DRAFT DETAILED GUIDELINE ON GOOD CLINICAL PRACTICE SPECIFIC TO ADVANCED THERAPIES REGULATION
Irish Medicines Board Comments - Draft 1, 25th August 2008

General comment:

For consistency and standardisation, it is recommended that:

- The format and flow of the guidance document be parallel with ICH GCP E6. As such,
  - section 1 should contain additional relevant definitions (glossary);
  - section 2 additional principles;
  - section 3 ethic committee responsibilities;
  - section 4 investigator responsibilities;
  - section 5 sponsor responsibilities;
  - section 6 protocol;
  - section 7 investigator brochure;
  - section 8 essential documents:
- A parallel numbering system to ICH GCP E6, such as AT2.0 through to AT8.0, would also be useful.

Scope of Guideline:

All references to Blood Establishments and Blood Directives should be removed. With the exception of haemopoietic stem cells, the ATMP Regulation does not apply to products derived from Blood – these are blood derived medicinal products and are covered by existing legislation. (for example medicinal products manufactured from fractionation of blood)

Note: (Haemopoietic Stem Cells are covered by the Tissues and Cells Directive and as part of an ATMP they would be covered in this guideline.)

The only reference to Blood in Directive 1394/2007 is in relation to the establishment of a traceability system for ATMPs that is compatible with the system described in the Tissues and Cells Directive and the Blood Directive.

Section 2.2: Overarching GCP principles:

Principle 1, 2 and 4**:** It is recommended that consideration is given to incorporation of a sentence within the overarching principles that equates to the sentence for IMPs - 'they should be used in accordance with the approved protocol', from principle 2.12 of ICH GCP E6

Principle 4: As this relates to a manufacturing step, it may be more suited in supplementary GMPs for ATIMPs rather than GCPs.

Principle 2: The language used is very specific. The nuances of long term follow up will be specific to each trial and as of yet largely unknown. To prevent unavoidable non compliance, this principle could already be seen to be incorporated as part of the current ICH GCP E6 principle 2.6 – compliance with the protocol. Therefore each follow up plan will be evaluated as part of the clinical trial assessment and compliance with the protocol can be inspected.

It is foreseen that nuances may occur that require non compliances with principle 2.7 of GCP in the context of AT clinical trials. The need for the presence of a representative of the sponsor in administration of the ATIMP, may necessitate in certain circumstances for that representative to make decisions that have an impact upon the medical care given – which can be construed as a medical decision, for example – to abort the procedure due to an immediate risk assessed by that representative, based on their knowledge of the product. This should be considered fully and an additional principle or addendum to principle 2.7 should be provided to prevent unavoidable non compliance with 2.7 at the investigator site.

Section 2.3: Traceability

Whilst different parties will be responsible for using the system as the ATIMP passes through the chain, one party, namely the sponsor should be ultimately responsible and have oversight. It is not clear if this is the case from Section 2.3. For example, if different systems are used at different points e.g. a tissue establishment using paper based system for traceability and the manufacturing site using an electronic system –the sponsor should ensure that the traceability systems used from start to finish are compatible.

The information related to traceability in this section is complicated. As the minimum data set specified in this guideline has been mostly copied from Annex VI of Directive 2006/86/EC (traceability requirements for human tissues and cells) this should be specified. No changes should be made to this information for tissue establishments as it has already been defined as a legal requirement in Directive 2006/86/EC.

It would be preferable to state that this minimum data set as defined in Annex VI of Directive 2006/86/EC shall be maintained by the tissue establishments and organizations responsible for human application. The requirements for the manufacturer should be defined or agreed in a contract with the Tissue Establishment / Organisation responsible for human application / Investigator. This system should be overseen as suggested by the Sponsor.

Also for a tissue establishment, the above data set is only required to be maintained for 30 years after clinical use, not shelf life of resulting product which could be shorter than 30 years. This should be clarified.

Section 2.4: Safety Reporting and long term follow-up

Section 2.4.1 Notification of Adverse Events and Reactions

The reporting requirements for an ATMP should be clarified in terms of those reportable as SUSARS under the clinical trials directive and those reportable under the Tissues and Cells Directive.

A Serious Adverse Reaction, under the Tissues and Cells Directive, is an unintended response including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life threatening, disabling, incapacitating or which results in, or prolongs hospitalization or morbidity.

Only reactions that may be associated with the quality and safety of the tissues / cells should be reported to the Competent Authority for Tissues and Cells. It should also be clarified that these are often separate entities in different countries.

2.4.2 Long term follow-up

It is recommended that documentation is maintained that provides evidence that the long term follow up plan for each study was determined based on the nature of the ATIMP, the current state of knowledge regarding that ATIMP and a risk analysis. This could be included as an essential document in the sponsors file, 'prior to the conduct of the trial' section. It is recommended as it could be forseen that the long term follow up for a particular ATIMP will become a standard template text included in the protocols across and over the course of a clinical development programme, and that the necessary determination will not made by the sponsor for each trial based on the all information available at that time. It will be difficult to inspect if this is the case if a particular essential document is not required.

What is the contingency plan if the sponsor ceases to be a legal entity and no other sponsor assumes responsibility for long term follow up?

Are the websites/phone lines for patients to contact or for physicians – are there any data protection issues if for patients?

2.5: GCP and Ethics Committee

The issues that the Ethics Committee needs to consider and the issues which should be included in the patient information sheet should be split – similar to the current ICH GCP E6 guideline.

In the context of patient information, points 3, 7 and 8 are already expected to be included under the ICH GCP E6 guidelines.

2.6: GCP and Investigator/Institution

Should the Investigator be responsible for maintaining the traceability system and the sponsor responsible for establishment of that system? If the investigator is responsible for establishing the system (as stated in the fifth sub bullet), how shall compatible records are maintained in multi centre studies?

With regards to the Investigator knowledge of the ATIMP and the sponsor training of the Investigator – it should be more transparent that training relevant to the duties delegated by the Investigator to his team is required. The references to the Investigator alone and not Investigator and Investigators staff (as given in E6) in many of the sub bullets appears to remove a training requirement from the GCPs rather than supplement it with specifics for ATIMPs.

This section refers to the keeping of traceability clinical trial records. Is it required that clinical trial records are retained separate to the data set required for minimum traceability as defined in Directive 2006/86/EC? In section Section 2.10 a reference is made to keeping the clinical trial records for 5 years after the end of the follow-up period.

2.7: GCP and Sponsor

It is unclear why the requirement to notify the competent authorities of serious breaches to GCP is specific to ATIMPs. Is it mandated in any legislation that competent authorities are to arrange procedures in relation to handling these notifications?

2.8: Protocol

The following section appears to contradict itself:
'Instructions to ensure the blinding of the trial where the person involved at the clinical site in the preparation of the ATIMP cannot to be unblinded whilst the person responsible for the administration of the ATIMP needs to be blinded'

We would propose the following
'Instructions are required to ensure the adequate blinding of a clinical trial in an institution where the preparation of the ATIMP cannot be blinded. These instructions should ensure that the investigator / person responsible for administration are appropriately blinded, where applicable. This should not compromise the mechanisms for traceability in place.

2.10: Essential Documents

Section 2.10.2 is ambiguous. The information required to be maintained by Tissue Establishments has already been defined in Directive 2006/86/EC.