PPI) led activities, in particular the production of two PPI lay summaries.

This guideline is anticipated to serve as a useful resource for trialists, journal editors, peer reviewers, funders, regulators, and research ethics committees to promote best practice in the reporting of early phase dose-finding trials, facilitate trial interpretability and reproducibility of methods and results and improve completeness and transparency. To achieve these objectives, the dose-finding CONSORT Executive Committee will follow gold standard methods for developing healthcare reporting guidelines recommended by the CONSORT group (9, 12).

It is anticipated that the guidance will result in:

- Improving the transparency and adequacy reporting of the reporting of early phase dose-finding trials,
- Enhancing reproducibility of methods,
- Enhancing the interpretability of early phase dose-finding trials results,
- Providing a framework for peer review of early phase dose-finding trial reports,
- Indirectly helping researchers in designing early phase dose-finding trials,
- As a result of the above points, the generated guidance will ultimately benefit the overall clinical research community in contributing to reducing research waste, as well as patients.

13 Scope and General Principles

This CONSORT-DEFINE statement is intended to be used across a range of disease and therapeutic areas, for trials aiming to determine the safety profile of the intervention and/or to identify a recommended dosing regimen(s) (including radiotherapy, e.g., chemo-radiation studies or studies to escalate dose and/or intensity of fractionation). As terms like "early phase", "dose-escalation" and "dose-finding" are often used interchangeably, it is important to clarify the scope of the project, and the trials that it intends to cover as well as the general principles underpinning the project.

13.1 Scope

What is covers:

- Our focus is on early phase clinical trials (typically referred to as Phase I with or without dose expansion cohorts or Phase I/II), where interim dose-decisions are taken using accumulating trial data to either escalate, de-escalate, stay at the current level or stop a trial early. The dose assignment decisions could be based on safety, pharmacokinetic, pharmacodynamic or biological markers or a combination of these parameters.

- The guidance applies to all early phase dose-escalation (or de-escalation) clinical trials where more than one ascending (or descending) dosing regimens are investigated *sequentially*. This could be:
    - intra-participant escalation (where doses are increased sequentially over time *within* a participant),
    - inter-participant escalation (where each participant is allocated a specific dose and doses are increased sequentially over time for subsequent participants),
    - or both.

- Although this guidance does not specifically address the reporting needs of early phase trials that do not include interim dose decisions taken sequentially (e.g. trials with safety run-ins where only one dose is assessed for safety), some principles covered here may still apply to such trials.

- Trials where the dose-finding element is only a part of the whole trial in one or more experimental **arms / disease groups** (e.g. in basket, umbrella, platform trials or master protocols) are included.

What it does not cover:

- It excludes clinical trials which randomise patients simultaneously to several dosing regimens, without any initial sequential dose-decision evaluation, sometimes referred to as dose-ranging

trials. Dose-ranging trials with adaptations are covered by Adaptive designs CONSORT Extension (ACE). Dose ranging trials without adaptations are covered by CONSORT 2010, and other relevant extensions such as multi-arm trials.

- The guideline does not primarily address specific reporting needs for Phase 0/window of opportunity trials, phase II/III, food-effect [13, 14] or feasibility trials or animal studies, which incorporate interim dose-decisions, but some principles covered here may still apply to such trials.

13.2 Principles

- CONSORT-DEFINE covers general reporting principles to make it applicable to a wide range of current and future dose-finding trials in all disease settings and participant population (encompassing both adults and paediatric), which evaluate sequential dosing regimens in one or more interventional treatments.

- It presents the *minimum* essential requirements that should be reported but we also encourage authors to report additional information that may enhance the interpretation of trial findings.

- It intends to provide generic reporting guidelines relevant to all dose-finding designs, not to legitimize or discourage any dose-finding design, trial adaptation, underpinning methods (model or rule-based) or statistical framework used (frequentist or Bayesian methods).

