

Final Report – Efficient / innovative delivery of NIHR research – 2019 Projects

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Title of Project

Development of Guidance for Statistical Analysis Plans for Early Phase Clinical Trials

Abstract

Guidance for the content of statistical analysis plans (SAPs) for clinical trials was published in 2017 and focused on late phase, randomised controlled trials. The existing guidelines have been extended to broaden their applicability to early phase (phase I and non-randomised phase II) clinical trials. This extension is based on existing guidance; a comprehensive search to identify existing published protocols, SAPs, and SAP guidance; a survey of clinical trial funders and regulators; a survey of current practice by statisticians within Clinical Trials Units registered with the UK Clinical Research Collaboration; a critical appraisal and expert review meeting; and a pilot of the proposed guidelines. Of 55 original items in the current SAP content guidance, 30 have remained unchanged, 25 have been modified, and a further 11 new items have been proposed to ensure comprehensive and appropriate guidance for early phase clinical trials. The final paper is published here <https://doi.org/10.1136/bmj-2021-068177>

Introduction

This project details guidelines for the content of Statistical Analysis Plans (SAPs) for early phase clinical trials, presenting an extension to “Guidelines for the Content of Statistical Analysis Plans in Clinical Trials” by Gamble et al.(1)

Early phase (phase I and non-randomised phase II) clinical trials aim to determine the safety and initial indicators of efficacy of interventions prior to conducting potentially practice-changing phase III clinical trials. The undertaking of definitive late phase clinical trials is often a lengthy and costly process since these clinical trials ensure full-scale evaluation of the interventions efficacy and may involve analysis of its cost-effectiveness. Definitive clinical trials are predicated on accurate and robust conclusions from early phase clinical trials, with flaws in design and analysis potentially a reason for interventions failing to demonstrate a benefit in phase III clinical trials. Consequently, the design, conduct, and analysis of early phase clinical trials does not solely impact that specific study. Conclusions from early phase clinical trials have implications for all related subsequent clinical trials, as such these studies must be performed to the highest standards of rigour and quality, to ensure correct decisions are taken forward.

Historically, phase I clinical trials were conducted without significant statistical involvement and conformed to rule-based designs, for example, the 3+3 design, to determine the maximum tolerated dose (2,3). Recent recommendations propose that phase I studies should employ model-based designs (4), such as the continual reassessment method (CRM) (5–8), or model assisted designs, such as a modified toxicity probability interval (mTPI)

design (9). In addition, randomised dose finding phase I clinical trials (such as those which randomise to attain the optimal doses or dose schedules once safety has been assured (10)) and single arm phase II designs (11) are being used, all of which require significant statistical input before, during and at the analysis stage of the clinical trial. The use of these more statistically involved clinical trial designs has been accelerated by oncology clinical trials where examples of their use is more prevalent (12) however examples are emerging across other disease areas (13).

The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E9 guidelines state that ‘although the early phases of drug development consist mainly of clinical trials that are exploratory in nature, statistical principles are also relevant’ (14). As early phase clinical trials utilise statistical model-based designs, the requirement for good quality SAPs, including additional statistical parameters and progression criteria to later phase research, becomes an even greater necessity (15,16), with the trial statistician playing a key role in designing, and undertaking analysis of early phase clinical trials.

Guidelines for the content of SAPs were published in 2017 (1) and highlighted the need for a detailed SAP to improve transparency, clinical trial quality, and robustness. These guidelines were developed with the primary intention of being applicable to the analyses of later-phase randomised controlled trials (RCTs) and acknowledged that despite some recommendations being transferable, specific consideration and guidance are needed for early phase clinical trials. These guidelines were discussed at a UK Clinical Research Collaboration (UKCRC) Registered Clinical Trials Unit (CTU) Network Statisticians’ Operational Group meeting in April 2018, confirming that specific consideration and guidance for early phase clinical trials was an area of unmet need. This was based on the fact that early phase clinical trials are often not randomised, often use adaptive designs, and often otherwise have statistical considerations and requirements that are different in character from those of later-phase, RCTs. This discussion led to this extension of those 2017 guidelines to address the needs and considerations of SAPs for early phase clinical trials. Given the drug development pathway, early phase clinical trials are more prevalent than late phase (17), highlighting the importance and impact of this guidance.

As part of this project, we developed, disseminated, and published an extension to published guidelines for SAP content to broaden their applicability to early phase clinical trials. These recommendations are intended to guide the authoring of SAPs for all early phase studies, irrespective of the study design used (rule-based, model-based, model-assisted, or randomised phase I trials; or single arm phase II designs). Beyond the scope of this extension are randomised phase II trials given that they are covered by the existing guidelines.

