

## **N68 Clinical trials in small populations: methodological challenges and solutions**

### Investigators

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### Original Aims

The original aim of this project was to develop and host a two-day training and dissemination meeting with the following objectives:

- (i) Provide hands-on training in current methods relevant to trials in small populations to applied statisticians involved with such studies;
- (ii) Develop collaborative links between the CTU Network and the HTMR Network with a view to supporting future trials in small populations;
- (iii) Disseminate state-of-the-art statistical methods for trials in small populations;
- (iv) Bring together statisticians, patient representatives and regulators to set priorities for future methodological research.

### What was achieved

The two-day meeting was developed as planned and was held 30<sup>th</sup> November - 1<sup>st</sup> December 2015 at the Royal Statistical Society, London. Please see the Supplementary Material for agendas for both days. The first day of the meeting (referred to as the Groundwork Training Workshop) comprised a mixture of tutorials on state-of-the-art methods relevant for trials in small populations and six case-studies. The tutorials covered Bayesian methods and adaptive designs (outcome adaptive randomisation, group sequential designs, multi-arm multi-stage designs). In preparation for the meeting, a systematic review of software available for incorporating historical data into the design and interpretation of new clinical trials was also performed. We had planned and prepared for hands-on practical sessions, but on the day had to omit these due to time constraints. Despite this, hard copies of the training materials and solutions (including the software review) were made available to the workshop attendees on the day; electronic versions have since been made publicly available on the meeting website. Case-studies were contributed by statisticians and scientists from clinical trials units from the UK, Norway and Canada. The workshop was fully subscribed with 46 in attendance. Participants were drawn from academia (including members of the EU FP7-funded projects IDeAl and Asterix); public sector research institutes and clinical trials units (from UK, EU, Canada); the pharmaceutical industry and regulators.

The second day of the meeting (referred to as the Forwards-Looking Forum) comprised a series of 11 invited presentations from patient representatives and leading researchers. Talks were contributed by leaders of the EU FP7-funded projects (InSPiRe, IDeAl and Asterix), members of the MRC Hubs for Trials Methodology Research, the pharmaceutical industry and a patient representative. Presentations focused on novel methods for designing and interpreting trials in small populations.

Sixty people attended the meeting, again representing a broad range of stakeholders. In addition to the presentations, six posters were exhibited during the coffee and lunch breaks by early career researchers.

Six early career researchers were awarded travel bursaries to attend the two-day meeting. Four bursaries of £250 were awarded to statisticians from the UK; one bursary of £500 was awarded to a researcher from Germany; and one bursary of £700 was awarded to a statistician from Canada. The scholarship recipients either presented a case-study at the Groundwork Training Workshop or a poster at the Forwards-Looking Forum.

Feedback obtained immediately after both days of the meeting was positive and is summarised in the Appendix.

#### Outputs from the workshop:

- (i) A website for the workshop has been developed where the meeting programmes, training materials (tutorial slides; problem sheets; solutions; example code); invited presentations and posters have been archived. Audio recordings of a number of the invited presentations from the Forwards-Looking Forum have also been made available. The website is available at: <http://www.lancaster.ac.uk/mathsmall-trials/>.
- (ii) A postdoctoral researcher conducted a systematic review of software available for incorporating historical data into the design and interpretation of new clinical trials. The findings of this review were distributed at the Groundwork Training Workshop and an electronic copy has been made available on the meeting website: <http://www.lancaster.ac.uk/mathsmall-trials/day-1/>

The original funding application stated that the organising committee would explore whether it could prepare a commentary piece or a short paper summarising discussions from both days of the meeting. However, a number of reviews of innovative approaches to study and treat rare diseases have recently appeared in the literature. For example, see the series of 14 articles on this topic which appeared in Issue 3 supplement of Volume 29 of the *Journal of General Internal Medicine*. Discussion and review papers have recently appeared by Korn et al. (*Science Translational Medicine* 2013; 5:178sr3), O'Connor and Hemmings (*Expert Opinion on Orphan Drugs* 2014;2:765), the IRDiRC Scientific Secretariat ([http://www.irdirc.org/wp-content/uploads/2016/01/SPCT\\_DraftDocument.pdf](http://www.irdirc.org/wp-content/uploads/2016/01/SPCT_DraftDocument.pdf)) and Gange et al. (*BMJ* 2014;349:g6802). We do not believe that there is space for another commentary paper on approaches for studying rare diseases. Therefore, we do not intend to pursue this activity.

#### Impact of the workshop:

- (i) Following the workshop, the workshop organisers received a request for advice on the design of a trial in Duchenne Muscular Dystrophy from researchers at University of Sheffield's Clinical Trials Research Unit. This input will be included in a HTA monograph on the Hydrotherapy for Duchenne Muscular Dystrophy trial which is currently in preparation.
- (ii) In terms of establishing a dialogue between the HTMR Network and other stakeholders, on the basis of the meeting one of organising committee has since been invited to be involved in delivering a PSI (Statisticians in the Pharmaceutical Industry) webinar on statistical issues pertaining to rare diseases/orphan drugs.

Next steps over the coming 12 months:

- (i) We will follow up with the meeting participants in December 2016 to ask them to complete a follow-on questionnaire. This will trace:
  - whether and how they used the training material and software provided at the Groundwork Training Workshop
  - whether and how they have used the methods from both days in their working practices;
  - whether the meeting lead to subsequent collaborations or other types of interactions with other meeting delegates.
- (ii) The co-applicants will track collaborations on clinical trials and methodological projects that may have arisen/may arise from the meeting.

## **Appendix: Summary of feedback obtained immediately after the meeting**

### Day 1

Out of a total of 17 respondents, 94% said the workshop met expectations, 65% said that they planned to use the methods covered in their own work, and 88% assessed the tutorials as being of 'excellent' or 'good' quality.

### Day 2

Out of a total of 15 respondents, 93% said the meeting met expectations; the most useful aspects of the meeting were felt to be the opportunity for networking and the diversity of the presentations given; 73% intended to use the methods they had heard about in their future work.