EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 January 2018
EMEA/149995/2008 rev.1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products

Draft

Adoption by CHMP	November 2008
Date of coming into effect	31 December 2008
Adopted by PRAC	November 2017
Adopted by CAT	January 2018
Adopted by CHMP for release for consultation	January 2018
Start of public consultation	01 February 2018
End of consultation (deadline for comments)	30 April 2018

This guideline replaces 'Guideline on safety and efficacy follow-up - risk management of Advanced Therapy Medicinal Products' (EMEA/149995/2008)

Comments should be provided using this template. The completed comments form should be sent to: ATMPguideline@ema.europa.eu

Keywords	Advanced Therapy Medicinal Products, Post-authorisation efficacy and safety studies, Risk Management

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products

Table of contents

Executive summary **3**

1. Introduction (background) **4**

2. Scope **4**

3. Legal basis and relevant guidelines **4**

4. Pharmacovigilance system **5**

5. Safety and efficacy concerns for advanced therapy medicinal products **6**

5.1. Identification of the safety and efficacy concerns for ATMPs 6
5.2. Safety specifications 9

6. Pharmacovigilance activities **9**

7. Risk minimisation measures **10**

7.1. Routine risk minimisation measures 10
7.2. Additional risk minimisation measures 10
7.2.1. Administration site where the patient is treated 10
7.2.2. Educational programme 10
7.3. Effectiveness of the risk minimisation measures 12

8. Efficacy and safety follow-up **12**

8.1. Introduction 12
8.2. Methodological considerations 13
8.3. Objectives for long-term follow-up for efficacy 15
8.4. Objectives for long-term follow-up for safety 16
8.4.1. For cell based products 16
8.4.2. For gene therapy 16
8.4.3. For combined ATMPs 17
8.4.4. Other considerations on safety follow-up 17

9. Management and reporting of adverse reactions and PSURs **17**

10. Compliance monitoring **18**

Executive summary

The aim of this guideline is to provide the guidance for the Safety and Efficacy (S&E) follow-up and risk management for advanced therapy medicinal products (ATMPs) according to Article 14(4) of Regulation (EC) No 1394/2007. This regulation requires the European Medicines Agency (EMA) to develop a detailed guideline relating to the post-authorisation follow-up of efficacy and adverse reactions, and risk management for these products.

This is the 1st revision of the original ATMP guideline on safety and efficacy follow-up and risk management; the guideline has been revised to take into consideration the experience gained with the authorisation of these products and to define their risks and their risk minimisations measures. In addition, guidance on methodology in order to design post-authorisation S&E follow-up studies is provided.

Two documents from the Marketing Authorisation Holder (MAH) are directly impacted by this guideline – the Pharmacovigilance System Master File (PSMF) and the Risk Management Plan (RMP).

With regards to the description of the pharmacovigilance system within the PSMF, reference to the relevant GVP is provided.

During product development, guidance on how to identify the risks associated with the clinical use of an ATMP and their risk factors with respect to quality, safety and efficacy is provided in the guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to advanced therapy medicinal products. As part of the marketing authorisation evaluation, an assessment of the risks is carried out in order to determine the ones which should be minimised and/or further characterised post-marketing. A description on how to report, minimise and/ or further characterise in the RMP, the important risks which may be attributed to ATMPs is provided in this guideline.

Finally, guidance is provided on the methodology to follow in order to design post-authorisation S&E follow-up studies. This includes defining precisely the study objective(s), the appropriate study design (e.g. randomised controlled trial, cohort study, case control study, use of external controls, etc.), to consider the available data sources (e.g. clinical trial, registry, healthcare database) and to define a statistical analysis which will obtain a reliable estimate of the effect. It needs to be emphasised that both the S&E follow-up activities do not substitute for the adequate data to be provided at the time of marketing authorisation and enable a benefit-risk evaluation.

The consequences of non-compliance with the pharmacovigilance and risk minimisation activities agreed in the RMP, including financial penalties and regulatory measures are highlighted in this guideline. As follow-up systems and risk management may require the processing of sensitive personal data, the requirement to observe the applicable data protection legislation is also identified.

1. Introduction (background)

Scientific progress in cellular and molecular biotechnology has led to the development of advanced therapy medicinal products (ATMPs), such as gene therapy, somatic cell therapy, and tissue engineering products. Because of the novelty, complexity and technical specificity of ATMPs, these products are regulated under a specific legislative framework Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products, which introduces additional provisions to those laid down in Directive 2001/83/EC and Regulation (EC) No 726/2004. (hereafter, also referred to as the ATMPs Regulation).

2. Scope

According to Article 14 (4) of Regulation (EC) No 1394/2007, the Agency shall draw up a detailed guideline relating to the post-authorisation follow-up of efficacy of ATMPS and adverse reactions thereto, as well as risk management including an evaluation of the effectiveness of that system as well as the guidance on post-marketing studies.