Methods

A literature review was undertaken to identify peer-reviewed publications of applicable guidelines, and example clinical trial protocols and SAPs. The Enhancing the QUALity and Transparency Of health Research (EQUATOR) network repository was searched to identify

existing guidance; PubMed was searched to identify published SAPs; and a PubMed search of early phase (encompassing phase I and phase II) clinical trial protocols. The search of protocols was undertaken to capture the statistical detail contained within these documents, as SAPs may not always have been written for some early phase clinical trials.

The same clinical trial funders and regulators contacted during the original SAP guidance development (1) were contacted via email in January 2020. Funders were initially contacted to gauge whether they fund early phase clinical trials. Surveys were sent to all regulators and those organisations who confirmed the scope of their funding considerations would extend to early phase clinical trials. Consultation with clinical trial funders led to the identification of two additional dedicated early phase clinical trial funders who were also approached. The goal of these surveys was to ascertain funding and regulatory requirements of design, analysis and SAP contents for early phase clinical trials.

Additionally, we surveyed the CTUs in the UKCRC network. The survey was developed based on the original SAP guidance survey (1) and tailored to early phase clinical trials. The aim was to identify CTUs conducting early phase clinical trials and the current practice within those units for developing SAPs. A senior statistician at each CTU was asked to complete the survey to reflect practices and majority opinion within the statistician's CTU in May 2020.

Example SAPs shared by CTUs conducting early phase clinical trials were collated and reviewed for content to establish the current level of detail provided. To ensure as much coverage for study design types and disease areas, examples were sought from multiple scenarios, including design based (e.g., rule-based, model-based, or single-arm phase II) and disease based (oncology or non-oncology).

An expert panel of 21 statisticians from regulatory agencies, pharmaceutical companies, and academic and NHS CTUs was convened. After the initial draft of the guidelines had been produced, this panel was responsible for reviewing and critically appraising the guidelines. An international expert review meeting was held on the 26th October 2020 with contribution and attendance from the expert review meeting. Following incorporation of comments made during the expert review meeting, the guidance was re-circulated to the experts involved in the critical appraisal and review meeting for piloting over the period December 2020 to March 2021 at 6 UK CTUs on new and existing early phase trials. This piloting aimed to ensure the guidance produced was fit for purpose, appropriate to the needs of statisticians authoring SAPs, and to identify any items requiring further clarification.

Results and Conclusion

An extension to existing SAP guidelines have been developed to ensure guidance was apposite to early phase trials. These has been made publicly available and supports clinical trial statisticians, trialists and peer reviewers to facilitate an improvement in the quality of analysis, the reproducibility of methods and results, and the robustness of conclusions.

Of the original 55 items proposed in Gamble *et al.* (1), 30 items have remained unchanged, 25 have been modified to better reflect early phase trials, and a further 11 new items have been proposed. Significant alterations include:

- Increased details regarding trial design methodology, and where appropriate model choice.
- Update of outcome definitions to estimands following the wider adoption of ICH E9 (R1).
- Inclusion of simulation reports to justify trial design or sample size.
- Inclusion of code required for novel methodology.
- Inclusion of dose transition pathways, where appropriate.
- Amendments to wording to be more neutral to both frequentist and Bayesian methodology, to reflect that many early phase trials designs are underpinned by Bayesian methods.

Some of the more minor amendments include updates to extended descriptions to ensure pertinence to early phase trials.

An elaboration of each item is included in the appendix to the primary publication with illustrative examples covering various early phase trial designs and therapeutic areas also provided.

Dissemination

The primary output of this project is a table highlighting the proposed alterations to SAP content for early phase trial. This table, along with further details regarding methods and the aforementioned appendix (including extended descriptions and illustrative examples) has been published in the BMJ and is publicly available at <https://doi.org/10.1136/bmj-2021-068177>.

Moreover, this work was presented to the CTU network through a presentation given at the UK CRC statistics group meeting (in May 2021), presented to the wider statistical community at the Society for Clinical Trials (SCT) annual conference (also May 2021), at the NIHR Early Phase Statistics Group Annual Meeting in October 2021, and in a dedicated Trials Methodology Research Partnership webinar in February 2022.

A submission to the International Clinical Trials Methodology Conference (ICTMC) 2022 is planned. Depending on appetite and feedback from publication, a standalone workshop may be planned.

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Conflict of interest declaration

None declared.