- It aims to promote transparent and adequate reporting of dose-finding trials to maximise their potential benefits and improve the interpretability of their results and their reproducibility, without impeding their appropriate use or stifling design innovation. Therefore, the guideline does not specifically address the appropriateness of statistical methods.

- It emphasises the importance of access to information regardless of the source and form of publication. For example, use of appendices and citation of accessible material (such as protocols, statistical analysis plans (SAPs), or related publications) is sufficient.

- The order in which researchers report information does not necessarily need to follow the order of the checklist.

14 Study Management and membership

14.1 Establishment of an International Executive Committee and Independent Expert Panel

To support the development of the guidelines, and increase impact and uptake, an international Executive Committee has been formed, comprising of a multi-disciplinary team of international statistical methodologists and trialists (clinicians and statisticians conducting trials) in early phase trials in both academia and pharmaceutical industry, a CONSORT group representative and a patient and public representative. The Executive Committee will meet every 2-3 months to discuss progress and specific aspects of the project as required. The members of the Executive committee are:

- Professor Christina Yap, Institute of Cancer Research
- Dr Munyaradzi Dimairo, University of Sheffield
- Professor Christopher Weir, University of Edinburgh
- Professor Adrian Mander, Cardiff University
- Professor Thomas Jaki, Lancaster University / University of Cambridge
- Professor Jeff Evans, University of Glasgow
- Dr Rong Liu, Bristol-Myers Squibb
- Dr Shing Lee, Columbia University
- Mr Andrew Kightley, Patient and Public Involvement lead
- Dr Sally Hopewell, University of Oxford
- Professor Johann de Bono, Institute of Cancer Research
- Dr Alun Bedding, Roche.
- Dr Olga Solovyeva
- Ms Aude Espinasse

Expert advisors:

- Dr Stephen Hann, Flagship Pioneering
- Dr Kadhija Rantell, MHRA

In order to expedite the decision-making process, designated members of the Executive Committee will each co-lead specific project activities through specific working groups (e.g., Scoping review, protocol development, Public and Patient involvement) in consultation with the Executive Committee. Decisions or requests for input/feedback by the working groups to the Executive Committee will be communicated to the Executive Committee either at regular meetings or via email. These working groups will meet by webinar as required by the specific project activities until the task is complete. A small Project Team, which comprises of the Principal Investigator, the Trial methodologist, and the Clinical Trials Programme manager, will be tasked with the day-to-day management of the project and will meet weekly via webinar.

To provide independent oversight of the project, in particular the development of the Delphi survey and the Dose-Finding CONSORT extension guidelines prior to submission, an Independent Expert Panel has also been formed. Members include:

- Professor Elizabeth Garrett-Mayer [chair], American Society of Clinical Oncology, expert methodologist/trialist in dose-finding oncology trials.
- Professor Deborah Ashby, Imperial College London, expert methodologist/trialist in various diseases and was the independent chair of the ACE (Adaptive Designs) CONSORT extension.

- Professor John Isaacs, Newcastle University, expert clinician scientist in Rheumatology.
- Professor Melanie Calvert, University of Birmingham, expert in outcome methodology and was the lead of the SPIRIT-PRO (Patient Reported Outcomes) extension

15 Methodology

To achieve these objectives, the Dose-finding consort development group will follow gold standard methods for developing healthcare reporting guidelines recommended by the CONSORT group [15].

15.1 Stage one: Draft checklist generation

15.1.1 Rapid Methodological review

A rapid methodological review will be conducted in order to explore the current status of reporting of early phase dose-finding trials, identify any gaps and any specific features to dose-finding early phase trials not adequately covered by existing guidance, and to inform the drafting of the checklist. The review will also serve in providing a sampling frame for some of the stakeholder categories for the Delphi survey (see section 5.2). This rapid methodological review will be conducted in accordance with the Johanna Brings Institute (JBI) methodology for scoping reviews [16]. Through 3 iterative phases (inclusion/exclusion, pilot run and main extraction), a total of 476 papers reporting early phase dose-finding trials published between 2011 and 2020, stratified by setting (oncology/non oncology) will be reviewed. To standardise the review process, a detailed data extraction form will be generated, and a comprehensive accompanying guidance document produced. Agreement between reviewers will also be tested based on pre-established rules. The rapid methodological review will be the subject of a separate publication, and the protocol will be made publicly available [17].

