Reviewer’s report

Title: Ancillary Study Management Systems: A Review of Needs

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Reviewer: Wenle Zhao

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Major Compulsory Revisions

This revised manuscript titled “Ancillary Study Management Systems: A Review of Needs” researches the requirements for a new information system for the management of ancillary studies, named as ASMS. The primary research results are presented in the Result section (from page7 line 19 to 24 line 4) and the discussion section (from page 24 line 5 to page 29 line 14). There are 5 main parts included in these two sections:

1) an exploration of special characteristics that make ancillary studies different from primary studies
2) a brief review of current methods used for ancillary study managements
3) a detailed workflow of ancillary study management form hypothesis generation to publication
4) a comprehensive discussion of the pros and cons of having a separate ASMS versus combining ASMS functions into existing CTMS
5) a brief introduction of the LabKey Server system and current programming efforts covering ASMS functions presented in the result section

It is concluded that a separate ASMS is likely to be useful.

In part 1), five special characteristics of ancillary studies are explored: collection of additional measurements, conduction of a study by external investigators, cross-protocol data pooling and analysis, pre-existing and new participant consent, pre-existing data context and provenance. Ancillary studies are common in clinical trial fields, and these special challenges are well recognized. Some of them are not unique to ancillary studies, and could occur to primary studies when implementing significant protocol amendments during the course of the trials. One unique challenge comes from the fact that an ancillary study may involve multiple primary studies. The necessity of a separate ASMS could be better defensed in cases where the primary study does not have a CTMS, or the CTMS does not allow end user to configure for ancillary studies, or the ancillary study involves multiple primary studies.

The part 2) reviews the three strategies currently used for ancillary study managements, using CTMS, or ad hoc combination of software, or developing homegrown systems. From the data safety and management efficiency point of view, CTMS is the only alternative to ASMS. The other two alternatives lack the fundamental features to support real-time study management, especially in
multi-center cases. The debate on the limitation of using CTMS is not strong enough. Issues like adding new data item after primary study data lock, assign data access to external investigators may not be a real problem to a professionally developed CTMS. The real challenge is the cross-study data pooling.

The part 3) described the process (steps) of ancillary study management based on a “freezer study” scenario. As the main component of the manuscript, this part lists the functionality requirements for ASMS. Although the “freezer study” may be the most popular type of ancillary studies in some disease fields, a more challenging “cross-study” scenario could be better address the need for the ASMS.

The part 4) covers the debates of using or integrating CTMS versus developing separate ASMS. It is true that integrating ASMS features into a CTMS may not be feasible because commercial CTMS may not allow end-users to expand the originally designed functions. The key issue regarding developing a separate ASMS is the data integrity concern when the ancillary study started before the data lock of the primary study, or when cross-study involved. Without a solid exploring on this issue, people’s concern of using a separate ASMS may remain.

The part 5) briefly mentions the LabKey Server, on which the ASMS is currently under developing. It is understandable that this paper is not the ASMS design paper, rather to address the necessity of ASMS only. However, if the author could briefly answer few key questions regarding the main concerns of using separate ASMS, this manuscript will be much stronger. Here no programming details are needed. Some description on the system architecture design logics and strategies handling data reconciliations with the primary study database, as well as across multiple studies will be very useful. Such information is crucial to support the feasibility of the proposed ASMS.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests