GUIDELINE ON THE PRINCIPLES AND PROVISIONS FOR GOOD CLINICAL PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCTS 13 NOVEMBER 2015

1. PURPOSE This guideline has been prepared for the purpose of setting out the provisions concerning good clinical practice of advanced therapy medicinal products to be used for clinical trial purposes. 2. DEFINITIONS 2.1. Donation: The donation of human or animal tissues or cells for use in humans. 2.2. Human application: The use of tissues or cells in human recipients or in extracorporeal applications. 2.3. Tissue/cell centre: A hospital or any other legal entity, institution or organisation that undertakes activities of processing, preservation, storage or distribution of human tissues and cells. 2.4. Donor: Any human or animal source, living or deceased, from which human cells or tissues are obtained. 2.5. Efficacy follow-up: The systematic collection and compilation of data designed to enable information to be obtained on the efficacy or performance of a medicinal product. 2.6. Safety follow-up: The systematic collection and compilation of data designed to enable information to be obtained on the safety of a medicinal product. 2.7. Animal facility: A facility in which activities relating to xenogeneic cell-based medicinal products are carried out. 2.8. Advanced therapy medicinal product: Tissue and cell-based human medicinal products classified as gene therapy medicinal products, somatic cell therapy medicinal products, tissue engineered products and combined advanced therapy medicinal products. 2.9. Traceability system: The ability to locate and identify each individual tissue/cell unit at each stage of the supply chain from procurement through processing, testing and storage to distribution to the recipient or disposal units. This also means the ability to identify the manufacturing facility or tissue centre and the donor that receives, processes or stores the tissues/cells, and to identify the recipients at the medical facilities where such tissues/cells are applied to recipients. The traceability system also encompasses the capacity to locate and identify all relevant data relating to products and materials that come into contact with these tissues/cells. 2.10. Blood establishment: Any structure or body that is responsible for the collection and testing of human blood or blood components, irrespective of their purpose of use, and for their processing, storage and distribution when intended for transfusion. This does not include blood banks. 2.11. Clinical follow-up: The follow-up conducted by the investigator of volunteers/patients, including the prevention, screening, observation, diagnosis and treatment processes of diseases, as well as injuries, complications, adverse reactions and medical errors. 2.12. Procurement: The process by which tissues or cells are made available. 2.13. Procurement organisation: A healthcare facility, a hospital or any other institution or organisation that undertakes the procurement of human tissues and cells and that is not accredited, designated, authorised or licensed as a tissue centre. 3. DONATION, PROCUREMENT AND TESTING OF ADVANCED THERAPY MEDICINAL PRODUCTS IN THE RESEARCH PHASE 3.1. With regard to advanced therapy medicinal products in the research phase, tissue centres, blood establishments, procurement organisations, animal facilities and donors, as well as investigators, manufacturers/importers and other parties shall be considered, with the exception of the sponsor. The duties of these parties and the applicable relevant legislation must be taken into account.

3.2. The donation, procurement and testing of human cells and tissues used for the manufacture of advanced therapy medicinal products in the research phase shall be carried out in accordance with the "Regulation on the Safety of Human Tissues and Cells and the Related Centres". 3.3. In particular, in cases where the advanced therapy medicinal product in the research phase to be used in clinical trials contains human cells and tissues, the legal obligations relating to donors shall comply with the relevant legislation. 3.4. In cases of tissues or cells obtained from animal sources for the manufacture of the advanced therapy medicinal product in the research phase, the processes relating to donation shall comply with the Good Manufacturing Practice (GMP) guideline. 4. TISSUE CENTRES OR BLOOD ESTABLISHMENTS AND ANIMAL FACILITIES 4.1. The responsibilities of the tissue centre or blood establishment and the procurement organisation regarding the donation, procurement, testing, traceability requirements and other technical