This guideline provides dedicated and specific guidance for ATMPs with regards to the pharmacovigilance system, the identification of risks, the risk minimisation measures, the post-authorisation S&E studies, the management and the reporting of adverse reactions and of the evaluation of the effectiveness of the risk management system. The GVP modules apply and references are provided accordingly.

The two documents below should be updated throughout the lifecycle of the product and when new important safety information becomes available:

- The pharmacovigilance system master file
- The Risk Management Plan (module 1.8.2.): The applicants are referred to the RMP template and GVP Module V – Risk management systems.

This revision involves an update of all the main sections based on experience gained from the marketing authorisation applications received.

Follow-up systems, risk minimisation plans and traceability systems require access to personal data and in particular to data concerning health. Hence, reference is made to the obligations laid down in Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) and to any other applicable legal requirements concerning the processing of personal data.

3. Legal basis and relevant guidelines

This guideline should be applied in accordance with Regulation (EC) No 1394/2007 of the European parliament and of the Council of 13 November 2007 on advanced therapy medicinal products:

Directive 2001/83/EC on the Community code relating to medicinal products for human use and Regulation (EC) No 726/2004 for Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, in particular Part IV of Annex I of the Directive 2001/83/EC related to Advanced Therapy Medicinal Products.

To the extent that clinical trials are required in a post-marketing setting, Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.

Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.

Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

This guideline should also be read in conjunction with other relevant guidelines, namely:

Good Pharmacovigilance Practices (GVP) Modules:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c

Guideline on summary of product characteristics (SmPC)

Scientific guidance on post-authorisation efficacy studies (EMA/PDCO/CAT/CMDh/PRAC/CHMP/261500/2015).

ICH E9 Statistical principles for clinical trials.

ICH E10 Choice of control group and related issues in clinical trials.

Guidelines relevant for ATMPs, which can be found on the website of EMA:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000298.jsp&mid=WC0b01ac05800862bd

These include specific clinical guidelines for ATMPs e.g.:

Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products (EMA/CAT/CPWP/686637/2011),

Reflection paper on in-vitro cultured chondrocyte containing products for cartilage repair of the knee (EMA/CAT/CPWP/568181/2009) and the reflection paper on clinical aspects related to tissue engineered products (EMA/CAT/573420/2009).

ICH Considerations General Principles to Address Virus and Vector Shedding (EMEA/CHMP/ICH/449035/2009).

CAT reflection paper on the management of clinical risks deriving from insertional mutagenesis (EMA/CAT/190186/2012).

Guideline on follow-up of patients administered with gene therapy medicinal products (EMEA/CHMP/GTWP/60436/2007).

4. Pharmacovigilance system

As part of the application for marketing authorisation of a medicinal product, the applicant is requested to provide a summary of the pharmacovigilance system which will have to be in place once the

authorisation is granted. This is further detailed in the Guideline on good pharmacovigilance practices (GVP) Module II – Pharmacovigilance system master file.

Article 14(1) of the ATMPs Regulation requires the applicant to detail, in the marketing authorisation application, the measures envisaged to ensure the follow-up of efficacy of ATMPs and of adverse reactions thereto.

Therefore, within their pharmacovigilance system in place, the MAH for an ATMP should ensure that:

- Procedures for follow-up of reported adverse reactions which allows identification of the batch linked to the reported reactions are in place.
- When applicable agreements should be in place with registry owners in order to allow the use of patients' data collected for regulatory purposes. In these cases, patients' informed consent should be in place to allow the use of their data.

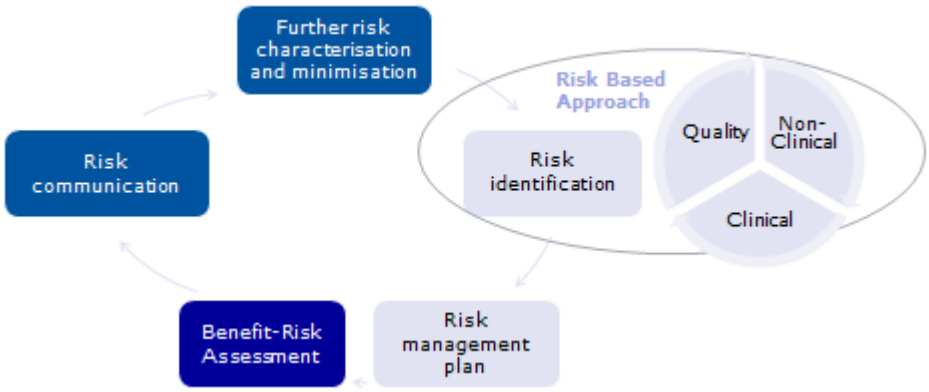
Pharmacovigilance inspections may be performed to ensure compliance with the legislation. The responsibility for performing the inspections resides with the national competent authorities (NCAs). Please refer to GVP Module III - Pharmacovigilance inspections.

