Reviewer's report

Title: Three Steps to Writing Adaptive Study Protocols in The Early Phase Clinical Development of New Medicines

Version: 3 Date: 31 May 2014

Reviewer: Frank Bretz

Reviewer's report:

The manuscript is of potential interest, but there are concerns.

The manuscript would benefit if a concrete case studies would be incorporated to illustrate the concepts. The authors state that they will include "examples from projects we have authorised and performed in the UK" (p. 2), but I could not locate those examples. Otherwise this manuscript remains fairly vague.

On p. 7 the authors state that "the data is usually reviewed in a blinded fashion". What do you mean by this? Are you really suggesting that in a SAD study dose escalation decisions (mostly based on safety data to determine the maximum tolerable dose) do not make use of the information on which treatment the patient was randomized to (placebo or drug, in most cases)? This would be opposite to standard practices. Please clarify.

I have the impression that this manuscript uses the term “adaptive design” not in the sense of, for example, the FDA (2010) guidance document. Please clarify whether you are indeed referring to adaptations incorporated via protocol amendments. As mentioned above, standard practice makes use of unblended data and revisions not previously planned and made or proposed after an unblinded interim analysis raise major concerns about study integrity.

On p. 5 you state “in an early phase protocol it is advantageous to make a wide range of possible adaptations available” and further on p. 11 “there is no further interaction with the CA/REC so long as the study proceeds within the protocol’s adaptive specifications”. Thus, my understanding is then that in future I will design my protocols as general as possible (i.e. with all sorts of adaptations I can think of) and since then I don’t expect any major changes to the protocol I can proceed with my study without further interactions. Is this your suggestion? I would have great difficulties with this proposal.

Level of interest: An article of limited interest

Quality of written English: Acceptable

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

Declaration of competing interests:
I declare that I have no competing interests.