Reviewer's report

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

Version: 3 Date: 20 May 2014

Reviewer: Weili He

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Major Compulsory Revisions:

1. This article attempts to define a universally acceptable terminology and describe a process of writing an adaptive study protocol for the early phase development of new medicines. However, it’s somewhat confusing to also mention in the abstract that “Adaptive study design avoids the delays associated with the creation and authorization of substantial protocol amendments.” Dragalin defined an adaptive trial (AD) as a multistage study design that uses accumulating data to decide how to modify aspects of the study without undermining the validity and integrity of the trial. The essential components of an AD trial include that changes are made by pre-specified algorithm(s) and not on an ad hoc basis and that adaptation is a design feature and not a remedy for poor planning. Therefore, adaptations made during the study should be pre-specified. Adaptations that were made during the study but were not pre-specified may lead to operational biases that should not be encouraged. Regardless of an adaptive design or regular study protocol, changes in study conducts outside of what a protocol described will result in protocol amendments.

2. Although the EMA reflection paper on AD trials and FDA draft guidance on AD trials focused on confirmatory trials, the guiding principle on key factors an adaptive trial study protocol need to include should apply to early study AD study protocols as well. Specifically, details not just vague languages regarding the adaptation features, algorithms for adaptations, decision rules, and other related information should be pre-specified in the study protocol or the DMC charter. If that’s the case, there should not be a need to amend the protocols later on based on adaptations outside of the boundaries and control mechanisms.

3. In summary, this reviewer is not certain whether the proposed protocol template languages for adaptive early trials will reduce the need for protocol amendments, if details, rather than vague languages, regarding specific adaptations in the study are not suggested to be included in the study protocol. In addition, languages such as these in Section on How to document adaptive changes to the protocol, “During the course of an adaptive study, decisions are made on study conduct and protocol leading to changes of the originally planned protocol. These changes need to be fully documented.” may add to the confusion.