Dear mr/mrs,

The CCMO has reviewed the document "*Risk proportionate approaches in clinical trials - Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use*"

- The Regulation provides the basis for developing a guideline on risk proportionate approaches in clinical trials. The CCMO is very much in favor of a risk proportionate approach, but realizes that it is difficult to predict in advance the accuracy of these risks. In the introduction of the document different factors are mentioned which can have an influence on the risks (line 58-63 of the document) and this is all true. However, much is still unknown and difficult to predict and one could say that by choosing for a risk proportionate approach an additional risk could be introduced (by less extensive research). The CCMO misses this nuance in the introduction. The proposals in the document with respect to trial management and logistics are welcome and feasible but as a whole the document is general in nature and the tenor of the document is much less than the introduction does suggest.
- Line 76-78 mention that this guideline applies to all sponsors, commercial as well as academic and all types of clinical trials, from early development of unauthorised products to clinical research conducted in the post-authorisation phase. But should it also not apply to Inspectorate and Regulatory bodies?
- Line 99-108, section 4.1, line 208 indicates that risks should be considered from a broad perspective. We completely agree. Therefore, in our Dutch template research protocol, chapter 13, investigators/sponsors have to make a structured risk analysis. We would appreciate if this is included in the guidance document as an example together with other examples (line 208) in the references in chapter 5. The following link could be added: http://www.ccmo.nl/en/standard-research-file (section C1. template research protocol, chapter 13 about structured risk analysis).
- Low intervention trials are primarily for authorized medicinal products . MEBs are more and more moving to adaptive licensing. What are the implications of this?
- Line 298; the example about oncology trials is a somewhat unfortunate example. New oncolytica are many times studied in combination with other toxic substances with unknown (and difficult to predict) interactions and adverse reaction. Therefore, not register these adverse events might not be a good example.
- Line 304 and further: the text about the need for a DSMB is not clear and not fully in line with current practice. Reference to EMA guideline about DSMB seems to be in place: "Data Monitoring Committees" (EMEA/CHMP/EWP/5872/03 dd 27 July 2005) (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003635.pdf).
- Line 330 and further: the CCMO supports very much the proposal (line 345-350) about traceability IMP in low intervention trials , namely conform the routinely maintained pharmacy documentation on receipt, storage and handling.

On behalf of the Central Committee on Research Involving Human Subjects (CCMO), The Netherlands

Central Committee on Research Involving Human Subjects (CCMO)
Parnassusplein 5 | 2511 VX The Hague, The Netherlands
PO Box 16302 | 2500 BH The Hague, The Netherlands
T +31 (0)70 340 6700 |E ccmo@ccmo.nl | I http://www.ccmo.nl