HICT

Cross-border healthcare for advanced therapies

TOWARD MORE TRANSPARENT, PREDICTABLE, AND EQUITABLE ACCESS

OPTIMISING HEALTHCARE

Amber Werbrouck, Lies Schoonaert, Sebastian Vermeersch (2023). "Cross-border healthcare for advanced therapies: Toward more transparent, predictable, and equitable access." Ghent, Hict.

Source of funding

PTC Therapeutics and Orchard Therapeutics have promoted and supported the project financially and logistically. This document does not focus on specific diseases or treatments, including, but not limited to, those commercialized or under development by the supporting companies.

Overview

This document, developed in cooperation with different stakeholders, provides an overview of the various issues related to planned cross-border healthcare for ATMPs and proposes a workflow to tackle all the different issues and optimize cross-border treatment.

The ***issues*** are subdivided into four different categories:

Our proposed **workflow** to tackle these issues consists of a stepwise approach:

This workflow can be seen as a whole. However, separate building blocks of the workflow can serve as starting points to further adapt and optimize practices and optimize patient access to ATMPs beyond national borders.

Further iterations with different stakeholders will be required for the practical implantation of our recommendations.

Introduction

ATMPs and the need for planned cross-border treatment

Advanced therapy medicinal products (ATMPs)[I] represent an emerging and rapidly evolving market, introducing innovative treatments that modify genes, cells, or tissues (1). Where traditional medicines generally target imbalances and symptoms caused by dysfunctions on the cell and gene levels, ATMPs aim to correct those cellular or genetic dysfunctions. This is another step in the evolution of pharmaceutical sciences towards more specific, targeted, and causal treatments (2).

ATMPs can be gene therapy medicines, somatic cell therapy medicines, and tissue-engineered medicines. Gene therapies can be ex-vivo, where cells are removed from the body, modified, and placed back into the body (e.g., CAR-T), or in-vivo, where new genes are inserted directly into the body. As approximately 80% of rare diseases are of genetic origin (3), ATMPs could have a particular role to play in these conditions with, up until now, little to no treatment options.

Due to the specific nature of these types of treatments, **specific expertise** might be required to prepare treatment or administer the treatment:

- Specific procedures or manipulations might be required **to prepare the ATMP**. In the case of ex-vivo gene therapy, patient material needs to be manipulated outside the patient's body. These manipulations can be done within the hospital laboratory, by the pharmaceutical company, or by an external organization (i.e., a contract development and manufacturing organization (CDMO)). In the case the manipulation needs to be done by the hospital pharmacy, dedicated staff will need to be trained to be able to do the manipulation for a specific treatment.
- In some cases, the **administration of the ATMP** is complex, requiring specific equipment, skills, or training to perform a particular procedure. In addition, not all physicians might feel comfortable with performing this procedure.

To acquire the necessary expertise to prepare or administer these products, dedicated staff must be trained to perform these tasks. Next to the **required training**, specific infrastructure might be needed to execute those tasks. However, it is expected to take at least one year to one year and a half to set up such a dedicated treatment center, including training and education of staff and installing the necessary infrastructure and equipment. These treatment centers must often fulfill specific criteria and conditions to receive and maintain recognition as Qualified Treatment Centers (QTC). For example, **treating a minimal number of patients per year is often required**. Fragmented care can have a negative impact on the quality of care as shown previously in the context of immune-oncology (4). In the case of (ultra)rare diseases, reaching the minimal number of patients, to justify the investment of time and resources to stay qualified if a specialized treatment center were set up in every European country, can be challenging.

Therefore, in some exceptional cases, **delivering these therapies in every country will not be feasible**, either temporarily (e.g., in anticipation of a locally recognized treatment center) or in the long term (e.g., due to the lack of a minimal critical mass to provide quality care). This implies that patients have to cross borders to access treatment.

[I] *Advanced therapy medicinal products (ATMPs) are classified into three main types:*

1. *Gene therapy medicines: these contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources;*
2. *Somatic-cell therapy medicines: these contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases;*
3. *Tissue-engineered medicines: these contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue;*

In addition, some ATMPs may contain one or more medical devices as an integral part of the medicine, which are referred to as combined ATMPs.

Scope

Two European legislations exist related to planned cross-border healthcare[II]: Social Security Regulations (EC) 883/2004 and 987/2009 (further referred to as "The Regulation"); and the Directive 2011/24/EU (further referred to as "The Directive"). These legislative routes were not developed to be implemented in the context of ATMPs, so several barriers might arise when applied to access this new generation of therapies. This document aims to identify these particular issues and their possible solutions.

We focus on ATMPs with permanent or temporary reimbursement in a country who cannot provide the treatment within the country and where cross-border healthcare is required. Issues related to early access or the reimbursement procedure are beyond this document's scope.

The **first part** of this document provides an overview of the different **issues related to planned cross-border healthcare for ATMPs**. The **second** part proposes a **workflow for optimal cross-border treatment** in the context of ATMPs.

Applied approach

This project was a follow-up project of a round table discussion held in Belgium in 2022, in which we mainly focused on the barriers that might arise for a cross-border treatment for ATMPs in (ultra)rare diseases, and a first set of minimal requirements was defined for a solution to overcome those barriers (5).

Starting from the information and insights from this previous project, we analyzed the different issues more in-depth to find possible solutions. As the different solutions might solve multiple issues and depend on the choice of other aspects, we developed a workflow to optimize cross-border treatment.

We continue to focus on the context of (ultra)rare diseases, where the number of patients within one country might not reach the minimal critical mass to foresee quality care or to obtain and maintain recognition as a Qualified Treatment Center.

Issues were analyzed in detail based on **desk research and semi-structured interviews**. The input and perspectives of different stakeholders (patients, hospitals, physicians, industry, and payers) were collected to ensure the suggested solutions are feasible and can be implemented in practice.

Our previous project focused on Belgian patients seeking ATMP treatment in another European country (5). There are several reasons why Belgium serves as a relevant example for cross-border healthcare in ATMPs. First, **Belgium** is a relatively small country. For (ultra)rare diseases, the lack of a critical mass can hamper receiving and maintaining quality labels. Second, a change in Belgian law was adopted in 2022, making an exception for ATMPs regarding the legal obligation of local availability and continuity for reimbursed products (6). This exception allows ATMPs to be reimbursed even when the treatment cannot be provided in a Belgian treatment center. The legislative change demonstrates payer awareness of the specific context of ATMPs and opens the road for planned cross-border delivery of ATMP care. Third, Belgium is among the countries most using cross-border healthcare in the EU (7).

In the current document, we have broadened our scope by considering the identified issues and proposed workflow relevant to each European country sending patients to centers abroad for treatment with an ATMP. Given that we build further upon insights from previous initiatives, many of our examples still refer to the Belgian context.

[II] *Cross-border healthcare is "a situation in which the insured person receives healthcare in a Member State other than the Member State of insurance." A distinction can be made between unplanned cross-border healthcare, planned cross-border healthcare, and healthcare for persons that reside in another country. We can restrict our focus to planned cross-border healthcare in the context of treatment with ATMPs for rare diseases .*

Part A | Issues related to cross-border treatment for ATMPs

Issues related to cross-border healthcare for ATMPs can be subdivided into four different categories (Figure 1):

1. The issues related to the **patient's treatment**, including the preparation and follow-up of the treatment.
2. The issues related to the treatment **financing** and all associated costs – between countries.
3. The issues related to the **authorization procedure** to request approval for the treatment across borders, guaranteeing (re)funding of treatment costs
4. The issues related to the **data** requirements, data collection, and data sharing related to cross-border treatment.

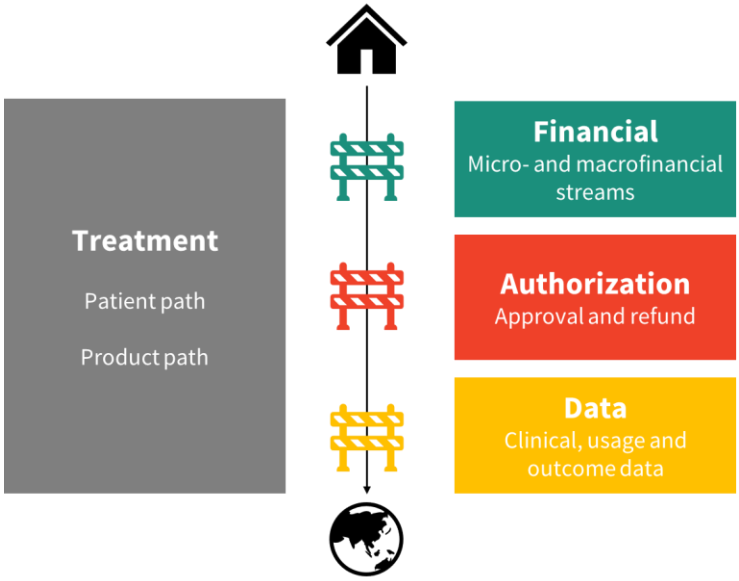

Figure 1. Schematic overview of the different types of issues related to cross-border healthcare for ATMPs

Treatment of people with rare diseases already brings many challenges with them. Hence, issues arising when this ATMP treatment is provided abroad should be clearly distinguished from issues inherently related to ATMP treatment for (ultra)rare diseases, even when they would be provided in the patient's home country. For each issue we discuss, we start by sketching the situation for an orphan ATMP with (temporary) reimbursement available in the home country. Hence, each issue begins with describing the situation when treated in the home country (displayed in the red box), followed by the issues that occur when needing to cross borders to get treatment.

