EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

8 October 2015

Submission of comments on GVP Module VIII – Post-authorisation safety studies (Rev 2) (EMA/813938/2011)

Comments from:

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

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When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(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 110,000 employees engaged in research activities around the world (including 30,000 in Europe), ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 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 research sponsors annually. ACRO welcomes this opportunity to comment on the draft revision of the Module VIII guidance on non-interventional post-authorisation safety studies (PASS). ACRO is concerned that requirements for the regulation of PASS have become unnecessarily complex and provide a potential source of compliance risk, both for	

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	organisations conducting PASS and for competent authority staff involved in their regulation. PASS requirements are detailed across numerous documents (pharmacovigilance legislation, guidelines on good pharmacovigilance practices, Regulation (EC) No. 1234/2008 on variations, post-authorisation measures: questions and answers, Periodic Safety Report (PSUR) and Risk Management Plan (RMP) templates, and fees legislation). Confusion resulting from this complexity has led to inconsistent implementation of the requirements by organisations conducting PASS and to inconsistent application of the requirements by competent authorities. ACRO recognises and welcomes that the current proposed revisions are intended to make clearer the requirements of the current Module VIII PASS guideline. In particular, ACRO welcomes and supports the approach to distinguish legal requirements from recommendations (while noting that, in practice, more could be done to improve the document in this regard). However, ACRO is disappointed that the opportunity has not been taken to produce a guidance document that pulls together, in a clear and consistent way, all of the requirements relevant to PASS arising from the different source documents. While recognising the scale this task, ACRO recommends and encourages the EU regulatory network	

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	to undertake such an initiative. ACRO also recommends and encourages the network to reach agreements on simplification of the PASS requirements, consistent with the legislation. Together, these initiatives would greatly improve the understanding of and compliance with PASS requirements.	

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)*
Line 106		Comment: ACRO welcomes and supports the addition of the clarification that collection of blood samples maintains the non-interventional status of a PASS. Proposed change (if any):	
Lines 124 - 128		Comment: ACRO welcomes and supports the proposal to make a distinction in the text of the guideline between legal requirements and recommendations. However, on reviewing the guideline, ACRO saw little evidence of this distinction in practice and recommends that the draft guideline is further amended to highlight these differences. Proposed change (if any): Further amend the draft guideline to ensure this distinction is made clear whenever appropriate.	
Lines 150 - 155		Comment: The list of changes given as examples that may be considered substantial amendments of the protocol is very high level. Within each category, there may be some changes that do and some that do not constitute a substantial amendment. This gives scope for differing interpretations between study sponsors, between competent authorities, and between sponsors and competent authorities. Consequently, ACRO recommends that a more precise list of changes that will be considered to be substantial amendments should be	

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		developed. Proposed change (if any): Include a more precise list of changes that will be considered substantial amendments.	
Line 162		Comment: Directive 2001/83/EC as amended by Directive 2010/84/EU defines a PASS in Article 1(15) as “any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.” This legal definition expressly does not include the use of other interventions, which are outside the scope of the Directive. ACRO therefore recommends that the phrase “class of medicinal product or other intervention as appropriate” is changed to “or class of medicinal product as appropriate.” Proposed change (if any): Change the phrase “class of medicinal product or other intervention as appropriate” to “or class of medicinal product as appropriate.”	
Lines 212 - 221		Comment: The pharmacovigilance legislation requires the EMA to publish in a publicly available register the protocols and abstracts of results of PASS imposed as an obligation by a competent authority. It also specifies that the final reports of such studies must provide the date of registration in this register. The EMA recommends that information about PASS which are initiated, managed or financed voluntarily by a MAH	

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		and which are required in the Risk Management Plan (RMP) to further investigate safety concerns or to evaluate the effectiveness of risk minimisation activities, or any other PASS should also be entered into this register in order to support the same level of transparency, scientific and quality standards. While ACRO recognizes and supports the concept of applying similar standards to all PASS, irrespective of the regulatory status of the study, ACRO is not aware of any legal basis that mandates registration of studies conducted outside the EU and which are not part of the EU RMP. The distinction between legal requirements and recommendations is not clear in this section of the draft guideline, and ACRO recommends that the text is modified accordingly. Proposed change (if any): Revise the proposed text to ensure that legal requirements and recommendations concerning use of the EU PAS Register are made clear.	
	Lines 225 - 228	Comment: ACRO welcomes and supports the proposed flexibility to permit redaction of the protocol that is made publicly available when necessary to protect the integrity of the study or intellectual property. ACRO is aware that this is an important issue for many PASS sponsors. Proposed change (if any):	
	344 - 358	Comment: ACRO welcomes and supports the proposed flexibility to justify the non-collection and/or non-expedited reporting of certain adverse events. In addition to maintaining	

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		the integrity of outcome studies, this will allow for simplification of study procedures to focus on the important risks. Proposed change (if any):	
Lines 421 - 425		Comment: The proposed text states that safety findings should be reported in Periodic Safety Reports (PSURs) and Risk Management Plans (RMPs). However, ACRO notes that guidance on the PSUR relative to findings from non-interventional studies states “This section should summarise relevant safety information or information with potential impact on the benefit or risk evaluations” (HMA/EMA Guideline on Good Pharmacovigilance Practices Module VII – periodic safety update report (Rev 1) and ICH E2C(R2) guidance: Periodic Benefit-Risk Evaluation Report). Similarly, the RMP should be proportionate to the identified risks (HMA/EMA Guideline on Good Pharmacovigilance Practices Volume V – risk management systems) and therefore focus on those risks identified as important and so, again, only relevant information (including information on the effectiveness of risk minimisation measures) should be summarised in the RMP. ACRO therefore recommends that the proposed text is revised to make clear that only relevant PASS findings or information with potential impact on the benefit-risk evaluation should be summarised in PSURs and RMPs. Proposed change (if any): Revise the text to make clear that	

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		only relevant PASS findings or information with potential impact on the benefit-risk evaluation should be summarised in PSURs and RMPs.	
Line 583 AND Lines 589 - 590		Comment: It is not clear what the sentence “This provision should be applied to all PASS” means. Is it a legal requirement for all PASS or a recommendation? ACRO recommends that clearer wording is used. Proposed change (if any): Make clear whether the provision is a legal requirement or a recommendation for PASS that are not imposed by a competent authority.	
Lines 648 - 653		Comment: There may be circumstances in which multiple MAHs do not agree to conduct a joint protocol. Consequently, ACRO recommends that these lines are not deleted as proposed but are retained to describe how the competent authorities will act under such circumstances Proposed change (if any): Retain the text that is proposed to be deleted. ACRO thanks the EMA for the opportunity to submit comments on this consultation. Please do not hesitate to contact us if we can provide additional information (knoonan@acrohealth.org or +1 202 464 9340).	

Please add more rows if needed.