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SPIRIT and CONSORT extensions for early phase dose-finding clinical trials: the DEFINE (Dose FIndiNg Extensions) study protocol

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Complete List of Authors:	Espinasse, Aude; Institute of Cancer Research Sutton, Clinical Trial and Statistical Unit Solovyeva, Olga; Institute of Cancer Research, Clinical Trials and Statistics Unit Dimairo, Munyaradzi; The University of Sheffield, School of Health and Related Research Weir, Christopher; University of Edinburgh, Edinburgh Clinical Trials Unit, Usher Institute Jaki, Thomas; University of Regensburg; University of Cambridge, MRC Biostatistics Unit Mander, Adrian; Cardiff University Centre for Trials Research Kightley, Andrew; Patient and Public Involvement Lead Evans, Jeffrey; University of Glasgow, School of Cancer Sciences Lee, Shing; Columbia University Bedding, Alun; Roche Products Ltd Hopewell, Sally; University of Oxford, Oxford Clinical Trials Research Unit / Centre for Statistics in Medicine, NDORMS Rantell, Khadija ; Medicines and Healthcare Products Regulatory Agency Liu, Rong; Bristol-Myers Squibb Co Chan, An-Wen; University of Toronto, Dept of Medicine, Women's College Research Institute De Bono, Johann; Institute of Cancer Research Yap, Christina; Institute of Cancer Research, Clinical Trials and Statistics Unit
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3 1 **SPiRiT and CONSORT extensions for early phase dose-finding clinical trials: the DEFINE (Dose**
4 **FiNDiNg Extensions) study protocol**

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11 6 Aude Espinasse¹⁺, Olga Solovyeva¹⁺, Munyaradzi Dimairo², Christopher J. Weir³, Thomas Jaki^{4,5},
12 7 Adrian Mander⁶, Andrew Kightley⁷, Jeffrey Evans⁸, Shing M. Lee⁹, Alun Bedding¹⁰, Sally Hopewell¹¹,
13 8 Khadija Rantell¹², Rong Liu¹³, An-Wen Chan¹⁴, Johann de Bono¹⁵, Christina Yap^{1,*}
14 9

15 9
16 10 + Joint first authors
17 11

18 11
19 12
20 12 ¹ Clinical Trials and Statistics Unit, The Institute of Cancer Research, Sutton, United Kingdom
21 13

22 13 ² School of Health and Related Research (SchARR), University of Sheffield, Sheffield, United Kingdom
23 14

24 14 ³ Edinburgh Clinical Trials Unit, Usher Institute, University of Edinburgh, Edinburgh, United Kingdom
25 15

26 15 ⁴ University of Regensburg, Regensburg, Germany
27 16

28 16 ⁵ MRC Biostatistics Unit, University of Cambridge, Cambridge, United Kingdom
29 17

30 17 ⁶ Centre for Trials Research, Cardiff University, Cardiff, United Kingdom
31 18

32 18 ⁷ Patient and Public Involvement lead, Lichfield, United Kingdom
33 19

34 19 ⁸ School of Cancer Sciences, University of Glasgow, Glasgow, United Kingdom
35 20

36 20 ⁹ Columbia University, New York, United States of America
37 21

38 21 ¹⁰ Roche, Welwyn Garden City, United Kingdom
39 22

40 22 ¹¹ Oxford Clinical Trials Research Unit / Centre for Statistics in Medicine, NDORMS, University of
41 23 Oxford, Oxford, United Kingdom
42 24

43 24 ¹² Medicines and Healthcare products Regulatory Agency (MHRA), London, United Kingdom
44 25

45 25 ¹³ Bristol Myers Squibb, New York, United States of America Columbia University, New York, United
46 26 States of America
47 27

48 27 ¹⁴ Dept of Medicine, Women's College Research Institute, University of Toronto, Toronto, Canada
49 28

50 28 ¹⁵ Division of Clinical Studies, The Institute of Cancer Research and Royal Marsden Hospital, Sutton,
51 29 United Kingdom
52 30

53 30
54 31 *** Correspondence:** Christina Yap, The Institute of Cancer Research, ICR-CTS, 15 Cotswold Road,
55 32 Sutton, SM2 5NG, UK
56 33

57 33 E-mail: christina.yap@icr.ac.uk
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3 35 **ABSTRACT**
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5 36 **Introduction:** Early phase dose-finding (EPDF) studies are critical for the development of new
6
7 37 treatments, directly influencing whether compounds or interventions can be investigated in further
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9 38 trials to confirm their safety and efficacy. There exists guidance for clinical trial protocols and reporting
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11 39 of completed trials in the SPIRIT 2013 and CONSORT 2010 statements. However, neither the original
12
13 40 statements, nor their extensions, adequately cover the specific features of EPDF trials. The DEFINE
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15 41 (DosE FIndiNg Extensions) study aims to enhance transparency, completeness, reproducibility and
16
17 42 interpretation of trial protocols (SPIRIT-DEFINE) and their reports of completed EPDF trials (CONSORT-
18
19 43 DEFINE), across all disease areas, building on the original SPIRIT 2013 and CONSORT 2010 statements.

20 44 **Methods and analysis:** A methodological review of published EPDF will be conducted to identify
21
22 45 features and deficiencies in their reporting and to inform the initial generation of the candidate items.
23
24 46 The early draft checklists will be further enriched through review of published and grey literature, real-
25
26 47 world examples analysis, citation and reference searches and consultation with international experts,
27
28 48 including regulators and journal editors. Development of CONSORT-DEFINE commenced in March
29
30 49 2021, followed by SPIRIT-DEFINE from January 2022. A modified Delphi process, involving worldwide,
31
32 50 multidisciplinary, and cross-sector key stakeholders, will be run to refine the checklists. An
33
34 51 international consensus meeting in autumn 2022 will finalise the list of items to be included in both
35
36 52 guidance extensions.

37 53 **Ethics and dissemination:** This project was approved by ICR's Committee for Clinical Research. The
38
39 54 Health Research Authority confirmed Research Ethics Approval is not required. The dissemination
40
41 55 strategy aims to maximise guideline awareness and uptake, including but not limited to dissemination
42
43 56 in stakeholder meetings, conferences, peer-reviewed publications, and on the EQUATOR Network and
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45 57 DEFINE study websites.

46 58 **Registration details:** SPIRIT-DEFINE and CONSORT-DEFINE are registered with the EQUATOR Network
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48 59 and the full protocols are accessible on the Equator website [\[1, 2\]](#)
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62 STRENGTHS AND LIMITATIONS OF THIS STUDY

- 63 ● This study aims to develop an international consensus-driven SPIRIT and CONSORT extensions
64 using gold standard methodological framework, for early phase dose-finding clinical trials across
65 all disease areas and regardless of trial design used. It will fill an important methodological gap in
66 protocol and trial reporting guidance and will be relevant to a significant number of trials.
- 67 ● A multidisciplinary international team of experts in both academia and pharmaceutical industries,
68 regulators, SPIRIT and CONSORT group representatives and a patient partner, has been brought
69 together to drive delivery of the project. An External Multidisciplinary Expert Panel will provide
70 independent oversight and quality control assurances throughout the project.
- 71 ● The stakeholders we will engage with for the Delphi survey and consensus meeting will represent
72 a diverse group of experts including clinical trials researchers, regulators, ethics committee
73 members, journal editors, funders and funding committee members, and patients and public
74 advocates.
- 75 ● The scope of our guidelines does not cover early phase trials where only one dosing regimen is
76 considered (i.e., no ascending (or descending) dosing regimens), However the basic principles may
77 still be applicable.
- 78 ● The Consensus meeting discussions will not be anonymous, which may impact the flow of
79 dialogue, however the voting process to determine inclusion of items will be anonymous.

82 INTRODUCTION

83 Background

84 Early phase dose-finding (EPDF) or dose-escalation trials, also referred to as Phase I or Phase I/II, are
85 critical in clinical therapy development. Depending on the drug and the endpoint of interest, the
86 studies may be conducted in healthy volunteers or in patients with the condition or disease. These
87 studies involve interim dose decisions and may provide data on safety, adverse effects,
88 pharmacokinetic (characterisation of a drug's absorption, distribution, metabolism, and excretion),
89 pharmacodynamics biomarker activity, clinical activity, and other information needed to choose a
90 suitable dosage range and/or administration schedule to inform further clinical studies. As such,
91 results from these trials directly influence decisions on further development and whether the selected
92 doses and schedules are sufficiently safe and have promising results on activity.

