29 April 2018

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

Comments from:

Name of organisation or individual
The Alliance for Regenerative Medicine (ARM) is the preeminent global advocate for regenerative and advanced therapies. ARM fosters research, development, investment and commercialization of transformational treatments and cures for patients worldwide. By leveraging the expertise of its membership, ARM empowers multiple stakeholders to promote legislative, regulatory and public understanding of, and support for, this expanding field. ARM convenes all stakeholders with an interest in regenerative and advanced therapies to provide a unified voice for our 280+ member organizations, including companies – especially small- to medium-sized enterprises (SMEs); academic/research institutions; non-profit organizations; patients, and other members of the advanced therapies community. Our aim is to connect all parts of the innovation lifecycle to address the unmet needs of patients, particularly through supporting commercialization objectives via legislative and policy frameworks that enable next generation therapies to reach those who need them. To learn more about ARM, visit http://www.alliancerm.org. As for last year consultation on the same topic, the consultation document on Good Manufacturing Practices for ATMPs has raised significant interest and engagement from ARM members. This contribution represents the consolidated view of ARM members. The full list of members is provided at the end of this document. Transparency register number ID: 244710319190-73

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)*
	ARM welcomes the revision and the consultation on this guideline. Generally, the proposed guideline is comprehensive, well written, addresses most of the key points and provides detailed examples of risks and associated risk mitigation measures that will be very useful to ATMP developers.	
	ARM is in favour of a regular revision of this guideline to reflect the evolving experience and position of the EMA on these topics.	
	Compared to traditional medicines, ATMPs may differ in the extent of safety and efficacy follow-up required post-approval due to different intrinsic properties, duration of effect and their more frequent approval via conditional pathway. Notwithstanding this, the safety and efficacy follow-up and risk management must be commensurate to risks, in compliance with regulatory requirements such as defined in Article 14 of Regulation (EC) 1394/2007, and, overall, the requirements for MAH to adequately characterise the safety and efficacy profile of an ATMP pre- and post-marketing should not be significantly different as for any other type of medicinal product. A confirmation of this general approach in the introduction of the guideline would be welcome.	
	Considering that Article 14(4) of Regulation (EC) N°	

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	1394/2007 required the EMA to develop a detailed guideline related to post-authorisation follow-up of efficacy and adverse reactions, and risk management and in view of the existence of another guidance on "Follow-up of patients administered with gene therapy medicinal products", ARM proposes to clarify that this guideline deals with the post-authorisation follow-up by changing its title into 'Guideline on post-authorisation safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products'. Several sections of this guidance (Section 4 lines 165-173), Section 5 (all but 5.2) and Section 8 – lines 384-389, 403-404 and 472-474), contain safety considerations that are also relevant to the pre-authorisation setting. Whilst ATMP developers (often academics and SMEs) could benefit from an understanding of the articulation between pre- and post-authorisation safety expectations, it is unclear whether some pre-authorisation safety considerations should be included in this guidance. ARM recommends considering whether the statements that apply to pre-authorization evaluations should be consolidated in an initial section of the guidance to provide context and general pre-authorisation expectations. Alternatively, it could be evaluated	

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	whether the pre-authorisation safety expectations for ATMPs might best be incorporated into a separate (new) PV guidance or whether other existing guidance documents could be expanded to include such ATMP specific information (risk-based approach or GCP guidance?). Such guideline would also help understand the EMA views on prospective, pre-development risk analysis and risk mitigation plans. If it is determined that a pre-authorisation section will be added, we would offer the following additional considerations: • It is recommended to consider the role of usability testing in risk identification and mitigation. User errors may affect safety or efficacy (e.g. reconstitution, delivery of ATMP via a medical device). In many cases usability testing will detect errors in the preclinical phase. • The effectiveness of educational materials 7.2.2 should be validated in a clinical setting.	
	Overall the guidance provides a quite comprehensive and holistic approach toward the definition of safety and efficacy concerns to be addressed in the risk management plan and efficacy and safety follow-up studies. Following the executive summary, lines 76-77, and figure in section 5.1 the guideline would benefit from	