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requirements (e.g. processing, preservation, storage and distribution) of human tissues and cells, including blood cells, to be used for the manufacture of the advanced therapy medicinal product in the research phase shall be as set out in the "Regulation on the Safety of Human Tissues and Cells and the Related Centres". 4.2. In cases where animal-derived tissues or cells are used in the manufacture of advanced therapy medicinal products in the research phase, the requirements for sourcing/donation, procurement and testing processes shall be as set out in the GMP guideline and the relevant legislation. 5. MANUFACTURE AND IMPORT OF THE ADVANCED THERAPY MEDICINAL PRODUCT IN THE RESEARCH PHASE 5.1. The requirements for the manufacture and import of advanced therapy medicinal products in the research phase are set out in the relevant legislation. 6. GENERAL PRINCIPLES 6.1. The use of each advanced therapy medicinal product in the research phase shall be traceable. Individual products shall be traceable through sourcing, manufacture, packaging, storage, transport, delivery to hospital/institution/private practice, management of volunteers/patients, reconciliation and destruction or final processing. 6.2. The number of links in the chain of custody (from the donation process through to administration to the volunteer/patient) shall not be greater than necessary. If a product or a part thereof is sourced from a donor, the records shall contain sufficient detail to allow links from the individual volunteer/patient who receives the product (or vice versa) to the donor from whom it originated. 6.3. Volunteers/patients shall be followed up during and after the conclusion of the clinical trial regarding their treatment processes in such a way as to allow data to be collected when required. The content of the follow-up and, where applicable, long-term follow-up after the conclusion of the trial shall be determined on the basis of the content of the advanced therapy medicinal product in the research phase, the risk analysis and the available information relating to the advanced therapy medicinal product in question. Processes shall be maintained throughout the required follow-up period and contact with volunteers/patients shall be maintained. 6.4. In cases where animal-derived tissues or cells are used in the manufacture of the advanced therapy medicinal product in the research phase, the specific animal-derived cells and tissues (e.g. cell lines used in the manufacture of viral vectors) shall be in compliance with the provisions of the relevant legislation.

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6.5. Medical care and medical decisions for volunteers/patients must be under the responsibility of a qualified and competent physician or dentist. However, the administration of the advanced therapy investigational medicinal product to the volunteer/patient also requires the presence of the sponsor's representative. This expert may provide advice and information to the principal investigator, but the principal investigator remains responsible for decisions to suspend or modify the method of administration. 7. TRACEABILITY 7.1. General Requirements 7.1.1. In cases where the advanced therapy investigational medicinal product contains human cells or tissues, the sponsor on site where the product is used, its manufacturer and the investigator/institution must ensure that an on-site traceability system is in place that is consistent with and complementary to the traceability requirements previously applied to tissue establishments and blood facilities, as set out in the relevant legislation. In cases involving animal-derived tissues or cells, the same traceability requirements apply as specified in the relevant legislation. 7.1.2. There must be a link between the donor/animal source and the donation process at the tissue establishment/animal facility, a link between the donation process and the product at the manufacturing site, and a link between the product and the volunteer/patient at the investigator's site. The traceability system must demonstrate operation in both directions, from the source to the volunteer/patient and from the volunteer/patient back to the source. 7.1.3. Good clinical practice includes accountability/transparency requirements for investigational products (IP). These requirements contribute significantly to the traceability process from the manufacturer to the release of the IP. Traceability requirements can be fulfilled by ensuring the existence of systems combining traceability and IP accountability in order to

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address each of the specific requirements. 7.1.4. Traceability requirements must be consistent with the requirements set out in the IMP guidelines. 7.1.5. In the event of the suspension or premature termination of the clinical trial, or the discontinuation of product development, the sponsor must retain its obligations to ensure the continuation of the traceability system. If ownership of the advanced therapy investigational medicinal product is transferred to another legal entity, the new owner must assume responsibility for maintaining traceability. In the event of the sponsor's bankruptcy or liquidation and where ownership is not transferred to another legal entity, the traceability records are transferred to the national competent authority. 7.1.6. The traceability methods and documentation process must be described in the clinical trial protocol and modified where required. 7.1.7. Traceability requirements must comply with the relevant legislation on the free movement of such data and the processing of personal data. Therefore, the system must permit full donor-to-recipient traceability criteria through anonymous coding systems, ensuring the following: 7.1.7.1. The identities of human donors are protected and such individuals are identified only by code numbers that can be linked to full identification processes solely by the tissue establishment/blood facility. 7.1.7.2. The volunteer/patient identity is protected and can be identified only by code numbers that can be linked to full identification processes solely by the site where the product is used and where the investigator is located.

