Response from Nuffield Department of Population Health, University of Oxford to the European Medicines Agency consultation document; "Risk proportionate approaches in clinical trials"

19 August, 2016

Overall comments:

This document seeks to provide further information on how a risk proportionate approach can be implemented in clinical trials and to highlight the areas identified in the clinical trials Regulation which support and facilitate such adaptations.

The new clinical trials Regulation provides a significant step forward for clinical trials, providing for flexible and proportionate approaches to quality management and oversight. This document very helpfully re-emphasises and illustrates how such flexibility can be best used to facilitate and enhance the quality of clinical trials to the benefit of both trial participants and the patients whose care may be influenced by the results. The document provides a helpful bridge between the legal requirements and their real-world application to clinical trials. As such this document is to be welcomed.

Specific comments:

Section 4.1:
Risk based quality management (lines 159-242)

The text uses the language of "risk" (e.g. risk based quality management, risk identification, risk evaluation, risk control, risk review, risk communication, risk reporting). While these concepts are good it would be helpful to incorporate some of the language of Quality-by-Design as has been proposed by the FDA Clinical Trial Transformation Initiative (http://www.ctti-clinicaltrials.org/files/QbD_toolkit/CTTI%20Quality%20by%20Design%20Recommendations_FINAL_1JUN15.pdf) [refs #1,#2 below] and is alluded to in the proposed addendum to ICH E6 ("Quality management includes the efficient design of clinical trial protocols, data collection tools and procedures, and the collection of information that is essential to decision making").

There is substantial overlap between these two areas but it would help the interpretation and application of this document if there was some acknowledgement that "risk based quality management" and "quality by design" (conventionally plan-do-check-act) were part of the same effort to focus attention on what matters, eliminate or control risks where possible (through better protocols, planning and design), monitor for those that cannot be eliminated and respond accordingly.

Ref #1 Landray MJ et al. Clinical Trials: Rethinking how we ensure quality. Therapeutic Innovation & Regulatory Science 2012 http://dij.sagepub.com/content/46/6/657.full.pdf+html

Ref #2 Meeker-O'Connell et al. enhancing clinical evidence by proactively building quality into clinical trials. Clinical Trials 2016 (http://ctj.sagepub.com/content/early/2016/06/21/1740774516643491.full.pdf+html)

Risk identification and evaluation (lines 196-199)

Current text: "the sponsor should ensure adequate and tailored training for the investigators and trial staff for those specific adverse events anticipated to occur in the trial subjects due to the nature of the IMP or the disease."

Suggested modification: "the sponsor should ensure adequate and tailored training for the investigators and trial staff for *ascertainment, reporting and management of any* specific adverse events anticipated to occur in the trial subjects due to the nature of the IMP or the disease."

Risk control (lines 222-223)

Current text: "...apply risk adaptations ("less stringent rules")..."

Suggested modification: It would be better to avoid the phrase "less stringent rules" since this may cause some to believe that "standards are lower" whereas the intention is that "standards are more appropriate to the situation"

Section 4.2: Safety reporting

(lines 251-253)

The current text implies that, in general, any adverse reaction (without the necessity of being serious) should be reported to the sponsor. As elsewhere in this section, it would be better to rewrite to emphasise a risk proportionate approach should be adopted in determining the nature and extent of safety reporting.

(line 269)

Current text: "... the level of detail and reporting requirements for adverse events may be adapted in the protocol..."

Suggested modification: "...the <u>extent (range of events) and level of detail of recording and reporting adverse events</u> may be adapted in the protocol..."

(lines 323-324)
Suggested addition: "Procedures for review, clarification, assessment, decision-making and onward reporting to regulators and other parties (including DSMB) should be clearly documented."

Section 4.3: IMP management

(lines 336-338) - Traceability and accountability

Suggest change to “The risk assessment and mitigation plan should include justifications for the <u>procedures and</u> documentation used to <u>allow</u> ~~reconstruct~~ drug traceability and the doses administered <u>to be reconstructed</u>.”

Suggestion: It would be helpful to include an example of risk adaptations for trials in which IMP is shipped direct to participants (e.g. a mailed study of aspirin vs placebo for cardiovascular disease prevention)

(lines 359-369):
This text is deals very helpfully with an important area of potential confusion

Section 4.4 Trial management – Monitoring **(line 390)**

Suggested addition: "…but the use and extent of such on-site monitoring should be tailored to suit the needs of the particular trial."

Section 4.5 Trial documentation

(lines 435-438): Content of the Trial Master File (TMF)

These refer to the appendix "Essential Documents" in ICH E6. In its current form, this is one of the weakest areas of E6. Either this cross-reference should be omitted / down-played in this document or E6 itself should be modified in this regard.

(lines 439-441):

Emphasising the flexibility / risk-proportionate nature of Article 57 is very helpful.

*** END ***