SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

**Response to Memorandum issued Dec 3, 2013 by Dr Curtis Meinert**

March 3, 2014

Dear Dr Meinert,

Thank you for commenting on the SPIRIT Statement and contributing to the important dialogue on trial protocols. As uptake and endorsement of SPIRIT continue to expand internationally, ongoing feedback is important for future revisions to make SPIRIT as useful as possible to all stakeholders. On behalf of the SPIRIT group, I wanted to take the opportunity to clarify and address some of the points raised in your memorandum:

**1) Definition of a protocol** -- We agree that the recommended SPIRIT items may in some cases be fully addressed in diverse documents. For some trials, a single protocol document with appendices contains all relevant information recommended in the SPIRIT checklist (see examples in BMJ explanatory paper), while for others (particularly large multicenter trials), there will be multiple documents. 'Standard' practice also varies among trial groups and sponsors with regard to what information is placed in the protocol versus other related documents. Recognizing this variation in practice, the SPIRIT Statement states:
"For some trials, relevant details may appear in related documents, such as statistical analysis plans, case record forms, operations manuals, or investigator contracts (35, 36). In these instances, the protocol should outline the key principles and refer to the separate documents so that their existence is known."

**2) Protocol amendments** – In the SPIRIT Statement and explanatory paper, we explicitly recognize that the protocol is an evolving document, and that "the implementation and communication of amendments are also burdensome and potentially costly."

We also agree that minimizing the number of IRB submissions is highly desirable, and the SPIRIT recommendations are not intended to increase the burden of conducting trials. Accordingly, we specify in the SPIRIT Statement that "**important** protocol amendments should be reported to IRBs… [my emphasis]." We also state in the BMJ explanatory paper:
"It is important that **substantive** protocol amendments be reviewed by an independent party [my emphasis], such as the REC/IRB, and transparently described in trial reports. The notion of "substantive" is variably defined by authorities, but in general refers to a protocol amendment that can affect the safety of trial participants or the scientific validity, scope, or ethical rigour of the trial."

**3) Variable protocol requirements** – We agree that lack of harmonization across IRBs and funders is inefficient, and it is encouraging that several regions and countries are moving towards centralized review. The REB/IRB community has been widely supportive of efforts such as SPIRIT to harmonize protocol standards, as protocols have been shown to lack relevant information. Although some IRBs

may require less information than others, preparing a single protocol version with sufficient detail to satisfy the most extensive IRB requirements should also satisfy IRBs with less extensive requirements.

**4) Authorship eligibility guidelines** – The Committee On Publication Ethics (COPE), representing journal editors and publishers, recommends that authorship discussions begin during the research planning stages in order to foster transparency and prevent later disputes. Many protocols explicitly state authorship guidelines (e.g., the NIH trial at http://www.spirit-statement.org/31b-authorship/).

**5) Participant time schedule** – Specifying time commitments is a routine requirement in consent forms mandated by IRBs. However the SPIRIT recommendations do not call for details about the duration of each visit, as can be seen by the model examples for Item 13 (http://www.spirit-statement.org/participant-timeline/). Item 13 refers to the timing/frequency of visits and procedures:
"…key information to convey includes the timing of each visit, starting from initial eligibility screening through to study close-out; time periods during which trial interventions will be administered; and the procedures and assessments performed at each visit…"

Thank you again for the opportunity to discuss SPIRIT and our common goal of promoting high-quality clinical trials.

Sincerely,

An-Wen Chan, MD DPhil
Chair, SPIRIT Initiative
on behalf of the SPIRIT group