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7.2. Responsibilities 7.2.1. With respect to the advanced therapy investigational medicinal product, the sponsor is responsible for establishing the traceability system and ensuring its continuation. The system must ensure that the individual product — including starting and raw materials and all materials coming into contact with the cells or tissues it contains — is tracked from source procurement at the investigator's site where the product is used, through manufacturing, packaging, storage, transport and delivery, and receipt by the volunteer/patient or other final disposition, through to the disposal or destruction of the product. 7.2.2. In cases involving multiple parties, the sponsor must ensure that the tasks of each party are complete and defined and that traceability integrity is maintained (for example, where the investigator obtaining tissue or cells from an autologous donor prior to manufacture of the advanced therapy investigational medicinal product is located at the same site as the one responsible for volunteer/patient management). 7.2.3. The sponsor must guarantee the establishment and maintenance of the traceability system through agreements concluded with the tissue establishment or blood facility or animal facility, the manufacturer and the investigator's site, by ensuring that the advanced therapy investigational medicinal product can be linked through the investigator's site where the product is used and the donor/donation procurement organisation. 7.2.4. The tissue establishment/blood facility, procurement organisations or animal facility are responsible for implementing a traceability system relating to the supply and donation of cells or tissues required for the manufacture of the advanced therapy investigational medicinal product, up to the delivery of the materials in question to the manufacturer. These activities must comply with the relevant guidelines. 7.2.5. The manufacturer is responsible for implementing a traceability system from receipt, from the procurement organisation, tissue/cell establishment or blood facility or animal facility, of the finished advanced therapy investigational medicinal product, through the manufacturing process until provision of the advanced therapy investigational medicinal product to the sponsor for use in the clinical trial and its delivery to the site where the clinical trial is conducted. The processes of provision or delivery of the advanced therapy investigational medicinal product to the sponsor are undertaken or controlled by the manufacturer. In cases where the sponsor is responsible for the delivery of the advanced therapy investigational medicinal product from the manufacturer to the site of the clinical trial, the sponsor is responsible for ensuring traceability through those process stages. 7.2.6. The investigator, or the pharmacist where delegated, is responsible for implementing the volunteer/patient and product traceability system at the clinical trial site. This system must contain the necessary details to allow the linkage

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of each product to the investigator or to the volunteer/patient who received it. 7.3. Archiving by the Sponsor, Manufacturer, Investigator and Trial Site for the Traceability Process 7.3.1. The sponsor on site where the advanced therapy investigational medicinal product is used must retain each part of the traceability records of the tissue establishment/procurement organisation, animal facility, manufacturer and trial site for at least 30 (thirty) years after the expiry date of the product, or for a longer period where required by the clinical trial authorisation conditions or under the agreement concluded with the sponsor. In the case of tissue establishments, where the period in question is longer than the period specified in the relevant legislation, the sponsor must ensure through agreements that the traceability records are retained for the specified period.

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7.3.2. The minimum data set to be retained by each party is provided in detail in the annex to this guideline. 8. SAFETY REPORTING AND LONG-TERM FOLLOW-UP 8.1. During the clinical trial, the reporting of adverse events and reactions by the sponsor and the responsible investigator is specified in the relevant legislation. New events related to the conduct of the trial and the development of the advanced therapy investigational medicinal product that may affect the safety of the participant (volunteer)/patient must be reported through the accelerated reporting process within the existing timeframe. These shall include, at a minimum, the following: 8.1.1. Serious adverse events related to the trial procedures that may require a modification of the conduct of the trial, 8.1.2. Significant hazards to the participant (volunteer)/patient population. 8.2. The sponsor shall provide the responsible investigator with the necessary information and training regarding any product-specific requirements for adverse event reporting or any additional protocol. The reporting process shall be clearly provided with details in the clinical trial protocol. In addition, attention shall be paid to the following safety issues: 8.2.1. Adverse events related to the product administration procedure (surgical or otherwise), 8.2.2. Suspected and confirmed cases of infection, 8.2.3. Unexpected reactions (e.g., hypersensitivity, immunological, toxic or other reactions resulting from a change in the manufacture or function of the viral vector, recombination yielding a replication-competent virus), 8.2.4. Adverse events related to product errors (including lack of efficacy), 8.2.5. Adverse events related to medicinal products mandatorily used in combination (e.g., immunosuppression), 8.2.6. Adverse events related to medical devices that form part of the product or are used for its administration. 8.3. A differentiated causality assessment related to the safety issues mentioned above shall be described in the clinical trial protocol and implemented in the adverse event reporting system. 8.4. In cases where a serious adverse reaction occurs in a clinical trial with an advanced therapy investigational medicinal product containing cells or tissues or a combined advanced therapy investigational medicinal product, all relevant parties shall be informed. 8.5. The necessity, duration and nature of the follow-up process shall be determined by the sponsor for each clinical trial based on a risk analysis including close contact, existing information on the advanced therapy investigational medicinal product, and the nature of the advanced therapy investigational medicinal product. The sponsor shall also take into consideration the relevant legislation concerning the follow-up and risk assessment of participants (volunteers)/patients treated with specific types of advanced therapy investigational medicinal products that provide further detailed information on the expected type and duration of follow-up. 8.6. The follow-up process shall be adapted to the specific evolving product requirements, described in the protocol, and modified as deemed necessary in the light of the development trials with the advanced therapy investigational medicinal product. It shall clearly define the follow-up activities. 8.7. The rationale for the selected follow-up, including existing supporting information, shall be documented and retained as required clinical trial documentation. 8.8. The follow-up process shall be considered with respect to the aspects set out below:

