Stakeholder	Alan Boyd Consultants Ltd
Category	Private company

Section	Comment	Rationale
-	It is noted that, although the scope of the guideline is intended to address issues related to GCP for ATMPs, many of the items covered do not relate to GCP itself (namely, many recommendations are not concerned with ensuring that the rights, safety and well-being of trial subjects are protected). We suggest that much of this content (including the examples called out in our comments) is more suited to a separate guideline on the design and conduct of clinical studies with ATMPs. This would mean that the GCP guideline could then address "true GCP" issues for ATMPs, such as site training (e.g. to cover the specialist procedures often required for product preparation and administration), the consent process (reflecting the complex administration procedures often associated with ATMPs), sample storage, and long-term follow-up of patients treated in a country other than that in which they reside. Alternatively, the title of the guideline could be amended to reflect its current broader focus.	The title of the guideline is not accurate, as the draft does not solely address GCP issues, but mostly rather those associated with clinical development as a whole.
-	The guideline is primarily focused on tissue and cell-based products, and the complexities of gene therapy medicinal products are not adequately reflected. It is suggested that the guideline is revised to address this, with a clear delineation between the different products.	The guideline should better reflect all types of ATMP (rather than tissue and cell-based products).
2. Clinical trial design (lines 91-93)	It is suggested to restructure the section so that similar points are discussed together, and a clear reference is made to the type of	This section covers several similar points dispersed across the whole section, which is confusing.

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	ATMP. For instance, the text on line 93 regarding sensitisation is more targeted to tissue and cell-based products. However, the challenges of re-administration are also discussed in several other places (e.g. lines 106 and 123, under separate sub-bullets), and the challenges of repeat dosing with gene therapy medicinal products is covered in line 127. It would be beneficial for e.g. sub-bullet (v) to be discussed in sub-bullet (i).	
Lines 99-101	It is recommended to change the text regarding development stage by age subgroup; as a minimum, it is recommended that, "i.e." is replaced by "e.g." to indicate that this age breakdown is purely an example and not a requirement.	The current text could be interpreted as an absolute requirement and is therefore too restrictive.
Line 111	It is recommended that the stated example ("For example, the investigational product could be injected into one eye and the untreated eye is used as a control. Comparison of local effects can be facilitated in this way by eliminating inter-subject variation.") is deleted. It is considered that a simple statement (such as "For some ATMPs an intra-subject control might be appropriate, with adequate justification.") would provide sufficient guidance.	This example (and likely others) does not take into account biodistribution or differences in disease progression (e.g. individual eyes may be at different stages of disease progression).
Line 131	It is recommended that the text reflects the need to justify the staggering interval between patients and cohorts.	The need for staggering is recognised; however, it is considered that the text in this section could more reflect the complexities of ATMPs and their administration. At present, the text may indicate that a standard NCE-type staggered dosing approach is suitable.
3. Application dossier (line 137)	It is recommended that this section is either moved to the introduction or (if possible) moved to the guidelines on GMP for ATMPs.	Reference to the Directive and other relevant documents is helpful for context but this is not part of GCP (as per general comment). This text concerns critical raw materials and would be better suited to manufacturing guidance.

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3.1 (i)(line 151)	It is suggested to delete the text regarding release specifications.	Release specifications are not relevant to GCP (and are covered by site training in the case of ATMPs).
(vii)(line 192)	It is recommended that this section is revised to reflect that the end of the trial (i.e., the point at which the database would be locked for analysis) may occur at the earliest point where maximal efficacy is reasonably expected to be achieved.	In order to avoid lengthy development programmes driven by the need to complete long follow-up studies as part of initial efficacy investigations, monitoring of longer-term efficacy and safety follow-up could continue in a long-term follow-up protocol (or similar), with longer-term safety and efficacy data provided at intervals thereafter.
(viii)(lines 193-197)	The text regarding the rationale for long-term follow up of patients is misleading; it is recommended to amend the text to ensure that long-term follow up is performed based on scientific and medical justification, with reference to existing guidelines (e.g. Guideline on follow up of patients administered with gene therapy medicinal products; EMA/CHMP/GTWP/60436/2007). Further, it is stated that, "For example, in the case of gene therapy medicinal products using integrating vectors, a follow-up of 15 years after administration is expected." This is not consistent with the above guideline. It should be clarified if the existing guidance is to be rescinded.	The need for long-term follow up of patients is not driven by prolonged biological activity. Instead, a risk-based assessment based on the product's characteristics should inform the duration and nature of the long-term follow-up activities. There is a discrepancy between the draft GCP guideline and the existing guideline.
-	It is recommended that, in the case of GMOs, sponsors should list the product's classification and provide guidance to investigators on recommendations for product handling.	Inclusion of recommendations would ensure that safe and consistent handling of GMO-containing products.
3.2 Specific considerations regarding the Investigator's Brochure (line 212)	The section should be amended to reflect the need for stopping criteria. Additionally, it is recommended that this section includes recognition of the need for appropriate nonclinical biodistribution studies to be performed to support study of the product in a specific clinical trial population.	Investigators should be provided with adequate information on grounds for stopping treatment and on the product's characteristics.

