30 October 2018

Comments on the Consultation Document: Good Clinical Practice for Advanced Therapy Medicinal Products

Comments from:

Name of organisation or individual
Alliance for Regenerative Medicine (ARM) 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 300+ 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. Transparency register number ID: 244710319190-73

1. General comments

General comments	
Support of the approach	ARM welcomes the opportunity to comment the new draft guideline specific to Advanced Therapy Medicinal Products that the European Commission has developed with the European Medicines Agency and the expert group of the competent authorities of the Member States. The consultation document focuses on ATMP specificities only and is to be applied in addition to the GCP Guidelines of The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ARM is in strong support of such approach and is pleased to send herewith comments from its members for consideration in finalising the guideline.
Change from prior guidance	ARM notes that some of the information contained in the previous guidance dated 3 Dec 2009 has been removed. In particular: - the 'Definitions' section has been removed - section 7 on 'Traceability' was longer and more detailed and a 4-page 'Annex-Traceability records' spelling out the responsibilities for multiple parties on traceability has been removed. - section 15 on 'Essential documents' describing document that should be available in the investigator and sponsor files has been removed and is missing in the new guidance. ARM is in favour of providing more details, with definitions and more guidance on traceability requirements and responsibilities. It is requested to consider re-including the information provided in the former guidance.
Overlap with 'Handling & shipping IMPs' guideline'	Several sections relate to handling of IMPs and may therefore more appropriately be included in the 'Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice' which was recently released for consultation (ref: EMA/202679/2018, dated 26 April 2018) . ARM provided comments to this guideline and questioned whether it is applicable to ATMPs or not. If applicable to ATMPs, ARM recommends incorporation of the following sections into this guideline, with the GCP guideline providing a cross-reference to the 'handling & shipping IMPs' guideline: - Section 3.2. – Reconstitution - Section 4.0 – Storage, transport, handling

General comments	
	- Section 7.0 – Retention of samples - Section 8.3 – Administration of out of specification products
References to other relevant guidelines	This guideline should focus exclusively on aspects that are specific to GCP with ATMPs and should avoid any duplication with other existing guidelines. As several other guidelines are applicable to ATMPs, it would be helpful to add a section or an annex to have the list of other relevant guidelines, EudraLex Volume 10 being added and cross-referred to in this guideline. In addition, as these Guidelines are to be read in conjunction with the ICH guidelines and good clinical practice guidelines ('plus/minus' approach), it would be useful to insert cross-reference to other relevant guidelines in each section. For example, informed consent has already been described for Clinical Trials in ICH E6 section 4.8. It is suggested that the guidance should indicate which item(s) from ICH E6 do(es) not apply to ATMPs, or in addition to all items in Section 4.8 of ICH E6, what else should be followed. Each section of the document should reference all applicable regulation/guidelines and identify what is added and what is not required.
Addition of a section with definitions	Convergence of definitions given to some specific terms (e.g. reconstitution) must be ensured across all guidelines for ATMPs. It would be helpful to include a section with definitions, including the different types of ATMPs, and any other terms used in the context of ATMPs.
Administration of out of specification products (section 8.3)	Convergence of regulatory guidance on the administration of out of specification products is required. Specifically, ARM recommends harmonisation with the Guideline on Good Manufacturing Practice for ATMPs, as adopted by the European Commission on 22 November 2017 (EudraLex Volume 4, Part IV). Making an out of specification product available to a patient on individual case-by-case basis does not fit the criteria for notification as an urgent safety measure (USM). USMs should be reserved for scenarios where a safety signal was detected, and an action had to be taken for the safety of patients and physicians need to be informed accordingly. Additionally, the responsibilities for the sponsor, and in particular the Qualified Person (QP), should be clarified. As a QP cannot release a product out of specification, some sponsors seek administration under a compassionate use framework (or 'specials' in the UK) so that administration can be carried out under the physician's responsibility. It is requested whether this approach is necessary or whether alternative options are available. More details, with examples to better clarify responsibilities for the QP (batch certification, batch release?), the sponsor and the investigator should be provided.
Collection/extraction of	In an autologous setting, the subject must undergo a medical intervention to collect cells/tissues prior to the manufacture and