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8.8.1. Follow-up for the protection of the participant (volunteer)/patient, 8.8.2. Follow-up established for the purpose of collecting specific data (may not be required for all participants (volunteers)/patients). 8.9. All participants (volunteers)/patients enrolled in a clinical trial with an advanced therapy investigational medicinal product shall receive from the responsible investigator an alert card, containing at a minimum the name of the participant (volunteer)/patient, the contact number of the responsible investigator, and information on the medical examination received, approved by the clinical trials ethics committee and authorized by the TİTCK (Turkish Medicines and Medical Devices Agency), and previously agreed upon by the sponsor. 8.10. The protocol shall define the end of the trial and the follow-up process to be addressed after the completion of the trial. While safety and efficacy follow-up requiring an active data collection process (such as trial visits) shall constitute part of the clinical trial, clinical follow-up and the passive data collection process shall take place after the completion of the trial. 8.11. Where follow-up after the completion of the trial is required, particularly where this occurs over a long period of time, the sponsor shall ensure that a process is in place for the follow-up of participants (volunteers)/patients treated with the product in cases where product development is discontinued or the (previous) sponsor ceases to exist as a legal undertaking. This process shall be described in the protocol in such a way that it can be modified when necessary and archived as indicated below: 8.11.1. Appropriate information on the follow-up of participants (volunteers)/patients after the completion of the clinical trial, to be provided to healthcare facilities serving as trial sites, 8.11.2. Telephone numbers providing data/consultation in case of complications, 8.11.3. In cases of serious adverse reactions, the need to notify the TİTCK (Turkish Medicines and Medical Devices Agency), the trial site and the sponsor, and in cases of safety/efficacy issues, other available sources of data and independent records, and participant (volunteer)/patient alert cards informing physicians about the product used shall contain, at a minimum, the name of the participant (volunteer)/patient, the investigator's 24-hour contact number, and information on the medical examination received. These shall be agreed upon in advance by the sponsor, approved by the clinical trials ethics committee, and also authorized by the TİTCK (Turkish Medicines and Medical Devices Agency). This may be the same as those used for the clinical trial in cases where there are changes or additional information that are not necessary to address long-term follow-up processes after the completion of the trial. 8.12. In cases where the participant (volunteer)/patient withdraws from the trial of their own will or based on the investigator's decision, the follow-up process shall be continued subject to the consent of the participant (volunteer)/patient. 9. PROCESS FOR THE TİTCK (TURKISH MEDICINES AND MEDICAL DEVICES AGENCY) AUTHORIZATION 9.1. Clinical trials of advanced therapy medicinal products shall not be conducted without the authorization of the TİTCK (Turkish Medicines and Medical Devices Agency). 9.2. When evaluating the authorization of a clinical trial of an advanced therapy investigational medicinal product, the TİTCK (Turkish Medicines and Medical Devices Agency) shall take into consideration the relevant legislation as well as the adequacy of the follow-up strategy and traceability arrangements, including the definitions of the completion of the trial and the risk assessment. 10. CLINICAL TRIALS ETHICS COMMITTEE APPROVAL PROCESS 10.1. In order to conduct clinical trials of advanced therapy medicinal products, it is mandatory to obtain the authorization of the TİTCK (Turkish Medicines and Medical Devices Agency) and the approval of a clinical trials ethics committee authorized by the TİTCK (Turkish Medicines and Medical Devices Agency).

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10.2. In forming its opinion on clinical trials requiring advanced therapy investigational medicinal products, in addition to the relevant legislation, the ethics committee of the clinical trial must also carefully verify the following matters: 10.2.1. Traceability arrangements regarding the provisions for volunteer/patient data protection and confidentiality, 10.2.2. The information to be provided to the volunteer/patient for each use in the event of problems that may arise after the

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end of the trial (alert card) and the follow-up arrangements before and after the end of the trial, including the subsequent processes of volunteers/patients withdrawn from the trial, 10.2.3. The arrangements of the follow-up process regarding close contacts of recipients, 10.2.4. Written informed consent forms (ICF) and other documents regarding ethical issues concerning the suitability of specific advanced therapy investigational medicinal products, 10.2.5. The circumstances in which the sponsor's representative must be physically present during the administration of the advanced therapy investigational medicinal product belonging to the volunteer/patient, in the handling of the advanced therapy investigational medicinal product. 10.2.6. The irreversible content of the administration of certain advanced therapy investigational medicinal products and the information given to volunteers/patients for this purpose, 10.2.7. Special circumstances where the donor is a relative of the volunteer/patient to be included as a volunteer/patient, for the purpose of protection from "sibling/parent" pressure.