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	a deeper discussion in sections 8 and 9 on contribution of long-term follow-up of safety and efficacy toward cumulative evidence base for the product and implications for the iterative benefit-risk assessment. In particular, the specific context in which ATMPs impact the PSMF is not clear. The PSMF is routinely updated as information about the MAH's products changes, so any new MAs or changes to the PV system that are required to accommodate the specific requirements for ATMPs would be included on an ongoing basis. It is therefore requested to provide specificity about the impact of this guideline on the maintenance of the PSMF.	
	As was described in comments submitted when this guidance was originally issued in draft form (August 2008), the post-authorisation follow-up of efficacy and adverse reactions and risk management may be different for the various products types (somatic cell, tissue engineered, gene therapy, combined ATMPs). For example, while considerable time is spent on educational programmes (described in 7.2.2), based on the product type and setting for use, a significant educational programme may not be necessary. Section 8.4 is organized in a way that is particularly helpful for sponsors focusing on the development of a	

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	particular product type. Significant post-authorisation experience is available for tissue engineering products approved by EMA, yet it is not clear that recommendations specific to unique aspects of these product types have been included. ARM recommends to consider whether it is possible, in each section of the guidance, to clarify whether recommendations apply to all ATMPs or to specific ATMP types.	
	Additional regulatory guidance on the adoption of patient registries and other data sources (in addition to controlled clinical trials) to support safety and efficacy follow-up would be appreciated. ARM also suggests gathering guidance on relevant registries and other data source in a specific section of the guidance, rather than throughout the guidance. Would it be helpful to add reference to "Good Registry Practice" in addition to GCP in that section?	
	Relevant outcomes of EMA workshops on registries (e.g. the CAR-T registry workshop) should be incorporated in this guideline. Data from disease registries and product-based registries will likely be complementary in understanding use of the product in a specific indication.	

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	Due to the specificity of ATMPs, post-authorisation studies sponsored by the MAH for its product may necessitate the use of a product-based registry. We welcome further clarity on how EMA intends to align data collection in a ATMP-specific registry with disease registries to avoid duplication. Additionally, the flow of information between the registry holder, the MAH and regulators may not be so straightforward, with potentially direct access for regulators to the registry data and assessment of the data by the registry holder or a third party potentially without the involvement of the MAH, unless it is in relation to a mandated PASS or PAES. Registry holders and regulators have an important role to play in the long-term follow-up of ATMPs but this should be better explained and in context of the MAHs legal obligations. Most of the GVP modules are structured in this way with a section on 'operation in the EU network' where various roles and responsibilities of the key stakeholders (MAH and regulators) are elaborated and we feel a similar approach here would be beneficial.	

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)*
75-76		Comment: It should be emphasized that the extent of safety and efficacy follow-up activities should be proportionate to the specific risks of the ATMP and remaining uncertainty at the time of approval. We understand that ATMP development follows a more adaptive approach requiring cumulative evidence generation driven by data that is already being generated in ongoing and planned studies, which will reduce the level of uncertainty at the time of approval. As a consequence, the continuum of evidence should be a factor in determining the level of additional data on safety and efficacy in the planned follow-up studies. Proposed change: "It needs to be emphasised that both the S&E follow-up activities do not substitute for the adequate data to be provided at the time of marketing authorisation and enable a benefit-risk evaluation. The extent of safety and efficacy follow-up activities should be proportionate to the specific risks of the ATMP, the remaining uncertainty at the time of approval and consider evidence to be generated through the ongoing planned development."	
87		Comment: Combined ATMPs should be listed, consistent with the fact that combined ATMPs deserve specific considerations	

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		in the guideline. Proposed change: '…such as gene therapy, somatic cell therapy, ~~and~~ tissues engineered products and combined ATMPs"	
115-156 (Section 3)		Comment: In order to facilitate location of current guidance, could a link/links be provided to the location of relevant guidance (see example below)? For PV guidance, the following link: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001819.jsp&mid=WC0b01ac05800241de Alternatively, could relevant references be provided in an Appendix which references the need to consult EMA website(s) for updates? Additionally, it is suggested that the guideline be later updated with references to additional EMA guidance/recommendations of relevance, such as for instance those following the CAR T registry workshop.	
166-167		Comment: Regarding batch traceability, it would be important to know whether the GVP Module PII that requires explicit batch traceability statement to be included in the SmPC of all biologics will be applicable to ATMPs so that companies can plan for its implementation if applicable.	