General comments	
the cells/tissues	administration of the ATMP. Whilst these activities need to comply with GMP requirements, some will also need to comply with GCP requirements. The specific items which need to be governed by GCP relating to the collection of cells/tissues (including trial design, patient consent, collection procedure, traceability, biovigilance) are insufficiently covered in the proposed draft document, particularly when compared to specifics relating to the ATMP administration procedure. For example: - The possibility of having a blinded controlled study when cells/tissues need to be collected in an autologous setting may be challenging; such considerations should be added in section 3.1. 'Specific considerations concerning the protocol'. - Upstream interventions on subject should be added as a specific consideration in the Investigator's Brochure (section 3.2) - Potential risks associated to the collection of cells & tissues should be added in the information on the product in (section 3.2), safety of the clinical trial subject (section 3.2), and informed consent of the clinical trials subjects (section 8.1) - The need for training of the investigator and/or the presence of the sponsor during the collection procedures should be considered in the same way as for administration procedures in section 5. - Adverse events possibly related to the collection procedure should be considered in the safety reporting (section 9.) It would be helpful to reconsider each section having in mind cell/tissue collection-related aspects that are specific to the clinical testing of autologous ATMPs and relevant to GCP, with cross-reference to other existing guidelines where available.

2. Specific comments on text

Section and Line numbers	Comment and rationale; proposed changes
Section 1.1. – Lines 65-66	Comment: In line with the general comment above, to prevent confusion as to which guidance GCP guidance is applicable i.e. ICH or ATMP, it would be useful to indicate that ICH is applicable where specific ATMP guidance is not provided, and replace duplicated information with a cross-reference instead. Proposed change: It is proposed to change these 2 sentences as follows: *These Guidelines are to be read in conjunction with the ICH guidelines[2] on good clinical practice, which are also applicable to ATMPs. ~~To the extent that there is a difference in the requirements, the content of these Guidelines should prevail.~~ Where ATMP GCP guidance differs from ICH, specific guidance is provided herein.*
Section 1.2. – Lines 75-76	Proposed change: The following change is proposed, for sake of clarity: *Moreover, it is recognised that it may not always be feasible to generate ~~relevant~~ preclinical data ~~before the product is tested in humans~~ that are predictive for the human response.*
Section 2.(i) – Lines 95-105	Comment: Considerations under Bullet 2 relate to clinical trials involving paediatric populations but do not focus on ATMP specificities. It would be helpful to add some ATMP examples addressing aspects of paediatric trials that more specifically apply to ATMP development and are not currently addressed in other existing guidelines or regulations. Proposed change: ARM recommends providing some examples of specific considerations related to the risks and benefits for paediatric patients participating into clinical trials involving administration of ATMPs.

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Section 2.(i) - Lines 103-105	Comment: Where prior adult studies should have been performed prior to clinical trial in a paediatric population, please clarify to what extent adult data should be available as this could affect timing or initiation and development in paediatrics. Should adult studies be completed? Is establishment of risk benefit sufficient, or proof of concept and safety sufficient? A requirement for adult data prior to paediatric studies would preclude adolescents entering adult studies and delay paediatric study start. It is suggested to add examples where prior adult studies may not be relevant. Proposed change: Suggest amending as follows: *Prior studies in adults should have been performed if feasible for the condition in question, or else a rationale should explain why these are unethical, not feasible or not relevant (e.g. in cases of diseases exclusively affecting paediatric patients). <u>If the condition to be treated is similar in adults and adolescents, then adolescents could be included in the study.</u>*
Section 2. (ii) - Lines 111-114	Comment: A cross-reference to the Benefit/Risk section of the protocol can be beneficial.
Section 2. (ii) – Lines 111-114	Comment: Since this guidance is specific to Good Clinical Practice, ARM advises eliminating disease specific guidance which might be best offered in scientific guidance. With regard to tissue based therapies, we would submit that intra-subject controls are appropriate when systemic effects can be definitely ruled out *and* when the internal control is known to be truly independent. In practice these criteria are likely to be very difficult to meet for most ATMPs. Intra-subject control may be appropriate in other situations, not just for investigation of local effects e.g. pre- and post-treatment protein/enzyme levels for an established surrogate marker. It is suggested to provide additional examples. Proposed change: ARM proposes to add an example as follows: *(ii) For some ATMPs, an intra-subject control might be appropriate. For example:*