5. Safety and efficacy concerns for advanced therapy medicinal products

5.1. Identification of the safety and efficacy concerns for ATMPs

ATMPs provide new possibilities for restoring, correcting or modifying physiological functions, or making a medical diagnosis. At the same time, because of their novelty, complexity and technical specificity, they may cause new, risks to patients. The specific rules described in this guideline should facilitate early detection of such risks and provide a framework for effective mitigation of their consequences to patients.

The detection of the risks should start early and continue throughout the development of the ATMP in order to prevent and/ or minimise the risk when possible, reference is made to the guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to advanced therapy medicinal products. The aim of this section is to describe the safety and efficacy aspects that need to be managed through the risk management plan to be agreed as part of the marketing authorisation (please see below figure).



Only the safety concerns relevant to RMP should be added in the safety specification of the RMP as either as important identified or potential risks or missing information. For the efficacy concerns, these are likely to be followed-up through post-authorisation efficacy studies. The content and extent of the RMP must be proportionate to the risks of the ATMP.

Examples are presented below.

Flow chart of the logistics of the therapy

A high level flowchart of the manufacture up to the administration of the therapy should include, harvesting, transport, controls, manipulation, conditioning, administration and clinical follow-up.

The risks are listed below in the chronological order of the product manufacturing, handling, application and clinical follow-up:

Risks to patients in relation to quality characteristics, storage and distribution of the product

- Risk of transmission of diseases: Origin of cells or tissues (autologous vs. allogeneic), characteristics of the cell type used and the ability of cells to proliferate and differentiate (e.g. embryonic stem cells, iPSC, etc.). Depending on the origin of cells/tissues, there might be a risk related to transmissible diseases (viral, bacterial, parasitical infections and infestations).
- Risk of tumourigenicity: Characteristics of products (e.g. if the manufacturing process includes extensive culture for proliferating cells (e.g. mesenchymal stem cells), this may affect the differentiation capacity of the cells leading potentially to a risk a tumourigenicity, risk of “off target” mutations and unintended “on target” mutations when gene editing techniques are used).
- Risk related to the storage, transport and distribution of the product, for instance related to preservation, freezing and thawing, risks of breaking the cold chain or other type of controlled temperature conditions and risks related to stability of the product. This could impact on the biological activity of the ATMP potentially leading to treatment failure.

Risks related to patient associated conditions/disease or underlying disease, or concomitant treatment /interactions with other medicinal products

- Unwanted immunogenicity and its consequences (including anaphylaxis, graft versus host disease, graft rejection, neutralising antibodies, hypersensitivity reactions, immune deficiencies, cytokine release syndrome, inflammation, etc.).
- Risks related to conditioning of patients (e.g. in case of CD34 positive genetically modified cells, in oncology in case of CAR T cells).
- Risks related to both intended and unintended genetic modification of the patient’s cells (apoptosis, change of function, alteration of growth and/or differentiation, malignancy).
- Early and late consequences of homing, grafting, differentiation, migration and proliferation.
- Risks related to infection with vectors used in gene therapy medicinal products (type of vector, target cells, persistence, potential for latency and reactivation, potential for integration of genetic material into the host genome, prolonged expression of the transgene and altered expression of the host’s genes).

- Risks related to clinical follow-up (immunosuppression associated with the co-medication or when needed to treat the complications, or to facilitate the diagnostic procedures, etc.).

Risks to patients related to reconstitution procedures

- Dosing errors and/or maladministration which can be related to reconstitution procedures for administration of the product.

Risks to patients related to administration procedures and re-administration

- Risks associated with related medical or surgical procedures or administration of the medicinal product (such as infusion, transfusion, implantation, etc.).
- Risks related to repeated surgical or administration procedures (e.g. administration in the brain via burr holes).
- Risks related to an administration medical device (technical or mechanical aspects) leading to medication errors or maladministration.

Risks related to persistence of the product in the patient

- Availability of rescue procedures or antidotes and their risks.
- Late complications, particularly malignancies and autoimmunity.
- Considerations on the potential impact of previous, concomitant, or prospective therapies typical for the diagnosis or treatment of the respective disease on the product, or vice versa impact of the product on those other therapies (e.g. an immunoglobulin treatment later in life could impact on expression of the introduced gene by antibody interaction).
- Risk of non-specific integration into other cells with the potential of tumourogenicity.
- Risk of germ line integration of transgene, or other genetic transformation of the germ line.