93 A clinical trial protocol is a vital document that details the study rationale, proposed methods,
94 organisation, and ethical considerations ^[3]. By providing the details to guide the conduct of a high-
95 quality study, a well-written protocol is a shared central reference for the study teams [\[4, 5\]](#) and
96 facilitates appraisal of its scientific, methodological, safety and ethical rigour by external reviewers.
97 However, protocols can vary greatly in content and quality despite their importance [\[4, 5\]](#). To address
98 this, the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 ^[4]
99 statement was established to provide evidence-based guidance for the minimum essential content of
100 a clinical trial protocol and is widely endorsed as international standard for trial protocols. Although
101 the considerations of SPIRIT 2013 are largely applicable across many types of trials, some
102 circumstances require additional protocol items^[4]. In particular, guidance on content specific to EPDF,
103 including dose and schedule determination based on safety/tolerability either alone or jointly with
104 one or more pharmacokinetic or activity markers, is lacking. Examples of specific features unique to
105 such trials include:

- 106 ● starting dose and its justification;
- 107 ● how interim dose decisions will be undertaken (including clearly defined outcome measures
108 and their assessment window, and analysis populations for interim adaptations);
- 109 ● how future recommended dose(s) will be selected.

110 Incomplete or unclear information on the design, conduct and analysis in dose-finding **protocols** and
111 **reporting papers** hinder interpretability and reproducibility of the results from such studies, which
112 may impact on the overall clinical development timeline, lead to erroneous conclusion on safety and
113 efficacy, and compromise the safety of trial participants ^[6].

114 This is particularly relevant as a considerable number of early phase trials are sponsored and run by
115 academic institutions or publicly funded organisations with funding from non-commercial sources

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3 116 including Research Councils and medical charities (e.g., Cancer Research UK, Wellcome Trust, US
4 117 National Cancer Institute). In the UK, 159 out of 1157 (14%) phase I clinical trials, which started in
5 118 2014-2018, had non-industry sponsors (data from ClinicalTrials.gov). This emphasises the importance
6 119 of this research to public research institutions and industry alike. Based on results from
7 120 ClinicalTrials.gov of trials in all countries, there are substantially more phase I trials than phase III trials
8 121 (13826 phase I versus 9501 phase III which started in 2014-2018). Data from pharmaceutical trials in
9 122 the US in 2004-2012 show that the estimated average cost of a phase I trial across all therapeutic areas
10 123 ranged from US \$1.4 to 6.6 million^[7]; such high costs reinforces the importance of managing resources
11 124 efficiently. The attrition rate throughout the drug development process is high, and the success rate
12 125 between phase I studies and marketing authorization has been reported as between 9.8% and 13.8%
13 126 ^[8, 9], with failure being primarily attributable to either poor tolerability or lack of biological activity
14 127 (79% of failed studies over the period 2016–2018)^[10]. In this context, it is vital that EPDF trial results
15 128 are assessed accurately to avoid poor dose selection, which will often lead to failed trials (Phase II and
16 129 Phase III), delays in regulatory submissions, additional post-marketing commitments or dose changes
17 130 post approval due to excessive toxicities or lack of efficacy^[11].
18 131 The use of more efficient but undoubtedly more complex dose escalation designs such as model-
19 132 assisted or model-based designs is rising: 1.6% (20/1,235 phase I published cancer trials) used model-
20 133 based designs in 1991-2006^[12], which increased to 6.4% (11/172) by 2012–2014^[13]. Such designs are
21 134 more complex to implement than conventional designs^[14-17] and require the specification of more
22 135 design features. Further transparency and reporting demands are needed in such protocols and trial
23 136 reports to facilitate understanding of the design, ensure the methods and results are reproducible,
24 137 and how dose decisions will be and have been made^[9].
25 138 More than 580 biomedical journals now require that trial reports conform to the CONSolidated
26 139 Standards Of Reporting Randomised Trials (CONSORT) 2010 reporting guidelines for randomised
27 140 parallel group clinical trials or an appropriate CONSORT extension to improve transparency,
28 141 reproducibility, consistency and accuracy in reporting^[12, 18]. A total of 153 journals, as well as a growing
29 142 number of commercial and non-commercial funders, regulators, trial organisations and patients
30 143 groups have also endorsed SPIRIT. A systematic review, based on more than 16,000 trials, published
31 144 in 2012 showed that journal endorsement of the CONSORT guidelines was associated with more
32 145 completely reported randomised trials^[16].
33 146 Neither the original guidance, SPIRIT 2013 and CONSORT 2010, nor their extensions, adequately cover
34 147 the features of EPDF trials. The Dose Finding Extensions (DEFINE) study aims to enhance transparency,
35 148 completeness, reproducibility and interpretation of EPDF trial protocols and their reporting of results,

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3 149 across all disease areas, and to build on the checklists outlined in the SPIRIT 2013 and CONSORT 2010
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5 150 statements.

6 151 **Overall aim**

8 152 The overall aim of this research is to develop and disseminate to stakeholders an extension to the
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10 153 SPIRIT 2013 and the CONSORT 2010 statements tailored to the specific requirements of EPDF clinical
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12 154 trials across all disease areas ^[19].

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156 **METHODS AND ANALYSIS**

157 The strategy for the development of reporting guidelines follows the gold standard methodology
158 framework for guideline development as recommended by the Enhancing the QUALity and
159 Transparency Of health Research (EQUATOR) network^[15]. To ensure the guidance is as impactful and
160 as widely adopted as possible, an international Executive Committee was formed, comprising of a
161 multi-disciplinary team of methodologists and clinicians with expertise in early phase trials in both
162 academia and pharmaceutical industries, a representative each from the SPIRIT and CONSORT group
163 and a patient and public partner, with planned active engagement with regulators. An external
164 multidisciplinary Expert Panel will provide independent oversight and quality control assurances.

165
166 Development of CONSORT-DEFINE commenced in March 2021, followed by SPIRIT-DEFINE from
167 January 2022. Figure 1 below illustrates the development process and each stage will be addressed in
168 detail below.

169
170 <Figure 1>

173 **1. Stage one: Literature Review and Draft checklist generation**

174 The objectives for this stage are to (a) explore current practice in early phase dose-finding trials
175 reporting and identify any gaps and (b) generate candidate reporting (CONSORT DEFINE) and protocol
176 (SPIRIT-DEFINE) checklist items

177 **1. Methodological Review**

178 A methodological review ^[20] will be conducted in order to explore the current status of reporting of
179 EPDF trials, identify any gaps and any specific features to dose-finding trials not adequately covered
180 by existing guidance, and to inform the drafting of the checklist. The review will also serve in providing
181 a sampling frame for some of the stakeholder categories for the Delphi survey (see section “Stage two:
182 Delphi Survey”). A random sample of 476 papers in dose-finding trials published between 2011 and
183 2020, stratified by setting (oncology/non-oncology) will be evaluated. This sample size will provide a
184 two-sided 95% confidence interval for the reporting frequency of an individual reporting item which
185 has a width of at most 9% ($\pm 4.5\%$) based on a conservative sample proportion of 0.5 (which gives the
186 largest variance). To standardise the review process, a detailed data extraction form will be generated,
187 and a comprehensive accompanying guidance document produced and agreement between
188 reviewers assessed.

2. Candidate Item Generation

Based on the results of the methodological review as well as expert opinion from the Executive Committee, items considered to be relevant in constituting a minimum set of reporting requirements will be identified as potential checklist candidates for CONSORT-DEFINE. A literature review of multiple databases (PubMed and Embase) will be performed, alongside grey literature and regulatory or industry guidelines, to identify any existing relevant guidance. Recommendations will also be sought from experts including regulatory bodies. The SPIRIT-DEFINE candidate item generation process is presented in Figure 2 and described below.

<Figure 2>

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 EPDF trials from the CONSORT-DEFINE development work. The list will be further refined through expert opinions from the Executive Committee, grey literature which includes regulatory and industry guidance documents and protocol templates by professional groups^[21, 22]. 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., from trial registries) will be consulted and their protocol templates (if available) included in the review process.

Building on the review conducted for CONSORT-DEFINE, the search strategy will be updated to identify protocol recommendations in peer-reviewed literature. Relevant literature not picked up by the search strategy but recommended by experts will be included. Citation and reference searches of key articles will also be conducted. Throughout the stage one (draft checklist generation) process, the Executive Committee will review and refine the candidate items for both CONSORT-DEFINE and SPIRIT-DEFINE guidance through expert discussion.

2. Stage two: Delphi Survey

The draft candidate items for the SPIRIT-DEFINE and CONSORT-DEFINE checklists will be submitted for feedback to a wider stakeholder group through a Delphi survey. The Delphi process will be conducted according to existing methodological guidance^[23-25] and involves inviting participants to complete iterative rounds of a web-based survey, where results from earlier rounds will inform the design of subsequent rounds. Each candidate item will be scored on a 9-point Likert scale relating to the

224 participant's opinion of its importance grouped in three categories: (1-3) "not important", (4-6)
 225 "important but not critical" and (7-9) "important and critical". An option "unable to rate" will be
 226 provided for participants who are unable to give their rating opinions for any reasons. Free text fields
 227 will also be used to elicit comments on the candidate items, and in round one, participants will also
 228 have the opportunity to suggest additional items.

