Health Research Authority

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

Consultation Response from the Health Research Authority[1]

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Introduction:

1. The Health Research Authority (HRA) was established to promote and protect the interests of patients in health and social care research and to streamline the regulation of such research. We aim, with partners, to make the UK a great place to do health and social care research, to build confidence and participation in health and social care research, and so improve the nation's health. Our responsibilities include the appointment and operation of statutory research ethics committees.

2. The HRA particularly welcome the adoption of risk proportionate approaches to the conduct of clinical trials as 'proportionality' is a major theme underpinning the delivery of our strategic ambitions to streamline research and protect the interests of the public.

Our Comments:

3. It would be beneficial to state more clearly in the guidance whose responsibility it is to make judgments regarding the level of risk inherent in a trial, and thus the proportionate approaches to be used (the Sponsor), and whose responsibility it is to agree/approve these (the regulatory bodies).

4. One factor that will affect the level of risk involved in conducting a trial at the system level will be the experience and expertise of the unit/researchers doing the research. For example, an experienced high volume phase I unit is likely to present a lower risk in general than a physician undertaking a phase I study for the first time on a normal hospital ward. It might be helpful to adopt an accreditation scheme similar to the 'phase I accreditation scheme' introduced in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA). Such a scheme might be used to justify proportionate approaches based on the proven competence of the institution undertaking the trial. Under the MHRA scheme organisations have to exceed the basic regulatory good clinical practice (GCP) standards by having additional procedures that include the highest standards for avoiding harm to trial subjects and for handling any medical emergencies.

5. **Line 114:** In some low intervention clinical trials use of a placebo might be acceptable where standard care includes no treatment or a period of 'watchful waiting'.

6. **Line 117:** We suggest that the following condition should be added as the second condition:

   "ii) The investigational products are used routinely off-label (such as in paediatrics and in oncology etc.) where this off-label use is established practice and is supported by sufficient published evidence and/or guidelines; or"

[1] This response includes comments received by the Chief Scientist Office in Scotland.

7. **Line 132:** Whilst low levels of blood withdrawal might represent a 'minimal additional burden' to participants the burden, and risk, will increase with the withdrawal of larger volumes. The guidance might helpfully provide upper volume limits below which the withdrawal of blood could be considered to be of minimal burden.

8. **Line 342:** The suggestion that "*IMPs could also be provided directly to the sites by the trial sponsor*" should stipulate that where this is done the IMPs should be labelled for use in a clinical trial according to local requirements (e.g. in order that a compliance check can be carried out).

9. **Line 356:** Similarly, where "*unlicensed medicinal products are used as IMPs*" these should be labelled for use in a clinical trial.

10. **Line 345:** This paragraph appears to be unfinished as it sets up a conditional clause (i.e. by using "*if*") but does not go on to complete the clause (i.e. by use of "*then*"). In large scale, primary care based pragmatic trials, all the data will be entered into the electronic health record used for normal prescribing and the data are accessed centrally for analysis. In such studies there would be no need for a CRF as used in the example provided.

11. **Line 390:** It should be noted that source data verification will not be possible in pragmatic trials where the data is entered directly into the electronic health record using normal prescribing practices. In addition, if the consent is recorded electronically, there may be no need for onsite monitoring.

12. **Line 394:** It is unclear whether the suggestion that "*there may be no on-site visits in certain trials*" also includes site selection/initiation and close out visits as well as source data verification and investigator meetings. It would helpful to add further detail on the type of trials that this might apply to and the range of traditional on-site activities that would not need to take place on site. In the case of pragmatic trials involving 'standard of care' interventions, central monitoring (rather than on-site site visits) could be considered particularly where an Electronic Health Record (EHR) is used to record the data.

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