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171-173		Comment: There is nothing specific for ATMPs in making this reference. The scope already states that GVP modules (including GVP Module III) apply (line 100); therefore, this statement is not needed here.	
179		Comment: Typographic mistake, comma should be deleted after new. Proposed change: "…they may cause new~~,~~ risks to patients."	
182		Comment: Detection of risks is done during development and in the post-marketing setting. Proposed change: "The detection of the risks should start early and continue throughout the development and lifecycle management of the ATMP…"	
189-190		Comment: "Only the safety concerns relevant to RMP should be added in the safety specification of the RMP as either as important identified or potential risks or missing information". This sentence is not clear and would benefit from rewording.	
192		Comment: Both PAES and PASS are likely to be relevant for safety and efficacy follow-up of ATMPs and should be referenced in this context. It is important to create a link to the risk-based approach and benefit risk assessment cycle as pictured in the figure above.	

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		Proposed change: "The content and extent of the RMP and any PAES and PASS must be proportionate to the risks of the ATMP and uncertainty, which may be reduced following the iterative benefit-risk assessments."	
194-196		Comment: The section on flow chart of the logistics of the therapy appears out of place in examples of safety concerns relevant to RMP. If the Agency wants to see a flow chart, it should be clarified in which section of the RMP it would be appropriate to include it. Furthermore, the meaning of 'clinical follow-up' in regard to 'flow chart of the logistics of the therapy' is unclear: does this refer to the fate of the product after administration, e.g. destruction at site, return to manufacturer, …? Proposed changes: • It is suggested to delete lines 194-196 or possibly, to consider its relocation earlier in the text. • The sentence in lines 195-196, if kept, could be changed into: 'A high level flowchart of the manufacture up to the administration of the therapy should include, harvesting, transport, controls, manipulations, conditioning, storage, and administration ~~and clinical follow-up~~. Please clarify which section of the RMP is appropriate to include a flowchart.	

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199-212		Comment: Does the Agency propose that the risks listed on lines 199-212 should be included as formal Safety Concerns in the EU-RMP or is the expectation that the MAH should conduct an assessment of the application for those risks to the specific product and then include as Safety Concerns only those risks that meet the GVP Module V criteria? Proposed change: Clarification on this question in the text would be welcome.	
199-212		Comment: A robust system for traceability, from cell/tissue collection to patient administration, is also an essential aspect for securing patient safety. Any risks related to traceability should be included in this section Proposed change: Add another bullet "Risk related to traceability, for instance an unforeseen break in the chain of identity."	
218-219		Comment: It is proposed to clarify the notion of conditioning and to replace "oncology" with "hematology/oncology" Proposed change: "Risks related to conditioning treatment prior to administration of an ATMP ~~of patients~~ (e.g. in case of CD34 positive genetically modified cells, in hematology/oncology in case of CAR T cells."	

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223		Comment: We suggest to not use the word "infection" with regards to vector administration as this terminology can be misleading. Proposed change: "Risks related to ~~infection~~ <u>administration</u> of vectors used in […]"	
253		Comment: It is proposed to clarify the wording Proposed change: "Replication-competent virus / vector might persist in the patient for extended periods and can <u>cumulate</u> ~~increase in amount~~."	
280		Comment: The mention of impossibility of retreatment may be misconstrued to apply to all ATMPs. It is proposed to delete this wording or to move it in front of the parentheses to indicate this applies to the example of graft dysfuction/rejection. Proposed change: "Treatment failure (e.g. graft dysfunction and/or rejection)~~, impossibility of re-treatment~~."	
298		Comment: Consider including additional examples that would be acceptable as active pharmacovigilance monitoring methods. We would consider that not all ATMPs (e.g. tissue engineered products) will be limited to administration in centres of excellence.	