229

230 The Executive Committee will meet between each round to discuss the results and agree on any
 231 required changes (see section "Analysis"). The DEFINE Delphi survey will be hosted on the University
 232 of Liverpool's DelphiManager, a purpose-built web-based platform, and the Executive Committee will
 233 pilot the survey prior to launch.

234

235 1. Identification of participants

236 A wide cross-section of stakeholders will be approached to take part in the Delphi survey. In the
 237 context of this study, stakeholders will be considered to be direct users or beneficiaries of the guidance
 238 and those involved in research conduct, governance, approval, commissioning, funding or publishing
 239 EPDF.

240 Potential participants will be approached through a combination of individual and group approaches
 241 through publicly available contact details and various professional organisations or advocacy groups.
 242 Table 1 below references the identified stakeholder groups as well as contact platforms and
 243 organisations. The survey will also be advertised on social media and a link to the survey will be
 244 provided on the DEFINE study website (www.icr.ac.uk/DEFINEstudy)

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Stakeholders	Platforms
Clinical Trials Researchers (including Clinicians/ Clinical Pharmacologists, Trial management staff, Statisticians, Trial methodologists)	<ul style="list-style-type: none"> • Medical Research Council - National Institute for Health and Care Research Trial Methodology Research Partnership (MRC-NIHR TMRP) (UK) • UK Clinical Research Collaboration (UKCRC) Network of Registered clinical trial Units • 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)

	<ul style="list-style-type: none"> • Clinical Conferences such as the National Cancer Research Institute (NCRI) annual conference (NCRI), European Society for Medical Oncology (ESMO) congress, American Society for Clinical Oncology (ASCO), the Experimental Cancer Medicine Centres (ECMC) events, European Centre for Rare Diseases and orphan products (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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • UK Health Research Authority (HRA) (targeting Research Ethics Committees (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)

	<ul style="list-style-type: none"> • South Korea Institutes Review Board • Executive Committee members professional contacts
Journal editors, associate editors and Conference Abstracts Review Committee Members	<ul style="list-style-type: none"> • 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 review Committee members from leading conferences presenting Phase 1 results (see above). • Executive Committee members professional contacts
Funders / Funding Committee members	<ul style="list-style-type: none"> • Funding panels such as Medical Research Council (MCR), National Institute for Health and care Research (NIHR), Cancer Research UK (CRUK), Blood Cancer UK, Wellcome Trust, Melinda and Bill Gates Foundation, Great Ormond Street Hospital (GOSH) and other selected charities funding phase 1 work as applicable • USA National Institutes of Health (NIH) • Pharmaceutical companies • Executive Committee members professional contacts
Patients and Public	<ul style="list-style-type: none"> • 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 Clinical Trials Units portfolios) • Executive Committee members' professional contacts

Table 1: Delphi survey stakeholders and methods of access

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 "Identification of participants" above), years of experience in clinical research, and in early phase trials. Information on data processing and handling will be provided on the participant information sheet via email invitation and website.

2. Sample size

As this is a prospective exercise and a multi-faceted survey, the sample size was decided on pragmatically, to be both achievable and 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 giving an overall target of at least 90 participants. To achieve this, as many potential participants as possible will be approached. The registration and survey response rates, both overall and by stakeholder categories will be monitored by the Executive Committee.

3. Survey administration

Potential participants will be invited to take part and nominate additional experts to be contacted by the 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. 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 approximately 4 weeks and reminders sent weekly during this period. Participants will be allowed to complete a round even if they haven't completed the previous one, provided they have registered for the first round.

4. Pilot

The Delphi Survey will be piloted by the members of the Executive Committee, before launching the main survey.

Particular attention will be paid to piloting the Delphi survey to ensure patient and public engagement and representation can be optimised. Selected consumers representatives with substantial experience 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 Patient and Public Involvement and Engagement (PPIE) experts in order to identify a core set of SPIRIT-DEFINE and CONSORT-DEFINE items relevant to PPI contributors. This core set will then be submitted for feedback to a wider PPIE audience through a separate process.

5. Analysis

The response observed for the initial 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

290 presented based on the background characteristics data collected. For each item, distribution of
291 scores as well as summary statistics (median, interquartile range, minimum and maximum), will be
292 computed and presented. Summary statistics will be presented by the key stakeholder categories
293 defined in section "Identification of participants" and overall, and the geographical and professional
294 background characteristics data may be used to explore the data further if relevant.

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

297 After each round, members of the Executive Committee will be sent the results of the survey and meet
298 to discuss the output and any changes required. Items scored 1-3 'not important' by at least 80% of
299 the participants may be dropped between rounds subject to confirmation by the Executive
300 Committee. Notes will also be made of any feedback relevant to the development of the E&E
301 document.

302 Participants will also be presented the distribution of the ratings, their own ratings from the previous
303 round, as well as feedback on how suggestions and comments from the free text fields were dealt
304 with.

305 At further rounds, participants will be given the opportunity to change their ratings, and such changes
306 will be monitored. The change in participants' ratings between subsequent rounds will be analysed at
307 item level and interest will be on participants who moved from one category to another (e.g., from
308 not important" to "important but not critical)

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

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

- 313 a) percentage agreement; percentage of participants with the same rating between rounds
314 relative to the total responders to all rounds,
- 315 b) weighted Cohen's kappa coefficient using absolute error weights^[22].

316 The analysis will be performed in R version 4.1.2 ^[26].

317

318 6. Stopping Criteria

319 The Executive Committee will decide to stop the Delphi Survey process once consensus and stability
320 of ratings have been achieved. It is anticipated that 2 rounds will be sufficient to achieve this objective,
321 however, the Committee may proceed to a third round based on the observed level of agreement and
322 stability, and an assessment on whether a subsequent round is likely to yield any further information.

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3 324 **3. Stage three: Consensus Meeting:**
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5 325 The objectives of the Consensus meeting will be to discuss and finalise the full list of items to be
6 326 included in the guidance, guided by the information on item importance and level of agreement
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8 327 gleaned during the Delphi survey process, as well as the structure of the E&E document. The
9
10 328 Consensus meeting will follow the recommended methodology for such exercise ^[15]
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12 329

13 330 1. Definition of Consensus
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15 331 For the purpose of automatic inclusion into the checklist, items rated 7-9 (“Critically Important”) by at
16 332 least 70% of the Delphi survey respondents will be considered as having reached consensus.
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19
20 334 2. Identification of participants

21 335 The Executive Committee will be responsible for the selection of relevant experts in each of the key
22 336 stakeholders’ categories (see Table 1) to be invited to participate in the Consensus meeting. Responses
23
24 337 to the invitations will be tracked, to ensure balanced representation across the key stakeholder
25
26 338 groups.

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28 339 Checklist items having reached consensus (see section “Definition of Consensus”) will be automatically
29
30 340 recommended for inclusion. Items that did not reach consensus will be discussed for inclusions and/or
31
32 341 modification based on the overall importance rating achieved in the last round of the Delphi Survey.
33
34 342 Following the discussion, consensus group members will anonymously be given an opportunity to
35
36 343 make individual decisions about the inclusion of a specific item; ‘keep’, ‘discard’, and ‘unsure or no
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38 344 opinion’. A decision to retain a reporting item will be based on achieving at least 50% support of group
39
40 345 members deciding/wishing to keep the item, however the Executive committee will retain the
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42 346 prerogative to discuss and make final decision for low scoring items or items where a consensus is
43
44 347 difficult to achieve. The rationale to guide decisions will be whether the item addresses elements
45
46 348 unique to dose-finding early phase trials and whether they belonged in a minimum reporting set of
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48 349 items. Notes will be taken, and the discussions audio-recorded, with the participants’ consent.
49
50 350 Particular attention will be paid to any feedback or discussion requiring inclusion in the E&E document.
51
52 351 Following the meeting, a summary report will be produced and shared with the meeting attendees,
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54 352 as well as the Delphi survey participants.
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58 354 **4. Stage four: Development of a reporting guidance and explanatory support document**
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3 355 The objectives of this stage are to finalise the SPIRIT-DEFINE and CONSORT-DEFINE guidance and
4
5 356 supporting documentation including the corresponding explanation and elaboration documents.
6
7 357 After the consensus meeting, the Executive Committee will continue working on refining the content
8
9 358 and wording of both guidelines, as well as preparing the E&E documents, intended to provide
10
11 359 explanation on the rationale and elaboration of the items, as well as evidence and examples applied
12
13 360 in the literature. Feedback from the Delphi survey and the consensus meeting will be checked for any
14
15 361 information relevant for inclusion in the E&E document.

16 362

17 363 Both guidelines will be piloted with real-world examples by a selection of key stakeholders with
18
19 364 expertise in developing and reporting EPDF trials to test their usability and provide insight into issues
20
21 365 that should be addressed in detail in the E&E documents. The Committee will discuss feedback from
22
23 366 the pilot and decide on whether further modifications are required, either to the checklist itself or the
24
25 367 E&E document.