11. PRINCIPAL INVESTIGATOR AND OTHER INVESTIGATORS 11.1. Principal investigators and other investigators involved in clinical trials of advanced therapy investigational medicinal products are responsible for complying with the provisions of the relevant legislation and must also pay attention to the following matters: 11.1.1. They must establish and maintain a traceability system at the clinical site. 11.1.2. They must retain their portions of the traceability records for the relevant person. 11.1.3. They must be aware of the process for reporting adverse events and reactions, including reactions related to the administration of the advanced therapy investigational medicinal product. 11.1.4. They must have knowledge of the risk analysis of the advanced therapy investigational medicinal product. 11.1.5. They must have knowledge of the requirements for the storage, use, handling, and destruction and disposal of the advanced therapy investigational medicinal product, including risks that may arise to the environment and hazards related to close contact and use of the product. 11.1.6. They must have information on the requirements for the use, administration, implementation or handling of the advanced therapy investigational medicinal product and for clinical, efficacy and safety follow-up. 11.1.7. They must ensure that special requirements for the administration of the advanced therapy investigational medicinal product, such as the standardization of surgical methods and training of healthcare professionals, are communicated by the investigator to the trial site, including the necessary surgeons or other specialists. 11.1.8. They must inform the volunteers/patients in the trial and, where applicable, their legal representatives about matters arising from the advanced therapy investigational medicinal products.

12. INFORMED CONSENT FORM 12.1. The informed consent form (ICF) prepared for volunteers/patients or any written information must also contain, in addition to the provisions specified in the relevant legislation, in particular the following matters:

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12.1.1. Traceability arrangements, including provisions on volunteer/patient data protection and confidentiality, 12.1.2. The information to be provided to the volunteer/patient for each use in the event of problems that may arise after the end of the trial and the follow-up arrangements before and after the termination of the trial, including the subsequent processes of volunteers/patients withdrawn from the trial, 12.1.3. Where applicable, the disadvantages of long-term follow-up, 12.1.4. The definition of the termination of the trial and its relationship with the follow-up process after the termination of the trial, 12.1.5. Where applicable, the irreversible nature of the advanced therapy investigational medicinal product, 12.1.6. Where applicable, the need for the presence of the sponsor's representative for assistance and support during the handling of the advanced therapy investigational medicinal product, 12.1.7. Risks and precautions, including those related to the shedding processes of advanced therapy investigational medicinal products requiring gene therapy, 12.1.8. Guidance information on how information during any follow-up process and the risks to close contacts who may be at risk should be communicated.

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13. DUTIES AND RESPONSIBILITIES OF THE SPONSOR 13.1. It is obliged to comply with the legislation on clinical trials and the basic principles of good clinical practice (GCP). 13.2. It must establish and maintain a traceability system at the clinical site. 13.3. It must retain the portions of the traceability records for the relevant period. 13.4. It must implement the reporting process for adverse events and reactions required by the legislation on advanced therapy investigational medicinal products. 13.5. Through the trial brochure or its updates or the informed consent forms (ICF) or their updates, it must provide the information and documents stating that an ongoing risk analysis based on the current product type and intended use information is carried out and provided to the volunteer/patient and to the investigator serving in the clinical trial. 13.6. For combined products, the risk analysis and the risk management plan of the device component must be shared with investigators. 13.7. It must define the need, duration and nature of the necessary clinical, safety or efficacy follow-up, including the subsequent processes after the withdrawal of volunteers/patients from the trial. 13.8. It must provide the special requirements for the administration of the advanced therapy investigational medicinal product, such as the standardization of the surgical procedures and training processes of the principal investigator and other investigators. 13.9. It must have knowledge of the requirements for the storage, use, handling, and destruction and disposal of the advanced therapy investigational medicinal product, including risks that may arise to the environment and hazards related to close contact and use of the product. 13.10. It must provide training to investigators regarding the use, administration, implantation or handling procedures of advanced therapy investigational medicinal products that may require surgical procedures that may have an impact on the safety and efficacy of the special treatment and product to be acted upon together. During clinical development, information on the standardization and optimization of these procedures must be provided. The sponsor must also determine whether the involvement of its own personnel in these procedures is required and must address these circumstances in the agreements concluded with the clinical trial site and in the clinical

