Health Research Authority

Definition of Investigational Medicinal Products (IMPs) and use of Auxiliary Medicinal Products (AMPs) 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

v1.0 31/08/2016

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.

Our Comments

2. It would be helpful if the guidance provided or referred to a definition of a 'medicinal product' (e.g. that used in EU Directive 2001/83/EC:

   "Medicinal product:

   (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
   (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.")

3. We recommend incorporation of advice, similar to the Medicines & Healthcare Products Regulatory Agency's (MHRA) useful guidance on IMP versus non-IMP designation (available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/343441/Mock_examples.pdf), in order to help sponsors determine whether substances administered in clinical trials are Investigational Medicinal Products (IMPs) (comparator or placebo), AMPs (e.g. a licensed medicine used in an interaction study as a CYP3A4 substrate but which is not expected to be co-prescribed with the IMP), or non-AMPs (e.g. alcohol used in an interaction study).

4. It would be helpful to clarify whether products (such as alcohol used in an interaction study) that do not meet the definition of an AMP do not need an AMP dossier or to be manufactured to GMP standards (whilst recognising that they must be of suitable quality for use in the trial). It would be useful to echo the wording used in "Volume 4 - EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Annex 13" with regards to "*Products other than the test product, placebo or comparator may be supplied to subjects participating in a trial.*" i.e. that "The advice and involvement of a Qualified Person is recommended in this task."

5. **Lines102–109:** This paragraph is unclear and appears to be incomplete.

6. **Line 142:** A full stop is required after '*authorisation'*

7. **Line 172:** The section "*While all SAEs and SARs should be included in the annual safety report of the relevant IMP, and non serious adverse events and non serious suspected adverse reactions should be reported in the Clinical Study Report. Further details, also with regard to adverse reactions possible interacting with IMP, please see safety section of the Questions and Answers Paper Version XX.*" appears to be incomplete or ungrammatical. In addition it is not clear where serious adverse events/reactions associated with an *unauthorised* AMP should be reported? Whilst this section refers to all SAEs and SARs being included an "annual safety report of the 'relevant IMP'" it is not clear what the 'relevant IMP' would be?

8. **Line 182: Annex 1 -** The title is "*Types of AMPs with examples*", but the annex includes the challenge agent tyramine, which is not a medicinal product and therefore doesn't meet the definition of an AMP. The title of the annex is therefore somewhat misleading. It would be helpful to include more examples of non-AMPs, such as methacholine, used for bronchial challenge, and PET ligands, microdoses of which are used only to measure receptor occupancy.

9. **Line 192: Annex 1 - Section 1 "Rescue medication":** It might be helpful to explain that rescue medicines may also be used to treat a side effect of a trial procedure (e.g. beta-2 agonist given as needed after inhaled allergen challenge or spirometry).

10. **Line 215: Annex 1 - Section 1**: Rescue medicines for an *emergency situation* should be available in *all* clinical pharmacology studies, not just first in human trials of biological products. So the example given is not useful. All early phase research units should have a wide range of licensed medicines for emergency situations, such as anaphylactic shock available at all times on the ward. It would be unnecessarily burdensome for investigators, sponsors and regulators to specify that SmPCs for all routinely stocked emergency medicines should be included in applications for authorisation. It might be helpful and proportionate if medicines routinely stocked to treat emergencies or common adverse events (e.g. paracetamol, antihistamine) were explicitly classed as non-AMPs.

11. **Line 223: Annex 1 - Section 2 "Challenge agents":** It might be helpful to add PET ligands that are not used in medical practice for diagnosis as examples of non-AMP 'challenge agents'. They are not medicinal products and are administered in very small doses only to measure receptor occupancy by IMPs.

For further information, please contact Clive Collett, HRA Ethics Guidance & Strategy Manager, Health Research Authority (clive.collett@nhs.net).

www.hra.nhs.uk