Comment of the Network of Coordinating Centers for Clinical Trials (KKS-Network), Germany

on the

Consultation document "Risk proportionate approaches in clinical trials" (01/06/2016)

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

General Comments:

The recommendations are good and helpful in providing information regarding the implementation of the risk proportionate approach. The flexibility the paper provides is appreciated. However, in some areas the recommendations could be a little bit more precise. Furthermore, as lot of information is also available in other guidelines, we would find it helpful if the terms used would be defined and be aligned with those in other guidelines/regulatory texts. A glossary might be helpful for this.

As a risk-based approach should shift the focus from 100% data integrity to accuracy where it matters it would be good if the concept of "data integrity" could be formulated as a goal without being mandatory. However, some parts in the document (lines 180, 224) mention data integrity irrespective of the impact on the validity on conclusions. These parts should be rephrased. For instance we would prefer if the term "data integrity" could be changed to "data validity" in the phrasing in lines 166-7 which focusses on scientific outcomes. Data integrity as a goal for safety variables appears in line 224.

The scope section mentions in the first sentence that the goal of the regulation is to foster innovation whilst ensuring the protection of the participants in clinical trials and the quality and integrity of the trial outcomes. Starting at line 89 the text does not mention any risk issues beyond patients' safety. The scope for the recommendation should also contain both protection of participants' safety/privacy and validity of conclusions as objects of risk analysis.

The objective of the recommendations is to "provide further information on how such risk proportionate approach of the Regulation (EU) 536/2014 can be implemented and also highlights the areas identified in the Regulation which support and facilitate such adaptations." For the implementation of the approaches in practical life, those should be cross-checked with other requirements (e. g. FDA, ICH E6). The procedure / process chosen should be justified accordingly in the protocol.

Specific comments:

Lines 68, 83, 183-184:

Lines 68 and 83 mention the term “risk proportionate”, suggesting that risk is viewed as the product of damage and occurrence rate. This definition is made explicit in lines 183-4. While this is a common definition of risk, practitioners should be cautioned against deriving a risk class and basing the action on the risk class only. The mitigation strategy for a low-damage, high-rate event may be very different to one for a high-damage, low-rate event.

4.2. Safety reporting:

The paper should mention that for risk analysis criteria for searches regarding adverse events need to be available, e.g.:

- A procedure for signal detection which should be documented. The risk based quality management should take the results of the search into account
- A safety monitoring plan

Line 305ff:

Starting in 305, a suggestion is made to tackle the problem of erroneous documentation at its root by reducing the burden of documenting adverse events. This is a laudable approach with a realistic suggestion to handle possible risks to safety. We would welcome similar suggestions for the documentation of concomitant medication, which has been noted before as a domain with a very poor documentation/conclusion ratio (see O’Leary et al 2013, <doi:10.1177/1740774513491337>).

One aspect by which patients’ identity/privacy may be imperiled is the occurrence of a rare disease as an adverse event, where the rarity could allow to pinpoint the identity even beyond the study population with extraneous information. Clinical trials dedicated to rare diseases are very prone to unwanted patient identification; the special risk to be considered should be mentioned.

4.4. Trial management

Section 4.4 contains a whole subsection on monitoring but no dedicated text passage on data management. Given that most risk based management approaches shift the burden from monitoring to data management, more about the changing role of risk detection and mitigation using centralized data and the resulting obligations for data management should find its way into a separate subsection.

Line 404-407:

The escalation in case of „non-compliance“ is of general importance and should possibly be highlighted at a more prominent place of the recommendation.

Köln/Berlin, 31.08.2016