ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

29 August 2016

Directorate General for Health and Food Safety DG SANTE
Unit B4 "Medical products – Quality, Safety and Innovation"
European Commission
F101 08/058
B-1049 Brussels

RE: Public consultation on the revision of the "Definition of Investigational Medicinal Products (IMPs) and use of Auxiliary Medicinal Products (AMPs)" (previously called "Guidance on Investigational Medicinal Products (IMPS) and Non-Investigational Medicinal Products (NIMPs))

Dear Sir/Madam:

The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through pivotal studies assessing the safety and effectiveness of new products – as well as post-approval and pharmacovigilance research. With over 33,000 employees engaged in research activities in Europe, and more than 120,000 worldwide, ACRO member companies advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 9,000 clinical trials involving nearly two million research participants in 142 countries. On average, each of our member companies works with more than 500 pharmaceutical, biotech, and medical device sponsors of clinical trials each year.

ACRO's comments are organized into 3 sections:

- general comments
- suggested revisions to specific line numbers in the consultation document
- topics omitted from the consultation document and recommended for inclusion in the final document

I. General comments

ACRO welcomes and supports the draft recommendations on the Definition of Investigational Medicinal Products (IMPs) and use of Auxiliary Medicinal Products (AMPs) developed by the European Commission's expert group on clinical trials for the implementation of Regulation (EU) No 536/2014. ACRO is pleased to note that, in contrast to current guidance on non-investigational medicinal products, concomitant medications administered to patients as part of their standard care for a condition which is not the indication for which the IMP is being tested, will not be considered as auxiliary medicinal products. ACRO welcomes this change from current guidance.

II. Suggested revisions to specific line numbers

Line Numbers	Current text	Issue/question	Suggested language
54-56	"It follows that medicinal products with a marketing authorisation are IMPs too when they are to be used as the test product, reference product or placebo in a clinical trial."	Minor edit might be useful for clarification	"It follows that medicinal products with a marketing authorisation are also considered IMPs, when they are to be used as the test product, reference product, or placebo in a clinical trial."
70-72	"For instance, some clinical trial protocols require the use of medicinal products such as rescue medication, challenge agents, medicinal products used to assess end-points in the clinical trial and background treatment."	Minor edits might be useful for clarification	"For instance, some clinical trial protocols require the use of medicinal products as a rescue medication, a challenge agent, to assess end-points in the clinical trial, or as background treatment(s)."
76 - 78	"AMPs should not include concomitant medications; medications unrelated to the clinical trial and not relevant for the design of the clinical trial."	Minor re-wording might be useful for clarification	"AMPs should not include concomitant medications unrelated to the clinical trial and not relevant for the design of the clinical trial."
92-94	"Where there are problems with respect to the availability of authorised AMPs, unauthorised AMPs may be used in a clinical trial in justified cases."	It is not clear how "justified cases" should be defined and documented. ACRO recommends that the justification should be included in the clinical trial protocol.	"Where there are problems with respect to the availability of authorised AMPs, unauthorised AMPs may be used in a clinical trial in justified cases. The justification should be included in the clinical trial protocol."
95 - 98	"Subjects should not have to pay for IMPs, AMPs, medical devices used for their administration and procedures specifically	ACRO agrees that subjects should not have to pay for procedures specifically required by the	"Trial subjects should not have to pay for IMPs, AMPs, medical devices used for their administration, and procedures specifically required by the

	required by the protocol, unless the law of the Member State concerned provides otherwise."	protocol, and recommends that the guidance should make clear that this also extends to their health insurance provider. ACRO also acknowledges that the payment framework of medicines used in clinical trials varies significantly from country to country due to specific national legislations. This can sometimes generate significant heterogeneity in the procurement / sourcing / reimbursement of those therapies between the different countries. There is a particular issue with regard to interpretation of the phrase "procedures specifically required by the protocol," which should be clarified in the final guidance. When the protocol requires that an IMP is added to treatment that is standard of care in a member state, that standard of care treatment may continue to be reimbursed if the patient is already receiving the standard	protocol, unless the law of the Member State concerned provides otherwise. The phrase "procedures specifically required by the protocol" means additional treatments/procedures required by the protocol and not treatments considered to be standard of care (whether implemented at the time of entry to the trial or earlier)."

		of care treatment prior to enrollment in the clinical trial. However, if a patient is started on such standard of care treatment at the same time as they are entered into the trial, the standard of care treatment may not be reimbursed and is expected to be provided by the sponsor.	
102 - 109	"Medicinal products that do not have a marketing authorisation, but prepared in accordance with a magistral formula, i.e. prepared in a pharmacy in accordance with a medical prescription for an individual patient, and medicinal products prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and intended to be supplied directly to the patients served by the pharmacy in question, i.e. officinal formula, as referred to in Article 61 (5) of the regulation (EU) No 108 536/2014.."	It might be helpful to more clearly state the purpose of this paragraph and its relevance to auxiliary medicinal products. Also, it appears that a statement might be missing from the end of the paragraph to confirm that these products may also be auxiliary medicinal products.	"Medicinal products that do not have a marketing authorisation, but are prepared in accordance with a magistral formula, i.e. prepared in a pharmacy in accordance with a medical prescription for an individual patient, and medicinal products prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and intended to be supplied directly to the patients served by the pharmacy in question, i.e. officinal formula, as referred to in Article 61 (5) of the regulation (EU) No 108 536/2014 may also be auxiliary medicinal products."
141 - 142	"dossier for IMPs also apply to AMPs irrespective their marketing authorisation Regulation (EU) No 536/2014 Annexes I and II set out the"	Minor re-wording might be useful for clarification	"dossier for IMPs also apply to AMPs irrespective of their marketing authorisation. Regulation (EU) No 536/2014 Annexes I and II set out the"
161	"which cover authorized AMPs.-"	Minor re-wording suggested to delete hyphen	"which cover authorized AMPs."
170 - 171	"Nevertheless, sponsors are highly encouraged to report	Article 40(1) of the regulation requires that	The procedure to be followed should be defined by the expert