26 368

27 369 **5. Data Management and Confidentiality**

28 370 All data generated and collected during the DEFINE study will be handled, processed and stored
29
30 371 according to all applicable data protection legislation. Data collected during the Delphi Survey will be
31
32 372 stored on stored in a MySQL database hosted on a dedicated DelphiManager server hosted by the
33
34 373 University of Liverpool's Data Centre. Following closure of the Delphi survey, data will be downloaded
35
36 374 for analysis, audio recordings and transcripts from the Consensus meeting will be stored on secure
37
38 375 servers at the Institute of Cancer Research Clinical Trials and Statistical Unit. Access to any DEFINE
39
40 376 study data will be access restricted to the team members conducting the analyses and stored for a
41
42 377 minimum of five years after the end of the study.

43 378

44 379 **6. Patient and Public Involvement**

45 380 The DEFINE Study Patient and Public Involvement and Engagement (PPIE) lead (AK) was involved in
46
47 381 the study design from inception, and contributed to the development of the protocol. Additional PPIE
48
49 382 representatives from both the oncology and non-oncology disease areas will also be consulted on the
50
51 383 checklists items to ensure optimum representation of this particular patient group. The DEFINE study
52
53 384 also comprises of a specific PPIE work package aimed at producing lay publications to chart the
54
55 385 development of both the SPIRIT-DEFINE and CONSORT-DEFINE guidelines (see section Ethics and
56
57 386 Dissemination).

58 387

59 388 **ETHICS AND DISSEMINATION**

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2
3 389 This project has been formally assessed for risk and approved by the Institute of Cancer Research
4
5 390 Committee for Clinical Research as sponsor. The Health Research Authority has been consulted and
6
7 391 confirmed Research Ethics Approval is not required.

8 392 The Executive Committee will devise a detailed dissemination strategy to maximise guideline
9
10 393 awareness and uptake. Broadly, the strategy will comprise of the following:

- 11 394 ● Direct feedback will be provided to the Delphi Survey participants, Consensus meeting
12 395 contributors and the stakeholders groups identified in Table 1.
- 13 396 ● The guideline will be accessible via the CONSORT and EQUATOR network website, as well as
14 397 on the DEFINE study's own website, which will also be kept updated throughout the project.
- 15 398 ● Dissemination at specific UK and international study groups that run phase I trials, such as the
16 399 UK National Cancer Studies Groups, as well as to funders for early phase trials (including MRC,
17 400 CRUK, NIHR Biomedical Research Centres, ECMC and NCI), and to industry via The Association
18 401 of British Pharmaceutical Industry (ABPI) and pharma partners' networks
- 19 402 ● Maximising publications in high impact scientific journals.
- 20 403 ● Presentation at meetings of UK Clinical Research Collaboration (UKCRC) Clinical Trials Unit,
21 404 UKCRC Statistics Operational Group and NIHR Early Phase Statistics Group; national and
22 405 international methodological conferences (e.g. International Clinical Trials and Methodology
23 406 Conference, Society of Clinical Trials or International Society of Clinical Biostatistics), and at
24 407 pharmaceutical conferences/meetings via our industry partners (e.g., PSI, EFPSI, DIA) and
25 408 clinical conferences (e.g., NCRI, ESMO, ASCO, ECRD).
- 26 409 ● Practical Dissemination workshops will be organised, one specifically aimed at journal editors
27 410 in order to promote use of the guideline and encourage endorsement.
- 28 411 ● Patient and public engagement will also be sought via the publication of PPI lay summary
29 412 papers, including the production of a lay study report template, liaison with patients' groups
30 413 (including the Royal Marsden Patients and Carers Review Panel and the Independent Cancer
31 414 Patient's Voice), as well as dissemination at local and national PPI events.
- 32 415 ● Broader communication with the public will also be pursued via the Institute of Cancer
33 416 Research's website and social media, including blogs, posts on Twitter, Facebook and
34 417 LinkedIn, press releases and potentially thought leadership pieces on trials reporting in the
35 418 media.

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8 426 [network.org/wp-content/uploads/2022/05/DF-CONSORT-protocol-v1.2_FINAL.pdf](https://www.equator-network.org/wp-content/uploads/2022/05/DF-CONSORT-protocol-v1.2_FINAL.pdf).
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18 434 [medical-research-involving-human-subjects/](https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/).
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3 490 **AUTHORS' CONTRIBUTIONS**

4 491 CY and CW conceived the idea. CY, CW, MD, TJ, AM, AK, JE, SL, SH and JdB obtained funding for
5 492 CONSORT-DEFINE. AE, OS, MD, CW, TJ, AM, AK, JE, SL, SH, AC, JdB and CY contributed to the design of
6 493 the study. AE, OS and CY wrote the first draft of the manuscript. All authors contributed to the
7 494 refinement of the study methods and critical revision of the manuscript. All authors read and approved
8 495 the final version of the manuscript.
9

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23 505 However, research outputs will be published in line with the funders' publication policy requirements.
24 506 SPIRIT-DEFINE part did not receive any external funding. For the purpose of open access, the author
25 507 has applied a Creative Commons Attribution (CC BY) licence to any Author Accepted Manuscript
26 508 version arising from this submission.
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37 510 **COMPETING INTERESTS**

38 511
39 512 Professor Johann de Bono has served on advisory boards and received fees from many companies
40 513 including Amgen, Astra Zeneca, Astellas, Bayer, Bioexcel Therapeutics, Boehringer Ingelheim,
41 514 Cellcentric, Daiichi, Eisai, Genentech/Roche, Genmab, GSK, Harpoon, ImCheck Therapeutics, Janssen,
42 515 Merck Serono, Merck Sharp & Dohme, Menarini/Silicon Biosystems, Orion, Pfizer, Qiagen, Sanofi
43 516 Aventis, Sierra Oncology, Taiho, Terumo, Vertex Pharmaceuticals.
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49 518 funding or other support for his research work from AZ, Astellas, Bayer, Cellcentric, Daiichi,
50 519 Genentech, Genmab, GSK, Janssen, Merck Serono, MSD, Menarini/Silicon Biosystems, Orion, Sanofi
51 520 Aventis, Sierra Oncology, Taiho, Pfizer, Vertex, and which has a commercial interest in abiraterone,
52 521 PARP inhibition in DNA repair defective cancers and PI3K/AKT pathway inhibitors (no personal
53 522 income).
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3 523 Professor Johann de Bono was named as an inventor, with no financial interest for patent 8,822,438,
4
5 524 submitted by Janssen that covers the use of abiraterone acetate with corticosteroids. He has been the
6
7 525 CI/PI of many industry sponsored clinical trials.

8 526 Professor Johann de Bono is a National Institute for Health Research (NIHR) Senior Investigator. The
9
10 527 views expressed in this article are those of the author(s) and not necessarily those of the NHS, the
11
12 528 NIHR, or the Department of Health.

13 529 The remaining authors declare no conflicts of interest.
14
15 530

16 531

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21
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23
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25 536

26 537 **Figure legends:**

27
28 538 Figure 1. Project overview for the development of SPIRIT-DEFINE and CONSORT-DEFINE guidelines.

29
30 539 Figure 2. SPIRIT-DEFINE candidate item generation development process.
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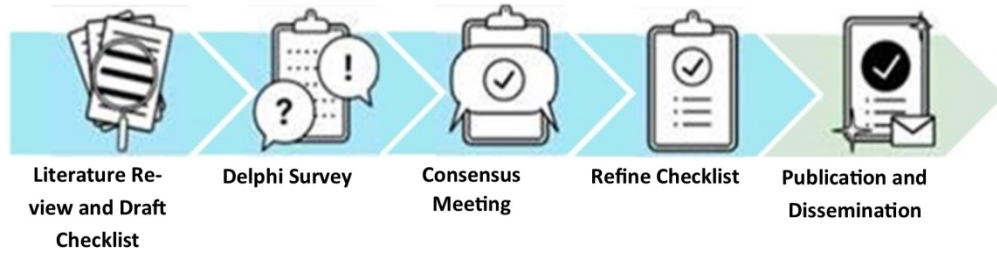


Figure 1. Project overview for the development of SPIRIT-DEFINE and CONSORT-DEFINE guidelines.

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Figure 2. SPIRIT-DEFINE candidate item generation development process.