Risks to healthcare professionals, care givers, offspring and other close contacts and its risks to the environment

- If a risk to healthcare professionals, care givers, offspring and other close contacts with the product or its component, or with patients is identified, this risk should also be considered in the safety specification (this is based on the environmental risk assessment for instance). Replication-competent virus /vector might persist in the patient for extended periods and can increase in amount. Therefore, the potential for shedding can be higher with replicating virus / vector and could result in a greater likelihood of transmission. For replicating virus / vector, analysis of molecular variants will also be important and could impact virus / vector shedding. Reference is made to ICH Considerations General Principles to Address Virus and Vector Shedding (EMEA/CHMP/ICH/449035/2009).
- A gene therapy medicinal product containing or consisting of a genetically modified organism (GMO) capable of replication and dissemination or transmission can pose a risk of being transmitted into the environment. Adverse effects may be related to inserted genes and their products, but also to an unforeseen change of the host range or tissue tropism, infectivity, virulence, or latency of the generated GMO. All these effects have to be taken into account, either by making theoretical assumptions based on known science or by experimentally assessing pre-requisites or

consequences of such effects. Reference is made to the guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products (EMEA/CHMP/GTWP/125491/2006).

- Specific parent-child risks, for instance foetal transmission (of vectors, biologically active substances, cells, infectious agents, etc.), transmammary exposure of children for lactating women (to vectors, biologically active substances, cells, infectious agents, etc.).

For the identification of the risks in the RMP, a cross reference can be made to the relevant section of the CTD dossier where these aspects are addressed.

5.2. Safety specifications

Based on the examples of safety concerns listed above, applicants should set up the safety specifications which consist of a summary of the important identified and potential risks and potentially missing information. Additional guidance on safety specifications can be found in the GVP- module V – Risk management Systems.

This could include as appropriate:

- Transmission of infectious agents to the patient and to close contacts.
- Treatment failure (e.g. graft dysfunction and/or rejection), impossibility of re-treatment.
- Harm due to medication errors/maladministration.
- Induction of autoimmunity or immunogenic reactions.
- Induction of malignancies/tumour formation.
- Impossibility of discontinuing or removal of the product in case of emerging risks.
- Potential of the vector for latency and reactivation, integration of genetic material into host genome, prolonged expression of the transgene, altered expression of the host's genes, activation of oncogenes, potential for germline integration.
- Unwanted tissue formation including abnormal cell proliferation.

6. Pharmacovigilance activities

For ATMPs, additional pharmacovigilance activities may be introduced to identify, characterise or quantify a safety hazard, to measure the effectiveness of risk-management measures or to investigate missing information. The performance of pharmacovigilance activities should include the following considerations:

- Any specific aspects of routine pharmacovigilance if applicable, e.g. any increased requirements with regards to spontaneous reports, follow-up reports, specific methodology for signal detection. Reference is made to GVP Module VI – Management and reporting of adverse reactions to medicinal products.
- Active surveillance should often be put in place, particularly when the ATMP is expected to be used in "centres of excellence" that could serve as sentinel sites. Surveillance could potentially be accommodated within disease registries hosted by such centres; this would permit the product to be evaluated in the context of other treatments and the disease more broadly.

- In the case of ATMPs that contain tissues and/or cells, use of traceability data[1] for surveillance purposes (e.g. an established registry of batches of products distributed to a particular centre and its record linkage to the pharmacovigilance database of reports received from that centre).

The MAH should also consider appropriate measures to ensure the follow-up of patients for potential cases where the MA ceases to exist.

7. Risk minimisation measures

7.1. Routine risk minimisation measures

The routine risk minimisation measures refer to the management of risks as explained and minimised in the SmPC, the package leaflet, the labelling, the pack size and design and the legal (prescription) status of the product. Cross-references can be made to the section of the CTD dossier where these aspects are addressed. Reference is made to the guideline on Summary Product Characteristics (SmPC).

7.2. Additional risk minimisation measures

Based on the existing tools and feasible approaches to risk minimisation, this section describes examples of additional risk minimisation measures that could be considered to reduce some particular risks. It is stressed that the list is not exhaustive and that the examples are to be considered as appropriate depending on the specific product subject to the risk mitigation. Reference is made to GVP Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators.

7.2.1. Administration site where the patient is treated

In order to reduce the risks associated with the administration of the ATMP, the use of a controlled access programme by selecting accredited centres and adequately trained and experienced physicians might be necessary. Selection and accreditation of specialised centres by MAHs and/or NCAs, possibly in cooperation with an appropriate medical organisation might also be part of the risk minimisation plan. When the ATMP is only available in one or a few specialised centres in specific countries, considerations should be taken into account with regards to the follow-up of patients and awareness of physicians.

7.2.2. Educational programme

Educational programmes based on targeted communication could be developed to supplement the information in the SmPC and PL. Reference is made to GVP Module XVI - Risk minimisation measures.

<u>Educational materials for treating physicians relating to:</u>

- the conditioning of the patient (e.g. in oncology, bone marrow transplant).