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306-307		Comment: We would welcome clarity from the EMA on the options for the MAH to maintain contact with patients who have received these products in situations where there is no registry or other formalised non-interventional study. Does the EMA have examples of acceptable methods for patient tracking which are not via patient registries? If not, this would mean that the use of registries is indispensable to allow long term follow-up of patients.	
322-324		Comment: Considering that some Member States do not have restrictions on prescribing (physicians can prescribe any medicinal product approved in the country), it may be difficult for the MAH to control access to the ATMP. We would welcome the EMA view on how controlled access programmes and/or processes could be implemented to support controlled administrations in such situation.	
323-326		Comment: The previous version of the guidance seemed to allow specialised centres and did not mandate the centres to be accredited. This version of the guidance seems to emphasize on the selection of accredited centres. However, the Line 326 creates a slight uncertainty to the type of centres that is recommended to be selected. Accreditation would imply approval by an official body. It is proposed to replace accreditation by certification, i.e. a written assurance of conformity to specified requirements that could be left to the MAH's assessment and decision.	

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		Proposed change: "(…) by selecting <u>specialised</u> ~~accredited~~ centres and adequately trained and experienced physicians might be necessary. Selection and ~~accreditation~~ <u>certification</u> of specialised centers by MAHs and/or NCA (…)".	
Footnote page 10		Comment: Typographical error Proposed change: '(…) Article 15 of Regulation (EC) No 1394/20~~0~~17 (…)'	
332 -362		Comment: The addition of clarity about the educational materials is welcome. However, the sub-division of educational materials by target groups is not always clear: • The role of nurses and other clinical support personnel involved in the administration and treatment processes should be acknowledged. • It is not clear what is meant by 'personnel' on line 363 and why the paragraph on lines 363-366 could not be integrated with the previous one. The information mentioned on lines 364-366 is also useful to healthcare professionals. Proposed change: We propose to group together a category as follows "Educational materials for treating physicians, <u>and other healthcare professionals</u> relating to: (…)", possibly identifying within this category which are the materials more	

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		specifically intended for a sub-group of those. Materials for healthcare professionals could also include the information mentioned on lines 364-366. A second category could group together materials for patients, family and/or caregivers. An alternative option could be to list the different types of materials and indicate which are the target groups for each of these.	
347-349		Comment: The term patients' protection in this context is not clear. Proposed change: "Patients' ~~protection~~ safety, including – where appropriate -…" Comment: It is not clear what information on "disease registry" MAHs are expected to provide as educational materials to treating physicians if the MAH is not the registry holder. Reference to a disease registry here appears misleading, it would be more appropriate to mention post-authorisation studies which are sponsored by the MAH. Proposed change: "…on reporting of patient clinical information, treatment outcomes and adverse effects in the relevant ~~disease registry~~ post-authorisation study".	
361-362		Comment: Please refer to comment regarding line 349	

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		Proposed change: "the importance of reporting other information required in the post-authorisation studies ~~arising from the disease registry~~ that are relevant for the ATMP."	
353-362		Comment: The importance of being followed up should also be included in the educational materials for patients (and/or caregivers). Some ATMPs will require much longer follow-up than with conventional products and patients need to be aware of this otherwise MAHs will have difficulty completing post-authorisation studies due to patients being lost to follow-up. Proposed change: Add a bullet "the importance of compliance with follow-up procedures"	
367-369		Comment: To avoid confusion, it is suggested that the proposed wording for educational materials reflects the guidance in GVP Module XVI Addendum 1- educational materials, or that a cross-reference be provided instead. Proposed change: 'When applicable, key elements ~~an English draft version~~ of the educational materials should be ~~submitted for evaluation and~~ agreed as part of the marketing authorisation application. Thereafter, drafts of the educational material(s) addressing the key elements should be submitted to ~~This will serve as a basis for the implementation with~~ the	