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BMJ Open

SPIRIT and CONSORT extensions for early phase dose-finding clinical trials: the DEFINE (Dose FINDing Extensions) study protocol

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Primary Subject Heading:	Medical publishing and peer review
Secondary Subject Heading:	Medical education and training, Communication
Keywords:	EDUCATION & TRAINING (see Medical Education & Training), STATISTICS & RESEARCH METHODS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT



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3 1 **SPiRiT and CONSORT extensions for early phase dose-finding clinical trials: the DEFINE (Dose-**
4 **FiNdIng Extensions) study protocol**

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8 4 Keywords: early phase, clinical trials, SPiRiT guideline, CONSORT guideline, dose finding
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11 6 Aude Espinasse¹⁺, Olga Solovyeva¹⁺, Munyaradzi Dimairo², Christopher J. Weir³, Thomas Jaki^{4,5},
12 7 Adrian Mander⁶, Andrew Kightley⁷, Jeffrey Evans⁸, Shing M. Lee⁹, Alun Bedding¹⁰, Sally Hopewell¹¹,
13 8 Khadija Rantell¹², Rong Liu¹³, An-Wen Chan¹⁴, Johann de Bono¹⁵, Christina Yap^{1*}.
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10 + Joint first authors

12 ¹ Clinical Trials and Statistics Unit, The Institute of Cancer Research, Sutton, United Kingdom

13 ² School of Health and Related Research (SchARR), University of Sheffield, Sheffield, United Kingdom

14 ³ Edinburgh Clinical Trials Unit, Usher Institute, University of Edinburgh, Edinburgh, United Kingdom

15 ⁴ University of Regensburg, Regensburg, Germany

16 ⁵ MRC Biostatistics Unit, University of Cambridge, Cambridge, United Kingdom

17 ⁶ Centre for Trials Research, Cardiff University, Cardiff, United Kingdom

18 ⁷ Patient and Public Involvement lead, Lichfield, United Kingdom

19 ⁸ School of Cancer Sciences, University of Glasgow, Glasgow, United Kingdom

20 ⁹ Columbia University, New York, United States of America

21 ¹⁰ Roche, Welwyn Garden City, United Kingdom

22 ¹¹ Oxford Clinical Trials Research Unit / Centre for Statistics in Medicine, NDORMS, University of
23 Oxford, Oxford, United Kingdom

24 ¹² Medicines and Healthcare products Regulatory Agency (MHRA), London, United Kingdom

25 ¹³ Bristol Myers Squibb, New York, United States of America

26 ¹⁴ Dept. of Medicine, Women's College Research Institute, University of Toronto, Toronto, Canada

27 ¹⁵ Division of Clinical Studies, The Institute of Cancer Research and Royal Marsden Hospital, Sutton,
28 United Kingdom

29
30 * **Correspondence:** Christina Yap, The Institute of Cancer Research, ICR-CTSU, 15 Cotswold Road,
31 Sutton, SM2 5NG, UK

32 E-mail: christina.yap@icr.ac.uk
33

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3 34 **ABSTRACT**
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5 35 **Introduction:** Early phase dose-finding (EPDF) studies are critical for the development of new
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7 36 treatments, directly influencing whether compounds or interventions can be investigated in further
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9 37 trials to confirm their safety and efficacy. There exists guidance for clinical trial protocols and reporting
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11 38 of completed trials in the SPIRIT 2013 and CONSORT 2010 statements. However, neither the original
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13 39 statements nor their extensions adequately cover the specific features of EPDF trials. The DEFINE
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15 40 (DosE-FIndiNg Extensions) study aims to enhance transparency, completeness, reproducibility, and
16
17 41 interpretation of EPDF trial protocols (SPIRIT-DEFINE) and their reports once completed (CONSORT-
18
19 42 DEFINE), across all disease areas, building on the original SPIRIT 2013 and CONSORT 2010 statements.

20 43 **Methods and analysis:** A methodological review of published EPDF trials will be conducted to identify
21
22 44 features and deficiencies in reporting and inform the initial generation of the candidate items. The
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24 45 early draft checklists will be enriched through a review of published and grey literature, real-world
25
26 46 examples analysis, citation and reference searches and consultation with international experts,
27
28 47 including regulators and journal editors. Development of CONSORT-DEFINE commenced in March
29
30 48 2021, followed by SPIRIT-DEFINE from January 2022. A modified Delphi process, involving worldwide,
31
32 49 multidisciplinary, and cross-sector key stakeholders, will be run to refine the checklists. An
33
34 50 international consensus meeting in autumn 2022 will finalise the list of items to be included in both
35
36 51 guidance extensions.

37 52 **Ethics and dissemination:** This project was approved by ICR's Committee for Clinical Research. The
38
39 53 Health Research Authority confirmed Research Ethics Approval is not required. The dissemination
40
41 54 strategy aims to maximise guideline awareness and uptake, including but not limited to dissemination
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43 55 in stakeholder meetings, conferences, peer-reviewed publications, and on the EQUATOR Network and
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45 56 DEFINE study websites.

46 57 **Registration details:** SPIRIT-DEFINE and CONSORT-DEFINE are registered with the EQUATOR Network.
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3 60 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
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- 5 61 ● This study will develop international consensus-driven SPIRIT and CONSORT extensions using a
6 gold standard methodological framework, for early phase dose-finding clinical trials across all
7 62 disease areas and regardless of trial design used.
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10 64 ● A multidisciplinary international team of experts in both academia and pharmaceutical industry,
11 regulators, SPIRIT and CONSORT group representatives and a patient partner has been brought
12 65 together to drive the delivery of the project.
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15 67 ● A diverse group of stakeholders, including clinical trial researchers, regulators, ethics committee
16 68 members, journal editors, funders and funding committee members, and patients and public
17 69 advocates, will be involved in the Delphi survey and consensus meeting.
18
19 70
20 71 ● The scope of our guidelines does not specifically cover early phase trials with only one dosing
21 regimen or later phase dose-finding trials with dose (de-)escalations; however, we would expect
22 72 the basic principles may still be applicable.
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25 74 ● The Consensus meeting discussions will not be anonymous, which may impact the flow of
26 dialogue; however, the voting process to determine the inclusion of items will be anonymous.
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77 INTRODUCTION

78 Background

79 Early phase dose-finding (EPDF) or dose-escalation trials, also referred to as phase I or phase I/II, are
80 critical in clinical therapy development. Depending on the drug and endpoint of interest, the studies
81 may be conducted in healthy volunteers or patients with the condition or disease. These studies
82 involve interim dose decisions and may provide data on safety, adverse effects, pharmacokinetics
83 (characterisation of a drug's absorption, distribution, metabolism, and excretion), pharmacodynamics,
84 biomarker activity, clinical activity, and other information needed to choose a suitable dosage range
85 and/or administration schedule to inform further studies. Results from these trials directly influence
86 decisions on further development and whether the selected doses and schedules are sufficiently safe
87 and have promising results on activity.

88 A clinical trial protocol is a vital document that details the study rationale, methods, organisation, and
89 ethical considerations ^[1]. By providing the details to guide the conduct of a high-quality study, a well-
90 written protocol is a shared central reference for the study teams ^[2, 3] and facilitates appraisal of its
91 scientific, methodological, safety and ethical rigour by external reviewers. However, protocols can
92 vary greatly in content and quality despite their importance ^[2, 3]. To address this, the Standard Protocol
93 Items: Recommendations for Interventional Trials (SPIRIT) 2013 ^[2] statement was established to
94 provide evidence-based guidance for the minimum essential content of clinical trial protocols and is
95 widely endorsed as the international standard for trial protocols. Although the considerations of
96 SPIRIT 2013 are largely applicable across many types of trials, some circumstances require additional
97 items ^[2]. Guidance on content specific to EPDF trials, including dose and schedule determination based
98 on safety/tolerability either alone or with one or more pharmacokinetic or activity markers, is lacking.
99 Examples of features unique to such trials include:

- 100 ● starting dose and its justification.
- 101 ● how interim dose decisions will be undertaken (including clearly defined outcome measures
102 and their assessment window, and analysis populations for interim adaptations).
- 103 ● how future recommended dose(s) will be selected.

104 Incomplete or unclear information on the design, conduct, and analysis in dose-finding protocols and
105 reporting papers hinders the interpretability and reproducibility of the results from such studies,
106 which may impact the overall clinical development timeline, lead to erroneous conclusions on safety
107 and efficacy, and compromise the safety of trial participants ^[4].

108 This is particularly relevant as a considerable number of early phase trials are sponsored and run by
109 academic institutions or publicly funded organisations with funding from non-commercial sources,
110 including Research Councils and medical charities (e.g., Cancer Research UK, Wellcome Trust, US

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3 111 National Cancer Institute). In the UK, 159 out of 1157 (14%) phase I clinical trials, started in 2014-2018,
4 112 had non-industry sponsors (data from ClinicalTrials.gov). This emphasises the importance of this
5 113 research to public research institutions and industry alike. Based on results from ClinicalTrials.gov of
6 114 trials in all countries, there are substantially more phase I trials than phase III trials (13826 phase I
7 115 versus 9501 phase III which started in 2014-2018). Data from pharmaceutical trials in the US in 2004-
8 116 2012 show that the estimated average cost of a phase I trial across all therapeutic areas ranged from
9 117 US \$1.4 to 6.6 million ^[5]; such high costs reinforce the importance of managing resources efficiently.
10 118 The attrition rate throughout the drug development process is high, and the success rate between
11 119 phase I studies and marketing authorization has been reported as between 9.8% and 13.8% ^[6, 7], with
12 120 failure being primarily attributable to either poor tolerability or lack of biological activity (79% of failed
13 121 studies over the period 2016–2018) ^[8]. In this context, EPDF trial results must be assessed accurately
14 122 to avoid poor dose selection, which will often lead to failed trials (phases II and phase III), delays in
15 123 regulatory submissions, additional post-marketing commitments or dose changes post-approval due
16 124 to excessive toxicities or lack of efficacy ^[9].