[1] Traceability obligations are laid down in Article 15 of Regulation (EC) No 1394/20017 and are further developed in Section 6.6 of the European Commission Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products.

- the handling, product reconstitution, administration and product and/or implant trimmings disposal. To this effect, a surgical checklist and adequate Standard Operating Procedure (SOP) could be put in place. These should be in line with the Product Information and further detailed to ensure the effective and safe use of the ATMP. Training on the basis of the educational materials may be a requirement for the accreditation of healthcare establishments for the use of the product.
- the product characteristics and expected adverse reactions both associated with conditioning, administration and those post-administration and management of adverse reactions (e.g. in the case of CAR-T cells, a close monitoring of patients should take place to monitor for signs of Cytokine Release Syndrome so that immediate treatments can be given).
- clinical follow-up (e.g. need for rehabilitation and the detailed program).
- traceability aspects (e.g. recording batch number information in patient´s charts and on the patient´s alert card, providing batch number when reporting adverse reactions).
- Health Care Professional (HCPs) protection measures based on the environmental risk assessment.
- patients' protection, including – where appropriate- on mechanisms to ensure that patients are informed of the risks - on reporting of patient clinical information, treatment outcomes and adverse effects in the relevant disease registry.

<u>Educational materials for pharmacists relating to:</u>

- the product receipt and storage, the procedure for the reconstitution (e.g. when performed at a hospital's pharmacy), handling and disposal of the ATMP.

<u>Educational materials for patients (and/or caregivers) relating to:</u>

- brochures highlighting the important safety risks, such as adverse events and environmental risks (e.g. shedding) related to the ATMP.
- patient alert cards in line with GVP Module XVI - Risk minimisation measures: selection of tools and effectiveness indicators. There should be a batch recording on the alert card to facilitate the reporting of adverse events.
- a description of the administration process and treatment process.
- the importance of reporting adverse drug reactions.
- the importance of reporting other information arising from the disease registry that are relevant for the ATMP.

<u>Educational materials for support personnel, family and caregivers relating to:</u>

- early symptoms of important identified or potential risks, clinical follow-up procedures and post-treatment care and recommendation, or related to the accidental transmission of the vectors from patient to close contacts or caregivers through shedding.

When applicable, an English draft version of the educational materials should be submitted for evaluation and agreed as part of the marketing authorisation application. This will serve as a basis for the implementation with the NCAs in the Members States.

7.3. Effectiveness of the risk minimisation measures

Specific tools to measure effectiveness of risk minimisation via objective criteria can accompany the risk minimisation activity. Reference is made to GVP Module XVI - Risk minimisation measures: selection of tools and effectiveness indicators. In general all relevant data that is generated and comes to the knowledge of the MAH post-marketing should be used to evaluate the effectiveness of the RMP.

Examples may include:

- If there is a trend reflecting a large number of adverse events that may be associated to the administration procedure, there needs to be consideration whether the training material is adequate and should be updated.
- If an educational plan is in place, testing the knowledge and skills of the target audience that should have been improved by the particular educational plan can be conducted and evaluated when there is a reason for concern.

8. Efficacy and safety follow-up

8.1. Introduction

Safety and Efficacy (S&E) follow-up data generated during development is expected to be provided as much as possible to support the marketing authorisation application. There should be sufficient long-term S&E data generated in order to enable an adequate benefit-risk assessment of the products in line with the ATMP Regulation. When applicable, the remaining uncertainties around S&E as applicable at the time of MA will determine the extent, objectives and the design of the post-marketing S&E studies and according to Article 14 of the ATMP Regulation.

When studies are imposed at the time of granting the MA, the following information in this section should be taken into consideration for the design of these post-authorisation studies which can comprise extension phases of pre-authorisation trials, additional clinical trials and / or other observational studies which can be conducted based on the registry data.

All developers are encouraged to plan the development of the product holistically, considering data generation in the post-authorisation phase in addition to data obtained pre-authorisation. ATMP developers should ensure that the patients enrolled in clinical trials (starting at phase I) or in compassionate use are appropriately followed-up to allow generation of long-term S&E data. The use of disease registries or other data sources for collecting long-term S&E data should be considered early in the development process so that appropriate plans are in place by the time the MA is granted. In this regard, it is very important that appropriate agreements are in place between different parties (e.g. hospitals, registry owners, patients and ATMPs developers) to allow the legitimate use of patients' data collected in clinical trials (different sponsor), compassionate use programmes or through registries for specific regulatory purposes. Informed consent forms should be signed by patients to allow for these data to be provided for regulatory purposes.