15.1.2 Candidate Item Generation

Based on the results of the rapid methodological review (see section 5.1.1) as well as expert opinion from the group, items considered to be relevant in constituting a minimum set of reporting requirements will be identified as potential checklist candidates. In addition, a further literature review of multiple databases (PubMed and Embase), grey literature and regulatory or industry guidelines, will be performed for any existing relevant guidance. Feedback will also be sought from regulatory bodies, such as the MHRA and FDA.

The Executive Committee will then meet to discuss the list of candidate items generated from these findings. Through expert discussion, the Executive committee will seek to build a comprehensive list of potentially important reporting items to design the first round of the Delphi survey. In case of disagreement on inclusion or exclusion of an item following discussion, decision may be subject to a majority vote amongst the Committee members. This/these meeting(s) will be audio recorded and detailed minutes will be kept, in order to inform the rationale for selection of items. Generated items will be presented in logical order to match the ordering of the existing CONSORT 2010 checklist[5]. The Independent Expert Panel will be consulted on the preliminary list, and the Executive Committee will decide whether changes are required based on their feedback. Following this consultation, feedback will also be sought on the draft items from a range of key stakeholders from the main categories identified for the Delphi survey in table 1 below, focusing on categories with complementary expertise to the members of the Executive Committee. This is to provide a

high-level review of the proposed candidate items and to highlight modifications or additional items that should be considered in the trial publications for early phase dose-finding trials.

The Executive Committee may also decide to involve other working groups as appropriate for further feedback.

15.2 Stage two: Delphi Survey

Once a draft checklist of potentially important items has been developed, it will be submitted for feedback by a wider stakeholder group through a Delphi survey. The objective of the Delphi survey is to gather stakeholders' opinions on the importance of the drafted reporting items. The process will also gather feedback on any other aspect of reporting of early phase dose-finding trials the respondent feels is not covered by the proposed checklist through the use open-ended questions to allow free text feedback. The Delphi process will be conducted according to existing methodological guidance [18-20] and will involve inviting participants to complete iterative rounds of a web-based survey, where results from earlier rounds will inform the design of subsequent rounds and modify the design between rounds. It is anticipated the Delphi process will be completed in 2-3 rounds, and the Executive Committee will meet between each round to discuss the results and agree any required changes. Items may be added between rounds based on participants' feedback from the free text sections of the survey or dropped if they fail to meet a pre-specified threshold (see section 5.2.8).

15.2.1 Identification of participants

A wide cross section of stakeholders will be approached to take part in the Delphi survey. In the context of this study, stakeholders will be considered to be direct users or beneficiaries of the guidance and those involved in research governance, approval, commissioning or publishing and are deemed to fall in at least one of these categories:

- a) clinical trials researchers who have been involved in early phase dose-finding trials, have some knowledge and interest in early phase dose-finding trials, developed or have experience in conducting and reporting such trials. These include clinicians, trial statisticians, trial methodologists, trial/study managers,
- b) assessors and approvers of clinical trials such as regulatory assessors and ethics committees,
- c) beneficiaries or users of the resultant CONSORT guidance such as journal editors,
- d) commissioners of research grants such as funders,
- e) consumers of research results from early phase dose-finding trials and assessors of quality of evidence from such trials such as abstract reviewers,
- f) healthy volunteers, patients and patient representatives with experience of early phase dose-finding trials.

Potential participants will be approached through a combination of named and blind approaches through publicly available contact details and various professional organisations or advocacy groups, as referenced in Table 1 below.