trials shall be explained in the protocol submitted by the sponsor to the ethics committee and the Turkish Medicines and Medical Devices Agency (TİTCK) or in the accompanying documents. 13.11. Where applicable, the national competent authority should be consulted on biosafety matters. 14. PROTOCOL With regard to the content of the protocol, in addition to the matters specified in the relevant legislation, the sponsor shall, as a minimum, take into account the following matters: 14.1. In the protocol design specific to the use of medicinal products for advanced therapy trials, the protocol shall provide for the significant flexibility processes that may be required in order to address the diseases being treated and the variabilities inherent in the nature of the medicinal products in advanced therapy trials. For example; the acceptable ranges of cell counts and cell viability upon administration to participants (volunteers)/patients, the inclusion of criteria and appropriate acceptability windows for exclusion. 14.2. In cases where the medicinal product in advanced therapy trials contains human cells or tissues, the protocol shall include a brief description of the following matters: 14.2.1. Verification that the processes of donation, procurement and testing of human tissues and cells are in compliance with the relevant legislation, 14.2.2. The type of donor and whether the donation is part of the trial process, 14.2.3. Compliance of the eligibility criteria of the donated material with the defined requirements. 14.3. In cases where the medicinal product in advanced therapy trials contains a medical device (for example, a combined advanced therapy medicinal product), the protocol shall include a brief description of the following matters: 14.3.1. The characteristics, performance and purpose of the device, 14.3.2. The justification for the combination of the medicinal product in advanced therapy trials and the medical device, which may assist in understanding the effects either alone or in combination, 14.3.3. Compliance of this product with the essential requirements specified in the relevant legislation. 14.4. Where deemed necessary, detailed instructions for ensuring the blinding

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of the trial shall be provided (for example, cases where the person responsible for the randomisation of participants (volunteers)/patients for examination must remain blinded, or cases where the person present at the clinical site during the preparation stage of the medicinal product in advanced therapy trials cannot be blinded, necessitating the blinding of the person responsible for the administration of the medicinal product in advanced therapy trials). 14.5. Traceability procedures shall be specified. 14.6. Information on any specific requirements for safety reporting, including the processes during the follow-up following the end of the trial, shall be included. 14.7. The definition of the end of the trial and its relationship to the follow-up process following the end of the trial shall be specified. 14.8. There shall be justifications and objectives based on an appropriate risk assessment, and information on the follow-up strategy requested for the medicinal product in advanced therapy trials (including the follow-up process after the end of the trial). 14.9. Specific requirements regarding participants (volunteers)/patients who withdraw from the trial on their own initiative or on the initiative of the investigator shall be specified, particularly in relation to the follow-up strategy. 14.10. Where a procedure requiring special treatment applied jointly is at issue and where this procedure

necessitates surgical procedures that have an impact on the efficacy or safety of the product, information on the administration of the medicinal products in advanced therapy trials shall be included. This includes, where applicable, information on the standardisation and optimisation of the necessary processes, including surgical procedures. 14.11. Information shall be provided, together with the justification, on whether the sponsor's representative must be present during the administration of the medicinal product in advanced therapy trials to the participant (volunteer)/patient. 14.12. Instructions shall be included as to whether any local preparation or dilution is required. 14.13. In the case of medicinal products in advanced therapy trials requiring gene therapy, information on viral shedding and the necessary precautions shall be provided where applicable. 15. INVESTIGATOR'S BROCHURE With regard to the content of the investigator's brochure, in addition to the matters specified in the relevant legislation, the sponsor shall, as a minimum, take into account the following matters: 15.1. A description of the scope and adequacy of the existing data and their limitations, 15.2. Information obtained from the ongoing risk analysis based on the existing data on the intended use and product type, including risks associated with the method of administration (for example, surgical operations, concomitant medications and associated devices), 15.3. Information on the risk management plan (for products placed on the market), 15.4. Information on risks arising from product defects, 15.5. Information on the safe use, storage, prevention and disposal of the product, 15.6. Information on specific short-term and long-term safety concerns of medicinal products in advanced therapy trials, such as infections, immunogenicity/immunosuppression and malignant transformation, as well as those relating to medical devices for combined medicinal products in advanced therapy trials. 16. REQUIRED DOCUMENTS 16.1. With regard to the keeping of records, the rules specified in the relevant legislation shall apply. Traceability records shall be retained for a minimum of 30 (thirty) years after the expiry date of the product or for a longer period if required by the agreement concluded with the sponsor or by the conditions of the clinical trial authorisation. 16.2. In order to ensure two-way traceability processes linking, at the clinical trial site, the information of the participants (volunteers)/patients taking part in the clinical trial with the medicinal product in advanced therapy trials, and, at the supply area related to the medicinal product in advanced therapy trials, the donor information, while ensuring the legally required data protection for both the donor and the clinical trial participant (volunteer)/patient, each party shall have the necessary information available at all times before, during and after the completion or termination of the trial. 16.3. During the planning phase prior to the commencement of the clinical trial phase, the following documents shall be prepared and shall be included in the file before the trial officially commences: 16.3.1. Tissue establishment/blood establishment, manufacturer, sponsor and investigator/trial

