27 April 2018

Submission of comments on draft revision of the Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products (EMEA/149995/2008 rev.1)

Comments from:

Name of organisation or individual
ACRO (Association of Clinical Research Organizations)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	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 post-approval and pharmacovigilance research. With more than 130,000 employees engaged in research activities around the world (including 57,000 in Europe), ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 7,000 clinical trials involving 1.3 million research participants in over 100 countries. On average, each of our member companies works with more than 700 research sponsors annually. ACRO welcomes and supports the draft revision of the guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products, based on additional experience since the original guideline was introduced in 2008. ACRO considers this to be a comprehensive document that provides useful guidance for ATMPs with regards to the	

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	pharmacovigilance system, the identification of risks, the risk minimisation measures, the post-authorisation safety and efficacy studies, the management and the reporting of adverse reactions, and of the evaluation of the effectiveness of the risk management system. We note, however, that whereas the Good Pharmacovigilance Practices (GVP) modules have been written carefully to avoid redundancy, this seems to be less the case here and there is some unnecessary repetition of items captured in the GVP modules (e.g. inspection, enforcement, case management) which are identical in requirement to non-ATMP products. In particular, given that section 3 states that this guideline should be read in conjunction with the GVP modules, we see no need to repeat this in later sections of the document unless there are ATMP-specific issues to be taken into consideration. Several of our specific comments on the text reflect this view. Also, ACRO recommends the following additions to the draft guideline: • Lines 395-397 of the draft state “ATMP developers should ensure that the patients enrolled in clinical trials (starting at phase I) or in compassionate	

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	use are appropriately followed-up to allow generation of long-term S&E data." ACRO fully supports this advice and recommends that section 2 (Scope) of the draft guideline, which refers to "post-authorisation follow-up" should make clear that this includes appropriate follow-up post-authorisation of patients enrolled in pre-authorisation development to allow generation of long-term safety and efficacy data. • Section 5.1 of the draft guideline (Identification of the safety and efficacy concerns for ATMPs) highlights potential risks to patients, healthcare professionals, care givers, offspring and other close contacts of the patient. We recommend that these examples should also include potential risks to living donors related to conditioning and procurement of cells and tissues (e.g., immunosuppression, surgical/medical procedures, etc.). • ACRO welcomes the recognition that 'pragmatic' trial designs may be relevant for some trial objectives (line 522). However, given the current high level of stakeholder interest in the use of real world evidence for regulatory purposes, and the recommendation to use "an observational study, perhaps in a healthcare database or disease registry" when feasible (lines 516-519), ACRO recommends the inclusion of additional text to address the advantages and disadvantages of real world data in	

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	patient follow-up and risk management of ATMPs.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Lines 60-61		Comment: ACRO fails to see how the Pharmacovigilance System Master File (PSMF) is impacted by this guidance; PSMF requirements for ATMPs are same as for non-ATMPs. Proposed change (if any): Either provide explanation of the impact or delete the reference to the PSMF.	
Lines 76-77		Comment: Please note that adequate data must be provided at the time of Marketing Authorisation Application (not Marketing Authorisation) to allow for the benefit-risk evaluation. Proposed change (if any): Add “application” after “Marketing Authorisation.”	
Line 104		Comment: This line implies that the PSMF contains clinical data, which it does not. It also implies there is some ATMP-specific consideration for the PSMF (compared to non-ATMP products), which there is not. The PSMF contains limited product-specific information and is unlikely to be materially impacted as more safety information becomes available on a given product. Proposed change (if any): As noted earlier, either provide explanation of the impact or delete the reference to the PSMF.	

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Lines 158-160		Comment: This simply reiterates the GVP Module II requirement, with no specific additional considerations for ATMP. Proposed change (if any): Delete this paragraph.	
Lines 166-167		Comment: This is not specific to ATMPs and is addressed in GVP module VI. Proposed change (if any): Delete this paragraph.	
Lines 168-170		Comment: Informed consent is not mentioned in GVP Module VI in relation to all other non-interventional studies. It is not clear, therefore, why it is mentioned here, as it is not a specific requirement for ATMP-related studies. Proposed change (if any): Delete this sentence.	
Line 179		Comment: Incorrect use of comma in 'they may cause new, risks to patients'. Proposed change (if any): Change to "they may cause new risks to patients. The specific rules…"	
Lines 189-190		Comment: The meaning of the following sentence is not clear: "Only the safety concerns relevant to RMP should be added in	

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		the safety specification of the RMP as either as important identified or potential risks or missing information." Proposed change (if any): Reword the sentence to make the meaning clear.	
Lines 190-191		Comment: It is not clear why cases of lack of efficacy with an adverse clinical outcome would not be included in the list of safety concerns (e.g. life-threatening lack of efficacy). Proposed change (if any): Either add a statement that cases of lack of efficacy with an adverse clinical outcome should be included in the list of safety concerns or explain why they should not.	
Lines 251-252		Comment: It is not clear where these risks, other than those to patients, should be included in the safety specification of the risk management plan. Proposed change (if any): Add text to clarify where discussion of these risks should be located in the safety specification of the risk management plan.	
Lines 268-270		Comment: The current text refers specifically to parent-child risks (i.e., second generation effects). ACRO recommends that the text should be expanded to take into account the consequences of third generation effects (e.g., as shown by	

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		emerging evidence for diethylstilboestrol treatment). Additionally, reference to inter-generational risks raises potential issues regarding data privacy and the protection of personal data. Comment: Expand the text to address inter-generational risks more widely, and the impact of the General Data Protection Regulation (No. (EU) 2016/679).	
Lines 275-276		Comment: The phrase “potentially missing information” should read simply “missing information” Proposed change (if any): Revise the text to read “…specifications which consist of a summary of the important identified and potential risks and missing information. Additional guidance on safety specifications…”	
Lines 295-297		Comment: The reference provided (GVP Module VI) covers only individual case study report (ICSR) management and not signal detection. Proposed change (if any): Revise the text to read “…with regards to spontaneous reports, follow-up reports, specific methodology for signal detection. Reference is made to GVP Module VI – Management and reporting of adverse reactions to medicinal products and GVP Module IX – Signal management. “	
Lines 361-362		Comment: It is not clear what the bullet “the importance of	

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		reporting other information arising from the disease registry that are relevant for the ATMP“ refers to. It would be helpful to explain in more detail and/or provide some examples. Proposed change (if any): Explain this bullet in more detail and/or provide some examples.	
Lines 603-621		Comment: The content of section 9 contains multiple references to signal detection, but the title indicates only management and reporting of adverse reactions and periodic safety reports (PSURs). As several bullets refer to signal management, it would be preferable to move the reference to GVP Module IX from lines 611-612 to the beginning of the section (lines 605-606). Furthermore, there is no content regarding PSURs in the section other than a reference. Proposed change (if any): Change the title of section 9 to read “Signal detection, and management and reporting of adverse reactions.” Move the reference to GVP Module IX to lines 605-606. Delete line 621, as it says nothing that is specific to ATMPs.	
Lines 618-620		Comment: The term “adverse event” is not recognised in currently applicable legislation on medical devices. Rather, the manufacturers of medical devices are required to report adverse incidents. The correct terminology should be used.	

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		Proposed change (if any): Revise the sentence to read "…adverse events related to the device performance should be reported as adverse incidents."	
		ACRO thanks the Agency for the opportunity to comment on this draft revision of the Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products (EMEA/149995/2008 rev.1). Please contact ACRO (knoonan@acrohealth.org) if we can provide additional details or answer any questions.	

Please add more rows if needed.