1. Issues related to treatment

TREATMENT IN THE HOME COUNTRY

When looking at the context of (ultra)rare diseases, there are different challenges related to treating these patients, even when treatment can be provided in the patient's home country.

First, there might be limited knowledge of the disease and the different symptoms associated with (ultra)rare diseases (8). This can delay diagnosis (9) and result in diverse – possibly suboptimal – treatment approaches. To improve this, care pathways have been developed on a national level (e.g., by Vlaams Netwerk Zeldzame Ziektes (VNZZ) in Flanders (Belgium), United for Metabolic Diseases (UMD) in the Netherlands (10)) and the European level (e.g., by the European Reference Networks (ERN)) (8,11) for several (ultra)rare diseases. ERNs were set up[III] to transfer knowledge and expertise on (ultra)rare diseases across Europe.

Second, different specialists and hospitals might be involved in treating the disease, which can lead to ambiguity of clinical responsibilities. If innovative treatment options are available, this will be delivered by an expert center, possibly involving a multidisciplinary team. If the patient is stable on treatment, follow-up could be done by a more peripheral center closer to the patient's residence. Although ATMPs are often a one-off treatment, long-term follow-up is usually required due to the innovative nature of these products and the possibility of specific long-term adverse events. EMA mentions a follow-up duration of up to 15 years for some ATMPs (12). Care coordination is required across different clinical experts and hospitals.

TREATMENT ABROAD

Issue 1: Lack of uniformity of care

In those rare cases where transferring knowledge across borders would not suffice, and there is a need for the patient to go abroad to receive treatment, it is again vital to **standardize care delivery** and to **ensure the quality of care**. Compared with receiving treatment in the home country, **having a clear overview of the totality of care upfront** becomes much more critical. If specific steps of the treatment trajectory are overlooked, this has more significant consequences as the patient might have to travel several times, or particular actions do not happen accurately (e.g., follow-up).

Patient pathways developed by the ERNs can guide the planning and organization of care that requires patients to cross borders but might need more details of a particular ATMP treatment to ensure that every step in the treatment trajectory is considered.

Issue 2: More ambiguous clinical responsibilities

In a context where cross-border healthcare is required, **at least two centers** are involved: the treatment center in the home country and the treatment center abroad. In theory, it could be possible that the treatment center abroad provides the totality of care, including all precare and follow-up, which would create little room for confusion about clinical responsibilities. However, it can be questioned if it is desirable, for several reasons:

- Follow-up for numerous years will most likely be needed (12).
- It limits the transfer of knowledge and expertise to the home country (i.e; ERN).
- Patients can have preexisting comorbidities, for which they are already being treated in their own country.

A more realistic scenario is that the treatment center abroad only delivers that aspect of care that cannot be provided in the home country. Preparatory care and care and follow-up afterwards are done as much as possible in the home country. Follow-up could be imbedded in the patient's broader treatment plan as a whole (e.g. treatment of comorbidities). In that case, close collaboration between these centers will be required, and clinical responsibilities must be clarified upfront.

[III] *The European Reference Networks (ERNs), launched in 2017, are organized in 24 specialized virtual networks, linked to certain disease areas.*

2. Issues related to treatment financing

TREATMENT IN THE HOME COUNTRY

When an ATMP treatment is reimbursed within the home country, a list price (i.e., public price) and reimbursement basis (i.e., the level of health insurance coverage) is determined on a national level. If the patient is treated in a hospital, the hospital orders the product from the manufacturer and pays the list price to the manufacturer (Figure 2). The hospital gets the reimbursement basis paid by the payer. The potential difference between the list price and the reimbursement basis must be covered by the patient (i.e, co-payment) or the hospital (e.g., in case of specific categories of products where co-payment is not allowed).

Bringing innovative therapies quickly to market, available for patients, often comes with uncertainty about whether the product offers value for money. To mitigate these uncertainties, a managed entry agreement (MEA) can be negotiated between the manufacturer and the payer (13). This agreement is made nationally between the manufacturer and the payer, and the compensation is arranged directly between the manufacturer and the payer.

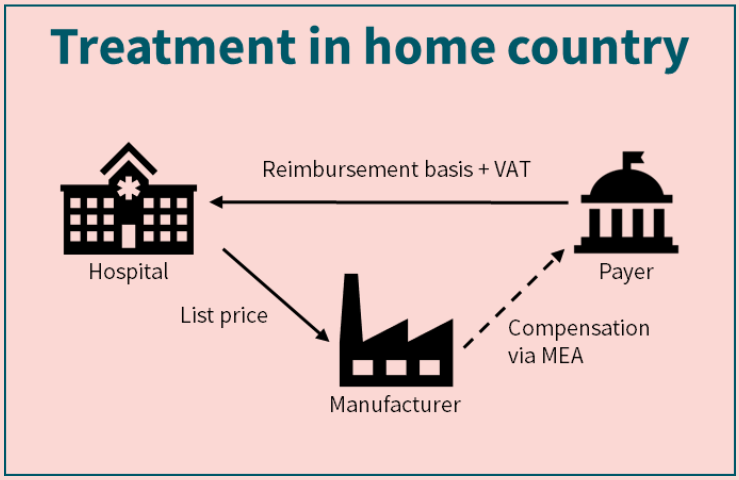

Figure 2. Financial streams for reimbursement of a patient treated in their home country.

The national insurance system generally covers other (medical) costs.

TREATMENT ABROAD

By looking more in-depth at the financial streams in a cross-border context, the underlying premise is that going abroad is a necessity and not the result of an individual choice or preference. Therefore, the aim should be **to assure coverage** of all associated costs.

Cross-border healthcare costs not only include the expenses related to drugs and administration of the product itself. Following ancillary treatment costs should also be considered (5):

- Procedures required to administer the product (e.g., surgical interventions).
- Pre-care and aftercare: patients might need additional testing that can only be done in the guest country, follow-up, complications or adverse events requiring specific expertise, etc.
- Travel- and accommodation: Accommodation might be needed before or after a hospitalization. If different tests or consultations are planned in ambulatory care, spread over multiple days, then the patient might need accommodation to bridge that period. If the patient is accompanied by a parent (or another informal caregiver), this person will also need accommodation, including the periods of hospitalization. Several separate travels could be necessary depending on the entire care trajectory (e.g., pre-care and aftercare, as mentioned above).

The medical costs can include laboratory tests, imaging, consultations, pharmaceutical products (other than the ATMP itself) , etc., both during hospitalization and in ambulatory setting. In some European countries, these costs are based on the fee-for-service principle. They are covered mainly by obligatory health insurance, often accompanied by additional patient co-payment (which can again (partially) be covered by a different private health insurance). In other European countries, such as Germany, these costs are grouped into a diagnosis-related group (DRG)-based system. Several countries, such as Belgium, combine both financing systems.

When a patient needs to go abroad for one or multiple steps in the treatment pathway, the payment and reimbursement of all treatment-related costs become more complex as additional stakeholders are involved (i.e., the treating hospital and payer of the guest country). In addition, travel-related costs should be taken into account if the patient needs to travel abroad to receive treatment.

Issue 1: Differences in actual price

There might be differences between the guest's and home country's actual price (Figure 3). The differences in actual price may be due to a difference in list price, a discount negotiated directly between the treated hospital and the manufacturer, or a discount negotiated in an MEA. As the agreements have been made on the national level, each stakeholder might only be willing to pay maximally the actual price as agreed on within its own country. Further differences in the actual price may also arise from different tax policies, such as VAT (see next issue).