	adverse reactions to the Eudravigilance Database as described in Article 40 (1) of the regulation."	reporting will be as provided for in articles 42 and 43. Both articles relate to reporting of reactions associated with the IMP. Additional text is required to describe the procedure for reporting adverse reactions related to an unauthorized AMP to EudraVigilance, in order to ensure the adverse reaction is correctly classified as related to the unauthorized AMP rather than the IMP.	group on clinical trials for the implementation of Regulation (EU) No 536/2014.
172-177	"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."	1. Rewording of the first sentence might be useful for clarification. 2. "SAE" and "SAR" are not defined	1. "All SAEs and SARs should be included in the annual safety report of the relevant IMP, and non-SAEs and non-SARs should be reported in the Clinical Study Report. For further details regarding adverse reactions possible interacting with IMP, please see safety section of the Questions and Answers Paper Version XX." 2. The abbreviations "SAE" and "SAR" should be defined when first used in the document. Use of the acronym or the full terminology should be used consistently throughout the document.

		3. It is not clear what is meant by "adverse reactions possible interacting with IMP"	3. The meaning of "adverse reactions possible interacting with IMP" should be clarified, using examples if necessary.
182-183	"Annex 1 – Types of AMPs with examples"	Minor formatting issue	"Annex 1 – Types of AMPs with examples" should be formatted as a header.
192-195	"Rescue medications are medicines identified in the protocol as those that may be administered to the patients when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation."	Minor edits might be useful for clarification	"Rescue medications are medicines identified in the protocol as those that may be administered to patients when the efficacy of the IMP is not satisfactory, the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation."
197-201	"Rescue medication allows patients to receive effective treatment, e.g. placebo controlled clinical trials where a standard treatment is available or dose response studies where lower doses might be ineffective. Rescue medications are sometimes called "Escape medications" in protocols. Usually these AMPs are authorised AMPs and are used according to the authorised conditions."	Minor edits might be useful for clarification	"Rescue medication allows patients to receive effective treatment while enrolled in placebo-controlled clinical trials where a standard treatment is available, or in dose-response studies where lower doses might be ineffective. Rescue medications are sometimes called "Escape medications" in protocols. Usually these AMPs are authorised AMPs and are used according to the authorised conditions."
219 - 220	Feedback requested: You are invited to elaborate further on "early escape" procedures.	Early escape trial designs allow patients to stop or escape the randomized treatment assignment when the patient fails to meet a pre-specified level of improvement or if the	

		patient's condition worsens. Early escape trial designs are relatively new clinical trial designs that minimize placebo exposure, or exposure to less effective treatment arms, and have proven to be more user-friendly than conventional parallel randomized controlled trial designs. A patient in an early escape trial may stop or escape the randomized treatment assignment in various ways, depending on the specific design of the trial, and not all of these involve use of rescue medication. Where rescue medication is used and specified in the protocol, it is ACRO's view that it should be treated as an auxiliary medicinal product in the same way as rescue medication in traditional trial designs.	

III. Omissions in consultation document recommended for inclusion in final document

There are two issues the Commission may wish to consider including in the final document. First, the draft guidance does not address the situation where an AMP may need to be used at a different dosage, route of administration, or application form from that described in the authorized summary of product characteristics (SmPC). ACRO recommends that a statement, such as the following, is added to the guidance document to confirm that, where this is necessary for the clinical trial, a justification should be included in the trial protocol. *"The route of administration, dosage and application form of an authorized AMP should in principle be according to the authorized SmPC. However, if the route, dosage and/or application form of an authorized AMP needs to be different due to protocol requirements or study design, a justification must be included in the clinical trial protocol."*

Second, the draft guidance does not address the situation where a subject experiences injury from use of an authorized AMP. ACRO recommends that a statement, such as the following, is added to the guidance to confirm that this situation should be covered by the sponsor's clinical trial insurance. *"Injury of a subject caused by use of an authorized AMP within a clinical trial should be covered by the patient insurance obtained by the sponsor of the clinical trial."*

ACRO thanks the Commission for the opportunity to comment on this public consultation on the revision of the "Definition of Investigational Medicinal Products (IMPs) and use of Auxiliary Medicinal Products (AMPs)."

Please contact ACRO if we can provide additional information or answer any questions (knoonan@acrohealth.org).

Respectfully submitted,

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EU Transparency Register:
ACRO's public ID number in the Transparency Register is: 150920420956-26