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site file: the process, responsibilities and documentation details necessary to document the link from the donor to the participant (volunteer)/patient receiving the product, or vice versa, 16.3.2. Sponsor file: 16.3.2.1. Documents used to determine the follow-up strategy,

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16.3.2.2. Information on the follow-up strategy requested for the advanced therapy investigational medicinal product, together with justifications and objectives based on an appropriate risk assessment (including the follow-up process after the termination of the trial). 16.4. During the conduct of the clinical trial, the following documents shall be kept in the file: 16.4.1. Tissue centre/blood or animal facility file: 16.4.1.1. Traceability records linking the donor/animal source to the donated material, 16.4.1.2. Updates to the process, responsibilities and documentation details required to document the link from the donor to the volunteer/patient receiving the product, or vice versa. 16.4.2. Manufacturer file: 16.4.2.1. Traceability records linking the donated material to the advanced therapy investigational medicinal product manufactured, 16.4.2.2. Updates to the process, responsibilities and documentation details required to document the link from the donor to the volunteer/patient receiving the product, or vice versa. 16.4.3. Sponsor file: 16.4.3.1. Traceability records for linking the advanced therapy investigational medicinal product manufactured to the trial site and to the patient code of the trial site, 16.4.3.2. Updates to the process, responsibilities and documentation details required to document the link from the donor to the volunteer/patient receiving the product, or vice versa, 16.4.3.3. Any update to the documentation used to determine the follow-up strategy, 16.4.3.4. Information on the follow-up strategy requested for the advanced therapy investigational medicinal product, together with justifications and objectives based on an appropriate risk assessment (including the follow-up process after the termination of the trial). 16.4.4. Principal investigator/trial site files: 16.4.4.1. Traceability records for linking the advanced therapy investigational medicinal product manufactured to the trial site, and from the trial site to the patient code, patient identification and medical file, 16.4.4.2. Updates to the details of the process, responsibilities and documentation required to document the link from the donor to the volunteer/patient receiving the product, or vice versa. 16.5. After the completion or termination of the trial, all documents specified in this guide and retained by each relevant party shall be kept in the file together with the following: 16.5.1. Tissue centre/blood establishment/animal facility file: Final traceability records enabling a link to be established between the donated material and the donor/animal, 16.5.2. Manufacturer file: Final traceability records enabling a link to be established between the advanced therapy investigational medicinal product manufactured and the donated material, 16.5.3. Sponsor file: 16.5.3.1. Final traceability records enabling a link to be established between the advanced therapy investigational medicinal product manufactured for the trial site and the trial site and the patient code, 16.5.3.2. Follow-up procedures, collected information and contact information, clinical follow-up, safety follow-up and efficacy follow-up documentation are required. 16.5.4. Principal investigator/trial site file:

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16.5.4.1. Final traceability records enabling a link to be established between the advanced therapy investigational medicinal product delivered to the trial site and, from the trial site, the patient code and the medical file through patient identification, 16.5.4.2. Follow-up procedures, collected information and contact information, clinical follow-up, safety follow-up and efficacy follow-up documentation are required. 18. REPEALED PROVISIONS The "Guide on the Principles and Requirements for Good Clinical Practices for Advanced Therapy Medicinal Products", put into effect by the Approval of the Authority dated 17.04.2013 and numbered 43020, has been repealed. 19. ENTRY INTO FORCE This guide enters into force on the date of its approval.