Recommended clinical follow-up in the form of laboratory and clinical investigations for patients treated with the product should be described in the SmPC and package leaflet (e.g. annual visits recommended in order to conduct a complete blood count with differential, biochemistry and thyroid stimulating hormone in the view of detecting any tumour formation). Reference is made to the guideline on follow-up of patients administered with gene therapy medicinal products (EMEA/CHMP/GTWP/60436/2007). Where possible, S&E follow-up studies should be combined. These

recommendations should always take into account existing general guidelines for clinical follow-up of patients continuing in an extension study and in post-authorisation studies. Therefore, when designing a post-authorisation study, it is always necessary to take into account any existing requirements and guidelines for follow-up of subjects in clinical trials, as well as the follow-up system that was, or still is, in place for subjects of clinical trials with the particular ATMP.

The objectives of the S&E follow-up should be based on the ATMP characteristics and its intended indication. For the safety aspects, these should be based on the important risks or missing information identified for the ATMP (please refer to section 5).

While the objective of long-term safety follow-up is structured according to the categories of ATMPs defined in accordance with Regulation (EC) No 1394/2007 (somatic cell therapy, gene therapy, tissue engineered and combined ATMPs), it is stressed that S&E issues are more related to specific characteristics of these products than to the product classification. Accordingly, developers should consider which type of measure is most appropriate for the specific product. For example, most genetically modified cells will be classified as a gene therapy medicinal product, but in some cases they may be classified as cell therapies, when their therapeutic effect is not linked to the recombinant nucleotide sequence. However, in both instances the active substance is based on genetic modification which in turn requires specific follow-up for S&E.

When designing S&E follow-up studies, applicants should consider ICH E9, E10 and the EMA scientific guidance on post-authorisation efficacy studies (PAES) and GVP Module VIII- Post-authorisation safety studies as appropriate. Cell and gene therapy clinical guidelines in general specifically the guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products, the reflection paper on in-vitro cultured chondrocyte containing products for cartilage repair of the knee (EMA/CAT/CPWP/568181/2009) and the reflection paper on clinical aspects related to tissue engineered products (EMA/CAT/573420/2009).

8.2. Methodological considerations

Given the nature of some ATMPs and the characteristics of certain diseases being targeted by ATMPs, only limited efficacy data may be available at the time of the marketing authorisation application (e.g. slow dynamics of the disease and effects of the treatment, rare diseases, etc). Comprehensive evidence of efficacy, including for example maintenance of clinical benefit, evidence of benefit on long-term clinical outcomes and evidence of a cure may need several years of follow-up. As a consequence, there might be situations that require obtaining data on long-term durability of efficacy and / or the manifestation of efficacy in a “real-life” setting.

As provided for, under Article 14 of the ATMP Regulation, as part of the marketing authorisation application, applicants are to consider measures to ensure the follow-up of efficacy of ATMPs and of adverse reactions thereto. This may be addressed in a post-authorisation study which should be designed and conducted to give interpretable results which could impact on the licensing status or product labelling. The choice of study design will be based on the scientific uncertainty to be addressed. Any post-authorisation efficacy study should be designed and conducted to be feasible and ethically acceptable to allow collection of reliable and interpretable results in relation to its primary objective. The scientific guidance on PAES covers, at a high level, aspects with regards to the methodology to follow in order to design efficacy studies. Structured thinking and justification is promoted, firstly to precisely define the study objective(s) (see 8.3 and 8.4), then to consider the appropriate study design (e.g. randomised controlled trial, observational studies (e.g. case control study, cohort study, etc…)) and the data source to use (e.g. clinical trial, registry, healthcare database,

use of external controls etc.), and finally to define a statistical analysis plan which will obtain a reliable estimate of the effect.

Comprehensive methodological guidance on the design of clinical trials and observational studies in the post-authorisation setting is outside the scope of this guideline. Scientific guidelines are already available (as outlined in section 3), and should be consulted in relation to the following considerations: (i) study design; (ii) the type of product; and (iii) specific therapy-areas.

Number of patients for follow-up:

S&E follow-up may be required for all recipients of an ATMP. Based on the epidemiology of the target population (disease), the objectives and endpoints chosen for S&E follow-up and the anticipated frequency of adverse drug reactions, all exposed patients may be followed or follow-up might be limited either to a defined subset of patients relevant to the objective or to the proportion of those exposed that is adequate to collect sufficient data to address the identified research question.

When a subset of exposed patients is used, scientific justification should be provided. A subset is normally not acceptable for medicinal products in orphan diseases due to the low number of exposed subjects. In many cases, ATMPs are developed in indications for which there are a limited number of patients. For these cases the principles described in the guideline on clinical trials in small populations should be carefully considered (CHMP/EWP/83561/2005).

Where long-term follow-up is required to address the study objective (e.g. long-term safety), efforts should be made to ensure that the number of patients enlisted considers any implications for the potential withdrawal of patients over the years of follow-up.

