Response in respect of the ICH E17 Draft Guidelines on "Multi-Regional Clinical Trials"

December 2016

Below are the comments submitted in response to the consultation on the ICH E17 Draft Guidelines on "Multi-Regional Clinical Trials on behalf of the following UKCRC Registered Clinical Trials Units:

Barts & the London Pragmatic

Barts Clinical Trials Unit

Cambridge Clinical Trials Unit

Centre for Healthcare Randomised Trials (CHaRT)

Clinical Trials Research Centre, University of Liverpool

Edinburgh Clinical Trials Unit

Imperial Clinical Trials Unit

Leeds Clinical Trials Unit

Manchester Academic Health Science Centre- Trial Coordination Unit

Norwich Clinical Trials Unit

Nottingham Clinical Trials Unit

PRIMENT Clinical Trials Unit

Royal Marsden

Sheffield Clinical Trials Research Unit

Swansea Trials Unit

1. Sample size. In section 1.4, paragraph 4 (and also line 386), it is stated that 'the sample size allocation to regions or pooled regions should be determined such that clinically meaningful differences in treatment effect among regions can be described without substantially increasing the sample size requirements based on the primary hypothesis'. Around line 397, several suggestions are given, but none seem to be met with much enthusiasm. Is it actually possible to detect clinically meaningful differences in treatment effect among regions and keep the sample size the same? Doesn't the statement on line 521 about treatment by region interactions contradict the desire to investigate regional differences without increasing sample size?

2. Section 2.2.4, line 295 makes a statement about regulatory approvals that are based on different primary endpoints at different regional authorities not needing a multiplicity adjustment. This doesn't follow on from any other statement about multiplicity adjustment, and it seems something is missing. When are multiplicity adjustments necessary?

3. On line 485, it is stated that for blinded studies, the statistical analysis plan (SAP) should be finalised prior to unblinding the treatment assignments (at interim or final report). This should be clarified – the SAP for the final analysis can presumably be finalised after an interim analysis, as long as it is finalised by people who are not unblinded. The statement assumes that there is a single point of unblinding everyone involved, but in reality different groups can be unblinded at different times, allowing for greater flexibility. In academic trials the Data Monitoring Committee are usually unblinded part way through the study, but the trial team remain blind.

4. Line 498 describes minimising the need for data driven investigations. This statement is too soft. Data driven investigations should absolutely not be encouraged.