**SPIRIT-DEFINE AND CONSORT-DEFINE**

**Feedback on Round One of Delphi Survey**

In Round One of the DEFINE Delphi survey we received 44 suggestions regarding adding new items, 17 general comments and 290 comments on specific items.

**Addition of new items**

The DEFINE Executive Committee carefully considered all suggestions regarding adding new items into the checklists and decided to add one new item (n = 1 item) into Round Two: “Access (or link to) code/functions used for simulation studies”. Other suggested items were either already covered by existing items or the main SPIRIT 2013/CONSORT 2010 statements (n = 14 items), or are not specific for early-phase dose-finding trials and therefore more applicable to updates to the main SPIRIT/CONSORT statements (n = 14 items), or can be addressed as modification of the existing items (n = 12 items), or were rather general comments (n = 3 items).

**Comments on specific items**

All 290 comments on items were reviewed internally and with the DEFINE Executive Committee. In total, we modified 29 items, either in the item wording or within the helping text. In the Delphi survey, such items are marked with a \*-sign.

Here, we would like to highlight those items that would benefit from further clarification and are most commented, and our feedback.

**Patient and Public Involvement (PPI)**. “Patient advocate” is the more commonly used term rather than PPI in some countries (e.g., USA). We have modified this item and the helping text for clarity. There was a suggestion that patient partners involvement may not be on the treatment itself but on the ethical side especially on the burden to the participants, the administration, etc.

**Lay summary**. We have reworded this item to improve clarity in Round Two: “Lay summary of the trial synopsis” for SPIRIT-DEFINE and “Lay summary of the results” for CONSORT-DEFINE.

**Estimand Framework**. We are aware that clinical trials are adopting the Estimand Framework following the ICH E9(R1) addendum and have considered this when we generated our candidate items. As the Estimand Framework is not specific for dose-finding trials, the inclusion of this framework is more applicable to updates to the main SPIRIT/CONSORT statements. We have referred this to the main SPIRIT/CONSORT group to consider in their next update. We have, however, purposefully ensured our existing candidate items include all information on attributes that are required to utilise the Estimand Framework, and will provide illustrative examples in our guidance within the Explanation and Elaboration (E&E) document. It is our intention to update SPIRIT/CONSORT-DEFINE guidelines once the main guidance is updated.

**Confidentiality**. There was a very helpful comment that in rare disease trials, individuals may be easily identifiable if baseline data are summarised per dose per group. Thus, we modified this item and the accompanying help text to reflect this.

**Skipping of dose level**. This item was modified for clarity that it is only applicable in settings where there are pre-defined dose levels, where doses could be skipped, e.g., from dose level 3 to 5.

**Dose transition pathways (DTP)**. This can take the form of a flow table or a flow diagram to map out in advance how a proposed design would recommend doses (escalate, de-escalate, stay or stop) based on participants’ key outcomes (e.g., if we observe no significant adverse events in 2 participants, we will escalate to the next higher dose but if both participants experience significant adverse events, we will de-escalate etc). Depending on the design used, it may sometimes only be feasible to project in advance the first few patients/cohorts.

**General Comments**

* Three (1.5%) respondents shared their concerns that several items are oncology-focused and cannot be utilised for non-oncology or healthy volunteers trials. Based on the feedback, we have reworded a few items to ensure we improved the applicability to those settings. Our scope covers all early-phase trials with dose escalation or de-escalation components with safety being a key objective (see below). It includes dose-escalation oncology trials, as well as non-oncology and healthy volunteers trials with typical randomised, placebo-controlled designs involving single ascending doses, multiple ascending doses, with or without crossover. If you are involved in healthy volunteer trials or non-oncology trials and have suggestions on how wording of any items can be further improved to aid the applicability to those settings, please get in touch via define-icrctsu@icr.ac.uk or leave your comments/suggestions within Round Two of the survey.

**SPIRIT-DEFINE and CONSORT-DEFINE scope**

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.
* Another general comment: “oncology phase 1 trials should not define a phase 2 dose, but only a range of doses”. We have intentionally kept our items broad to allow for the flexibility to define a dose or a range of doses for further evaluation, depending on the trial’s objectives.

For additional information, please contact the Principal Investigator Professor Christina Yap (Christina.Yap@icr.ac.uk) or Project Manager Ms Aude Espinasse (DEFINE-icrctsu@icr.ac.uk).

We would like to take this opportunity to thank everyone again who participated, and who suggested amendments and additional items during Round One. We sincerely appreciate your contribution.

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|  | **Thank you** |

Yours faithfully,

The DEFINE Team