Stakeholder consultation on the document Good Clinical Practice for Advanced Therapy Medicinal Products

31 October 2018

To whom it may concern,

We welcome the opportunity to comment on the **Consultation Document Good Clinical Practice for Advanced Therapy Medicinal Products**.
University College London (UCL) has a particular interest and expertise in the development of novel gene and cell-based therapies. The comments below represent the feedback from three UCL Clinical Trials Units who design, conduct and analyse academically sponsored clinical trials with advanced therapies.

1.1 Scope

General comment: There are no references to Directive 2005/28/EC.

3.1. Specific considerations concerning the protocol

General comment: Detailed instructions of the cell/tissue procurement procedures are often contained in separate study specific documents (e.g. SOPs, work instructions) provided to the site, which are referred to in the protocol.

Section 3.1 (iii) - Rows 167 to 172: suggestion to include also allogeneic setting

The example describes the autologous situation, however similar risks to the donor and product exist also in the allogeneic setting.

Row 171: There is a full stop missing at the end of the sentence.

Section 3.1 (vii) and (viii) - Rows 187 to 200: additional guidance would be helpful

In regards to long term follow up, the National Competent Authority has previously advised in email correspondence: "*It is presumed you will be collecting both safety and efficacy data for the gene therapy in question, and we would expect safety data collection as a minimum. This therefore means the trial follow-up falls within the remit of the CT Directive and requires a valid clinical trial authorisation. There are no options for a purely observational study as there would be no mechanisms for informing of safety issues such as SUSARs.*"

Additional guidance or examples would be helpful describing how safety reporting as part of long term follow-up could be managed, where the long term follow-up is planned as part of a non-interventional study or registry.

Section 3.1 (ix) - Rows 201 to 209: Combined ATMPs: more guidance would be welcome on how clinical trials should be managed e.g. expectations in regard to reporting of deviations, safety reporting.

If compliance of the medical device component of the combination product with the relevant general safety and performance requirements set out in Annex 1 of the Medical Regulation 2017/745 cannot be confirmed, it is unclear what is expected to be included in the protocol? It would be useful to include an example where it is justified to include a device that doesn't meet these requirements.

3.2 Specific considerations regarding the Investigator's Brochure (IB)

Rows 229 and 234: Suggestion to replace "etc."

As a stakeholder seeking guidance from this document we would welcome if the list could either be extended with further pertinent examples or reference is added to alternative guidance documents.

Rows 245 and 246: Change of sentence to replace "should" with "where appropriate"

Certain cell-based therapies are thawed in a water bath at the subject's bedside. It may not be necessary or feasible to describe the rate of temperature change for the product. Instead the dose could be adjusted to account for anticipated loss of cells during the thawing process.

4. Quality of the investigational ATMPs

Row 292: It would be useful to add reference to 'from reconstitution' as well as manufacture i.e. 'in relation to time from manufacture / reconstitution'.

6. Traceability

General comment: There is no mention of tissue/cell procurement organisations in this section, or the sponsor's responsibility to ensure that procurement organisation have in place a traceability system as set out in EU Tissues and Cells/Blood Directives. Where tissues and cells are being procured for the purposes of starting materials for further manufacture into the ATMP, the previous GCP for ATMP guidance document was clear that the sponsor would need to ensure (through contracts/due diligence) that all parties (sponsor, site, manufacturer, procurement organisation) have in place their part of the traceability system.

The previous GCP for ATMP guideline document contained a very useful annex providing more detail for each stake holder around traceability documentation/information required. We would welcome if this could also be included in the updated guidance document.

Row 315: Addition of further guidance

Suggestion that the guidance includes the possibility that the ATMP may be used for future ethically approved research purposes where the donor/subject have specifically consented for such use of the product and their donated material.

Row 323: Suggestion to add reference in footnote

A reference for the 'Guidelines on Good Manufacturing Practice for ATMPs' document (in a footnote) would be useful, to match the footnoted reference to the same document in section 4, Row 282.

