الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Guideline on good pharmacovigilance practices (GVP)

Product- or Population-Specific Considerations III: Advanced Therapy Medicinal Products

Version 1.0

Date of issue	12 April 2026
Date of implementation	12 April 2027

Guideline on good pharmacovigilance practices (GVP)

Product- or Population-Specific Considerations III: Advanced Therapy Medicinal Products

Version 1.0

Saudi Food & Drug Authority

Drug Sector

For Comments and Inquiries *Drug.Comments@sfda.gov.sa*

Please visit SFDA's website at
https://www.sfda.gov.sa/en/regulations?tags=2

for the latest update

Saudi Food and Drug Authority

Vision and Mission

Vision

To be a leading international science-based regulator to protect and promote public health

Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

Document Control

Version	Author	Date	Comments
Draft	Pharmacovigilance Executive Directorate	14 September 2025	-
Version 1.0	Pharmacovigilance Executive Directorate	12 April 2026	Final

Table of Contents

P.III.A. INTRODUCTION

Due to the novelty and the complex nature of advanced therapy medicinal products (ATMPs) (e.g. gene therapy, somatic cell therapy, and tissue engineering products), the SFDA established this Product- or Population-Specific Considerations III: Advanced Therapy Medicinal Products of the Good Pharmacovigilance Practice (GVP). It is primarily based on the European guidelines on Safety and Efficacy Follow-up and Risk Management of ATMPs. It aims to provide guidance to marketing authorisation holders (MAHs)/applicants to facilitate appropriate pharmacovigilance for ATMPs with comprehensive guidance on safety and efficacy follow-up and risk management for ATMPs.

The SFDA acknowledges the rapid evolution of science and technology and the limited worldwide experience with ATMPs. At the time of ATMP registration, there is usually a lack of information on the long-term safety and efficacy of ATMP use.

Therefore, it is crucial to have a well-established pharmacovigilance system and comprehensive guidance on pharmacovigilance activities for ATMPs. This guideline applies to ATMPs as defined in the SFDA Guideline on Classification of Advanced Therapy Medicinal Products.

Considering that the general guidance on pharmacovigilance processes in Saudi Arabia is provided in SFDA-GVP Modules I to XVI, this guidance provides dedicated and specific guidance of pharmacovigilance activities for ATMPs.

P.III.A.1 Related guidelines

GVP P.III is intended to be used in conjunction with the Saudi GVP Modules I–XVI and does not replace these modules or introduce additional regulatory requirements beyond those already covered in the existing modules.

This guideline should also be read alongside the SFDA Guideline on Classification of Advanced Therapy Medicinal Products, which provides the definition for ATMPs in Saudi Arabia

P.III.B. STRUCTURES AND PROCESSES

P.III.B.1. Risk management plan

Risk Management Plans (RMPs) aim to document the risk management system necessary to identify, characterise, and minimise the important risks associated with a medicinal product (GVP Module V). Similar to conventional medicinal products, the RMP of an ATMP should include a comprehensive scientific assessment of the identified or potential risks, as well as any important missing information. Applicants should address possible specific risks when drafting safety specifications for ATMPs. For all three categories of safety concerns, recognition in the summary of safety specifications typically implies that additional pharmacovigilance activities for data collection and/or risk minimisation measures may be required (refer to GVP Modules V and XVI). ATMPs may present specific risks not typically associated with other medicinal products. These risks include risks to living donors, germline transformation risks, and vector transmission risks.

P.III.B.1.1. 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.

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.

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 of 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 types 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, caregivers, offspring and other close contacts and its risks to the environment**

- If a risk to healthcare professionals, caregivers, 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.

- 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.

- 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.

P.III.B.1.2. Summary of 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.

- Induction of autoimmunity or immunogenic reactions.
- Induction of malignancies/tumour formation.
- Impossibility of discontinuation 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.

P.III.B.2 Management and reporting of adverse reactions

Reference is made to GVP Module VI- Collection, management and submission of reports of suspected adverse reactions to medicinal products. The following points should be considered in particular for ATMPs:

- 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 the 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 treatments (e.g. arthroscopy).