Table 1: Delphi survey stakeholders and methods of access

Stakeholders	Platforms
Clinical Trials Researchers (including Clinicians/ Clinical Pharmacologists, Trial management staff, Statisticians, Trial methodologists)	• MRC-NIHR TMRP (UK) • UK Clinical Research Collaboration (CRC) Network of Registered CTUs • Targeted conferences or organisations such as Society for Clinical Trials, International Clinical Trials Methodology Conference (ICTMC), International Society for Clinical Biostatistics (ISCB), Statisticians in the Pharmaceutical Industry (PSI), European Federation of Statisticians in the Pharmaceutical Industry (EFSPI), Drug Information association (DIA • Clinical Conferences such as NCRI, ESMO, ASCO, ECMC, ECRD • Sponsors from industry (via organisations such as Pharmaceutical Research and Manufacturers of America (PhRMA) in US, European Federation of Pharmaceutical Industries and Associations (EFPIA) in Europe) or the Association of British Pharmaceutical Industry (ABPI) • Publications (including corresponding authors of papers selected through the Methodological review process) • Executive Committee members professional contacts • Targeted professional social network groups
Regulators	• US Food and Drug Administration (FDA) • European Medicines Agency (EMA) • UK Medicines and Healthcare products Regulatory Agency (MHRA), • Japan Pharmaceuticals and Medical Devices Agency (PMDA) • China National Medical Product Association Centre for Drug Evaluation (NMPA CDE) • Australia Therapeutic Group Administration (TGA) • Drugs Controller General of India (DCGI) • Health Products and Food Branch (HPFB), Health Canada. • Ministry of Food and Drug Safety, South Korea. • Executive Committee members professional contacts
Ethics Committee / Ethics Committee members	• UK Health Research Authority (HRA) (targeting RECS specialised in reviewing early phase trials). • EUREC (European Network of ethics Committees) • US Institutional Review Boards • Australia Health Research Ethics Committees registered through the National Human Medical Research Council. • India Institutional Ethics Committees • Health Canada and Public Health Agency of Canada Research Ethics Board (PHAC REB) • South Korea Institutes Review Board • Executive Committee members professional contacts
Journal editors, associate editors and Conference Abstracts Committee Members	• Leading medical research journals in publishing clinical trials, and targeted journals will be informed by journal where many Phase I trials have been published (identified through Methodological review) • International Committee of Medical Journal Editors (ICMJE) • Abstract Committee members from leading conferences presenting Phase 1 results (see above). • Executive Committee members professional contacts

Funders / Funding Committee members	• Funding panels such as MRC, NIHR, CRUK, Blood Cancer UK, Wellcome Trust, Melinda and Bill Gates Foundation, Great Ormond Street Hospitaland other selected charities funding phase 1 work as applicable • USA NIH • Pharmaceutical companies • Executive Committee members professional contacts
Patients and Public	• Patient and Public engagement platforms • European Patients' forum https://www.eu-patient.eu/ • International disease specific advocacy groups • Patient representatives on Phase 1 trials management groups (through CTUs portfolios) • Executive Committee members' professional contacts

The survey will also be advertised on social media and a link to the survey will be provided on the DEFINE STUDY website (https://www.icr.ac.uk/DEFINEstudy). The Delphi survey is available at:

https://delphimanager.liv.ac.uk/dosefinding/

15.2.2 Consent, withdrawal and confidentiality

Consent to take part in the Delphi survey will be sought from every participant via the web-based survey application. No personal identifiable data will be collected aside from name and email address. Data gathered will include professional background characteristics of participants, including geographical location, self-identified stakeholder group (as defined in section 5.2.1 above), years of experience in clinical research, and in early phase trials. Information on data processing and handling will be provided on the website prior to consent.