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	• *the investigational product could be injected into one eye and the untreated eye is used as a control.* • *To investigate pre- and post-treatment biomarker levels for an established surrogate* *Comparison of local effects or pre- and post-treatment effects can be facilitated in this way by eliminating inter-subject variation.*
Section 2 (iv) - Line 121-122	Comment: It is proposed to add a reference to the informed consent form (ICF) as the document where the risk posed by the procedure should be explained. Proposed change: *The risk posed by the procedure should be duly explained in the protocol and the informed consent form.*
Section 2 (v) - Lines 127-130	Comment: It is suggested to refer to the observed non-clinical safety margin for the therapeutic dose to be given in once only administrations. Proposed change: *In early phase trials where it is not possible to re-administer the product (e.g. certain gene therapy) or when the re-administration involves the additional risk of a surgical procedure, the exploratory dose chosen should aim to be a therapeutic dose for the subject, taking the observed non-clinical safety margin into consideration.*
Section 2. (vi) – Lines 131-133	Comment: This consideration is not specific to the testing of ATMPs. This paragraph could also be reworded to better emphasize that staggered treatment is required and its absence should be duly justified. The current wording 'should be considered as appropriate' seems not strong enough. Proposed change: ARM recommends rewording this sentence as follows: *Depending on the degree of safety concern, in early phase clinical trials, the absence of staggered treatment of individual subjects*

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	within each new cohort and between cohorts should be duly justified. Adding some examples that would be specific to the staggered administration of ATMPs would also be helpful.
Section 3 - Lines 141-143	Comment: The term "in accordance" on line 142 is vague, the directive is transposed at national level and the requirements vary slightly from country to country. It may be helpful to add guidance text for 3rd countries where the principles of the EUTCDs will be followed Proposed change: The following rewording is suggested: *The confirmation that the donation, procurement and testing of the cells and tissues used as starting materials are ~~in accordance~~ in compliance with Directive 2004/23/EC or Directive 2002/98/EC.*
Section 3.1(i) – Lines 151-154	Comment: Please clarify the level of information on 'release specifications' to be included in the protocol. Detailed information on 'release specifications' should be provided in the investigational medicinal product dossier (IMPD). Information required in the protocol should be limited to a discussion on the potential variability due to the nature of ATMP. Proposed change: The following rewording is suggested: *(i) Release specifications: The variability in the nature of the ATMPs (in particular in the case of autologous products or allogeneic products in a matched donor scenario), should be duly considered when defining the release specifications (e.g. cell numbers/range of call number, transduction efficiency) in the investigational medicinal product dossier. A discussion on the potential variability may be included in the protocol with reference to the IMPD.*
Section 3.1. (ii) - Lines 160-161	Comment: The presence of inactive particles may also interfere with transduction and reduce the potency of an ATMP. It is suggested to reword this example. Additionally, it would be helpful to elaborate the definition of inactive particles, with examples, to avoid any

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	possible confusion with inactive ingredients/excipients. Proposed change: *Early phase clinical trials should attempt to define the dose range to be used in the pivotal trial. However, unique difficulties may arise in determining the dose for some ATMPs in early phase clinical trials, for example:* • *The cells that are active may be difficult to identify and may be different from those causing adverse drug reactions (ADRs).* • *In some instances, the ATMP may contain inactive particles (e.g. empty capsids or virus-like particles) which may impact ~~assist in the mechanism of action of the ATMP, for example~~ ~~in~~ transduction efficiency and potency.* • *For some autologous products or subject specific allogeneic donor products, the cell numbers may vary for each dose due to the intrinsic variability of the starting materials.* *Therefore, it is acknowledged that in the case of some ATMPs it may not be possible to perform formal dose finding studies.*
Section 3.1. (v) – Lines 180-181	Comment: In practice, detailed information on product handling (including containment and disposal) is normally presented in a separate document (for example, an Investigational Product Preparation Instructions) available at the sites. Proposed changes: It is recommended to revise this section as follows: *(v) Safety conduct:* *Detailed information should be provided on the product handling, containment and disposal. If this information is provided in a separate document, the protocol should reference that document.*
Section 3.1. (vi) - Lines 184-185 and Section 3.2. (vi) - Lines 268-271	Comment: Each of these sections refers to risk minimisation measures and different language is used to describe measures that should be taken? It should be clarified whether this information is needed in both the protocol and the Investigation Brochure (IB), or in one of these documents only. In addition, the measures to be taken should be clearly described. It would be helpful to represent each circumstance that can be conceived as separate items with the recommended risk-minimisation measures provided where possible.