Duration of follow-up:

The duration of the S&E follow-up can only be established on a case by case basis (e.g. it is expected to be longer for example if the maintenance of effect has to be demonstrated or late adverse reactions can occur e.g. insertional oncogenesis). It is therefore advisable to follow the patients in clinical trials, clinical trials extensions, or compassionate use programmes until the granting of the marketing authorisation, and beyond, if those patients can contribute data to address questions on long-term S&E. For gene therapy medicinal products using integrating vectors or have the potential for latency followed by reactivation, it is usually expected to follow the patients up to 15 years. The duration of the S&E follow-up will be agreed at the time of marketing authorisation and then reviewed when data from the post-authorisation studies become available.

Building on the clinical trial experience for the design of the post-authorisation study, detection of early complications (infectious diseases, complications linked to the related surgical procedures) and late complications (malignant diseases, emerging diseases, etc.) are likely to need different approaches to trial design and analysis. Moreover, they need to be considered in conjunction with the possible gradual increase or decrease of efficacy of the administered product over time. Design of the studies needs to take into account such dynamics, and good medical practice that may require specific timing of procedures, treatment adjustments, and laboratory investigations to be tailored for individual patients. Reasons for discontinuation of therapy or discontinuation of follow-up, and cases of re-administration or re-initiation of therapy are of particular interest for efficacy follow-up. Where relevant, research questions should be framed to be clear on which effect of treatment is of interest in respect of these different events.

Considerations on trial design:

Methodological approaches that are promoted in pre-authorisation clinical trials to ensure reliable estimates of effect, such as randomisation and pre-specification, are equally relevant in the post-authorisation setting.

S&E studies should use usual clinical practice for follow-up whenever compatible with the trial objectives and methodological design, to limit additional procedures and interventions. This should enable wider use of pragmatic trials and observational studies.

The choice of endpoints will be determined by the agreed scientific objective of the study and depend on the nature of the product. For example, for tissue engineered products, structural endpoints such as the tissue functionality and structural aspects of the regenerated, repaired and/or replaced tissue, as well as their persistence in the human body are specific attributes of these products and are relevant.

When feasible and when appropriate, long-term S&E studies should normally be of comparative design (reference is given to ICH Topic E10 Choice of Control Group in Clinical Trials). The choice of comparator (e.g. surgery, standard-of-care treatment, historical controls) or lack thereof should be justified (e.g. in the case of gene therapy medicinal product intended for a curative effect). It is acknowledged that changes in the standard of care over time may influence the conduct of such studies. In these situations, the integration of studies within disease registries may be of value in elucidating standard-of-care treatment, especially where this may differ between countries, in providing historical controls, and in permitting the inclusion of patient-reported outcomes.

Similarly to conventional medicinal products, feasibility aspects, such as design and duration, should be taken into consideration when designing post-authorisation studies. An observational study, perhaps in a healthcare database or disease registry may be more feasible than a controlled clinical trial to investigate incidence of a rare adverse event or clinical outcome in the long-term or in an orphan indication where there is a limited number of patients. An “explanatory” clinical trial will be more appropriate where a high degree of internal validity is required to minimise the risk of errors and biases influencing the results, though options for internal control groups might be limited. A ‘pragmatic’ trial will be more relevant for some trial objectives offering more opportunity to use existing databases or disease registries as a data source and might permit longer-term follow-up, while preserving the benefits of randomisation.

8.3. Objectives for long-term follow-up for efficacy

Specific considerations relevant to ATMPs might include:

- When cells or tissues are expected to engraft and exert a therapeutic effect after engraftment, studies to assess the duration of the effect/efficacy in the patient might be related to e.g. cell persistence or to metabolic events as result of cell engraftment. Longer follow-up may be required to fully assess the duration of efficacy and at which point the replaced tissue becomes/continues to be fully functional.

- Cell therapy medicinal products with a short shelf life may require an efficacy follow-up system that monitors dynamics of efficacy. In addition, information on the need for re-administration can be collected.

- Immunogenicity aspects are also a critical point to consider for efficacy assessment of a cell based product. Depending on the origin and on the manipulation of the cells during the manufacturing process, acute or chronic rejection needs to be considered as a risk. Immune

response may be either deleterious for long term therapeutic effect or, alternatively, constitute the basis of the therapeutic benefit and therefore its maintenance should be documented.

- The evaluation of the long term efficacy is also a key issue for gene therapy as studies in the pre-marketing setting are typically carried out in a limited number of patients and with limited duration. Sustainability of efficacy over time can only be answered by long-term efficacy follow-up post-marketing. The form and length of such follow-up will depend on the disease, the mode of administration of the product and the immune response to the therapeutic protein. All these points should be considered in addressing efficacy concerns for PAES.

- If combined ATMPs are used, the efficacy may rely on the suitability and persistence of the medical device part of the product. Therefore, this should be part of the evaluation of the long-term efficacy of the product when needed.