Data will be processed and stored in accordance with all applicable data protection laws. During the survey, data will be stored on a secure server at the University of Liverpool (see section 5.2.5). Following completion, data from the survey will be downloaded and stored on a secure, access restricted server at ICR-CTSU and in accordance with all applicable data protection laws.

Participants will be able to withdraw at any point, however data collected up to the point of withdrawal will be kept unless deletion is specifically requested.

15.2.3 Sample size

As a prospective exercise and a multi-faceted survey, it is difficult to ascribe a defined sample size. However, in order to ensure meaningful representation of all the stakeholder categories, the survey will seek to obtain responses from at least 15 participants in each of the identified stakeholder categories. To achieve this, as many potential participants as possible will be approached. The registration and response rates will be monitored by the Executive Committee, who may decide to invite further potential participants if required.

15.2.4 Scoring

Each candidate item will be scored on a 9-point Likert scale relating to the participant's opinion of its importance. Unsure or Don't know / not my expertise options will be provided for participants who are unable to give their rating opinions for any reasons. Free text fields will also be used to elicit comments on the candidate items, and in round one to invite potential additional reporting items, which may have been missed or considered less important previously.

15.2.5 Software

The Delphi survey will be run using the University of Liverpool's DelphiManager, a bespoke piece of software written in C# 4.0 using MVC 4.

Data will be stored in a MySQL database hosted on a dedicated DelphiManager server hosted by the University's data centre. The University shall ensure that:

a) access to the University's datacentre is restricted to authorised personal only.
b) the DelphiManager server sits behind the University's firewall that uses a 256 bit SSL certificate.
c) only authorised University personnel, specifically the DelphiManager team have access to the DelphiManager server.
d) all Personal Data stored on the DelphiManager server is encrypted.
e) access to the DelphiManager software instance is set up by the DelphiManager team and then password protected

15.2.6 Survey administration

Potential participants will be approached as described in the table above and recipients of the invitation will be encouraged to forward the invitation to other potentially interested stakeholders. A combination of named and blind approaches will be used, where pre-selected named potential participants will be invited to take part and nominate additional experts to be contacted by the CONSORT-DEFINE team, and various professional or advocacy groups will be approached for dissemination amongst their members. Interested stakeholders will be asked to register on the survey website prior to the survey launch. For named approaches, a follow-up to the initial invite will be sent week before the survey launch. Once registered, consented participants will be alerted to the survey launch by an email containing the link to the survey. Each round of the survey will be opened for 4-weeks and reminders will be sent weekly during this period. Participants will be allowed to complete a round even if they haven't completed the previous one.

15.2.7 Pilot

The Delphi Survey will be piloted by the members of the Executive Committee to troubleshoot and check technical functionality, wording, logical flow or identify any other concerns, before launching the main survey. The Executive Committee may approach other external stakeholders from other key categories to participate in the pilot as appropriate.

Particular attention will be paid to piloting the Delphi survey to ensure patient and public engagement and representation can be optimised. Selected patient representative with extensive experience in the field of dose-finding trials will be approached to take part in the pilot, and their feedback will be sought to ensure the survey is accessible to this particular stakeholder category. Should the Delphi

survey not allow lay participants to fully contribute, due to the complexity, technicality or number of items to be assessed, a focus group will be organised with PPI experts in order to identify a core set of CONSORT-DEFINE items relevant to PPI contributors. This core set will then be submitted for feedback to a wider PPI audience through a separate process.

15.2.8 Analysis

The response observed for the initial blind and named approaches will be explored in a narrative summary. Following each round, response rate will be calculated based on the number of participants registered and having completed the survey. Descriptive summary analysis of the responding population will be presented based on the background characteristics data collected. For each item, distribution of scores as well as summary statistics (median, interquartile range, minimum and maximum), will be computed and presented. Summary statistics will be presented by the key stakeholder categories defined in section 5.2.1 and overall, and the geographical and professional background characteristics data may be used to explore the data further if relevant.