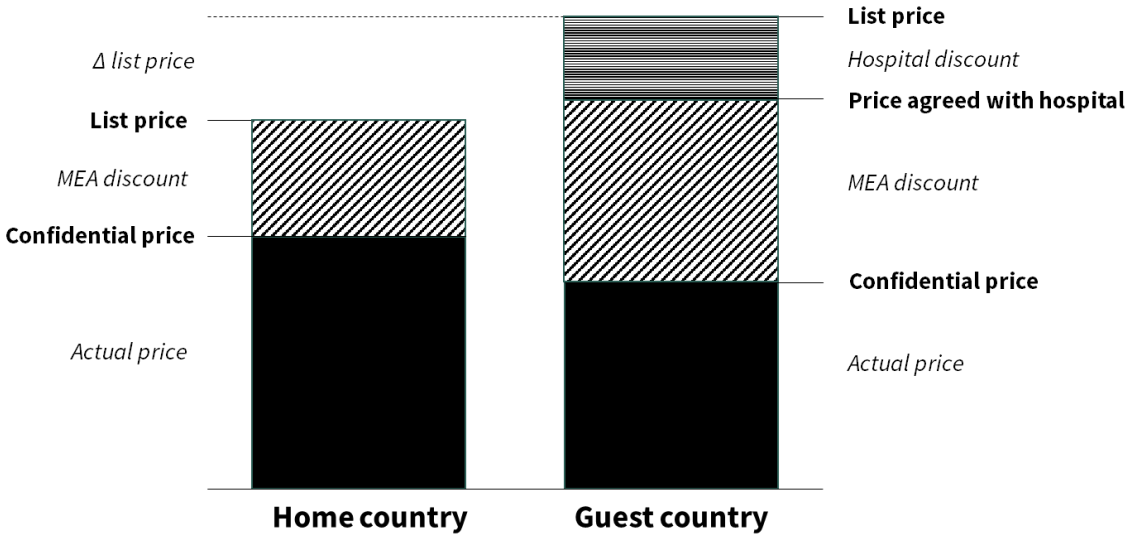

Figure 3. Overview of possible differences in actual price between home country and guest country

- In case two countries have **different approved list price**, the payer of the home country will prefer to adhere to his national (net) price, which - especially in the context of ATMPs – might substantially differ from the list price of the guest country.
- A **hospital discount** can be agreed upon between the treating hospital and the manufacturer. This confidential agreement between the hospital and the payer will not impact the cost paid by the payer of the home country for a patient treated abroad. However, even though this is theoretically possible, it is unclear if this will occur in ATMPs for (ultra)rare diseases. In addition, note that direct negotiations between the hospital and manufacturer are prohibited in some countries.
- Innovative products such as ATMPs are often conditionally reimbursed under an MEA. These agreements usually consist of a confidential discount and resulting **confidential price**. Due to the confidential nature of these contracts, the payers and possibly even national entities of pharmaceutical companies do not know the confidential discounts applied in other countries.

Issue 2: Differences in VAT rates

Next to differences in actual price (Issue 1), differences can also be caused by differences in value-added tax (VAT) rates between the home country and the guest country. Differences in VAT rates can be caused by **differences between countries** (i.e., different VAT tariffs apply for pharmaceutical products) or by differences in VAT rates used for **public and private patients**.

Issue 3: Prepayment requirements

Depending on the legislation used, there is a possibility that the costs need to be (pre)paid by the patient, and coverage by the national payer is only taken care of afterwards. Even when the patient prepays for care, approval upfront can be required to receive these costs back from their national payer (see section 'Directive 2011/24/EU' in Part B).

Issue 4: Confidentiality and practical implementation of MEA

When the ATMP is reimbursed under an MEA, this implies an agreement between the payer in the home country and the manufacturer in the home country and/or an agreement between the payer in the guest country and the manufacturer in the guest country. Issues might also appear related to the confidentiality and practical implementation of MEA.

- Both the payer and the treating center will **not be aware of the characteristics and details of the MEA** in the home country. Similarly, if an MEA is agreed upon in the guest country, the payer of the home country will not be aware of the characteristics and details of the MEA in the guest country. When an outcome-based agreement is set up, the MEA in each country might have different features and requirements, e.g., different types of outcome parameters that need to be measured.
- If there is an agreed MEA both in the home country and the guest country, there is a **risk that both the payer from the home country and the guest country will request MEA compensation** from the manufacturer in their country (Figure 4).

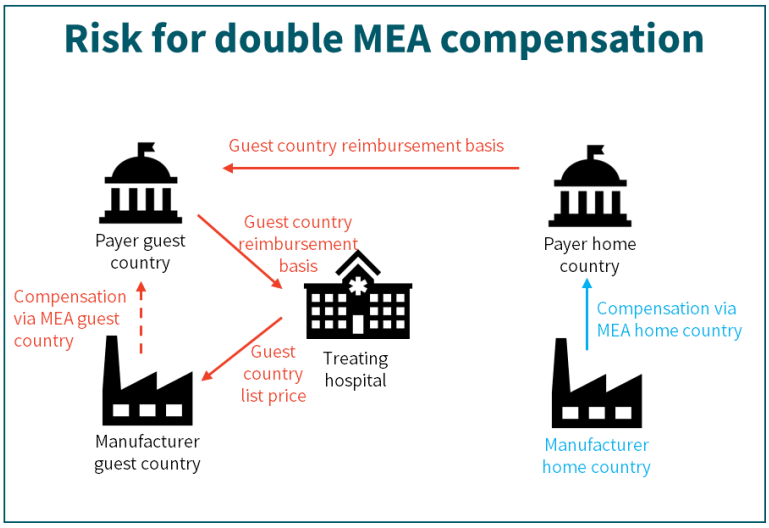

Figure 4. Risk for double MEA compensation when using existing EU regulations for planned cross-border healthcare.

- If a financial-based MEA is agreed upon, this is often linked to the manufacturer's revenue. However, if the treating hospital reimburses the product to the manufacturer in the guest country, the **manufacturer in the home country will not have any revenue** to execute the agreement.

3. Issues related to authorization

TREATMENT IN THE HOME COUNTRY

When looking at the situation where an (orphan) ATMP would be available in the home country, prior authorization is usually required to receive reimbursement for an orphan drug before treatment is initiated.[IV] A reimbursement request is submitted if the patient fulfills the national reimbursement criteria. The request is often initiated by a healthcare provider, such as the treating physician or a pharmacist (5,14,15). The request is then evaluated by a health insurer or other authorized body, which can be done by one centralized entity or multiple (i.e., decentralized) entities (5,14,16). If different entities evaluate requests, a central committee may be in place to support and align the decision-making process.

TREATMENT ABROAD

In the case of cross-border treatment, the entitled entity again has to consider if the patient fulfills the reimbursement criteria. In addition, they have to decide if the **conditions to approve planned cross-border healthcare** are fulfilled. These conditions are different, depending on the legislative route that would be used (see Table 1 in the introduction).

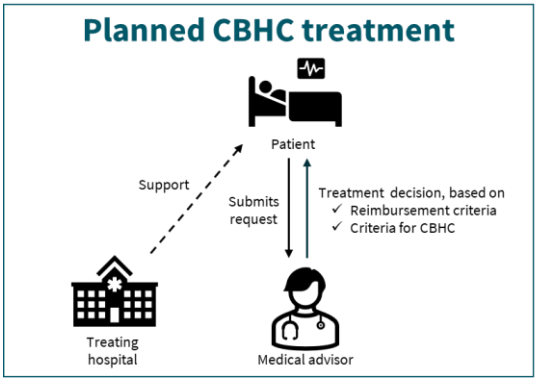

Figure 5. Authorization process for cross-border healthcare.

In the case of highly specialized treatment, some issues arise in the authorization process.

[IV] *For example, in Belgium prior authorization is required for 'Chapter IV' products. The treating physician will initiate the authorization request, which will be evaluated by the medical advisor affiliated to one of the seven sickness funds. In some cases, an Orphan Drug college supports the medical advisor in this decision. Based on the advice of the Orphan Drug college, the medical advisor is responsible for the authorization of reimbursement*

Issue 1: Lack of a standardized approach

It has been argued that the authorization process for cross-border healthcare in the context of ATMPs needs more predictability, uniformity, and transparency (5). It was suggested that many contextual factors influence the authorization process and decisions:

- In a decentralized authorization procedure, **decisions are made by different entities**, which might lack expertise about particular (ultra)rare diseases, which can lead to inconsistencies for similar patients. Supporting committees to provide advice to individual medical advisors are often less established, as up until now, planned cross-border healthcare was not often used in the context of highly specialized treatments, but this is expected to increase in the future.
- **Dependence on the knowledge and support provided by the treating physician** or center of the home country to compile an authorization dossier;
- **Lack of clear guidelines** on what an authorization dossier for receiving treatment abroad should entail, leading to incomplete requests, which can introduce delayed authorization decisions. Critical time can be lost in ATMPs for (ultra)rare diseases: a patient can quickly no longer be eligible for treatment in rapidly progressive diseases.