8.2. Long-term follow-up

8.2.2. Remote follow-up - Rows 374 to 383: Given the potential long duration of follow-up in many trials with ATMP, it can become onerous for subjects to attend the clinical trial site for many years after administration of the ATMP. Perhaps consideration could be given to the option to allow satellite sites closer to the subject's place of residence, if located in same country as the clinical trial site (e.g. if the subject is attending only for safety bloods or an annual physical check). The suggestion is not to have to open these satellite sites as full clinical trial sites, therefore reducing the amount of set-up work and costs this invariably involves.

Row 378: Change 'Detail' to 'Detailed'

8.2.4 Patient alert cards

Row 395: addition of example(s) would be helpful

As a stakeholder seeking guidance from this document we would welcome if examples could be included where it may not be necessary to provide subjects with a patient alert card.
This follows a query relating to an ATMP protocol where subjects randomised to the control arm (receiving standard of care but not the cell therapy) were not provided with an alert card, whereas the subjects receiving the ATMP did receive a patient alert card. A query was submitted to the National Competent Authority (NCA) to confirm that the control subjects do not require a patient alert card. The NCA replied quoting paragraph 42. from the *Detailed guidelines on good clinical practice specific to advanced therapy medicinal products (ENTR/F/2/SF/dn D(2009) 35810)* stating that "All subjects participating in a clinical trial with an ATIMP should receive from the investigator an alert card".

8.3 Administration of out of specification products

General comment: Further clarity on the provision of the out of specification product in the context of the clinical trial would be helpful. In our experience in the UK to date, we have only been able to provide out of specification products (which cannot be QP released for the trial) if they have been subsequently released under a specials license (or hospital exemption license, if available) for administration to the subject. This is done outside of the context of the clinical trial, at the treating physician's specific request and under the hospitals (not the sponsors) responsibility with separate (non-clinical trial) consent sought for this treatment. If out of specification products may be provided within the context of the clinical trial (e.g. as an urgent safety measure or a breach of predefined specification) can the patient still to be considered on trial, and can the data still be used and evaluated as part of the trial?

Row 404: Change 'case' to 'cases'

General comment - Rows 404 to 408: The text would read better if broken down into more than one sentence.

Rows 409 to 410: Refers to sponsor evaluation of the risks. For academically sponsored trials it would be the investigator/chief investigator who provides the evaluation of such risk and not the sponsor.

9. Safety reporting

General comment: In this section it is overall unclear whether there are increased safety responsibilities in addition to routine safety surveillance and whether these responsibilities apply to the sponsor and/or the investigators.

Rows 418 and 422: Please clarify whether the differentiated causality assessment is only required for novel application processes (e.g. differentiated causality assessment is not required for injections, infusions).

Rows 418-419, 430: The terminology here differs from standard terminology used for clinical trials (Eudralex volume 10). Please clarify whether "required concomitant medications" and "mandatory concomitant medications" equate to Non-Investigational Medicinal Products, NIMPs (or Auxiliary Medicinal Products, AMPs). If yes, please consider replacing with standard terminology. If no, please include a definition to clarify which legislation they fall under.

Row 421: Please expand on what it is intended with the statement "the following safety issues should be specifically considered". It is not apparent what additional responsibilities or activities are laid on the investigator or the sponsor with this statement, e.g. reporting requirements, signal detection, etc.

Rows 426-428: Please clarify whether this is intended to be different from the routine collection of SAE in a clinical trial.

Row 429: Could examples be added where the requirement to report lack of efficacy would be requested? For certain cell/gene therapy products efficacy is an endpoint of the clinical trial and as such not reported as a safety issue.

Row 430: Please clarify whether this reporting process is between the investigator and the Sponsor only. The Sponsor will consider the new safety information for relevant changes to the IB, protocol and other relevant trial documents. However please confirm that additional reporting requirements (e.g. Expedited reporting of SUSARs) from the Sponsor to the Competent Authorities is not foreseen. The latter would indeed be quite problematic as it is not included in Directive 2001/20/EC or the Regulation 536/2014. In addition there would be no Reference Safety Information for these products.

Yours sincerely

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