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Detailed guidelines on good clinical practice specific to advanced therapy medicinal products

Please note: These guidelines have been developed to address specific issues related to good clinical practice for clinical trials involving advanced therapy medicinal products.

The final adoption of these guidelines by the College of Commissioners is foreseen once more practical experiences have been gained with the specificities of clinical trials involving advanced therapy medicinal products.

Pending the final adoption of this guideline, it is recommended to apply the rules and principles set out in this text.

1. INTRODUCTION AND SCOPE

1. Article 4(2) of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004¹ requires the Commission to draw up detailed guidelines on good clinical practice (“GCP”) specific to advanced therapy medicinal products (“ATMP”).
2. These guidelines do not replace but supplement the principles and detailed guidelines set out in the Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.² They should be read in conjunction with the detailed guidelines set out in Volume 10 of the Rules Governing Medicinal Products in the European Union³, including in particular the Note for guidance on Good Clinical Practice⁴, as well as other guidelines specific to advanced therapies.⁵

2. DEFINITIONS

3. The definitions set out in Directive 2005/28/EC and in Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the

¹ OJ L 324, 10.12.2007, p. 121.

² OJ L 91, 9.4.2005, p. 13.

³ http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm

⁴ CPMP/ICH/135/95

⁵ <http://www.emea.europa.eu/htms/human/mes/advancedtherapies.htm>

laws, regulation and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use⁶ apply.

4. Moreover, for the purpose of these guidelines, the following definitions shall apply:
- ‘advanced therapy investigational medicinal product’ (“**ATIMP**”) means a ATMP as defined in Article 2(1) of Regulation 1394/2007 which is tested or used in accordance with Article 2(d) of Directive 2001/20/EC;
 - ‘procurement organisation’ means a health care establishment or a unit of a hospital or another body that undertakes the procurement of human tissues and cells and that may not be accredited, designated, authorised or licensed as a tissue establishment;⁷
 - ‘traceability’ means the ability to locate and identify each individual unit of tissue/cell during any step from procurement, through processing, testing and storage, to distribution to the recipient or disposal and vice versa. This also implies the ability to identify the donor and the tissue establishment or the manufacturing facility receiving, processing or storing the tissue/cells, and the ability to identify the recipient(s) at the medical facility/facilities applying the tissue/cells to the recipient(s); traceability also covers the ability to locate and identify all relevant data relating to products and materials coming into contact with those tissues/cells;⁸
 - ‘tissue establishment’ means a tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells;⁹
 - ‘procurement’ means a process by which tissue or cells are made available;¹⁰
 - ‘human application’ means the use of tissues or cells on or in a human recipient and extracorporeal applications;¹¹
 - ‘blood establishment’ means any structure or body that is responsible for any aspect of the collection and testing of human blood or blood components,

⁶ OJ L 121, 1.5.2001, p. 34.

⁷ Cf. Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells (OJ L 204, 25.10.2009, p. 32).

⁸ Idem.

⁹ Cf. Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (OJ L 102, 7.4.2004, p. 48).

¹⁰ Idem.

¹¹ Idem.

whatever their intended purpose, and their processing, storage, and distribution when intended for transfusion. This does not include hospital blood banks;¹²

- ‘animal facility’ means a facility where the activities as described in the guideline on xenogenic cell-based medicinal products¹³ are carried out;
- ‘clinical follow-up’ shall mean a follow-up of individual subjects conducted by healthcare professionals. It includes prevention, screening, monitoring, diagnosis and treatment of diseases, injuries, complications, adverse reactions and medical errors;¹⁴
- ‘safety follow-up’ shall mean any systematic collection and collation of data that is designed in a way that enables learning about safety of a medicinal product. It may include passive or active surveillance, observational studies, or clinical trials;¹⁵
- ‘efficacy follow-up’ shall mean any systematic collection and collation of data that is designed in a way that enables learning about efficacy or effectiveness of a medicinal product. It may include passive or active surveillance, observational studies, or clinical trials;¹⁶
- ‘donor’ shall mean any human or animal source, whether living or deceased, of human cells or tissues;
- ‘donation’ shall mean donating human or animal tissues or cells intended for human applications.