Issue 2: Separate authorization requests for different aspects of care

In many cases of cross-border healthcare, different routes for reimbursement are combined to achieve as much cost coverage for the patient as possible. For example:

- For planned care that requires a **hospital stay** abroad, prior authorization is always needed. Generally, patients are recommended to seek authorization via the S2 route (i.e., the Regulation).
- For planned **ambulatory care**, it is not required to request prior authorization, as it is possible to request reimbursement afterward via the Directive. This implies that patients have to pay everything upfront. However, prior approval is again required for particular imaging during ambulatory care.
- Financial support for **travel- and accommodation costs** could be retrieved via a separate fund (see section 'National fund' in Part B). In many cases, this must be requested before traveling abroad.

Separate authorization dossiers can lead to different decisions and costs only partially covered. In that case, the patient's financial possibilities can determine access to ATMP treatment abroad.

Issue 3: Patient as initiator

Patients are obliged to initiate and follow up on their authorization request. Some patients will be OK with bearing this responsibility, while some might need more skills to initiate and follow up a request. As it is often unclear what an authorization dossier should entail, patients largely depend on the knowledge and support provided by the treating physician or center. Incomplete dossiers might induce delays (see Issue 1 of the authorization path), which might become even more significant **when the patient (or caregiver) has to go back and forth between the treating physician and the entitled entity handling the request** (5).

Issue 4: Timing constraints

Best outcomes are usually expected when treatment is delivered in an early disease stage. It is critical to provide treatment as soon as possible before clinical symptoms appear, possibly making the patient ineligible for treatment (17,18). This might change rapidly for some diseases, leaving a very short time frame for treatment.

As mentioned earlier, delays in diagnosing (ultra)rare diseases often occur. Further delays can be induced in the authorization process due to incomplete dossiers, the need for separate requests for different aspects of care, or the patient becoming a middleman between the treating physician and the authorizing body, as discussed in the previous three issues.

4. Issues related to data

TREATMENT IN THE HOME COUNTRY

In (ultra)rare diseases, **multiple clinical experts are involved** in the treatment and follow-up of the patient. Clinical data must be shared between all stakeholders to ensure a proper follow-up. Data needs to be shared between specialists to treat the different aspects and symptoms of the disease properly. In addition, if a patient is followed up in a peripheral hospital, data must be shared between the peripheral hospital and the expert center to ensure proper treatment and follow-up.

Suppose data needs to be collected in the context of an outcome-based MEA. In that case, a data collection system must be in place to provide all necessary information to the payers to arrange possible compensation.

TREATMENT ABROAD

When a patient is treated abroad, data must be shared between clinicians from the home country and clinicians from the guest country. The sharing of personal data within the European Union is strictly regulated by the European Commission (19). Next to clinical data, extra information will be required when a patient is treated abroad:

- **Usage data** so the payer knows how many patients are treated abroad. As strict eligibility criteria often apply for these products, there is a risk that the patient will no longer fit the eligibility criteria in the timeframe between the authorization approval and the actual treatment. Hence, the number of patients who received approval (i.e., information that the payer has) might not be equal to the number of patient who finally received treatment.
- If an outcome-based MEA is agreed upon in the home country, these **outcome parameters** must be captured in the treating center and the hospital responsible for the patient's follow-up.

Some additional issues appear related to the capturing and sharing this data in a cross-border context.

Issue 1: Separate data per country

When a patient is treated abroad, all data captured will be collected in their local data system. Extra actions will be required to separate patients' data from different countries.

Issue 2: Delays in data transfers

If the payment is arranged between the payers in the guest and the home country, it will take much time before the correct information is with the dedicated person. In the case of an MEA, this information will be required in a timely matter to (re)negotiate the conditional reimbursement of the product. If the data transfer between countries is too slow, issues might appear with payment and refund of the product.

Part B | **Workflow for optimal cross-border treatment**

A workflow has been developed to tackle all the issues that might arise when a patient is treated abroad (as discussed in Part A). This workflow consists of a stepwise approach that addresses the issues and is visualized in Figure 6.

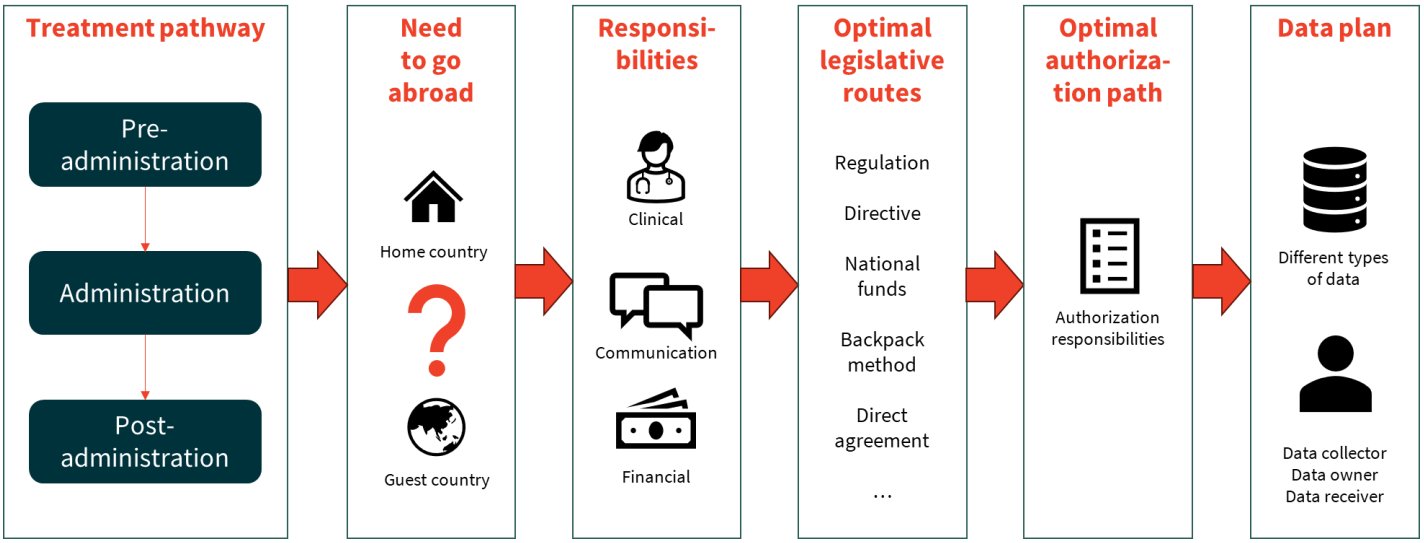

Figure 6. Workflow for optimal cross-border healthcare treatment

1. Define treatment pathway

An ATMP treatment pathway aims to **provide a clear view of the totality of care** by including all the possible aspects relevant to ATMP treatment. This should ensure that specific steps are noticed and primarily addresses the issue of the need for uniformity of care (see Part A, Treatment path). Although the actual treatment pathway differs between ATMPs, a generic pathway can help reflect on the steps needed in such a treatment. In a generic ATMP treatment pathway (Figure 7), we propose distinguishing **three separate phases: pre-administration, administration, and post-administration.** In addition, a difference is made between the patient and product pathways.

- The pre-administration phase starts with the **correct diagnosis** (or confirmation of the diagnosis) of the disease for which the ATMP is indicated. Next, the patient's **eligibility** for the specific ATMP needs to be confirmed, after which the product can be ordered, and the product pathway can start. In some cases, **patient material must be collected** to manufacture the product. The pre-administration phase ends when the product is correctly delivered and stored at the center where the ATMP will be administered.
- The administration phase starts with preparing **the patient and the product**. Regarding the preparation of the patient, eligibility may need to be reconfirmed shortly before the product is administered (e.g., in case of a rapidly progressive disease). Preparation can also entail preparatory treatments, such as conditioning treatment or other premedications. Preparation of the patient and the product must be coordinated so that everything is ready simultaneously. Then, the **product can be administered to the patient**. The complexity of the administration of the product can vastly differ, generally ranging from intravenous infusion to more invasive procedures such as surgery. Afterward, the patient will need to **stay under observation**. Regarding the product, specific procedures may be required after administration.
- In the post-administration phase, the patient must be **monitored and followed up**. As mentioned earlier, follow-up for numerous years might be required for ATMPs. In the context of innovative treatments, it is possible that patient outcomes need to be collected in the context of an MEA.
- With any procedure performed on the patient, **complications or adverse events** can occur. This can happen at any step of the patient pathway. If particular complications regularly occur, the recommended treatment approach can be discussed upfront between the treatment center abroad and the treatment center of the home country.