17 125 The use of more complex dose-escalation designs such as model-assisted or model-based designs is
18 126 rising: 1.6% (20/1,235 phase I published cancer trials) in 1991-2006 ^[10], to 6.4% (11/172) by 2012–
19 127 2014 ^[11]. Such designs are more complex to implement ^[12-14] and require the specification of more
20 128 design features ^[15]. Further transparency and reporting demands are needed in such protocols and
21 129 trial reports to facilitate understanding of the design, ensure the methods and results are
22 130 reproducible, and explain how dose decisions will be and have been made ^[16-18].

23 131 More than 580 biomedical journals now require that trial reports conform to the CONSolidated
24 132 Standards Of Reporting Randomised Trials (CONSORT) 2010 reporting guidelines for randomised
25 133 parallel group clinical trials or an appropriate CONSORT extension to improve transparency,
26 134 reproducibility, consistency and accuracy in reporting ^[19-21]. A total of 153 journals, as well as a growing
27 135 number of commercial and non-commercial funders, regulators, trial organisations, and patient
28 136 groups, have also endorsed SPIRIT ^[22]. A systematic review based on more than 16,000 trials published
29 137 in 2012 showed that journal endorsement of the CONSORT guidelines was associated with more
30 138 completely reported randomised trials ^[23].

31 139 Neither the original guidance, SPIRIT 2013 and CONSORT 2010, nor their extensions adequately cover
32 140 the features of EPDF trials. The Dose Finding Extensions (DEFINE) study aims to enhance transparency,
33 141 completeness, reproducibility, and interpretation of EPDF trial protocols and their reporting of results,
34 142 across all disease areas, and to build on the checklists outlined in the SPIRIT 2013 and CONSORT 2010
35 143 statements.

144 **Overall aim**

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145 The aim of this research is to develop and disseminate an extension to the SPIRIT 2013 and CONSORT
146 2010 statements tailored to the specific requirements of EPDF clinical trials across all disease areas
147 [24]. The full study protocols are accessible on the Enhancing the QUALity and Transparency Of health
148 Research (EQUATOR) website [25, 26].

149

For peer review only

150 **METHODS AND ANALYSIS**

151 The strategy for the development of reporting guidelines follows the gold-standard methodology
152 framework for guideline development recommended by the EQUATOR network [27]. To ensure the
153 guidance is as impactful and widely adopted as possible, an international Executive Committee was
154 formed, comprising a multi-disciplinary team of methodologists, clinicians with expertise in early
155 phase trials in both academia and pharmaceutical industry, a representative each from the SPIRIT and
156 CONSORT groups and a patient and public partner, with planned active engagement with regulators.
157 An independent multidisciplinary Expert Panel will provide oversight and quality control assurances.

158
159 Development of CONSORT-DEFINE commenced in March 2021, followed by SPIRIT-DEFINE from
160 January 2022. Figure 1 illustrates the development process, and each stage will be addressed in detail
161 below.

162
163

164 **1. Stage one: Literature Review and Draft checklist generation**

165 The objectives for this stage are to (a) explore current practice in EPDF trials reporting and identify
166 gaps and (b) generate candidate reporting (CONSORT-DEFINE) and protocol (SPIRIT-DEFINE) checklist
167 items.

168 **1. Methodological Review**

169 A methodological review [28] will be conducted to explore the current status of reporting of EPDF trials,
170 identify gaps and specific features of dose-finding trials not adequately covered by existing guidance,
171 and inform the drafting of the checklist. The review will also serve in providing a sampling frame for
172 some of the stakeholder categories for the Delphi survey (see section “Stage two: Delphi Survey”). A
173 random sample of 476 papers in dose-finding trials published between 2011 and 2020, stratified by
174 setting (oncology/non-oncology), will be evaluated. This sample size will provide a two-sided 95%
175 confidence interval for the reporting frequency of an individual item with a width of at most 9%
176 ($\pm 4.5\%$) based on a conservative sample proportion of 0.5 (which gives the largest variance). To
177 standardise the process, a detailed data extraction form and comprehensive guidance will be
178 generated, and agreement between reviewers assessed.

179

180 **2. Candidate Item Generation**

181 Based on the results of the methodological review as well as expert opinion from the Executive
182 Committee, items considered relevant to constituting a minimum set of reporting requirements will
183 be identified as checklist candidates for CONSORT-DEFINE. A literature review of multiple databases

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3 184 (Medline via PubMed and Embase) will be performed, alongside grey literature and regulatory or
4
5 185 industry guidelines, to identify relevant guidance. Recommendations will also be sought from experts,
6
7 186 including regulatory bodies. The SPIRIT-DEFINE candidate item generation process is presented in
8
9 187 Figure 2 and described below.

10 188

11 189 An initial draft of the SPIRIT-DEFINE checklist will be prepared, building on the original SPIRIT 2013,
12
13 190 and enriched by the items identified as specific to EPDF trials from the CONSORT-DEFINE development
14
15 191 work. The list will be refined through expert opinions from the Executive Committee, grey literature,
16
17 192 including regulatory and industry guidance documents and protocol templates by professional groups.
18
19 193 Key stakeholder groups identified in the CONSORT-DEFINE development protocol (clinical trials units,
20
21 194 including MHRA-accredited phase I units, funders, and ethics committees) and experts from other
22
23 195 protocol standard initiatives relevant to dose-finding trials (e.g., from trial registries) will be consulted
24
25 196 and their templates included.

26 197

27 198 Building on the review conducted for CONSORT-DEFINE, the search strategy will be updated to identify
28
29 199 protocol recommendations in peer-reviewed literature. Relevant literature not picked up by the
30
31 200 search strategy but recommended by experts will be included. Citation and reference searches of key
32
33 201 articles will also be conducted. Throughout the stage one (draft checklist generation) process, the
34
35 202 Executive Committee will refine the candidate items for both CONSORT-DEFINE and SPIRIT-DEFINE
36
37 203 guidance.

38 204

39 205 **2. Stage two: Delphi Survey**

40 206 The draft candidate items for the SPIRIT-DEFINE and CONSORT-DEFINE checklists will be submitted for
41
42 207 feedback to a wider stakeholder group through a Delphi survey. The Delphi process will be conducted
43
44 208 according to existing methodological guidance ^[29-31] and involves inviting participants to complete
45
46 209 iterative rounds of a web-based survey, where results from earlier rounds will inform the design of
47
48 210 subsequent rounds. Each candidate item will be scored on a 9-point Likert scale relating to the
49
50 211 participant's opinion of its importance, grouped into three categories: (1-3) "not important", (4-6)
51
52 212 "important but not critical" and (7-9) "important and critical". An option "unable to rate" will be
53
54 213 provided for participants who are unable to give their rating opinions for any reason. Free text fields
55
56 214 will also be used to elicit comments on the candidate items, and in round one, participants will also
57
58 215 have the opportunity to suggest additional items.

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3 217 The Executive Committee will discuss the results between each round and agree on any required
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5 218 changes (see section “Analysis”). The DEFINE Delphi survey will be hosted on the University of
6
7 219 Liverpool’s DelphiManager, a purpose-built web-based platform, and the Executive Committee will
8
9 220 pilot the survey before launch.

10 221

11 222 1. Identification of participants

12
13 223 A wide cross-section of stakeholders will be approached to take part in the Delphi survey. For this
14
15 224 study, stakeholders will be considered to be direct users or beneficiaries of the guidance and those
16
17 225 involved in research conduct, governance, approval, commissioning, funding, or publishing EPDF trials.
18
19 226 Potential participants will be approached through a combination of individual and group approaches
20
21 227 through publicly available contact details and various professional organisations or advocacy groups.
22
23 228 and encouraged to disseminate the invitation further. Professional contacts of the Executive
24
25 229 Committee experts will be contacted, and events and conferences used to garner participation. Table
26
27 230 1 below references the identified groups as well as contact platforms and organisations. The survey
28
29 231 will also be advertised on social media, and a link provided on the DEFINE study website
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31 232 (www.icr.ac.uk/DEFINestudy).