3. DONATION, PROCUREMENT AND TESTING OF ATIMPs

5. As regards ATIMPs, apart from the sponsor, investigator and manufacturer/importer, other actors have to be considered, including tissue/blood establishments, procurement organisations, animal facilities and donors. It is important to put the role of these parties, and the applicable legislation, in the context of the roles and responsibilities for clinical trials.
6. The donation, procurement and testing of human cells and tissues used for the manufacturing of an ATIMP are carried out in accordance with the
 - Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells;¹⁷ and

¹² Cf. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (OJ L 33, 8.2.2003, p. 30).

¹³ EMEA/CHMP/CPWP/83508/2009.

¹⁴ EMEA/149995/2008.

¹⁵ Idem.

¹⁶ Idem.

¹⁷ OJ L 102, 7.4.2004, p. 48.

- Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC,¹⁸
7. as well as their implementing acts:
- Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells¹⁹ ;
 - Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells²⁰
 - Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components.²¹
 - Commission Directive 2005/61/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events²²; and
 - Commission Directive 2005/62/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards Community standards and specifications relating to a quality system for blood establishments²³
8. In particular, where an ATIMP to be used in a clinical trial contains human cells or tissues, the legal obligations in relation to the donors (e.g. consent, eligibility of donors, compensation, data protection and confidentiality, selection, evaluation and procurement) are laid down in Directive 2004/23/EC (Articles 12, 13, 14 and 15) and its implementing Directives, . Regarding human blood cells, they are laid down in Directive 2002/98/EC (Articles 16- 24) and its implementing Directives.
9. Where tissues or cells are sourced from an animal origin for the manufacture of an ATIMP the processes related to donation are covered by the Annex 2 to the Good Manufacturing Practice (“GMP”) Guidelines²⁴ and the guideline on xenogenic cell-based medicinal products.²⁵

¹⁸ OJ L 33, 8.2.2003, p. 30.

¹⁹ OJ L 38, 9.2.2006, p. 40.

²⁰ OJ L 32, 25.10.2006, p. 294.

²¹ OJ L 91, 30.3.2004, p. 25.

²² OJ L 256, 10.2.2005, p. 32.

²³ OJ L 256, 1.10.2005, p. 41.

²⁴ http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4_en.htm

²⁵ EMEA/CHMP/CPWP/83508/2009.

4. TISSUE OR BLOOD ESTABLISHMENTS AND ANIMAL FACILITIES

10. The responsibilities of the tissue or blood establishment and procurement organization with respect to donation, procurement, testing, traceability requirements, and other technical requirements (e.g. processing, preservation, storage and distribution) of human tissues and cells, including blood cells, to be used for the manufacture of an ATIMP are set out in the Directives referred to in section 3.
11. When tissues or cells of animal origin are used in the manufacture of ATIMPs the requirements for sourcing/donation, procurement and testing are set out in Annex 2 to the GMP Guidelines and in the guideline on xenogenic cell-based medicinal products.

5. MANUFACTURING AND IMPORTATION OF ATIMP

12. The requirements for the manufacture and import of ATIMPs are laid down in Article 13 of Directive 2001/20/EC.

6. OVERARCHING PRINCIPLES

13. The use of each ATIMP should be traceable. The individual product should be traceable through the sourcing, manufacturing, packaging, storing, transport, delivery to the hospital/institution/private practice, administration to the subjects, reconciliation and destruction or final disposition.
14. The number of links in the chain of custody (from donation to subject application) should be no more than necessary. If the product or part of it originates from a donor, records should contain sufficient detail to allow linking from the donor to the individual subject who received the product and vice versa.
15. Subjects should be followed-up during and, if necessary, after the end of the clinical trial both for their own care and to allow data collection as needed. The nature of follow-up and, if applicable, long-term follow-up after the end of the trial should be determined based on the nature of the ATIMP, the current state of knowledge regarding that ATIMP and a risk analysis. Processes should be established to enable contact with subjects to be maintained throughout the required follow up period.
16. In some situations, e.g. human embryonic stem cells, tissue establishments may also need to undertake significant processing activities to derive stem cell lines to the point that they have clinical value before their transfer to a manufacturer of the ATIMP.
17. Where tissues or cells of animal origin are used in the manufacture of an ATIMP, the sourcing procurement and testing should be carried out in accordance with the Annex 2 to the GMP Guidelines and the guideline on xenogenic cell-based medicinal products, unless for some specific cells and tissues of animal origin (e.g. cell lines used for production of viral vectors) other guidelines have become available in the light of experience and further developments.

18. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or a qualified dentist.²⁶ However there may be circumstances where a representative of the sponsor experienced in the administration of the ATIMP needs to be present during the application of the ATIMP to the subject. This expert 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.