For each ATMP treatment, a specific treatment pathway needs to be developed. Starting from a generic ATMP pathway, a reflection must be made on which steps are required (i.e., not all steps might be applicable) and the actual content for each step.

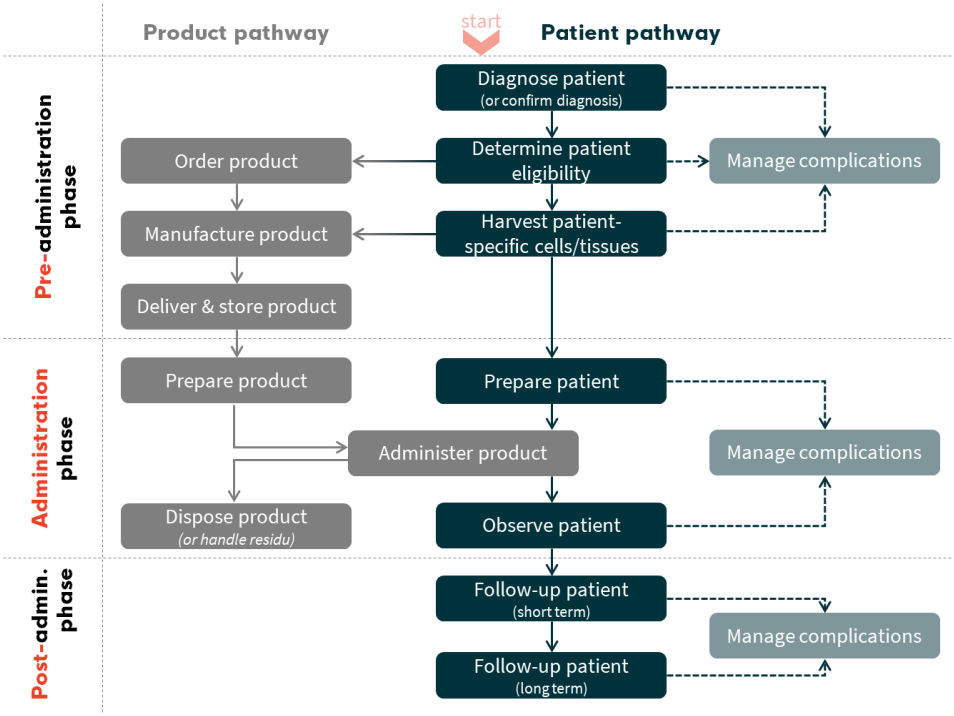

Figure 7. Generic pathway of an ATMP

Patient pathway

To specify the actual content and applicability of each step in the patient pathway for a specific ATMP, primarily **clinical input is required**, for which sufficient knowledge of the disease and the ATMP itself is needed. Outlining this process in detail with the particular cross-border context in mind can be appropriate to avoid ambiguities or miscommunication and to have a clear view of the totality of care, including long-term follow-up.

This patient pathway should be discussed between the treating physician from the treatment center abroad and the physician from the home country. A multidisciplinary team can support both. It can be relevant to involve an ERN. The pharmaceutical company or the CDMO can be consulted if publicly available evidence, such as the Summary of Product Characteristics (SmPC), is unclear.

Questions to guide the development of this patient pathway are shown in Table 1.

Table 1. Questions per step to develop the treatment-specific patient pathway.

Pre-administration phase	
Diagnose (or confirm diagnosis)	How is the diagnosis confirmed? Which tests are required? Which cut-off values?
	If there is room for interpretation of the diagnosis, how is this minimized?
Determine eligibility	How will eligibility be determined/confirmed? Which tests are required? Which cut-off values?
	If there is room for interpretation in determining eligibility, how is this minimized?
Collect patient material	Which procedures are required for cellular source collection? How should the preferred choice be determined in the case of different options?
Manage complications	What are possible complications related to diagnosis, eligibility, or cell/tissue harvest?
	What can be done to avoid or minimize the change of the complication(s) to occur?
	How should the complication(s) be treated?
Administration phase	
Prepare patient	Does eligibility need to be (re)confirmed shortly before administration? *If yes, reconsider questions related to patient eligibility.*
	Are there specific requirements regarding the condition of the patient?
	What are other practical/operational requirements before the patient preparation can be started?
	Which preparatory treatment is required?
Administer product	Which procedures are required to administer the product?
Observe the patient	What are specific points of attention after the product has been administered?
	How long should the patient be observed in case no complications occur?
Manage complications	What are possible short-term complications related to patient preparation or administration?
	What can be done to avoid or minimize the change of the complication(s) to occur?
	How should the complication(s) be treated?
Post-administration phase	
Follow up with the patient (routine follow-up)	How often and when should the patient be followed up?
	Which parameters should be assessed during follow-up? Which tests are required? Which cut-off values?
	Which follow-up data needs to be collected to meet MEA requirements? (parameters)?
Manage complications	What are possible long-term or delayed complications?
	What can be done to avoid or minimize the change of the complication(s) to occur?
	How should the complication(s) be treated?

For all steps in the patient pathway considered relevant for a specific ATMP, the actual content can be further finetuned by **translating the content into medical resource use**. Categories of medical resource use are:

- Visits and consultations (e.g., treating specialist, other specialist, teleconference between home/guest country, physiotherapist, psychologist, nurse, nurse assistant, etc.)
- Tests (e.g., blood test, urinalysis, ...)
- Imaging (e.g., X-ray, ultrasound, MR, CT, ...)
- Procedures (e.g., blood transfusion, biopsy, lumbar punction, ...)
- Pharmaceutical products other than the ATMP

Depending on what care is needed, the specific content of the step, and the associated risks, it can be determined whether this should be done during a **hospital stay** or if it's feasible to provide it in an **ambulatory** setting.

Product pathway

Next to the patient pathway, an overview of the product pathway and its requirements must be made for the ATMP. Many of these aspects are often described in existing documents such as for example the SmPC and Standard Operating Procedures (SOP) and many challenges are inherently related to ATMPs, even when they would be provided in the patient's home country. However, reviewing this process with all relevant stakeholders upfront can be appropriate, considering the additional complexity of a cross-border context (e.g., having more stakeholders involved). Depending on who prepares the product, input from the pharmaceutical company or the hospital pharmacy of the treatment center abroad is required.

Questions to guide the development of this product pathway are shown in Table 2.

Table 2. Questions per step to develop the treatment-specific product pathway.

Pre-administration phase	
Order product	How is the product ordered? Who prescribes the product?
Manufacture product	Where is the product manufactured?
	What happens if the product does not meet manufacturing standards?
	How is the traceability of the product assured throughout the entire product pathway?
Deliver product	What are the shipment conditions and delivery window?
Store product	How should the product be preserved? Are there restrictions on duration?
Administration phase	
Prepare product	What are the preparatory actions required for product administration?
Administer product	
Dispose of product (or handle residue)	Which procedures are required when the product cannot be administered?
	Which procedures are required after the product is administered?
Post-administration phase	
Not applicable	

2. Need to go abroad

The need to go abroad must be defined after the treatment-specific pathway is determined for a specific ATMP. **Each step separately** needs to be assessed as to whether the required care in this step can be provided in the home country (potentially in collaboration with the treatment center abroad) or if the patient needs to go abroad.

The most likely options are, per phase in the treatment pathway:

- Pre-administration phase:
  - The treatment pathway always starts in the home country, as a physician in the home country will at some point diagnose a patient or at least suspect a particular diagnosis. To confirm diagnosis or eligibility, it is possible that traveling abroad is already desirable. However, in many cases, it is possible to confirm diagnosis and eligibility in the home country in close cooperation with the treatment center abroad. If required, samples could be sent to the treatment center abroad.
  - If patient material needs to be collected, the collection will often need to be performed in the treatment center abroad. However, the option to do this in the home country should still be explored on a case-by-case basis, keeping in mind the possible difficulties and barriers (e.g., having the authority to perform the procedure (e.g., linked to certification), the complexity of the procedure to harvest, arrange transport of materials, possible timing constraints related to transportation and manipulation, ...).
- Administration phase:
  - The need for planned cross-border healthcare in the context of ATMPs often arises because the product cannot be delivered in the home country. In other words, the product administration will likely happen abroad.
  - In theory, it is possible that aspects of patient preparation could happen in the home country. However, it should be assessed if it is possible and desirable that the patient travels between preparatory steps and the actual product administration. In many cases, delivering the therapy, including all necessary preparatory steps abroad, e.g., combined in one hospital stay, is clinically justifiable.
- Post-administration phase:
  - Some follow-up in the treatment center might be inevitable, given their expertise about the disease, treatment, and potential complications. This may involve short-term follow-up, for which the patient might be able to stay abroad after treatment, or follow-up on longer term, requiring the patient to travel again.