P.III. B.3. Periodic safety update reports (PSURs)

The requirements for PSURs are detailed in GVP Module VII – Periodic benefit risk evaluation report/ periodic safety update report. In addition, the points below shall be discussed in the PSUR of an ATMP:

- The risks related to transmission and occupational exposure to the product or its components by patients, living donors, or close contacts, such as healthcare professionals, caregivers, and offspring.
- Risks related to administration procedures, surgical procedure and follow-up treatments.

- Age- and sex-specific patients exposure data from post-marketing experience should be included (in the PSUR section 'Estimated exposure and use patterns'), where available. In addition, information regarding cumulative numbers of exposed patients and the method of exposure calculation should be provided if the source of exposure data includes studies designed to obtain such data, including registries and formal drug utilisation studies.
- Where applicable, the subsection "Long-term follow-up" should provide efficacy/safety information from long-term follow-up of subjects from clinical trials of investigational ATMPs. Long-term efficacy studies should normally be of comparative design. The choice of comparator or lack thereof should be justified. It is acknowledged that changes in the standard of care over time may influence the conduct of such studies. This should be discussed with regulators on a regular basis in the PSUR.
- Results of newly finished post-authorisation safety and efficacy studies.

P.III.B.4. Post-authorisation safety and efficacy studies

When studies are imposed at the time of granting the marketing authorisation, 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) are appropriately followed-up to allow generation of long-term safety and efficacy data. The use of disease registries or other data sources for collecting long-term safety and efficacy data should be considered early in the development process so that appropriate plans are in place by the time the marketing authorisation 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 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 Summary of Product Characteristics

(SPC) 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). Where possible, safety and efficacy follow-up studies should be combined. When designing safety and efficacy follow-up studies, applicants should consider ICH E9, E10, GCP and GVP Module VIII- Post-authorisation safety studies as appropriate.

The objectives of the safety and efficacy 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 (refer to section P.III.B.1.).

While the objective of long-term safety follow-up is structured according to the categories of ATMPs (somatic cell therapy, gene therapy, tissue engineered and combined ATMPs), it is stressed that safety and efficacy 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 safety and efficacy.

P.III.B.4.1. 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 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 post-authorisation efficacy study (PAES) covers, at a high level, aspects with regard 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 P.III.B.4.2. and P.III.B.4.3.), 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.

Number of patients for follow-up:

Safety and efficacy 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 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.

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 safety and efficacy 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 or clinical trials extensions until the granting of the marketing authorisation, and beyond, if those patients can contribute data to address questions on long-term safety and efficacy.

For gene therapy medicinal products using integrating vectors or having the potential for latency followed by reactivation, it is usually expected to follow the patients up to 15 years. The duration of the safety and efficacy follow-up will be agreed at the time of marketing authorisation and then reviewed when data from the post-authorisation studies become available.

The design of the post-authorisation study should build on the experience gained from the clinical trials. Detecting early complications (infectious diseases, complications linked to the

related surgical procedures) likely requires a different approach to trial design and analysis compared to detecting late complications (malignant diseases, emerging diseases, etc.). 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.

Safety and efficacy 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 safety and efficacy studies should normally be of comparative design. 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, 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 randomization.

P.III.B.4.2. 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.

P.III.B.4.3. 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.

P.III.B.4.3.1. 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, Induced pluripotent stem cells). This is particularly a concern for autologous cells that will not be rejected after transplantation.

P.III.B.4.3.2. 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.
- 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.

P.III.B.4.3.3. For combined ATMPs

- With regard 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.

P.III.B.5. Signal management

P.III.B.5.1 Definition and processes

By definition, the signal is information that arises from one or multiple sources, including observations or experiments, which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action (GVP Module IX). Like other registered medicinal products in Saudi Arabia, the ATMPs will go through the same signal management processes described in GVP Module IX – Signal management. These processes include signal detection, signal validation, signal analysis and prioritisation, signal assessment and finally signal recommendations.

P.III.B.5.2 Signal detection: Sources of information

The sources for identifying new signals are diverse. They potentially include all scientific information concerning the use of ATMPs including: spontaneous reporting, product quality, non-clinical, clinical (including pharmacovigilance and pharmaco-epidemiological data). For more information about the sources of ATMPs signals, please refer to GVP Module IXB.1- Sources of Data and Information.