7. TRACEABILITY

7.1. General requirements

19. Where an ATIMP contains human cells or tissues, the sponsor of the trial, the manufacturer and the investigator/institution where the product is used should ensure that there is a traceability system in place complementary to, and compatible with, the requirements laid down in the Directives referred in section 3, which already set out the traceability requirements for tissue and blood establishments. Where the tissues or cells are of animal origin the same requirements for traceability apply as indicated in the guideline on xenogenic cell-based medicinal products.
20. This means that at the tissue establishment/animal facility there has to be a link between the donor/animal source and the donation, at the manufacturing site there has to be a link between donation and product and at the investigator/institution site there has to be a link between the product and the subject. The traceability has to work in both directions from source to subject and from subject to source.
21. GCP contains requirements for accountability of IMPs. These requirements contribute significantly to the traceability of an IMP from the point of release of the IMP from the manufacturer onwards. The requirements for traceability may be achieved by ensuring that the systems established for traceability and for IMP accountability are integrated so that the special requirements of each are addressed.
22. Traceability requirements should also be compatible with the requirements in Annexes 2 to the GMP Guidelines and 13 to the GMP Guidelines as amended for the specific requirements of ATIMPs.
23. The guideline on traceability referred to in Article 15(7) of the Regulation 1394/2007 should also be applicable to clinical trials on ATIMPs.
24. In the event that the clinical trial is suspended or prematurely ended or the product development discontinued, the sponsors retains their obligations to ensure that the traceability system is maintained. If the ownership of the ATIMP is transferred to another legal entity, the new owner should take responsibilities for maintaining the traceability. In case of bankruptcy or liquidation of the sponsor, and in the event that the ownership is not transferred to another legal entity, the traceability records shall be transferred to the national competent authority.

²⁶ Principle 2.7 of CPMP/ICH/135/95.

25. The traceability procedures and the documentation process should be described in the clinical trial protocol and amended as needed.
26. The requirements for traceability are without prejudice to the provision of Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.²⁷ Therefore the system should allow full traceability from the donor to the recipient through anonymous coding systems ensuring that:
 - The identities of the human donors are protected and that they are only identified by code numbers that can be linked to their full identity by the tissue/blood establishments; and
 - The subject identity is protected and is only identified by code numbers that can be linked to their full identity by the investigator/institution where the product is used.

7.2. Responsibilities

7.2.1. Responsibility of the sponsor

27. The sponsor of a clinical trial with an ATIMP is responsible for ensuring that a traceability system is established and maintained. The system should ensure that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the investigator/institution where the product is used, application of the product to the subject or other final reconciliation, disposal or destruction of the product.
28. Where multiple parties are involved the sponsor should ensure that the role of each is clear (*e.g.* where the surgeon obtaining the tissue or cells from an autologous donor prior to the manufacturing of the ATIMP is located at the same site as the investigator responsible for its administration to the subject) and that the integrity of the traceability is maintained.
29. The sponsor should guarantee the establishment and maintenance of the traceability system through contractual agreements with the tissue or blood establishment or animal facility, the manufacturer and the investigator/institution, ensuring that the ATIMP can be linked via the procurement organisation to the donor/donation and via the investigator/institution where the product is used to the subject, and *vice versa*.

7.2.2. Responsibility of the tissue/blood establishment, procurement organisations, or animal facility

30. The tissue or blood establishment or procurement organisation or animal facility is responsible for implementing a traceability system with respect to the donation and procurement of the cell or tissue material needed for the manufacturing of the ATIMP, up to the delivery of that material to the manufacturer. These activities are addressed in the Directives referred to in section 3 for human tissues, cells and blood

²⁷ OJ L 281, 23.11.1995, p. 31,.

and in Annex 2 to the GMP Guideline, and in the guideline on xenogenic cell-based medicinal products for cells/tissues of animal origin. The Directives referred to in section 3 also cover the data protection and confidentiality of the human donors.

7.2.3. *Responsibility of the manufacturer of the ATIMP*

31. The manufacturer is responsible for implementing a traceability system during the manufacturing process from receipt from the procurement organisation, tissues/cell/blood establishment or animal facility up to the release of the finished ATIMP to the sponsor for use in the clinical trial and its delivery to the clinical trial site, where the latter is also undertaken by the manufacturer or under their control. Where the sponsor takes care of the delivery of the ATIMP from the manufacturer to the clinical trial site the sponsor is responsible for ensuring traceability through that step of the process.