Optimal planning and organization of cross-border care in the context of an ATMP will most likely result from an **iterative process** where the needs of the patient and the parent(s) or caregiver(s) should be heard. The underlying premise should be to only bring the patient abroad for those steps in the treatment pathway that cannot be delivered in the home country, as this will minimize the burden for the patient and the costs for the healthcare payer.

Knowledge transfer should still be encouraged so the need to go abroad can change. When a new ATMP becomes available, the treatment center abroad should be able to build up expertise in the product and the disease. In a later phase, the treatment center can share this knowledge and expertise and guide other centers in providing particular aspects of the treatment pathway.

3. Define responsibilities

In a context where cross-border healthcare is required, there will always be more entities involved than in a situation where treatment can be provided in the patient's home country, which can lead to unclarities or miscommunication about responsibilities (see also Part A, treatment path), or more specifically, **the point where responsibilities transfer** from one entity to another. Therefore, the responsibilities need to be defined for each step in the treatment pathway. Depending on which steps will happen abroad, responsibilities will lie differently.

Clinical responsibilities need to be defined as different clinicians are involved throughout the different steps in the treatment pathway. For example, losing critical time can be avoided if it is clear who is responsible for making the correct diagnosis and determining eligibility, and treatment can be initiated as quickly as possible. In case adverse events or complications occur, it should be clear who the patient needs to contact and who is responsible for following up. The clinical responsibilities related to the particular ATMP treatment should be imbedded in the patient's broader treatment plan as a whole (e.g. treatment of comorbidities).

Responsibilities regarding the ATMP itself might largely fall under the hospital pharmacy, though there should be no ambiguity about this either. This comprises ordering the product, follow-up of transport, storing and preparing the product, etc. Some steps of the product might be outsourced to other hospital departments or even external entities.

Responsibilities regarding communication should also be clear upfront. This includes communication with the patient, for which a single point of contact could be appointed. Furthermore, there should be clear communication concerning preparation and prescription with the product's manufacturer. As mentioned in the product pathway, many of these aspects are already defined in SOPs, but additional agreements can be required to account for the cross-border context.

Other stakeholders also have responsibilities depending on the **legislative routes and authorization procedures** in place. For example, the payer might need to set up agreements with treating hospitals and manufacturers, while health insurers and physicians must help prepare the dossier.

When discussing responsibilities, it can be relevant to **formalize particular agreements**.

4. Choose optimal legislative route(s)

Depending on the steps and the number of steps in the treatment pathway for which there is a need to go abroad, the optimal legislative route(s) must be determined to **assure coverage for all treatment-associated costs**. This optimal route can consist of one solution to cover all treatment-associated costs or a combination of different solutions so each can cover a part of the cost.

Below, an overview of all possible solutions and their limitations in the context of ATMPs is provided. This overview consists of existing European Directive 2011/24/EU and Social Security Regulations (EC) 883/2004 and 987/2009 ("S2 route")), national legislations, and possible new solutions. Even though these existing procedures are limited in the context of ATMPs in rare diseases, they might be helpful in specific contexts to cover parts of the total treatment costs.

Social Security Regulations (EC) 883/2004 and 987/2009 ("S2 route")

Under the Regulation, the treatment center abroad considers the patient as **insured under the local, national healthcare system**, i.e., patients seeking care with public healthcare providers and private hospitals contracted with the national health system, which does not cover treatments in private institutions. Therefore, the payer of the home country is bound to pay the total treatment cost of the guest country (i.e., reimbursement basis guest country and the applicable VAT tariff of the guest country) (Figure 8). This means that the list price for the product as negotiated between the company and the payer of the home country will not be applicable.

One of the challenges of the Regulation in the context of ATMP is when there are differences between the guest country's list price and the home country's list price (Figure 3). It is counterintuitive that every stakeholder agrees to a list price nationally, which would eventually not be applicable. Hence, the difference between the list price of the guest country and the list price of the home country and the MEA discount as agreed within the home country could be compensated by the manufacturer (20). However, if one follows the Regulation's underlying intention of equality across patients (treated within the same center), therefore relying on cross-country solidarity, the price differences should be accepted by the national payers (21).

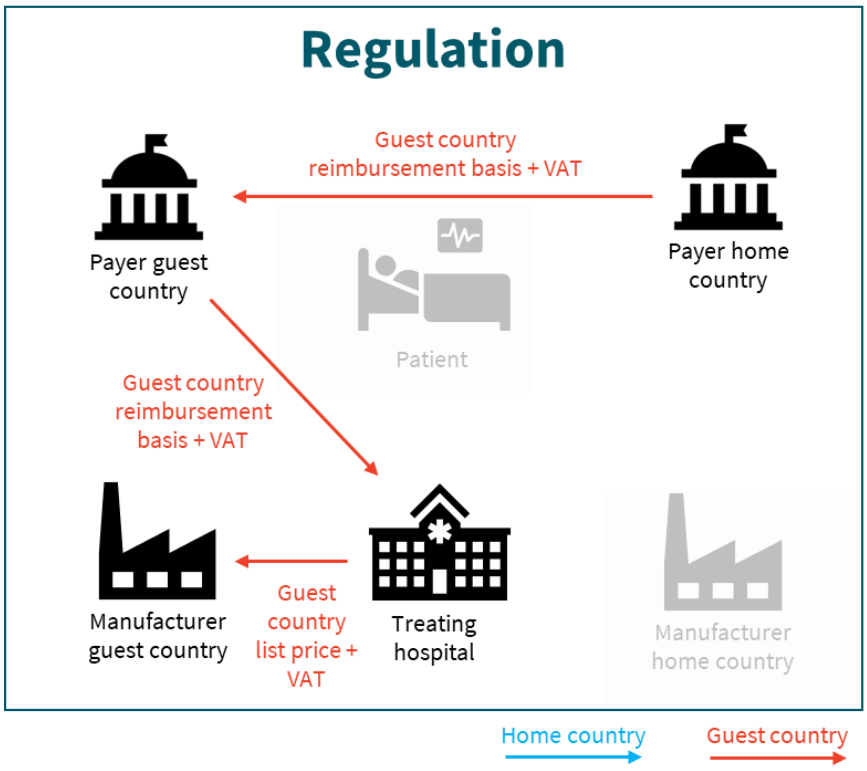

Figure 8. Financial streams as applied in the Regulation. VAT: value-added tax.

Directive 2011/24/EU

Under the Directive, the treatment center abroad will consider the patient as a **private patient**, which implies that the **patient needs to prepay** the cost of the treatment to the treating hospital and that a specific VAT rate for private patients might apply (Figure 9). Hence, prepayment to the treating hospital consists of the guest country's reimbursement basis and the guest country's applicable VAT tariff. If the authorization was granted before treatment was provided, the patient gets compensation from the payer of the home country. This compensation consists of the home country's reimbursement basis and the home country's applicable VAT tariff. The **patient must cover the difference in total cost in the guest country and total cost in the home country**[V]. In the case of ATMPs, the prepayment and the difference in total cost will be unrealistically high for an individual patient (20).

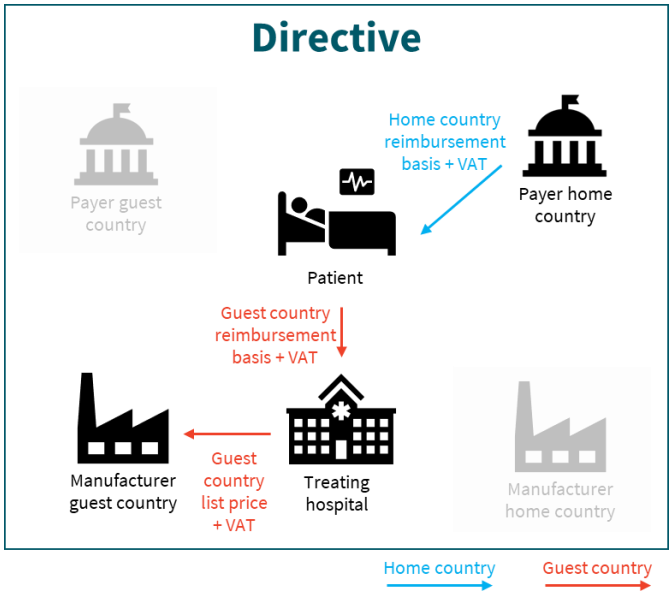

Figure 9. Financial streams as applied in the Directive. VAT: Value-added tax

In addition, the Directive does not provide specific preconditions that need to be met for authorization to be granted, leaving **more room for the decision-maker to refuse requests** at their discretion (20).