When establishing long-term efficacy, the use of comparator(s) has to be carefully considered in order to allow for a proper evaluation of the effect of the ATMP. Biomarkers can be used to learn more about differential efficacy or benefit-risk across strata of the disease (e.g. by mutation status or other disease classification) or based on a targeted mechanism of action of the ATMP. Reference is made to ICH E16 Genomic biomarkers related to drug response: context, structure and format of qualification submissions (EMA/CHMP/ICH/380636/2009), the guideline on key aspects for the use of pharmacogenomics in the pharmacovigilance of medicinal products (EMA/CHMP/281371/2013), the qualification of novel methodologies for drug development: guidance to applicants (EMA/CHMP/SAWP/72894/2008), as well as the guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/rev.4).

8.4. Objectives for long-term follow-up for safety

As a consequence of the identification and evaluation of the risks pre-marketing should guide the objectives of safety follow-up post-marketing. To help identify the safety objectives for long term follow-up, the following examples are provided and based on the safety specifications which have been presented above. When cells or tissues are genetically modified, safety issues related to both cell-based products and gene therapy medicinal products should apply.

8.4.1. *For cell based products*

Safety issues related to cell-based products will depend on the origin and manipulation of the cells. By means of illustration:

- Monitoring long-term immunity and/or rejection in case of xenogeneic and allogeneic cells. However, long term immunity towards specific cell types or specific haplotypes should be considered for patients susceptible to receive organs, tissues or cells for future treatments.
- Monitoring malignant transformation/mutagenesis in case of heavily manipulated cells in particular those that can differentiate into other lineages (e.g. mesenchymal stem cells, embryonic stem cells, iPSCs). This is particularly a concern for autologous cells that will not be rejected after transplantation.

8.4.2. *For gene therapy*

- The potential risk of insertional oncogenesis following integration of the recombinant genome is a key safety issue that should be evaluated in the case of gene therapy products where an

integrated vector is used. Reference is made to the reflection paper on management of clinical risks deriving from insertional mutagenesis (EMA/CAT/190186/2012).

- Monitoring immunisation towards the therapeutic protein expressed and vector is a specific issue which should be considered.
- When applicable, monitoring of complex administration of the product in direct *in vivo* gene therapy (e.g. direct multiple injections in the brain via burr holes) should be considered in order to assess the administration in routine use as it is not as closely monitored as a clinical trial.

8.4.3. *For combined ATMPs*

- With regards to combined ATMPs, any issues identified during the marketing authorisation evaluation that require follow-up should be addressed. This includes, for example, the capacity of the medical device to retain its therapeutic function or to maintain a sufficient level of integrity needed to ensure the safety of the combined ATMP (e.g. when allogeneic/xenogeneic cells are contained in a close compartment in the recipient). Premature alteration in the structure of the medical device may result in safety issues related to leaking of cells or tissues in the recipient's body.

8.4.4. *Other considerations on safety follow-up*

When a need for safety follow-up of close contacts and offspring is identified, feasibility is an important feature in the design of such a study.

9. Management and reporting of adverse reactions and PSURs

Reference is made to GVP module VI- Management and reporting of adverse reactions to medicinal products.

<u>The following points should be considered in particular for ATMPs:</u>

- Adverse reaction reports which do not contain the batch number of the ATMP product should be followed-up to obtain this information to enable traceability of reports to product.
- Signal detection and monitoring should be optimised for identifying new risks and any changes in existing risks. Transmission and occupational exposure should be monitored, as described in GVP Module IX - signal management.
- Signal monitoring should encompass detection of safety signals for any conditioning/pre-treatment (e.g. any adverse events associated with regimes required prior to bone marrow aspiration or stem cell transplantation).
- Signal monitoring should also include adverse events related to administration procedures, surgical procedure and follow-up treatment (e.g. arthroscopy).
- In the case of a medical device which is not contained within the product e.g. extracorporeal devices containing cell therapy medicinal products, adverse events related to the device performance should be reported.

With regards to PSURs, reference is made to GVP Module VII – Periodic safety update report.

10. Compliance monitoring

MAHs are required to monitor compliance with pharmacovigilance obligations according to Article 11 of Regulation (EC) No 520/2012. National competent authorities should conduct, in coordination with EMA, pharmacovigilance inspections, as described in GVP module III – Pharmacovigilance inspections. Reference is also made to GVP module IV - Pharmacovigilance audits.

EMA must inform the European Commission about issues of non-compliance, including non-compliance with risk management plans pursuant to Article 14(3) of Regulation (EC) No 1394/2007. The European Commission may impose financial penalties for infringement of certain obligations in connection with MAs according to Regulation (EC) No 658/2007. In addition, if the breach of the obligations imposed has an impact on the benefit-risk of the product, the marketing authorisation may be suspended or the product information revised.