7.2.4. *Responsibility of the investigator/institution*

32. The investigator or pharmacist or other individual who is designated by the investigator is responsible for implementing a system for subject and product traceability at the clinical site. That system should contain sufficient detail to allow linking of each product delivered to the investigator to the subject receiving it and *vice versa*.

7.3. Archiving by the sponsor, manufacturer and the investigator/institution for traceability

33. The sponsor of the trial, the tissue establishments/procurement organization, the animal facility, the manufacturer and the investigator/institution where the ATIMP is used, should keep their parts of the traceability records for a minimum of 30 years after the expiry date of the product, or longer if required by the terms of the clinical trial authorization or by the agreement with the sponsor. In the case of the tissue establishments, if that period is longer than provided in the Directives referred to in section 3, the sponsor should ensure through contractual agreements that the traceability records are kept for that longer period.
34. The minimum data set to be kept by each party is outlined in the Annex.

8. SAFETY REPORTING AND LONG TERM FOLLOW-UP

8.1. Notification of Adverse Events and Reactions

35. The requirements for notification of adverse events and adverse reactions by the investigator and the sponsor in the context of clinical trials are laid down in Articles 16 and 17 of Directive 2001/20/EC and their implementing guidelines.²⁸ New events related to the conduct of the trial or the development of the ATIMP and likely to affect the safety of the subjects should be reported according to the existing timelines for expedited reporting. This includes:

²⁸

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm

- serious adverse events which could be associated with the trial procedures and which could require modification of the conduct of the trial;
 - significant hazard to the subject population.
36. The sponsor should provide information and training to the investigator on any additional protocol and/or product specific requirements for the reporting of adverse events and this reporting process should be outlined clearly in the clinical trial protocol. The following safety issues are of particular concern:
- Adverse events related to the product application process (surgical or other);
 - Suspected or confirmed cases of infection;
 - Unexpected reactions (e.g. hypersensitivity, immunological, toxic or other as consequence of a change in the construction or function of the viral vector (e.g. generation of replication competent virus);
 - Adverse events related to product failure (including lack of efficacy);
 - Adverse events related to mandatory concomitant medication (e.g. immunosuppression);
 - Adverse events related to medical devices which form part of the product or are used for application of the product.
37. Differentiated causality assessment concerning the safety issues mentioned above should be described in the clinical trial protocol and implemented in the adverse event reporting system.
38. The national competent authority of the Member State where a serious adverse reaction occurs in a clinical trial with an ATIMP containing cells or tissues or a combined ATIMP should inform the relevant national authorities responsible for the implementation of the Directives referred to in section 3 (only applicable to ATIMP containing human cells or tissues) and the relevant national authority responsible for the Directives on medical devices (applicable to both, ATIMP containing human or animal cells or tissues).

8.2. Follow up

39. The need for, the duration and the nature of follow up should be determined by the sponsor for each clinical trial based on the nature of the ATIMP, the current state of knowledge regarding that ATIMP and a risk analysis, including the risk for close contacts and offspring. The sponsor should also take into account any Community guidance on risk assessment and follow-up of subjects treated with particular types of ATIMPs which may provide more details on the follow up period and kind of follow up to be expected.
40. The sponsor may wish to discuss the duration of follow up with the concerned national competent authority. This follow up should be aligned with the specific requirements of the product under development, should be described in the protocol, and amended as needed in accordance with the evolving experience with the ATIMP,

and should make clear which follow up activities should take place prior to and after the end of the clinical trial. The rationale for the chosen follow up, including the available supporting information, should be documented and kept as an essential clinical trial document as indicated in section 15.

