ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

9 October 2018

Directorate-General for Health and Food Safety
Unit SANTE B/5
European Commission
BE-1049 Brussels

RE: ACRO comment on European Commission public consultation on:
Targeted stakeholder consultation (TSC) on the draft Guidelines on Good Clinical Practice (GCP) for Advanced Therapy Medicinal Products (ATMPs)

Association of Clinical Research Organizations (ACRO)
EU Transparency Register public ID number: **150920420956-26**

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 post-approval and pharmacovigilance research. With 57,000 employees in Europe engaged in research activities (and more than 130,000 around the world), ACRO members advance 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 the European Commission's consultation document on good clinical practice (GCP) for advanced therapy medicinal products (ATMPs). In particular, ACRO welcomes the recognition that ATMPs are complex and innovative products that may pose specific challenges to the design and conduct of clinical trials, and therefore that GCP requirements for clinical trials with these products must be sufficiently flexible, while meeting ICH E6(R2) GCP standards utilising a risk-based quality management approach to clinical trials, to take account of the specific characteristics of individual products and trials. ACRO is pleased to provide the following specific comments on the consultation document.

Comments
Lines 98-102:
ACRO welcomes the recognition that "in some other cases (e.g. severe genetic diseases), treatment of the subject at a very young age may be necessary without a staggered approach", which recognizes the ethical and pragmatic need to include relevant patient populations in the clinical development programme. To some extent, however, this is negated by the preceding statement that "in some cases, it may be advisable to stagger trials by age i.e. first enrolling subjects between 18 and 12 years, then between 12 and 6 etc." Together, the two statements imply that, unless there are compelling reasons not to do so, the "staggered" approach should be used. This appears counter to the European Commission's guideline on Ethical Considerations for Clinical Trials on Medicinal Products Conducted with Minors (dated 18 September 2017), which states that "a 'staggered' medicine development approach, starting by the older and going sequentially to the younger age groups, may lead to delays in data availability, and result in prolonged off-label use in younger age groups."

ACRO acknowledges that the clinical development of ATMPs presents challenges that are not seen with conventional medicines but maintains the view that clinical trial programmes for all medicines should be sufficiently flexible to ensure inclusion of appropriate patients without delay if the benefit-risk assessment supports this. Consequently, ACRO recommends the deletion of lines 98-102 as the remaining statement in lines 95-98 provides adequate guidance: "When the clinical trial subjects involve a paediatric population or foetuses (in utero treatment), consideration should be given to the implementation of additional safeguards, which should be adapted to the specific characteristics of the product, the treated disease and the developmental stage of the population."

Lines 193-198:
ACRO agrees that long-term follow-up of subjects who receive an ATMP may be necessary "based on a risk-assessment having regard to all information available to the sponsor" and that this "may need to go beyond the end of the trial". However, ACRO is concerned that the statement which follows ("in the case of gene therapy medicinal products using integrating vectors, a follow-up of 15 years after administration is expected") may be too dogmatic. The evidence supporting this proposed requirement is not referenced in the draft guideline and there may be situations where shorter or longer periods of observation would be more appropriate. Consequently, ACRO recommends that lines 196-198 are replaced with the following: "This strategy may require an observation period for many years beyond the end of the trial. The appropriate observation period should be determined as part of the risk assessment, taking into account the observed duration of *in vivo* vector persistence, the observed duration of *in vivo* transgene expression, the prior, concomitant and post-gene therapy exposures of the study population, the expected survival rates of the study population, and other factors that may be relevant to the feasibility and scientific value of conducting long-term follow-up observations."

Line 209:
We believe the phrase "Medical Regulation 2017/7457" should read "Medical Device Regulation 2017/7457".

Line 255:
We believe the phrase "When the administration process is not standardised" should read "When a standard administration process is not used".

Line 297:
"The administration procedure should be clearly explained by the sponsor"; We suggest to add something like: …should be clearly explained by the sponsor, and documented in …Or: ..clearly explained and documented by the sponsor.

Line 305:
This currently states "If the presence of the administration is envisaged before the start of the clinical trial, this should be explained in the informed consent." We believe "administration" should be replaced with "sponsor (or a representative thereof)".

Line 310:
We recommend that the phrase "the clinical trial subject should be informed *a posteriori*" should be amended to read as follows: "the clinical trial subject and the relevant ethics committee should be informed *a posteriori*"

Lines 312-315:
We suggest to add 'chain of custody' within this section, as this appears to be what is meant here.

Lines 321-328:
Given the importance of traceability requirements to subject safety, ACRO recommends that this paragraph should be expanded. The last sentence of the paragraph states "In the case when the sponsor ceases to exist, the custody of the traceability data should be discussed with the competent authorities." However, it does not specify who is responsible for initiating this discussion if the sponsor no longer exists. Further, changes are possible for all actors in the traceability chain (manufacturers may also cease to exist, investigators may retire) and therefore ACRO recommends that the guideline should set out in detail the responsibilities of each of the relevant parties should they cease to operate.

Lines 347-348:
ACRO agrees with the concept that "In cases where a sample of the investigational product cannot be kept, photographs or copies of the label should be retained". However, given that it is possible for both photographs and copies to be manipulated, ACRO recommends that the sentence is amended to read as follows: "In cases where a sample of the investigational product cannot be kept, photographs or copies of the label, certified as true copies, should be retained

or, in the case of digital photographs or copies, the associated metadata should confirm that the image has not been altered."

Line 376:
We believe the phrase "a long period time" should read "a long period of time".

Line 378:
We believe the word "Detail" should read "Detailed".

Line 379:
We recommend that the sentence currently ending "…..an associated document" should end with "…..an associated document referenced in the protocol."

Lines 379-383:
In accordance with requirements set forth for long term follow-up, most protocols include the long term - follow-up scheme. We recommend that more explanation is provided regarding the expectation for approval to be asked from Member States/EAA countries involved in the long term follow-up, but not in the treatment period, when treatment period and follow-up are described in a single protocol.

Lines 384-393:
This section appears to be no different than what occurs in any other type of trial and so may not be required.

ACRO thanks the Commission for the opportunity to provide comments on this Targeted stakeholder consultation (TSC) on the draft Guidelines on Good Clinical Practice (GCP) for Advanced Therapy Medicinal Products (ATMPs).

Please do not hesitate to contact ACRO if we can provide additional details or answer any questions at all.

Respectfully submitted,

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