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Stakeholders	Platforms
<p>Clinical Trials Researchers (including Clinicians/ Clinical Pharmacologists, Trial management staff, Statisticians, Trial methodologists)</p>	<ul style="list-style-type: none"> ● Medical Research Council - National Institute for Health and Care Research Trial Methodology Research Partnership (MRC-NIHR TMRP) (UK) ● UK Clinical Research Collaboration (UKCRC) Network of Registered clinical trial Units ● Targeted conferences or organisations such as the 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 the National Cancer Research Institute (NCRI) annual conference (NCRI), the European Society for Medical Oncology (ESMO) congress, American Society for Clinical Oncology (ASCO), the Experimental Cancer Medicine Centres (ECMC) events, European Centre for Rare Diseases and orphan products (ECRD) ● Sponsors from industry (via organisations such as Pharmaceutical Research and Manufacturers of America (PhRMA) in the US, European Federation of Pharmaceutical Industries and Associations (EFPIA) in Europe) or the Association of British Pharmaceutical Industry (ABPI) ● Publications: Corresponding authors of papers selected for the Methodological review as well as papers identified but not sampled. If necessary, further searches without data limitation may be performed ● Executive Committee members' professional contacts ● Targeted professional social network groups
<p>Regulators</p>	<ul style="list-style-type: none"> ● 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

	<ul style="list-style-type: none"> • Executive Committee members' professional contacts
Ethics Committee / Ethics Committee members	<ul style="list-style-type: none"> • UK Health Research Authority (HRA) (targeting Research Ethics Committees (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 Review Committee Members	<ul style="list-style-type: none"> • Leading medical research journals in publishing clinical trials, and targeted journals will be informed by journals where many phase I trials have been published (identified through Methodological review) • International Committee of Medical Journal Editors (ICMJE) • Abstract review Committee members from leading conferences presenting phase 1 results (see above) • Executive Committee members' professional contacts
Funders / Funding Committee members	<ul style="list-style-type: none"> • Funding panels such as Medical Research Council (MRC), National Institute for Health and care Research (NIHR), Cancer Research UK (CRUK), Blood Cancer UK, Wellcome Trust, Melinda and Bill Gates Foundation, Great Ormond Street Hospital (GOSH) and other selected charities funding phase 1 work as applicable • USA National Institutes of Health (NIH) • Pharmaceutical companies • Executive Committee members' professional contacts
Patients and Public	<ul style="list-style-type: none"> • 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 Clinical Trials Units portfolios) • Executive Committee members' professional contacts

Table 1: Delphi survey stakeholders and methods of access

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3 236 Consent to take part will be sought via the web-based survey application. No personal identifiable
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5 237 data will be collected aside from name and email address. Data gathered will include professional
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7 238 background characteristics, including geographical location, self-identified stakeholder group (as
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9 239 defined in section "Identification of participants" above), and years of experience in clinical research
10 240 and early phase trials. Information on data processing and handling will be provided on the participant
11 241 information sheet via email invitation and website.
12
13 242

15 243 2. Sample size

16 244 As this is a prospective exercise and a multi-faceted survey, the sample size was decided on
17 245 pragmatically, to be both achievable and ensure a meaningful representation of all the stakeholder
18 246 categories. The survey will seek to obtain responses from at least 15 participants in each of the
19 247 identified stakeholder categories, giving an overall target of at least 90 participants. To achieve this,
20 248 as many potential participants as possible will be approached, identified through the authors list from
21 249 the methodological review, approaches from professionals following professional meetings and
22 250 presentations, as well as recommendations from the Executive Committee and Independent Expert
23 251 Panel. The registration and survey response rates, overall and by stakeholder category and country,
24 252 will be monitored by the Executive Committee. If a low rate of intake or response is observed, targeted
25 253 further approaches will be made as appropriate.
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35 255 3. Survey administration

36 256 Potential participants will be invited to take part and nominate additional experts to be contacted by
37 257 the DEFINE team, and various professional or advocacy groups will be approached for dissemination
38 258 amongst their members. Interested stakeholders will be asked to register on the survey website
39 259 before the survey launch. Once registered, consented participants will be alerted to the survey launch
40 260 by an email containing the link to the survey. Each round of the survey will be open for approximately
41 261 4 weeks, and reminders sent weekly during this period. Participants will be allowed to complete a
42 262 round even if they haven't completed the previous one, provided they have registered for the first
43 263 round.
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50 264 4. Pilot

51 265
52 266 The Delphi Survey will be piloted by the members of the Executive Committee, before launching the
53 267 main survey.
54 268 Particular attention will be paid to piloting the Delphi survey to ensure patient and public engagement
55 269 and representation can be optimised. Selected consumer representatives with substantial experience
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3 270 will be approached to take part in the pilot, and their feedback will be sought to ensure the survey is
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5 271 accessible. Should the Delphi survey not allow lay participants to fully contribute due to the
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7 272 complexity, technicality, or number of items to be assessed, a focus group will be organised with
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9 273 Patient and Public Involvement and Engagement (PPIE) experts to identify a core set of SPIRIT-DEFINE
10 274 and CONSORT-DEFINE items relevant to PPI contributors. This core set will be submitted for feedback
11 275 to a wider PPIE audience through a separate process.
12
13 276

15 277 5. Analysis

16 278 The response observed to the initial approaches will be explored in a narrative summary. Following
17 279 each round, the response rate will be calculated based on the number of participants who registered
18 280 and completed the survey. A descriptive summary analysis of the responding population will be
19 281 presented based on the background characteristics data collected. For each item, the distribution of
22 282 scores as well as summary statistics (median, interquartile range, minimum and maximum) will be
23 283 computed and presented. Summary statistics will be presented by the key stakeholder categories
24 284 defined in section "Identification of participants" and overall. Geographical and professional
25 285 background characteristics data may be used to explore the data further.

26 286 Qualitative data from the free text section of the survey will be thematically analysed to identify
27 287 potential new items for inclusion.

28 288 After each round, members of the Executive Committee will discuss the output and any changes
29 289 required. Items scored 1-3 "not important" by at least 80% of the participants may be dropped
30 290 between rounds, subject to confirmation by the Executive Committee. Notes will also be made on any
31 291 feedback relevant to the development of the E&E document.

32 292 Participants will also be presented with the distribution of ratings, their ratings from the previous
33 293 round, as well as feedback on how suggestions and comments from the free text fields were dealt
34 294 with.

35 295 At further rounds, participants will be given the opportunity to change their ratings, and such changes
36 296 will be monitored. The change in participants' ratings between subsequent rounds will be analysed at
37 297 item level and interest will be on participants who moved from one category to another (e.g., from
38 298 not important" to "important but not critical).

39 299 For each reporting item, the distribution of the changes in rating scores and proportion below 15%
40 300 change will be reported.

41 301 To gauge the level of agreement between round 1 and round 2 ratings, the following statistics will be
42 302 calculated and reported for each reporting item with associated 95% confidence intervals ^[32]:

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3 303 a) percentage agreement; percentage of participants with the same rating between rounds
4 304 relative to the total responders to all rounds,

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6 305 b) weighted Cohen's kappa coefficient using absolute error weights ^[33].

7
8 306 The analysis will be performed in R's latest version at the time of analysis ^[34].

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10 307

11 308 6. Stopping Criteria

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13 309 The Executive Committee will decide to stop the Delphi Survey process once consensus and stability
14 310 of ratings have been achieved. It is anticipated that 2 rounds will be sufficient to achieve this objective;
15 311 however, the Committee may proceed to a third round based on the observed level of agreement and
16 312 stability and an assessment of whether a subsequent round is likely to yield any further information.

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18 313

19 314 3. Stage three: Consensus Meeting:

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21 315 The objectives of the Consensus meeting will be to finalise the full list of items to be included in the
22 316 guidance, guided by the information on item importance and level of agreement gleaned during the
23 317 Delphi survey, as well as the structure of the E&E document. The Consensus meeting will follow the
24 318 recommended methodology for such exercise ^[27].

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26 319

27 320 1. Definition of Consensus

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29 321 For the purpose of automatic inclusion into the checklist, items rated 7-9 ("Critically Important") by at
30 322 least 70% of the Delphi survey respondents will be considered as having reached a consensus.

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32 323

33 324 2. Identification of participants

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35 325 The Executive Committee will be responsible for the selection of relevant experts in each of the key
36 326 stakeholder categories (see Table 1) to be invited to participate in the Consensus meeting. Responses
37 327 to the invitations will be tracked to ensure a balanced representation across the key stakeholder
38 328 groups.