41. The follow up should be considered from the following aspects:
 - follow up for the protection of the subject i.e. clinical follow up;
 - follow up for the purpose of collection of specific data (which might not involve all subjects) i.e. safety follow up and efficacy follow up.
42. All subjects participating in a clinical trial with an ATIMP should receive from the investigator an alert card, which has been previously agreed by the sponsor and approved by the Ethics Committee, containing as minimum the name of the subject, the investigator contact number and information regarding the medical treatment received.
43. The protocol should define the end of the trial and which follow up should take place after the end of the trial. The safety and efficacy follow up involving active data collection (study visits etc.) should form part of the clinical trial whereas clinical follow up and passive data collection may take place after the end of the trial.
44. Where follow up after the end of the trial is required, in particular when this occurs over a long term, the sponsor needs to ensure that there is a process in place for follow up of the subjects treated with the product even in cases where the product development is discontinued or the (former) sponsor ceases to exist as a legal entity. This process should be described in the protocol, which should be amended as needed, and may be achieved, for instance, by:
 - appropriate information about follow up of the subjects after the end of the clinical trial provided to healthcare establishments that served as centres for the particular clinical trial;
 - websites/phone-lines that provide data/consultation in case of complications;
 - subject alert cards that inform treating physicians about the product used and any independent registries or other sources of data available in case of safety/efficacy issues, and of the need to inform the national competent authority, the investigational sites and the sponsor in the event of certain serious adverse reactions. These alert cards should contain as minimum the name of the subject, a physician contact number and information regarding the medical treatment received. They should have been previously agreed by the sponsor and approved by the Ethics Committee. This may be the same as the one used for the clinical trial if changes or additional information is not required to address further follow up after the end of the trial.
45. Where a subject is withdrawn from a trial at their own request or based on a decision of the investigator the follow up should be maintained, subject to the consent of the subject.

9. NATIONAL COMPETENT AUTHORITIES

46. The national competent authorities when assessing the request for authorisation of a clinical trial involving an ATIMP should consider in particular the adequateness of traceability arrangements and the follow up strategy, including the definition of the end of the trial and risk-assessment.

10. ETHICS COMMITTEE

47. As regards clinical trials involving an ATIMP, the Ethics Committee should in particular check:
- (a) The arrangements for traceability as regards provisions for subject data protection and confidentiality (see section 7);
 - (b) The arrangements for follow up before and after the end of the trial, including after subjects withdraw from the study and including the information (alert card) to be provided to each subject for use in the event of problems arising after the end of the trial (see section 8.2);
 - (c) The arrangement when follow up needs to include close contact and offspring of the recipients;
 - (d) The written informed consent as regards ethical concerns of particular relevance for ATIMPs. (see informed consent issues in section 10);
 - (e) The circumstances where a representative of the sponsor experienced in the administration of the ATIMP needs to be present during the application of the ATIMP to the subject.
48. The following should be taken into account by the Ethics Committees when assessing the ethics of a clinical trial involving an ATIMP:
- The irreversible nature of certain ATIMP applications, and the information provided to subjects in that context;
 - The peculiarities of situations where the donor is a relative of the subject to be included in the trial, in particular the protection from “sibling/parent” pressure.

11. INVESTIGATOR

49. In the context of clinical trials with ATIMPs, investigators should:
- (a) establish and maintain a system for traceability at the clinical site (see section 7.1 and 7.2.4);
 - (b) keep their part of the traceability records for the required period (see section 7.3 and 15);
 - (c) be aware of the adverse event and adverse reaction reporting process, including reactions related to application of the ATIMP (see section 8.1);

- (d) have knowledge of the risk analysis of the ATIMP (see section 12(d));
- (e) have knowledge of the requirements for storage, handling, administration, and destruction or disposal of the ATIMP including any hazard to those handling the product and close contacts and the risk to the environment;
- (f) have knowledge on the use, application, implementation or administration of the ATIMP and the requirements for clinical, efficacy and safety follow up;
- (g) ensure that the particular requirements for the application of the ATIMP, such as standardisation of surgical procedures and training of the healthcare professionals involved, are communicated to the investigator site team including the surgeons or other specialists involved;
- (h) inform the trial subject and where applicable their legal representative of the particular issues that arise for ATIMPs. In particular, both the informed consent form and any other written information to be provided to the subjects should include explanation of the following:
 - The arrangements for traceability including provisions for subject data protection and confidentiality (see section 7);
 - The arrangements for follow up before and after the end of the trial, including after subjects withdraw from the study and including the information (alert card) to be provided to the subject for use in the event of problems arising after the end of the trial (see section 8.2);
 - The inconveniences of long term follow up, where applicable (see section 8.2);
 - The definition of the end of the trial and its relationship to the follow up after the end of the trial (see section 8.2);
 - The irreversible nature of the ATIMP, where applicable;
 - The need, where applicable, for the presence of a representative of the sponsor for assistance during the administration of the ATIMP and the rationale for this;
 - Risks and precautions including for example those related to shedding in the context of ATIMPs involving gene therapy;
 - Guidance on how to communicate risks to close contacts and offspring where they could be at risk and information on any follow up involving them.