National fund

In some countries, separate funds exist that can provide financial compensation for medical treatments of severe conditions (e.g., Special Solidarity Fund (SSF) in Belgium). This can be seen as **additional safety nets on top of the regular health insurance system**. In the case of the SSF in Belgium, you can only apply in specific instances, including the need for treatment abroad, and receive financial support for (a part of the) travel and accommodation-related costs. However, the SSF has a fixed and limited budget and will be very restrictive in terms of the number of requests they approve. It does not seem opportune to rely on additional safety nets within a system as a default route.

[V] *The compensation by the payer of the home country will never exceed the total cost the patient has paid i.e. if the total cost in the guest country is lower than the home country, the payer of the home country will not pay this additional difference to the patient.*

"Backpack" method

In this suggested solution, a more pragmatic and out-of-the-box proposal which – to our knowledge – has not formally been utilized, the home country hospital will order the product with the manufacturer in the home country. Still, the product will be delivered to the treating hospital in the guest country. The term 'backpack method' draws an analogy to how patients would essentially bring the products to the treating hospital, mimicking the idea of a personal backpack. Note that the pharmaceutical company and the treating center will arrange actual product transport and delivery abroad. With this approach, the patient is considered as **treated in the home country**. In this way, the reimbursement of the product and MEA compensation can be arranged similarly to when the product would be administered in the hospital in the home country (Figure 10).

In essence, the cross-border aspect is being bypassed regarding the product itself, avoiding several issues (see also Part A, Issues related to treatment financing) related to the cross-border context. Hence, the main advantages of this route are:

- The product is ordered within the home country at the tariffs agreed on at the national level.
- There are no differences in VAT between countries to deal with.
- There is revenue for the manufacturer in the home country, making it possible or easier to execute MEA compensations, if applicable.

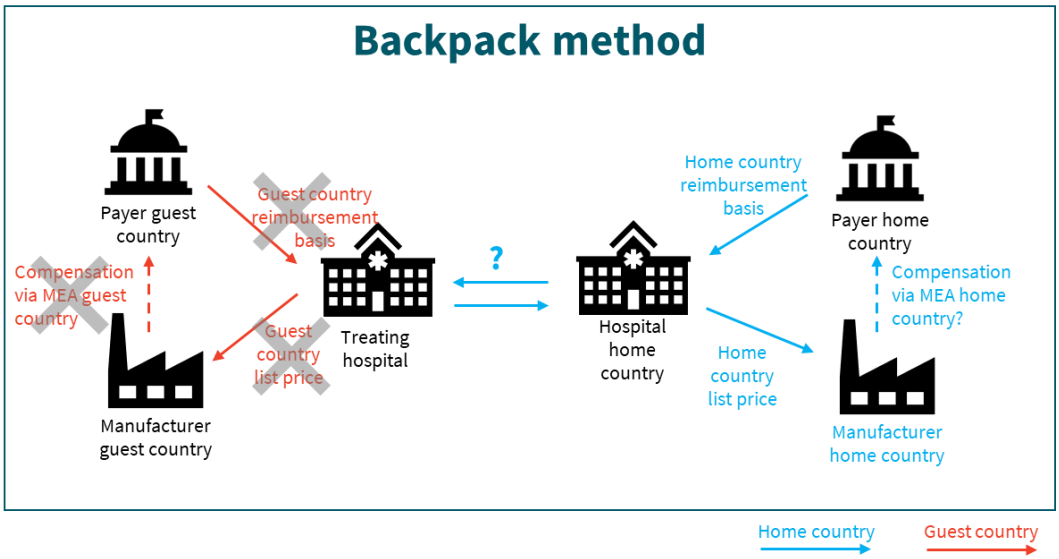

Figure 10. Financial streams as applied in the "backpack" method

This method can only bring a solution for the cost of the ATMP itself. In other words, a disadvantage of the 'backpack' method is that is will always need to be combined with other routes to cover other costs. Moreover, based on the feedback from a couple of hospital pharmacists from different countries, there are currently legal restrictions. For example, in some countries, it is impossible to administer a treatment that has not been prescribed within that hospital. Also, hospitals may still need to charge local VAT rates (which may differ from the guest country VAT rates).

Direct agreement with a hospital

In this suggested solution, **the payer of the home country sets up an agreement directly with the treatment center abroad**. In this type of agreement, different treatment-related costs can be included, for example, an administrative fee or specific treatments not reimbursed yet. As the payment is directly arranged between the payer of the home country and the treating center, the **payer of the guest country is not involved**. Due to the administrative work of the payer of the home country related to setting up these arrangements with each treatment center separately, the payer of the home country might limit the number of treatment centers abroad. This agreement can also include a fixed financial contribution for the referring hospital in the home country to cover the administrative work related to the referral.

This approach has been applied in Belgium in the context of hadron therapy. A separate executive order was created to enable Belgium's compulsory Health Care Insurance to grant financial contributions for proton therapy in one of these centers. Treatment-, travel- and accommodation costs are covered for patients who meet the predefined eligibility criteria and are referred by one of the certified radiotherapy centers following a fixed referral procedure. Tariffs and criteria have been aligned with those funded via other national routes (20,22).

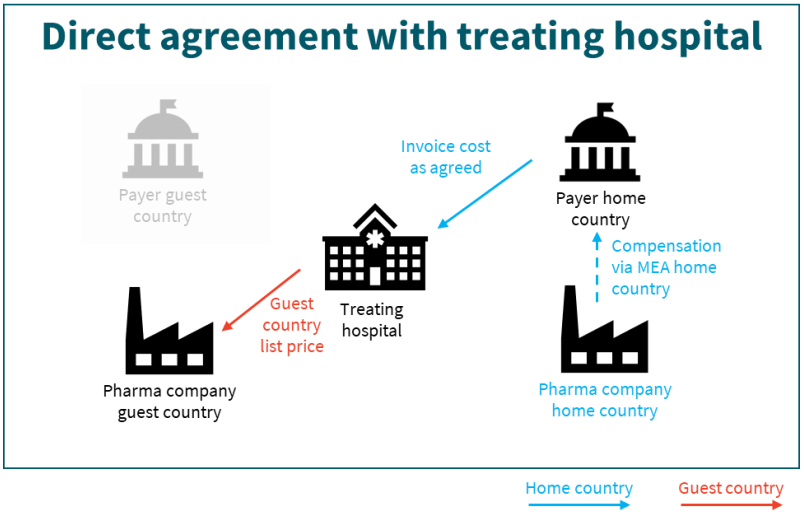

Figure 11. Financial streams as applied in the direct agreement

Feasibility of different legislative routes

Each of the different legislative routes described above has advantages and disadvantages or barriers that block implementation in practice (see also Table 3).

Theoretically, the "**backpack" method** seems to be a desirable solution to arrange the costs of the pharmaceutical product to avoid many issues, such as potential differences in actual price between the home country and the guest country and difficulties in MEA implementation. However, in practice, this solution is currently not legally feasible. Further, in-depth analysis would be needed to evaluate which legal changes would be required or whether solutions such as collaboration agreements could be found to tackle existing barriers. A pilot project or case study could uncover the actual feasibility of this approach. It should be kept in mind that this method can only cover costs related to the product itself, so other routes would still be required to cover all additional costs.

In the case of an ATMP, the required prepayment and the difference in cost that needs to be covered by the patient make the **Directive** an unsuitable option to cover the costs of the product itself. For other treatment-related costs, the Directive still might be a plausible option. However, this still implies the patient to prepay these costs, which might lead to inequitable treatment access. In addition, the Directive cannot be used to cover travel and accommodation costs. If available, a **national fund** could be used to cover travel and accommodation costs or even a part of the other treatment-related costs. However, using such a fund is not a sustainable solution, given the limited budget and nature (i.e., additional failsafe rather than a structural solution) of such a fund.

The most feasible options are the **Regulation** and the **direct agreement with the hospital**. Both options have the advantage of including multiple types of medical costs within one authorization request. Some countries (e.g., France) even include the coverage of travel- and accommodation costs in the same authorization approval. Within a direct agreement with the treating hospital, an agreement can be made on a specific treatment package or for treatment-related costs not (yet) reimbursed. Next to the treatment-related costs, this agreement can also cover a fixed financial compensation (e.g., for the referring hospital in the home country to cover the administrative work related to the referral and preparation of the authorization request).

