

## **Project R44: Development of Guidance for Statistical Analysis Plans for Clinical Trials**

### **Original objectives:**

Objective 1: Review Guidance/ recommendations from national and international regulatory/professional/ funding bodies

- The HTM funded project on development of a Trial Steering Committee Terms of Reference conducted a survey of the UKCRC registered CTUs and has established a list of 69 organisations (national and international, government, charitable, industry) funding RCTs. These organisations will be contacted to ascertain requirements/guidance.

The following regulatory authorities will be contacted: MHRA, FDA, EMA

Achieved: From the list of 69 organisations, 39 organisations were eligible having been suggested by more than one CTU. The organisations were contacted and we received responses from 28 (72%) which confirmed an absence of guidance with only a few organisations specifying reference to ICH E9.

- Peer reviewed publications of trial specific SAP documents including evidence for different types and phases of trial

A pubmed search on 'statistical analysis plan' restricted to titles identified 20 relevant publications. Statistical analysis plans included within HTA monographs will also be identified.

Achieved: 38 standalone publications of SAPs were identified in peer-reviewed journals with the first being published in 2009. The majority of the SAPs were published in Trials and Critical Care and Resuscitation. Around 50% of the published SAPs were published in 2014.

There were 155 HTA monographs identified in total relating to RCTS including parallel group designs, feasibility/pilot studies and cluster-randomised studies. There were only 10.3% (16/155) HTA monographs that included SAPs with 25.2% (39/155) monographs mentioning SAP but not including it within. 62.5% (10/16) of the HTA monographs that included SAPs were published between 2013 and 2014.

- Guidance documents covering items relevant to statistical analysis plans will be identified via a search of the EQUATOR database.

Achieved: ICH E9, the SPIRIT guidelines and the CONSORT guidelines cover items that were found to be of relevance to SAPs.

Objective 2: Survey of practice

- Survey of current practice through engagement with UKCRC registered CTUs. The survey will be targeted at the statistical representatives from each CTU who attend the UKCRC Statistics Operational Group meetings which take place every six to nine months. At the July 2013 meeting this project was raised with attendees and there was wide spread agreement to take part. The survey will identify current practice; obtain unpublished examples of SAPs, SOPs for SAPs, and other related documents for a mapping exercise. As part of the mapping exercise the researcher for the project will travel to up to 8 CTUs identified with pre-planned questions/ requests to lead discussion and develop a greater understanding of the reasons behind divergent processes and the specific implications for statistical resources. The results of this exercise will be presented at the UKCRC Registered CTUs Statistics Group meeting.

**Achieved:** The survey was developed and piloted prior to being distributed across the registered CTU statisticians network. A 100% response rate was achieved. In response to the survey we received 20 unpublished SAPs and 25 SAP SOPs. The project was tabled at two UKCRC registered CTU statisticians meetings which provided opportunity for wide spread discussions across CTUs removing the need to travel to individual CTUs. Survey results and later those from the Delphi were presented with open discussion around differences in practice. The main factors highlighted were: how established the CTU was as practices develop and tighten over time and inspections; statistical resources as some CTUs do not have multiple statisticians at various levels; time with most agreeing that time frames for SAP development were pushed back due to other workloads.

### Objective 3: Development of Guidance

- A Delphi survey will be conducted. The first round of the Delphi will be based on the outputs of objectives 1 and 2. Participants in the Delphi will include senior statisticians from UKCRC registered CTUs, contributors to CONSORT and SPIRIT guidelines, journal editors publishing statistical analysis plans, peer reviewers, and clinical trial regulators.

Following the Delphi survey, which will consist of a maximum of three rounds, the co-applicants will meet to review the results of the Delphi survey and determine the structure of a face-to-face consensus meeting.

The result will be a comprehensive guidance document on the suggested content and format of statistical analysis plans developed by the writing committee.

**Achieved:** The Delphi survey was undertaken. The Delphi had two rounds followed by an expert panel consensus meeting.

The first round of the Delphi was sent to 73 participants with 56 responding. In the second round the Delphi was sent to 56 participants with 54 responding. To encourage response to the second round entry, a prize draw was offered to those responding within 10 days.

The consensus meeting was convened in May. The expert panel included representation from the MHRA, senior statisticians from a US based pharmaceutical company, journal editors, and experienced statisticians in UKCRC registered CTUs. Following this meeting the Guidance was drafted.

- A structured template will be developed to aid consistent application of the guidance together with an explanatory document. The guidance will be aimed at later phase trials but will include consideration of its application to early phase and other types of studies.

**Achieved:** The development of a template was discussed at the UKCRC meetings. While some statisticians thought this would be helpful a majority felt that this would not be beneficial as they were bound to the templates they had developed within their CTUs.

**Next steps:** Rather than develop a further template a resource will be made available consisting of examples of SAPs. This will include published and currently unpublished SAPs (with permissions) which will be made available online to be used/considered by CTUs when developing or reviewing their templates for structure/format.

- A 'Points to consider' document will be developed for a SOP for SAPs. This will bring together existing documents from ICH, PSI, and MRC toolkit and the mapping exercise of SAP SOPs undertaken in objective 2.

**Achieved:**

25 SAP SOPs were returned as part of the survey. Relevant documents have been identified as listed above.

**Next steps:** The 'Points to consider' document will be completed following final approval of the SAP guidance document.

#### Objective 4: Critical review

It is important that the guidance produced is acceptable to statisticians within CTUs responsible for the development of SAPs. The UKCRC registered CTU statisticians meeting has highlighted this as an important area and some members have already provided examples of SAPs. We will consult all Statisticians on the UKCRC CTU Statisticians group, as well as those Statisticians nominated to attend the meetings, to gain views on the acceptability of the guidance and incorporate feedback prior to piloting the guidance.

**Achieved:** The Guidance document was tabled at the April 2015 UKCRC registered CTU statisticians meeting. 48 statisticians from across 39 registered CTUs attended. Attendees were split into groups to review the document and then to feedback. To ensure that each section of the document was critically reviewed each group were given a priority category to review and then to move on to other sections time allowing. In addition attendees were encouraged to discuss the draft with other statisticians in their CTU and to feedback additional comments/amendments by email. A further 12 sets of comments were received.

The Guidance was amended following critical review and is now with the expert panel who attended the Delphi consensus meeting. This stage of critical review is additional to that specified in the grant but will add to its value. Comments have been requested by 31<sup>st</sup> Aug 2015.

#### Objective 5: Piloting of the guidance

To pilot the SAP guidance we will identify a minimum of five clinical trials covering a range of conditions. The feedback from the experiences of applying the guidance will be incorporated prior to its finalisation.

#### **Achieved:**

Piloting has been split in to two stages. Stage one, undertaken after the critical review of the Guidance by registered CTU statisticians and stage 2 which is review by the expert panel convened for the Delphi consensus meeting. Stage one is complete with the Guidance piloted on two RCTs.

#### **Next steps:**

Stage two will be completed following incorporation of feedback from the expert panel. A total of 8 statisticians have agreed to pilot the guidance.

#### **Publications:**

There are three draft publications based on:

- 1) survey of current practice
- 2) Delphi survey
- 3) Guidance document

1) and 2) are under review within the team and may be joined as a single publication.

3) Will be a standalone publication and the current draft will be updated following comments from the expert panel and pilot.