12. SPONSOR

In the context of clinical trials with ATIMPs sponsors should:

- (a) establish and maintain a system for traceability (see section 7.1 and 7.2.1);
- (b) keep their part of the traceability records for the required period (see section 7.3);

- (c) implement the appropriate adverse event and adverse reaction reporting process as required by the legislation in the context of ATIMPs (see section 8.1);
- (d) ensure that an ongoing risk analysis, based on existing knowledge of the type of product and its intended use, is performed and provided to the investigator involved in a clinical trial with that ATIMP, through the investigators brochure or updates to it and to the patient through the informed consent or updates to it (see section 8.2);
- (e) for combined products, the risk analysis and risk management plan of the device part should be shared with the investigators;
- (f) identify the need for, duration and the nature of clinical, safety or efficacy follow-up required, including after subjects withdraw from the study (see section 8.2);
- (g) establish the particular requirements for the application of the ATIMP, such as standardisation of surgical procedures and training of the investigator involved;
- (h) train the investigator in the requirements for storage, handling, administration, and destruction or disposal of the ATIMP including hazards to those handling the product and close contacts and the risk to the environment;
- (i) train the investigator on the use, application, implantation or administration procedures of those ATIMPs that may require specific concomitant therapy and may involve surgical procedures that could have an impact on the safety or efficacy of the product. Information on the standardisation and optimisation of these procedures during clinical development should be provided. The sponsor should also identify when their personnel need to be involved in these procedures and describe this in the protocol or associated document that is included in the application to the competent authority and ethics committee and in the agreements with the clinical investigator site;
- (j) consult the national competent authorities for biosafety, where applicable.

13. PROTOCOL

50. The following should be considered by the sponsor in relation to the content of the protocol:

- (a) Variabilities in the nature of ATIMPs and the diseases for which they are used that need to be foreseen in the protocol design. The protocol should foresee any necessary flexibility that may be required for the handling of this variability inherent in the use of certain ATIMPs, for example:
 - The acceptable range of cell numbers and cell viability at the time of administration to subjects;
 - Appropriate windows of acceptability for inclusion and exclusion criteria.

- (b) Where an ATIMP contains human cells or tissues, the protocol should contain a brief overview of:
 - Confirmation that the donation, procurement and testing of the human tissues and cells are in conformity with the relevant Regulations, as referred to in Article 3 of the Regulation 1394/2007;
 - The donor type and whether the donation is part of the trial process;
 - The criteria for suitability of the donated material to comply with defined requirements.
- (c) Where an ATIMP incorporates a medical device (i.e. a combined advanced therapy medicinal product), the protocol should contain a brief overview of:
 - Characteristics, performance and purpose of the device;
 - Confirmation that this product is in conformity with essential requirements with the regulations referred to in article 6 of the advanced therapy regulation.
 - Rationale for combination of ATIMP and medical device to aid understanding of the effect of each individually and in combination.
- (d) Detailed instructions to ensure blinding of the trial where needed (e.g. where the person responsible for randomization of the subjects to treatment has to remain blind or where the person involved at the clinical site in the preparation of the ATIMP cannot be blinded whilst the person responsible for the administration of the ATIMP needs to be blinded);
- (e) Traceability procedures and documentation (see section 7);
- (f) Information on any particular requirements for safety reporting, including during follow up after the end of the trial (see section 8.1);
- (g) The definition of the end of the trial and its relation to the follow up after the end of the trial (see section 8.2);
- (h) Information on the follow up strategy expected for the ATIMP (including follow-up after the end of the trial) with the rationale and objectives based on appropriate risk assessment (see section 8.2);
- (i) Specific requirements relating to subjects withdrawn from the trial at their own initiative or that of the investigator, in particular relating to the follow-up strategy (see section 8.2);
- (j) Information on the application of the ATIMPs when this application may require specific concomitant therapy and may involve surgical procedures that could have an impact on the safety or efficacy of the product. This includes information on the standardisation and optimisation of the processes involved including where applicable the surgical procedures;

- (k) Information on whether the presence of a representative of the sponsor experienced in the administration of the ATIMP needs to be present during the application of the ATIMP to the subject and the rationale for this;
- (l) Instructions on any local preparation or reconstitution required;
- (m) In case of ATIMPs involving gene therapy, information on viral shedding and any precautions required should be provided where applicable;

14. INVESTIGATOR BROCHURE

51. The following should be considered by the sponsor in relation to the content of the Investigator Brochure:

- (a) A description of the scope and sufficiency of existing information and its limitations;
- (b) Information obtained from ongoing risk analysis based on existing knowledge of the type of product and its intended use including risk associated with the application method (e.g. surgery, concomitant medication, associated devices);
- (c) Information on the risk management plan (for marketed products);
- (d) Information on the risks due to product failure;
- (e) Information on the product safety handling, containment and disposal;
- (f) Information on short and long term safety issues particular to ATIMPs such as infections, immunogenicity/immunosuppression and malignant transformation as well as those related to medical devices for combined ATIMPs.