Qualitative data from the free text section of the survey will be thematically analysed to identify potential new items for inclusion.

After each round, members of the Executive Committee will be sent the results of the survey individually, prior to meeting (via video conference) to discuss the output and any changes required. Items scored 1-3 'not important' by at least 80% of the participants may be dropped between rounds subject to confirmation by the Executive Committee. Notes will also be made of any feedback relevant to the development of the E&E document. Additionally, the Executive Committee may decide to increase the number of participants, either overall or in certain stakeholder categories, based on observed registration and response rates.

Reports summarising the Delphi results will be produced and circulated to all participants after each round. Participants will also be presented with their own ratings from the previous round, as well as feedback on how suggestions and comments from the free text fields were dealt with. The Executive Committee will decide on the most appropriate format, content and manner of dissemination for these reports.

At further rounds, participants will be given the opportunity to change their ratings, and such changes will be monitored. The change in participants' ratings between subsequent rounds will be analysed at item level and interest will be on participants who changed:

1) 1-6 'not important' or 'important, but not critical' in round 1 to 7-9 in round 2 'critically important',

2) 7-9 'critically important' in round 1 to 1-6 'not important' or 'important, but not critical' in round 2,

3) 1-3 'not important' in round 1 to 4-6 'important, but not critical' in round 2,

4) 4-6 'important, but not critical' in round 1 to 1-3 'not important' in round 2.

For each reporting item, the distribution of the changes in rating scores and proportion below 15% change will be reported.

To gauge the level of agreement between round 1 and round 2 ratings, the following statistics will be calculated and reported for each reporting item with associated 95% confidence intervals [21]:

a) percentage agreement; percentage of participants with the same rating between rounds relative to the total responders to all rounds,

b) weighted Cohen's kappa coefficient using absolute error weights [22].

The analysis will be performed in R.

15.2.9 Stopping Criteria

The Executive Committee will decide to stop the Delphi Survey process once consensus and stability of ratings have been achieved. It is anticipated that 2 rounds will be sufficient to achieve this objective, however, the Committee may proceed to a third round based on the observed level of agreement, and an assessment on whether a subsequent round is likely to yield any further information. The Executive committee will make a decision based on their review of the Delphi survey results as described above and assess whether sufficient agreement and stability have been reached, aided by the stability and agreement criteria defined above.

15.3 Stage three: Consensus Meeting:

15.3.1 Objectives

The objectives of the Consensus meeting will be to discuss and finalise the full list of items to be included in the guidance, guided by the information on item importance and level of agreement gleaned during the Delphi survey process, as well as the structure of the E&E document.

15.3.2 Definition of Consensus

For the purpose of automatic inclusion into the checklist, items rated 7-9 ("Critically Important") by at least 70% of the Delphi survey respondents will be considered as having reached consensus.

15.3.3 Identification of participants

The Executive Committee will discuss and produce a list of experts in each of the key stakeholder categories described above to be approached for participation in the consensus meeting. If necessary, the Independent Expert Panel, as well as other professional groups may be approached to suggest potential candidates, subject to the Executive Committee sanction. The consensus meeting will be chaired by Professor Deborah Ashby.

15.3.4 Consensus meeting activities

The Executive Committee will prepare the agenda and meeting documentation to be shared with participants prior to the meeting, to include the results of the Delphi survey and the draft items checklist. The Consensus meeting will follow the recommended methodology for such exercise [8]. At the meeting Executive Committee members will first present the background and an update on work done to date, in order to facilitate the discussions. Session chairs then separately present items from the preliminary checklist, results of the Delphi study and feedback from stakeholders. Checklist items having reached consensus (see section 5.3.2) will be automatically recommended for inclusion. Items that did not reach consensus will be discussed for inclusions and/or modification based on the overall