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ANNEX-1 TRACEABILITY RECORDS

1. Tissue Centres and Procurement Organisation As specified in the relevant legislation. 2. Blood Establishments As specified in the relevant legislation. 3. Animal Facilities As specified in the relevant legislation. In addition: 3.1. Source animal identification 3.2. Donor identification comprising, as a minimum, the following: 3.2.1. Identification of the animal facility 3.2.2. Animal ID (identity) number 3.2.3. Location of the facility 3.2.4. Type of donation (for example, single and multiple tissue, living and deceased) 3.3. Product identification comprising at least the following: 3.3.1. Identification of the animal facility 3.3.2. Type of tissue and cell/product (basic terminology), anatomical class where applicable 3.3.3. Pool number (where applicable) 3.3.4. Split number (where applicable) 3.3.5. Expiry date 3.3.6. Tissue/Cell status (for example, in quarantine, suitable for use) 3.3.7. Description of the origin of the products, materials used in manufacturing steps, additives coming into contact with tissues and cells and their effects on quality or safety. 3.3.8. Identification of the establishment performing final labelling 3.3.9. Identification of user establishment and distribution dates 3.3.10. Distribution date/Disposal 3.3.11. Identification of the user establishment 4. Manufacturers 4.1. Information contained on the material obtained from the procurement organisation, as appropriate for whether it is a tissue centre or an animal facility: 4.1.1. Identification of the tissue centre/animal facility/any intermediary (where applicable) 4.1.2. Type of tissue and cell/product (basic terminology) 4.1.3. Pool number (where applicable) 4.1.4. Number of splits (where applicable) 4.1.5. Tissue/Cell status (for example, in quarantine, suitable for use) 4.2. Advanced therapy investigational medicinal product identification comprising at least the following: 4.2.1. Tissue/Cell status (for example, in quarantine, suitable for use) 4.2.2. Description of the origin of the products, materials used in manufacturing steps, additives coming into contact with tissues and cells and their effects on quality or safety 4.2.3. Identification of the sponsor, contract research organisation or principal investigator/institute/centre to whom the product is supplied 4.2.4. Product name/code 4.2.5. Pharmaceutical form, route of administration, dosage unit quantities and loss

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4.2.7. Trial reference code 4.2.8. Trial subject identification number 4.2.9. Expiry date 4.2.10. Date of distribution/Disposal 4.2.11. Release of the finished product by a qualified person 5. Sponsor 5.1. In accordance with the relevant legislation on good clinical practice, the following required documents shall be retained by the sponsor before, during and after the conduct of the trial: 5.1.1. Shipping records for the investigational product (IP) 5.1.2. Certificate of analysis of the IP 5.1.3. Documentation of treatment allocation and decoding 5.1.4. Traceability of the IP at the site, covering the final use of both used and unused product 5.2. These records and the information required for traceability purposes, including at least the specified minimum data set, shall be retained for 30 (thirty) years or longer from the expiry date of the product, in accordance with the conditions of the clinical trial authorisation or the agreement made with the sponsor. They shall include at least the following information: 5.2.1. Identification of the manufacturing site 5.2.2. Identification of the principal investigator / the organisation that used the advanced therapy investigational medicinal product 5.2.3. Product name/code 5.2.4. Pharmaceutical form, route of administration, dosage unit quantities and losses 5.2.5. Batch or code number 5.2.6. Trial reference code 5.2.7. Identification number of the participant (volunteer)/patient enrolled in the trial 5.2.8. Expiry date 5.2.9. Date of administration 5.3. In addition to the above, the latest version of the trial brochure and protocol shall be retained for the same period in order to provide information on the product and its administration. 6. Principal investigator and trial site responsible for human administration 6.1. In accordance with the relevant legislation on good clinical practice, the following required documents shall be retained by the sponsor before, during and after the conduct of the trial: 6.1.1. Shipment records for the IP 6.1.2. Certificate of analysis of the IP 6.1.3. Documentation of treatment allocation and decoding 6.1.4. List of participant (volunteer)/patient identification codes 6.1.5. Traceability of the IP covering the final use of both

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used and unused product 6.2. These records and the information required for traceability purposes, including at least the specified minimum data set, shall be retained for 30 (thirty) years or longer from the expiry date of the product, in accordance with the conditions of the clinical trial authorisation or the agreement made with the sponsor. They shall include at least the following information: 6.2.1. Identification of the principal investigator and the trial site 6.2.2. Where applicable, identification of the sponsor and the contract research organisation

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6.2.3. Identification of the manufacturing site 6.2.4. Product name/code 6.2.5. Pharmaceutical form, route of administration, dosage unit quantities and losses 6.2.6. Batch or code number 6.2.7. Trial reference code 6.2.8. Trial identification code 6.2.9. List of participant (volunteer)/patient identification codes (linking the name of the participant (volunteer)/patient to the trial participant (volunteer)/patient code) 6.2.10. Expiry/re-test date 6.2.11. Date of administration 6.3. The product name/code, trial reference code, trial participant (volunteer)/patient code, date of administration and dosage information shall also be included in the aforementioned medical records in order to enable retrospective product identification and further linkage with the sponsor's and investigator's traceability records. 6.4. Records containing the final status of any unused or destroyed product at the trial site shall be retained.

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