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42 330 Checklist items having reached consensus (see section "Definition of Consensus") will be automatically
43 331 recommended for inclusion. Items that did not reach consensus will be discussed for inclusions and/or
44 332 modification based on the overall importance rating achieved in the last round of the Delphi survey.
45 333 Following the discussion, consensus group members will anonymously be given an opportunity to
46 334 make individual decisions about the inclusion of a specific item; "keep", "discard", and "unsure or no
47 335 opinion". A decision to retain a reporting item will be based on achieving at least 50% support from
48 336 group members deciding/wishing to keep the item; however, the Executive committee will retain the

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3 337 prerogative to discuss and make final decisions for low-scoring items or items where a consensus is
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5 338 difficult to achieve. The rationale to guide decisions will be whether the item addresses elements
6
7 339 unique to dose-finding early phase trials and whether they belong in a minimum reporting set of items.
8
9 340 Notes will be taken, and the discussions audio-recorded, with the participants' consent. Particular
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11 341 attention will be paid to any feedback or discussion requiring inclusion in the E&E document.
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13 342 Following the meeting, a summary report will be produced and shared with the meeting attendees as
14
15 343 well as the Delphi survey participants.
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17 344

16 345 **4. Stage four: Development of a reporting guidance and explanatory support document**

18 346 The objectives of this stage are to finalise the SPIRIT-DEFINE and CONSORT-DEFINE guidance and
19
20 347 supporting documentation, including the corresponding explanation and elaboration documents.
21
22 348 After the consensus meeting, the Executive Committee will continue refining the content and wording
23
24 349 of both guidelines, as well as preparing the E&E documents, intended to provide explanations on the
25
26 350 rationale and elaboration of the items, as well as evidence and examples applied in the literature.
27
28 351 Feedback from the Delphi survey and the consensus meeting will be checked for any information
29
30 352 relevant for inclusion in the E&E document.
31
32 353

33 354 Both guidelines will be piloted with real-world examples by a selection of key stakeholders with
34
35 355 expertise in developing and reporting EPDF trials to test their usability and provide insight into issues
36
37 356 that should be addressed in the E&E documents. The Committee will discuss feedback from the pilot
38
39 357 and decide on further modifications, either to the checklist itself or the E&E document.
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41 358

40 359 **5. Data Management and Confidentiality**

42 360 All data generated and collected during the DEFINE study will be handled, processed and stored
43
44 361 according to all applicable data protection legislation. Data collected during the Delphi Survey will be
45
46 362 stored on a MySQL database hosted on a dedicated DelphiManager server hosted by the University of
47
48 363 Liverpool's Data Centre. Following closure of the Delphi survey, data will be downloaded and stored
49
50 364 on secure servers at the Institute of Cancer Research Clinical Trials and Statistical Unit, alongside audio
51
52 365 recordings and transcripts from the Consensus meeting. Access to study data will be restricted to
53
54 366 personnel conducting the analyses, and the data will be stored for a minimum of five years after the
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56 367 end of the study.
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369 6. Patient and Public Involvement

370 The DEFINE Study PPIE lead (AK) was involved in the study design from inception and contributed to
371 the development of the protocol. Additional PPIE representatives from both the oncology and non-
372 oncology disease areas will also be consulted on the checklists' items to ensure the optimum
373 representation of this particular patient group. The DEFINE study also comprises a specific PPIE work
374 package aimed at producing lay publications to chart the development of both the SPIRIT-DEFINE and
375 CONSORT-DEFINE guidelines (see section "Ethics and Dissemination").

376

377 ETHICS AND DISSEMINATION

378 This project has been formally assessed for risk and approved by the Institute of Cancer Research
379 Committee for Clinical Research as the sponsor. The Health Research Authority has been consulted
380 and confirmed Research Ethics Approval is not required.

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

- 383 ● Direct feedback will be provided to the Delphi Survey participants, Consensus meeting
384 contributors and the stakeholder groups identified in Table 1.
- 385 ● The guidelines will be accessible via the CONSORT and EQUATOR network website, as well as
386 on the DEFINE study website, which will also be kept updated throughout the project.
- 387 ● Dissemination at specific UK and international study groups that run phase I trials, such as the
388 UK National Cancer Studies Groups, as well as to funders for early phase trials (including MRC,
389 CRUK, NIHR Biomedical Research Centres, ECMC and NCI), and industry via The Association of
390 British Pharmaceutical Industry (ABPI) and pharma partners' networks.
- 391 ● Maximising publications in high-impact scientific journals.
- 392 ● Presentation at meetings of UK Clinical Research Collaboration (UKCRC) Clinical Trials Unit,
393 UKCRC Statistics Operational Group and NIHR Early Phase Statistics Group; national and
394 international methodological conferences (e.g., International Clinical Trials and Methodology
395 Conference, Society of Clinical Trials or International Society of Clinical Biostatistics), and
396 pharmaceutical conferences/meetings via our industry partners (e.g., PSI, EFPSI, DIA) and
397 clinical conferences (e.g., NCRI, ESMO, ASCO, ECRD).
- 398 ● Practical Dissemination workshops will be organised, one specifically aimed at journal editors
399 to promote the use of the guideline and encourage endorsement.
- 400 ● Patient and public engagement will be sought via the publication of PPI lay summary papers,
401 including the production of a lay study report template, liaison with patient groups (including

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3 402 the Royal Marsden Patients and Carers Review Panel and the Independent Cancer Patient's
4 Voice), as well as dissemination at local and national PPI events.

5 403
6 404 ● Broader communication with the public will also be pursued via the Institute of Cancer
7 Research's website and social media, including blogs, posts on Twitter, Facebook, and
8 405 LinkedIn, press releases and potentially through leadership pieces on trials reporting in the
9 406 media.
10 407
11 408

12 409 **AUTHORS' CONTRIBUTIONS**

13 410 CY and CJW conceived the idea. CY, CJW, MD, TJ, AM, AK, JE, SML, SH and JdB obtained funding for
14 411 CONSORT-DEFINE. AE, OS, MD, CJW, TJ, AM, AK, JE, SML, SH, AB, RL, KR and AWC, JdB and CY
15 412 contributed to the design of the study. AE, OS and CY wrote the first draft of the manuscript. All
16 413 authors contributed to the refinement of the study methods and critical revision of the manuscript.
17 414 All authors read and approved the final version of the manuscript.
18 415

19 416 **FUNDING STATEMENT**

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27 424 no involvement in the study design, collection, analysis, interpretation of findings, and reporting.
28 425 However, research outputs will be published in line with the funders' publication policy
29 426 requirements. SPIRIT-DEFINE part did not receive any external funding. For the purpose of open
30 427 access, the author has applied a Creative Commons Attribution (CC BY) licence to any Author
31 428 Accepted Manuscript version arising from this submission.
32 429

33 430 **COMPETING INTERESTS**

34 431 Professor Johann de Bono has served on advisory boards and received fees from many companies,
35 432 including Amgen, Astra Zeneca, Astellas, Bayer, Biocel Therapeutics, Boehringer Ingelheim,
36 433 Cellcentric, Daiichi, Eisai, Genentech/Roche, Genmab, GSK, Harpoon, ImCheck Therapeutics, Janssen,
37 434 Merck Serono, Merck Sharp & Dohme, Menarini/Silicon Biosystems, Orion, Pfizer, Qiagen, Sanofi
38 435 Aventis, Sierra Oncology, Taiho, Terumo, Vertex Pharmaceuticals.
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3 437 Professor Johann de Bono is an employee of The Institute of Cancer Research, which has received
4
5 438 funding or other support for his research work from AZ, Astellas, Bayer, Cellcentric, Daiichi,
6
7 439 Genentech, Genmab, GSK, Janssen, Merck Serono, MSD, Menarini/Silicon Biosystems, Orion, Sanofi
8
9 440 Aventis, Sierra Oncology, Taiho, Pfizer, Vertex, and which has a commercial interest in abiraterone,
10
11 441 PARP inhibition in DNA repair defective cancers and PI3K/AKT pathway inhibitors (no personal
12
13 442 income).

14 443 Professor Johann de Bono was named as an inventor with no financial interest in Patent No. 8,822,438
15
16 444 submitted by Janssen that covers the use of abiraterone acetate with corticosteroids. He has been the
17
18 445 CI/PI of many industry-sponsored clinical trials.

19 446 Professor Johann de Bono is a National Institute for Health Research (NIHR) Senior Investigator. The
20
21 447 views expressed in this article are those of the author(s) and not necessarily those of the NHS, the
22
23 448 NIHR, or the Department of Health.

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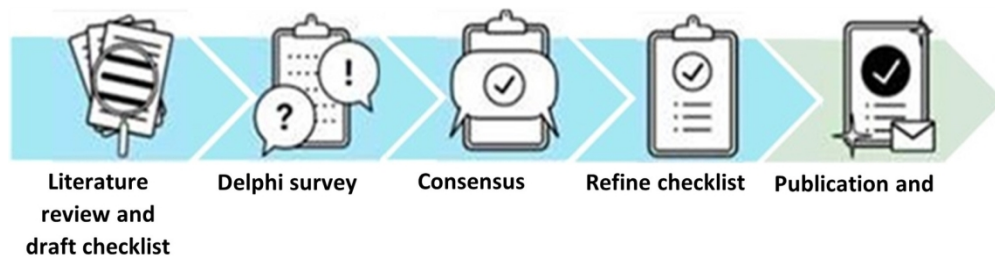


Figure 1. Project overview for the development of SPIRIT-DEFINE and CONSORT-DEFINE guidelines.

156x44mm (300 x 300 DPI)



Figure 2. SPIRIT-DEFINE candidate item generation development process.

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