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	Proposed changes: We recommend modifying this section as follows: *(vi) Risk-minimisation measures:* *Where appropriate, information should be provided on the measures that should be put in place to protect clinical trial subjects from identified risks. ~~For example, if the results of the sterility test of the product are not available at release, appropriate mitigation measures should be implemented, including liaison with clinical staff where out of specification test results are obtained after the release of the product.~~ Known examples include:* *- Sterility: if the results of the sterility test of the product are not available at release, appropriate mitigation measures should be described.* *- Out of specification test results (see Section 8.3.)*
Section 3.1. (viii) - Lines 197-198	Comment: Regarding the duration of the follow-up and the example given for gene therapy for integrating vector, current expectations may evolve as we gain cumulative experience and knowledge. Integrating vector technology has advanced significantly in recent years to improve safety. Rather than a standard approach of 15 years follow-up for gene therapy medicinal products using integrating vectors or having the potential for latency followed by reactivation, duration of follow-up should be based on the specific construct and characteristics of the product. The scientific justification for the expectation of 15 years follow-up should be included if this is expected. Proposed change: It is suggested to reword as follows: *The follow-up strategy should be based on a risk assessment having regard to all information available to the sponsor. This strategy may need to go beyond the end of the trial. For example, in the case of gene therapy medicinal products using integrating vectors, a follow-up of up to 15 years after administration ~~is~~ may be expected; a shorter duration of follow-up may be considered based on the specifics of the construct and/or characteristics of the product.*
Section 3.1. (ix) - Lines 204-209	Comment: In early development when the mode of action/classification of the product may not be clear, and/or when the device is not to be

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	approved separately, there may be little information that can be provided on the medical device until more is known about the product i.e. later in clinical development. It might therefore be difficult for early phase clinical trials. A more detailed guidance on what information is required would be helpful. This information would be more appropriate on the IMPD. Is this information relevant for the clinical protocol?
Section 3.2. (iv) - Lines 253-254	Proposed change: The following change is proposed, for sake of clarity: *Where appropriate (i.e. in the case of complex ~~reconstitution~~ administration procedure), training should be provided to those involved in the ~~reconstitution~~ process and documented.*
Section 3.2., (viii)– Lines 278-279	Comment: In practice, detailed information on traceability (Chain of Identity/Custody) is normally provided in the Investigational Product Preparation Instructions (IPPI) and not the protocol. Proposed change: It is recommended to modify this section as follows: *(viii) Traceability:* *In practice, detailed information should be provided on the measures that should be followed to ensure traceability of the cells/tissues contained in ATMPs. If this information is provided in a separate document, the protocol should reference that document.*
Section 5 – Lines 304-310	Comments: Lines 307-310 state that the presence of the sponsor during the administration of the ATMP to the clinical trial subject 'may be justified for reasons related to the protection of the clinical trial subjects or to detect and prevent errors of administration'. It would be helpful to provide some additional examples of circumstances where the presence of the sponsor during the administration procedure could be justified. ARM believes that the role of sponsor should be advisory and should not involve the provision of

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	healthcare. As mentioned in the previous guidance dated 03/12/2009, "*This expert (a representative of the sponsor experienced in the administration of the ATIMP) may provide advice and information to the investigator/responsible physician but the investigator/responsible physician remains responsible for any decision to halt or modify the application procedure.*" The word 'exceptionally' on line 307 is confusing: it is not clear whether this means that the presence of the sponsor is exceptional or whether that the fact that the presence of the sponsor has not been foreseen from the outset of the clinical trial and the clinical trial subject not informed *a priori* is exceptional. Finally, the word 'a posteriori' on line 310 is also confusing: does this mean that the clinical trial subject can be informed after the administration occurred? Proposed changes: Consider amending as follows: *The presence of the sponsor (or a representative thereof) during the administration of the ATMP to the clinical trial subject is only acceptable if it is duly justified. The role of the sponsor should be advisory and not involve the provision of patient care. [Add examples of situations where the presence of the sponsor would be justified]. If the presence of the ~~administration~~ sponsor during administration is envisaged before the start of the clinical trials this should be explained in the informed consent. If~~, exceptionally,~~ the presence of sponsor (or representative thereof) has not been foreseen from the outset of the clinical trial but is justified for reasons related to the protection of clinical trial subject or to detect and prevent errors of administration, exceptionally, the clinical trial subject should be informed ~~a posteriori~~ before administration of the ATMP.*
Section 6 - Lines 329-332	Proposed change: The following change is proposed, for sake of clarity: *The requirements for traceability are without prejudice to the provision Regulation (EU) 2016/679 (GDPR) of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data*