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		NCAs in the Members States for assessment and implementation upon approval.'	
376		Comment: The word 'large' may not be sufficiently defined Proposed change (if any): "If there is a trend reflecting ~~a large number~~ a significant increase of adverse events…"	
386-387		Proposed change: "…to enable benefit-risk assessment of the products on an ongoing and continuous basis in line with the ATMP Regulation…"	
390		Comment: While it is recognized that there may be studies imposed in the post-marketing setting for several types of ATMPs, this may not be true for all. In these latter cases, general active surveillance will be adequate. Line 390 states, "When studies are imposed at the time of granting the MA…", which infers that the remainder of the section is only applicable to PAS, rather than general active surveillance that could feed into the understanding of S&E. Proposed change: Consider removing: "When studies are imposed at the time of granting the MA" so that the scope of the section is all efforts on efficacy and safety monitoring."	
397-399		Comment: As this is the first mention of the data sources for efficacy and safety follow-up, we recommend adding reference	

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		to use of Real World Evidence ("real-life" setting referenced later in the document) to the sentence beginning with "The use of disease registries…."	
430-434		Comment: Typographical error on line 430 that says specifically. Proposed Change: Replace specifically with specify or other language as appropriate.	
448-450		Proposed change: "…in relation to its primary objective <u>to reliably reflect real world use as closely as possible."</u>	
482		Comment: The addition of an estimated follow-up period is welcome as the previous guidance version stated only life-long follow-up which was very vague. However, we would appreciate that the agreement on the follow-up duration is left to the MAA assessment, and discussion between the MAH and the CHMP based on risk-based approach, as this could be ATMP-specific. It is appreciated that this statement is present in the guidance (Line 483). For example, 15 years may be justified for young children, and 10 years may be sufficient for adolescents and adults. Proposed change: "… it is ~~usually expected~~ <u>advised</u> to follow-up the patients up to 15 years<u>, unless shorter periods of</u>	

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		observation may be appropriate based on supporting evidence and/or ATMP specific risk-based approach."	
503-506		Comment: As many products in development are in the oncology field, we propose to use another example in addition to the TEP example provided in this paragraph. Proposed change: Add a sentence such as the following: "In oncology, endpoints selected for post-authorisation safety and efficacy follow-up studies should reinforce the durability of surrogate endpoints used for approval and confirm the long-term effect."	
507-514		Comment: The need for long-term safety & efficacy studies and the design of such studies should consider the integration of cumulative body of evidence generated in the iterative development plan for additional lines of therapy and / or different patient populations. Considering different existing statistical approaches, non-comparative designs may also be informative in the perspective of the totality of evidence available.	
515-516		Comment: It is proposed to clarify the understanding of the paragraph by some rephrasing. Proposed change: "Similarly to conventional medicinal products, feasibility aspects, such as design and duration,	

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		should be taken into consideration along with the research objective when designing post-authorisation studies. Some options include: • An observational study… • An "exploratory study… • A "pragmatic" study…"	
519		Comment: We wonder whether the Agency means 'exploratory clinical trial' rather than 'explanatory clinical trial' Proposed change: Consider replacing 'explanatory' by 'exploratory'.	
529-531		Comment: Long term follow up is appropriate for many ATMPS, but the concept of a replaced tissue becoming or remaining "fully functional" may be difficult to define. The focus of long term follow-up should be on measurable patient outcomes. Proposed change: "Longer follow-up lay be required to fully assess the duration of efficacy ~~and at which point the replaced tissue becomes/continues to be fully functional~~."	
555-557		Comment: The guideline acknowledges that "*Biomarkers can be used to learn more about differential efficacy or benefit-risk across strata of the disease (e.g. by mutation status or other disease classification) or based on a targeted mechanism of*	

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		action of the ATMP". ARM would like to emphasize that developing companion diagnostics (CDx) can be very helpful for ATMPs. A CDx can represent the best way to prevent SAEs such as cytokine release syndrome for CAR-T cells therapies for instance. The usefulness of developing CDx could be clarified in this revised guideline, so the ATMP developers can take it more into consideration when designing long-term follow-up studies.	
564-569		Comment: Section 8 does not mention objectives for long-term follow-up safety of tissue engineered products. It is therefore proposed to add for these products.	
610		Comment: It is not clear exactly how the signal detection and monitoring is expected to be 'optimised' for ATMPs. Proposed change: Please clarify how the signal detection and monitoring should be 'optimised' for ATMPs.	