15. ESSENTIAL DOCUMENTS

52. As regards the keeping of records, the rules as set out in Directive 2001/20/EC and 2005/28/EC apply. The traceability records should be kept for a minimum of 30 years after the expiry date of the product, or longer if required by the terms of the clinical trial authorization or by the agreement with the sponsor.

53. Before, during and after completion or termination of the trial each party (see section 7.2) should hold the necessary information available at all time to ensure bidirectional traceability, linking the donor information at the procurement site to the ATIMP and the clinical trial subject information at the clinical trial site to the ATIMP, whilst ensuring the data protection legally required for both the donor and the clinical trial subject.

15.1. Before the Clinical Phase of the Trial Commences

54. During this planning stage the following documents should be generated and should be on file before the trial formally starts:

- (a) File of the tissue/blood establishment, manufacturer, sponsor and investigator/institution: Details of the process, responsibilities and documentation required to document the link from the donor to the subject receiving the product and vice versa;
- (b) File of the sponsor:
 - The documentation used to determine the follow up strategy;
 - The follow up strategy expected for the ATIMP (including follow-up after the end of the trial) with the rationale and objectives based on appropriate risk assessment.

15.2. During the Clinical Conduct of the Trial (see also Annex)

During the clinical conduct of the trial the following documents should be on file:

- (a) File of the tissue/blood establishment or animal facility:
 - Traceability records linking the donor/animal source to the donated material;
 - Any update to the details of the process, responsibilities and documentation required to document the link from the donor to the subject receiving the product and vice versa.
- (b) File of the manufacturer:
 - Traceability records linking the donated material to the manufactured ATIMP;
 - Any update to the details of the process, responsibilities and documentation required to document the link from the donor to the subject receiving the product and vice versa.
- (c) File of the sponsor:
 - Traceability records linking the manufactured ATIMP to the clinical trial site and from the clinical trial site to the patient code;
 - Any update to the details of the process, responsibilities and documentation required to document the link from the donor to the subject receiving the product and vice versa;
 - Any update to the documentation used to determine the follow up strategy;
 - Any update to the follow up strategy expected for the ATIMP (including follow-up after the end of the trial) with the rationale and objectives based on appropriate risk assessment.
- (d) File of the investigator/institution:

- Traceability records linking the manufactured ATIMP delivered to that clinical trial site and from the clinical trial site to the patient code, patient identification and medical file;
- Any update to the details of the process, responsibilities and documentation required to document the link from the donor to the subject receiving the product and vice versa.

15.3. After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections 15.1 and 15.2 and kept by each respective party should be in the file with the following:

- (a) File of the tissue/blood establishment/animal facility: Final traceability records linking the donor/animal source to the donated material;
- (b) File of the manufacturer: Final traceability records linking the donated material to the manufactured ATIMP;
- (c) File of the sponsor:
 - Final traceability records linking the manufactured ATIMP to the clinical trial site and from the clinical trial site to the patient code;
 - Follow-up procedures, contact information and data collected, to document the conduct of the clinical follow-up, safety follow-up and efficacy follow-up required.
- (d) File of the investigator/institution:
 - Final traceability records linking the manufactured ATIMP delivered to that clinical trial site and from the clinical trial site to the patient code, patient identification and medical file;
 - Follow-up procedures, contact information and data collected, to document the conduct of the clinical follow-up, safety follow-up and efficacy follow-up required.

ANNEX - TRACEABILITY RECORDS

By Tissue Establishments/Procurement Organisation:

As outlined in Annex VI of Directive 2006/86/EC implementing the human tissue and cell Directive 2004/23/EC.

By Blood Establishments:

As outlined in Annex I of Directive 2005/61/EC implementing the blood directive 2002/98/EC.