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Section 7 - Lines 338-342	Proposed change: *Due to this intrinsic limitation, it is justified not to keep samples of investigational medicinal product in the case of autologous ATMPs and certain allogeneic ATMPs (matched donor scenario) if this is not possible. In ~~other~~ all cases where the scarcity of the materials is also a concern, the sampling strategy may be adapted provided that this is duly justified.*
Section 8.1. – Lines 350-360	Comments: It would be helpful to add considerations regarding the informed consent and the practice to be adopted when genetic testing of cells is needed for product release and/or characterisation purposes (including the management of information that is generated as a result of this testing and is of potential interest for the patient, such as the extent of information to be provided, the transfer of such information, information on genetic mutations which may potentially have an impact on patient's health, etc.). As part of the informed consent procedure, the participant should also be informed about GDRP.
Section 8.2.4. - Lines 395-400	Comment: Patient alert cards are not specific to ATMPs and are covered by Eudralex Volume X. If needed, a sentence clarifying what happens when there is a change in sponsor would be welcomed.
Section 8.2.2. – Lines 373-383	Comments: It should be clarified how the arrangements for follow-up should be prospectively anticipated in cross-border situations where a subject travels to another country for treatment and returns to their home country during the follow-up period. Compliance with national laws of each country should be required. In the case of ATMPs which require long-term follow-up tracking, the movement of patient on an on-going basis from one country to another can present additional administrative challenges and may raise privacy concerns. The expectations and responsibilities for sponsors as well as investigators in the situation of remote follow-up should be clearly defined. Proposed changes: Consider adding:

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	'The clinical investigators should notify the study sponsor when a patient plans to move to another country. This will allow the Sponsor to submit a clinical trial application in the new country, if not already in place'
Section 8.3. – Lines 402-403	Comment: Please clarify that release specification should be defined in the IMPD (please see comment on section 3.1.). Proposed change: The following rewording is suggested: *'As explained in Section 3.1, the variability in the nature of the ATMPs should be taken into account when defining the release specification in the investigational medicinal product dossier in order to avoid or limit the occurrence of out-of-specification products.'*
Section 8.3. – Lines 404-413	Comment: Please clarify that treatment of a patient with an out-of-specification product made available to a patient and accepted by the investigator in accordance with this guideline does not require prior notification or approval from the National Competent Authority (NCA). This is critical to ensure timely access to potentially life-saving investigational products in populations with an unmet need. It would be helpful to ensure convergent regulatory advice on the handling of such situations. Specifically, ARM recommends harmonisation with the Guidelines on Good Manufacturing Practices for ATMPs, adopted by the European Commission on 22 November 2017. Notification as a 'breach of predefined specifications' should be sent to the NCA within 14 days after administration. The documentation required for notification should be harmonised and could include the investigator's request, the RBA and a CMC rationale supporting administration of the product. A decision whether to administer an out of specification product should be made based on the benefit-risk for the patient. If there is potential for benefit and risks are acceptable, then the product should be administered. The need for urgency may be a result of the impending expiration date, not an immediate need for the patient, as the benefits may be long term.

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	Making an out of specification product available to a patient on individual case-by-case basis does not fit the criteria for notification as an urgent safety measure (USM). USMs should be reserved for scenarios where a safety signal was detected, and an action had to be taken for the safety of patients and physicians need to be informed accordingly. Some sponsors currently seek administration under a compassionate use framework (or 'specials' in the UK) so that administration can be carried out under the physician's responsibility. It is requested whether this approach is necessary or whether alternative options are available. The consequences in term of data analysis should also be clarified. Additionally, the responsibilities for the sponsor, and in particular the Qualified Person (QP), should be clarified. See also comments under 'General comments' above. Proposed changes: The following rewording is proposed: *'Exceptionally, in case where the release specifications as set out in the ~~protocol~~ IMPD are not met but ~~the administration of the cells/tissues that are contained in a cell/tissue based ATMP is necessary to avoid an immediate significant hazard to the subject~~, the benefit:risk ratio of the administration of the cells/tissues that are contained in a cell/tissue based ATMP is evaluated to be positive, taking into account the alternative options for the subject and the consequences of not receiving the cells/tissues contained in the product, the supply of the product to the investigator is justified.* (…) *'The confirmation of the investigator to accept the product should be recorded by the sponsor ~~and the relevant competent authority should be notified of such events (as an urgent safety measure or breach of predefined specifications)~~.* *A patient can be treated with non-conforming product without prior notification or approval from national competent authority. In such case, notification by the sponsor to the relevant competent authority may be made after administration as a breach of predefined specifications. Notification should include the investigator's request, the sponsor's risk assessment and a rationale supporting administration of the product.'*
Section 10 - Lines 439-440	Comment: The language of this sentence is rather broad and not specific to ATMPs. ARM recommends to limit the text of the guideline to specific considerations for ATMPs, with a cross-reference to other guidelines as relevant. Further guidance on what is meant by

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	"adequately monitor" for ATMPs would be welcome, with additional examples of any specific requirements for monitoring clinical trials with ATMPs.