importance rating achieved in the last round of the Delphi Survey. Following the discussion, consensus group members will anonymously be given an opportunity to make individual decisions about the inclusion of a specific item; 'keep', 'discard', and 'unsure or no opinion'. A decision to retain a reporting item will be based on achieving at least 50% support of group members deciding/wishing to keep the item, however the Executive committee will retain the prerogative to discuss and make final decision for low scoring items or items where a consensus is difficult to achieve. The rationale to guide decisions will be whether the item addresses elements unique to dose-finding early phase trials and whether they belonged in a minimum reporting set of items. Notes will be taken, and the discussions audio-recorded, with the participants' consent. Particular attention will be paid to any feedback or discussion requiring inclusion in the E&E document.

Following the meeting, a summary report will be produced and shared with the meeting attendees, as well as the Delphi survey participants.

15.4 Stage four: Development of a reporting guidance and explanatory support document

15.4.1 Guideline development process

After the consensus meeting, the Executive Committee will continue working on refining the content and wording of the guidance, as well as preparing a detailed explanation and elaboration document. Feedback from the Delphi survey and the consensus meeting will be checked for any information relevant for inclusion in the E&E document

The E&E document is intended to provide detailed explanation on the rationale for inclusion of the items, as well as evidence and examples applied in the literature.

15.4.2 Piloting the guideline

The guideline will be piloted by a small selection of key stakeholders with expertise in developing and reporting early phase dose-finding trials to test its usability and provide insight into issues that should be addressed in detail in the Explanation & Elaboration statement. As part of the guideline development process, the Executive committee will decide on the most appropriate piloting strategy and potential stakeholders to be invited to pilot the checklist. The Committee will discuss feedback from the pilot and decide on whether further modifications are required, either to the checklist itself or the E&E document.

16 Stage 5: Dissemination plan

The Executive Committee will devise a detailed dissemination strategy to maximise guideline awareness and uptake. Broadly, the strategy will comprise of the following:

- Direct feedback will be provided to the Delphi Survey participants, Consensus meeting contributors and the stakeholders groups identified in Table 1.
- The guideline will be accessible via the CONSORT and EQUATOR network websites, as well as on the CONSORT-DEFINE project's own website, which will also be kept updated throughout the project.
- Dissemination at specific UK and international study groups that run Phase I trials, such as the UK National Cancer Studies Groups, as well as to funders for early phase trials

(including MRC, CRUK, NIHR BRCs, ECMC and NCI), and to industry via The Association of British Pharmaceutical Industry (ABPI) and pharma partners' networks
- Maximising publications in high impact scientific journals.
- Presentation at meetings of UK Clinical Research Collaboration (UKCRC) Clinical Trials Unit, UKCRC Statistics Operational Group and NIHR Early Phase Statistics Group; national and international methodological conferences (e.g. International Clinical Trials and Methodology Conference, Society of Clinical Trials or International Society of Clinical Biostatistics), and at pharmaceutical conferences/meetings via our industry partners (e.g. PSI, EFPSI, DIA) and clinical conferences (e.g. NCRI, ESMO, ASCO, ECRD).
- Practical Dissemination workshops will be organised, one specifically aimed at journal editors in order to promote use of the guideline and encourage endorsement.
- Patient and public engagement will also be sought via the publication of two PPI lay summary papers, liaison with patients' groups (including the Royal Marsden Patients and Carers Review Panel and the Independent Cancer Patient's Voice), as well as dissemination at local and national PPI events.
- Broader communication with the public will also be pursued via the Institute of Cancer Research's website and social media, including blogs, posts on Twitter, Facebook and LinkedIn, press releases and potentially thought leadership pieces on trials reporting in the media.

17 Ethics approval

This project has been formally assessed for risk and approved by the Sponsor's Committee for Clinical Research. The Heath Research Authority has been consulted and confirmed Research Ethics Approval is not required.

18 Funding and any additional support

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19 Declaration of Conflict of Interest

All Protocol Development Group members declare that they have no conflict of interest to disclose.

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