Reviewer's report

Title: Adaptive Clinical Trial Designs for European Marketing Authorisation - A Survey of Scientific Advice Letters at the European Medicines Agency

Version: 1 Date: 6 May 2014

Reviewer: Martin Jenkins

Reviewer's report:

This is a valuable article which compiles information not easily available to researchers and would be of interest to those seeking scientific advice from the EMA / CHMP.

Whilst there are no major errors as such with article as it stands I do not believe that the dataset which has been assembled has been made full use of and so I make the following suggestions. I have described some as compulsory, but in essence the method of addressing them is discretionary to the authors.

Major Compulsory Revisions

1) The abstract could include a sentence at the end to summarise the findings of the manuscript and what can be learnt from it rather than merely saying that opinion was generally positive. For example the fact that type I error rate control, bias and justification of the design are common points for feedback from the CHMP despite their description in guidance documents. This is worth highlighting.

2) It would be extremely illuminating to cross-tabulate the characteristics of the proposed adaptive designs included in these instances of scientific advice with the responses given. Currently the two are summarised separately, but are not linked so there is no opportunity to appreciate which types of adaptation are commonly accepted and which are more likely to be subject to concerns. This feels like an obvious question which the current draft of the manuscript leaves unanswered. In particular how many of the proposals in table 1 which were accepted / conditionally accepted / not accepted related to each type of adaptation or with early stopping? How often did these types of adaptation have issues regarding type I error rate control?

3) How often were stopping for futility, stopping for efficacy and the other types of adaptations combined together? This would be a fuller way to characterise the type of adaptation and this could potentially be combined with the above investigation. I appreciate limits need to be set on cross-tabulations if frequencies become too small however.

4) In a related point, on page 9 and in table 2 the issues raised with a number of proposals are described, but it isn't clear whether these issues relate to non-acceptance or to concerns raised in conditionally acceptance. The same
could be said for type I error rate control in table 1.

Minor Essential Revisions

5) Where specific methods are mentioned in the case studies it would be informative to include references. For example the method used to combine data before and after interim analyses in case study 1 or the closure principle and Dunnett test procedure.

Discretionary Revisions

6) Page 8, line 13 - Another question, related to the major points above, which could be answered is how many of the proposals with single pivotal studies related to orphan indications or rare diseases? This explanation is hinted at, but not supported by numbers.

7) Page 3, line 11 - Early interaction with regulators is not just important because of the limited experience available with adaptive designs. It is also important because many of the designs proposed will be non-standard and bespoke to the particular application being considered. Even in the future when the methodology is more well-practiced seeking scientific advice would still be sensible so that the specifics of the particular scenario in question can be considered. This could be mentioned here.

8) Figure 1 - The means used to project the number of submissions in 2012 could be described.

9) Page 8, line 11 - The authors may wish to comment on the fact that almost all examples of scientific advice related to confirmatory trials and whether this is surprising. This is likely a reflection of the stages at which risk lies more with the sponsor rather than the regulator rather than being an indication that adaptive designs are not used at earlier stages (not the the authors suggest this). Reference [16] found adaptive designs to be commonly used in early phases and that innovative methods were more often used compared to confirmatory trials. Would the authors suggest that there is value in consultation on adaptive designs used in earlier stages?

10) Page 8, line 24-28 - There are some trials mentioned where unblinded interim analyses are not performed by an external independent group. The situations in which this is deemed to be appropriate could be discussed. Incidentally a distinction could be drawn between instances where the sponsor is or isn't unblinded so as to explain why such a high proportion (80%) of studies include unblinded analyses. Some would consider unblinding to refer to the sponsor rather than a DSMB. I also note that in case study 3 blinded data is discussed for an open label trial.

11) Case studies 1 and 3 end in statements that leave the reader wondering whether these issues are of general concern to the CHMP. Perhaps more description could be given.
12) The issue of justification for the use of adaptive designs is mentioned in several places, including the discussion, as well as the efficiency and feasibility of such designs. It may be worth considering a discussion on whether this is the sponsor's risk or regulatory risk.

13) It may not be possible, but information on how many of the proposals were actually conducted would be interesting.

14) Again it may not be practical, but there is also the opportunity to consider patterns over time in proposal acceptance.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I am an employee and shareholder of AstraZeneca.