P.III.B.5.3 Roles and responsibilities of the MAH

It is vitally important for the MAH to monitor the safety of its registered products that belong to ATMPs group of medications. Similar to any signal, the MAH shall submit signal assessment and cover letter for each ATMP signal that arises from the various sources described in GVP Module IX.C.1. The MAH should have a system and perform routine

scanning on ATMPs signals at least once monthly. The MAH should assess the ATMPs' signals within the timeframe described in GVP Module IX.C.1.

P.III.B.6. Safety communication

The safety communication and RMM related communication aspects are outlined in GVP Module XV and GVP Module XVI should be followed for ATMP products. GVP Module XV provides an overview of different means of communication and stresses the importance of defining communication objectives. For ATMPs, the specific communication objectives relate to enabling healthcare professionals and patients to make informed decisions, promoting adherence to RMM, and supporting informed choices. Communication needs to address the specific information needs of healthcare professionals and patients regarding the risks and benefits of ATMP use.

The implementation of RMM for ATMPs also requires specific communication skills in relation to risks, benefits, and uncertainties, which may be more challenging than for conventional medicines. RMM targeted at healthcare professionals should provide them with information and tools to effectively inform and discuss risks and RMM with their patients.

To achieve the communication objectives, marketing authorisation holders are encouraged to address the following in the product information and any additional RMM, such as educational materials:

- Characterisation of the risks of adverse patient outcomes, including severity, seriousness, and frequency of potential adverse reactions related to the ATMP's quality characteristics, storage, distribution, patient-associated conditions, reconstitution, administration, persistence, and environmental aspects.
- Additional RMM, such as specific training, handling and disposal procedures, patient monitoring, and management of adverse reactions.
- Advice on the management of adverse reactions in patients, healthcare professionals, and other affected individuals.

Communication should be tailored for healthcare professionals (including general practitioners, specialists, nurses, and pharmacists) and patients or their representatives.

P.III.B.7. Risk Minimisation Measures

RMMs are interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient

should adverse reactions occur (see GVP Module V). Considering the nature of ATMPs, risks may arise that are not normally associated with other medicinal products (P.III.B.1.1.). RMMs aim to reduce the burden of adverse reactions or optimise benefits. The selection of RMMs and the determination of whether routine or additional measures are necessary should be based on the safety concerns outlined in the RMP.

P.III.B.7.1. Routine risk minimisation measures

The routine risk minimisation measures refer to the management of risks as explained and minimised in the SPC, the package leaflet, the labelling, the pack size and design and the legal (prescription) status of the product.

P.III.B.7.2. Additional risk minimisation measures

The following section explores additional risk minimisation measures that could be implemented. These examples are not exhaustive and should be considered on a case-by-case basis, taking into account the specific product and associated risks. Reference is made to GVP Module XVI - Risk minimisation measures: selection of tools and effectiveness indicators.

P.III.B.7.2.1. Controlled access programmes and centre accreditation systems

To mitigate the risks of administering ATMPs, a controlled access program might be necessary. This would involve selecting accredited centres and ensuring the physicians involved are adequately trained and experienced. The selection and accreditation of these specialised centers could be managed by the marketing authorisation holder, potentially in collaboration with a relevant medical organisation. This process would be a key component of the risk minimisation plan.

These programs should be tailored to local healthcare settings and agreed upon with the SFDA. The marketing authorisation holder should regularly provide updates on the implementation status of the controlled access program. These updates, which shall be documented through annual reports, should include any changes, including the addition of new centers. If the ATMP is only available in a limited number of specialised centers, the follow-up of patients and physician awareness must be carefully considered.

P.III.B.7.2.2. Educational programme

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

- Educational materials for treating physicians relating to:
  - the conditioning of the patient (e.g. in oncology, bone marrow transplant).
  - the handling, product reconstitution, administration and product 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).
  - healthcare professional (HCP) 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.

- Educational materials for pharmacists relating to:
  - 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.

- Educational materials for patients (and/or caregivers) relating to:
  - 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.

- Educational materials for support personnel, family and caregivers relating to:
  - 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.

English draft version of educational materials for HCPs, along with English and Arabic drafts for patients, should be submitted for evaluation and approval as part of the marketing authorisation application.

P.III.B.7.2.3. 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.