By Animal Facilities:

By analogy with Annex VI, of the Directive 2006/86/EC implementing the human tissue and cell Directive 2004/23/EC:

- Source animal identification
- Donation identification that will include at least:
 - Identification of the animal facility
 - Animal ID number
 - Date of procurement
 - Place of procurement
 - Type of donation (e.g. single v multi-tissue; living v deceased)
- Product identification that will include at least:
 - Identification of the animal facility
 - Type of tissue and cell/product (basic nomenclature)
 - Pool number (if applicable)
 - Split number (if applicable)
 - Expiry date
 - Tissue/cell status (i.e. quarantined, suitable for use etc.)
 - Description and origin of the products, processing steps applied materials and additives coming into contact with tissues and cells and having an effect on their quality and/or safety.
 - Identification of the facility issuing the final label
- Identification of user facility and distribution dates:

- Date of distribution/disposal
- Identification of the user facility

By the Manufacturers:

- Information on the material received from the Procurement organisation, tissue establishment or animal facility as applicable:
 - Identification of the tissue establishment/animal facility/any intermediaries if applicable
 - Type of tissue and cell/product (basic nomenclature)
 - Pool number (if applicable)
 - Split number (if applicable)
 - Tissue/cell status (i.e. quarantined, suitable for use etc.)
- ATIMP identification that will include at least:
 - Tissue/cell status (i.e. quarantined, suitable for use etc.)
 - Description and origin of the products, processing steps applied materials and additives coming into contact with tissues and cells and having an effect on their quality and/or safety.
 - Identification of the sponsor, contract research organization or investigator/institution to whom the product is supplied
 - Product name/code
 - Pharmaceutical form, route of administration, quantity of dosage units and strength
 - Batch and/or code number
 - Trial reference code
 - Trial subject identification number
 - Expiry date
 - Date of distribution/disposal
 - Release of the finished product by the Qualified Person

By the sponsor:

According to section 8 of the Note for guidance on Good Clinical Practice²⁹ the following essential documents should be kept by the sponsor before, during and after the conduct of the trial:

- Shipping Records for IMP (8.2.15, 8.3.8):
- Certificate of analysis of the IMP (8.2.16, 8.3.9)
- Treatment allocation and decoding documentation (8.2.17, 8.4.6)
- IMP accountability at the site (8.3.23, 8.4.1), including final disposition of both used and unused product.

These records contain information relevant for traceability purposes and at least the following minimum data set from these records should be kept for 30 years after the expiry date of the product, or longer if required by the terms of the clinical trial authorization or by the agreement with the sponsor:

- Identification of the manufacturing site
- Identification of the investigator/institution that used the ATIMP
- Product name/code
- Pharmaceutical form, route of administration, quantity of dosage units and strength
- Batch and/or code number
- Trial reference code
- Trial subject code
- Expiry date
- Date of application

In addition, the last version of the Investigator Brochure and the protocol should be retained for the same period to provide information about the product and its application.

By investigator and institution responsible for human application

According to section 8 of the Note for guidance on Good Clinical Practice³⁰ the following essential documents should be kept by the investigator before, during and after the conduct of the trial:

- Shipping Records for IMP (8.2.15, 8.3.8):

²⁹ http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm

³⁰ http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm

- Certificate of analysis of the IMP (8.2.16, 8.3.9)
- Treatment allocation and decoding documentation (8.2.17, 8.4.6)
- Subject identification code list (8.3.21, 8.4.3)
- IMP accountability at the site (8.3.23, 8.4.1) including final disposition of both used and unused product.

These records contain relevant information for traceability purposes and at least the following minimum data set from these records should be kept for 30 years after the expiry date of the product, or longer if required by the terms of the clinical trial authorization or by the agreement with the sponsor:

- Identification of the investigator/institution,
- Identification of the sponsor and contract research organization where applicable,
- Identification of the manufacturing site,
- Product name/code,
- Pharmaceutical form, route of administration, quantity of dosage units and strength,
- Batch and/or code number,
- Trial reference code,
- Trial subject code,
- Subject identification code list (8.3.21, 8.4.3) (links the name of the subject to the trial subject code),
- Expiry/retest date,
- Date of administration,

The subject medical records should also contain the product name/code, the trial reference code, trial subject code and administration dates and dose in order to ensure that a link can be made back to the identity of the product and the further traceability records of the investigator and sponsor.

The investigator site should also retain records of any product that was unused or destroyed and of its final status.