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3.2 Specific considerations regarding the Investigator's Brochure (lines 218-229)	The suitability and acceptability of data to support a clinical trial application is not within the remit of GCP. It is suggested that this text is moved to another suitable guideline.	The proposed text bears no relevance to the direct safety of patients or the Investigator's brochure.
3.2 Specific considerations regarding the Investigator's Brochure (lines 240-254, and 255-260)	The recommendations on provision of information on reconstitution and administration procedure is of value; however, the stated text is in the context of the protocol or pharmacy manual, not the Investigator's brochure. It is suggested to move this text from this section to section 3.1 (protocol).	The text refers to information to be provided in the protocol, not the Investigator's brochure.
(iii)(line 240)	It is recommended that the section on reconstitution is amended to reflect the need for stability and in-use expiry data.	The complexities of ATMP preparation are not fully reflected (e.g. time is most always needed for thawing, reconstitution, duration of time needed to take the product to the patient etc.). This is alluded to elsewhere in the guideline (line 291, where short shelf life products are mentioned).
	It is recommended that this section is expanded to include a section on control of thawing of the ATMP and a statement that detailed instructions should be provided on the process to be followed	No details are provided regarding the impact that differences in thawing may have on the efficacy of the ATMP
(iii) (line 248)	Typographical error to be corrected ("handing" should be "handling")	-
(vi) (line 265)	It is recommended that information on GMOs and shedding is also provided in this section.	Patients should be sufficiently informed of any safety risks arising from their participation in the study, and those of relevance to their carers.
(vii) (line 272)	It is recommended to expand this including risks to the patient, patient's family (some at-home precautionary measures may be required), investigator/site staff and the environment	Developers could benefit from more guidance on management of risks for GMO's and patients should be fully aware of those risks.
4 Quality of the investigational ATMPs (lines 291-293)	Related to the text on products with short shelf life, this should be covered in the detailed instructions reference in line 284. There are many factors that impact on the quality of the IMP stored/prepared at site for administration. This falls outside the GMP guidance.	

Section	Comment	Rationale
	Recommend focusing on and controlling all factors that may impact on product quality not only in use stability timings.	
5. Administration procedures (lines 304-307)	It is unclear why the presence of the sponsor during dosing is called out specifically for ATMPs, as this is not likely to be an issue specific to these products (and, in fact, some non-ATMP sponsors choose to have a representative on site on the first day of dosing). Further, the sentence, "If the presence of the administration is envisaged before the start of the clinical trial, this should be explained in the informed consent." is unclear and needs to be revised.	
6. Traceability (Line 319)	Retention of data for 30 years after the expiry date of the product is likely impractical. Recommendations on how and the format for doing this will be helpful.	The practicalities of data storage for 30 years in a readable format considering the rapid advances in technology should be considered for this guideline.
8.2.2 Long-term follow-up (line 374)	Logistics of long term follow up at sites should be planned and agreed in advance of patient visits.	Refer to rationale for line 381
(8.2.2) (line 381)	Recommend building flexibility in regulatory management of long-term follow-up. A patient who has been administered an ATMP in a clinical study, may decide at any point over the subsequent 15 years, to emigrate to any other country, including outside of the EU/EEA, and it would be challenging for sponsors to submit an CTA application in any country in the world to follow potentially one or two patients. Management of long term follow up should be carefully considered at a global level preferably. Development of patient centric approach may be an option.	Regulatory requirements for global registry studies varies considerably globally and, in some countries, particularly outside EU, requirements are unclear (Stakeholders personal experience).
(8.2.3) (line 386)	If the sponsor can contact/liaise with the patient all attempts should be made to maintain the patient in the long term, follow up. Additionally, support may be required to manage any stigma	Patients should be fully supported to manage any premature end of termination to long term follow up.

Section	Comment	Rationale
	associated with gene/cell therapy particularly for those patients treated in early childhood as they progress in to adult hood.	
(8.2.3) (line 390)	In the situation where the ATMP being developed and/or the company were acquired by another company, the acquiring company would need to assume the responsibilities of the acquired company.	Long term safety follow-up of patients is important and should be continued in any eventuality.
8.3 Administration of out of specification (line 409)	Recommend including the role the data safety monitoring board (DSMB)	Assessment of the risks and appropriate approaches should be discussed and agreed with DSMB
9 Safety reporting (Line 429)	Adverse events (AE) related to product failure including lack of efficacy should not be regarded as an AE. Recommend using wording such as adverse events related to the product' rather than the current wording. A sentence stating the categorisation for related and non-related AEs in the protocol is recommended.	Considering the complex nature of ATMP's, stage of development and that products targeting diseases that are rare and with unmet medical need, AE's associated with lack of efficacy maybe challenging to define at this time.
9. (line 434)	The reliability and quality of long term follow up AE reporting is questioned particularly where patients may not be able to remember specific events. Propose the following wording: 'In cases where long term follow up of trial subjects is foreseen, the Sponsor will define the expected duration for adverse event reporting in the protocol and will ensure that there is a robust process in place to capture all relevant AE data.	The quality of AE reporting during long term follow up is critical and drives future development of safe and efficacious IMP's.