However, both options have some **challenges for implementation in practice**. The Regulation mainly faces challenges if there is a substantial difference in the list prices between the home country and the guest country. Under the Regulation, the price that needs to be paid is the list price of the guest country, even though the payer of the home country has agreed to a different list price in the home country. Following the Regulation's underlying intention of solidarity, the national payers could accept the price differences (21). However, national healthcare systems are already under financial pressure, regardless of a cross-border context, so it can be argued that a national payer should be bound to the drug price as agreed on a national level (5). Differences are then expected to be covered by the manufacturer of the home country, which is challenged by the fact that the manufacturer does not have revenue in their home country. Under a direct agreement, for every new ATMP product requiring cross-border treatment, a separate agreement needs to be set up between the payer of the home country and the treatment center, which might come with a significant amount of administrative workload for the payer of the home country and will limit the number of treatment centers abroad for a specific treatment.

In addition, there might be challenges with the **practical implementation and execution of** MEAs. If an MEA has been agreed upon, the price might differ in both countries due to a confidential discount. This discount should be arranged between the manufacturer of the home country and the payer of the home country. In the case of **a simple discount**, the manufacturer of the home country will pay back the agreed discount to the payer of the home country. If the MEA contains **payment at outcomes achieved with annuity-based payment,** the manufacturer of the home country will first pay the guest country's full list price to the home country's payer. Depending on the outcomes achieved, the payer will then pay the manufacturer at specific time points.

Due to the confidentiality of these agreements, there is a risk of double MEA compensation both in the home country and the guest country (also shown in Figure 4). A solution for this problem could be to separately monitor the patients from the home country, the patients from the guest country, and patients from other countries. In this way, there is correct tracking of the patients treated abroad, for which MEA compensation can be requested in the home country and should not be requested in the guest country.

Table 3. Cross-border issues that are addressed via the different legislative routes

Main issues:	Difference in treatment cost	Payment system	MEA confidentiality	Other
Regulation				
Advantages	Different medical costs can be covered by the payer of the home country	Patient prepayment is not required[VI]		
Disadvantages	Reimbursement basis + VAT as agreed in the guest country Does not cover travel costs		Risk of double compensation No revenue for the manufacturer in the home country	
Directive				
Advantages	Reimbursement basis + VAT as agreed in the home country			
Disadvantages	Patient needs to cover the difference in total cost between the home country and guest country (reimbursement basis + VAT private patient) Does not cover travel costs	Patient prepayment required	Risk of double compensation No revenue for the manufacturer in the home country	
National fund (e.g. SSF in Belgium)				
Advantages	Can cover travel and accommodation costs	Patient prepayment is not required		
Disadvantages	Possibly limited budget (e.g. closed envelope system) Not a structural solution		Not addressed	
Backpack method				
Advantages	Reimbursement basis + VAT as treated in the home country	Patient prepayment is not required	Pharmaceutical company in the home country has revenue for MEA execution	
Disadvantages	Only relevant for pharmaceutical product			Legal restrictions
Direct agreement hospital				
Advantages	Treatment cost can be agreed between payer's home country and treating hospital	Patient prepayment is not required		
Disadvantages			Risk of double compensation No revenue for the manufacturer in the home country	Only valid for specific centers, which can limited the options Workload can rise with an increasing no of treatment centers

[VI] *In some cases, prepayment might still be required, even under the Regulation.*

5. Define the optimal authorization path

Centralized vs. decentralized decision-making body

Regarding the authorization path, we distinguish a decentralized approach, where different entities (e.g., different health insurers) are responsible for handling the authorization requests, and a centralized approach, where one entity bears this responsibility.

A **decentralized approach** allows one to make fast decisions. Moreover, these smaller entities can have the advantage of being more accessible to the patient. However, within such a system, it is **difficult to ensure uniformity** in the decisions (as discussed in Part A, Authorization path, issue 1)

A possible approach to make the authorization process more predictable and uniform is to install a **centralized approach** for ATMP treatments for (ultra)rare diseases, in which all the requests are handled similarly. The approval decision can be organized in two different ways:

- ***One individual*** could make the approval decision. In this case, this person understands the procedure and requirements for the authorization dossier and the difficulties that come with an ATMP treatment for (ultra)rare diseases. However, one person can't have detailed expertise about all different (ultrarare) diseases. Therefore, it is strongly advised that this person should reach out and rely upon (international) experts. This approach gives this person a good overview of the different approval requests to ensure uniformity. More importantly, fast decisions can be made. However, the decision-making responsibility lies with one person, which brings some risks. This way of working is used in France, specifically for the authorization of a cross-border treatment for ATMP.
- ***A committee or board*** can also make the approval decision. This way, more opinions and different points of view can be taken into account. In this way, specific disease experts can be invited to the committee, which will have a better knowledge of the disease and the treatment. However, this also implies that the composition of the committee can differ for every dossier, which might compromise the consistency and uniformity across dossiers. The most crucial downside to this approach is that it will require more time before deciding as it is challenging to bring different experts together on short notice. In the context of ATMPs of (ultra)rare disease, time-consuming procedures can lead to delayed treatment, which can have a substantial impact on patient outcomes or even eligibility to receive treatment.

Predictable throughput time of an authorization process

In the authorization process for ATMPs or orphan drugs, minimizing the time between the request to go abroad and the approval decision is essential. A **predefined maximal period** for permission is thus desirable. For example, in France, the patient must be notified of the approval decision within 14 days after receiving the request. If no reply is received within this period, the decision is made in favor of the patient (23).

Formalized guidance and patient support

Often, the patient must initiate and follow up on their authorization request, thus having a significant responsibility. Therefore, it is essential to guide them sufficiently: it should be clear how and where to start, where they can find information, and which documents they need. The national contact points should provide this guidance and feedback, or it should be provided via the patient's health insurer. In addition, treatment centers should help them and provide them with the necessary input for the request.

In addition, clear guidelines on what an authorization request should entail in the specific context of ATMPs can make dossiers sufficiently comprehensive. For example, it could be recommended to include a confirmation of the patient's eligibility as per the indication (at the time of application) determined by the qualified treatment center abroad. The decision maker must only assess whether the indication aligns with the national label.

6. Set up data plan

Next to sharing clinical information and clinical data between the treating physician and the specialist in the home country, other types of data might also need to be collected. ATMPs often come with strict eligibility criteria to which the patient must comply. The eligibility criteria are tested for the authorization request for the cross-border treatment and often need to be reconfirmed shortly before the patient receives the treatment. Considering patients becoming ineligible, failures in the manufacturing process, or other unexpected events, it is important not to assume that all patients who received approval for treatment will eventually be treated. **The payer requires the exact number of patients who finally received treatment** in the guest country to pay the total cross-border treatment cost and for the execution of an MEA (e.g., MEA discount).

Next to tracking the number of treated patients, collecting patient outcomes might also be essential. The physicians can use these outcomes for the follow-up of the patient. In addition, the collection of real-world evidence (RWE) might be required for the execution of an outcome-based MEA or the (re)negotiation of a conditional reimbursement. To avoid double MEA compensation (as discussed in Part A, Issues related to treatment financing), it will be required to track patients' information separately for each country.

A clear data plan will need to be set up to ensure the necessary data is transferred across borders to the dedicated persons. For data to be available, data needs to be collected, added to a registry or platform, and shared with the dedicated person(s). This requires to have a transparent overview of the following information:

- Types of data/information required
- When in the treatment pathway, the specific information is required
- Which stakeholders are involved, and what are their responsibilities
    - Data collector
    - Data owner
    - Data receiver

Existing initiatives regarding exchanging health data across the EU (19) should be explored and leveraged to the extent possible, before any new systems are initiated.

Patients should be aware that data collection and sharing will be required to receive cross-border treatment. Transparency will be essential to indicate to the patient the data collection purpose and with whom this information will be shared. Therefore, the **patient's consent will be required to collect and share the necessary data with the** stakeholders involved. It is possible that this will not be substantially different from other cross-border treatments. However, reviewing this process in the particular context of cross-border healthcare for ATMPs with all relevant stakeholders can be appropriate.

Next steps

This document, developed in cooperation with different stakeholders, provides an overview of the issues related to planned cross-border healthcare for ATMPs and proposes a workflow for optimal cross-border treatment. Further iterations with various stakeholders will be required for the practical implantation of our recommendations.

This workflow can be seen as a whole. However, separate building blocks of the workflow can serve as starting points to further adapt and optimize practices and patient access to ATMPs beyond national borders.

Abbreviations

ATMP	Advanced Therapy Medicinal Products
CDMO	Contract Development and Manufacturing Organization
DRG	Diagnosis-Related Group
EMA	European Medicines Agency
ERN	European Reference Network
EU	European Union
MEA	Managed Entry Agreement
RWE	Real-World Evidence
SmPC	Summary of Product Characteristics
SOP	Standard Operation Procedure
SSF	Special Solidarity Fund
VAT	Value-Added Tax

References

1. EMA. European Medicines Agency. 2018 [cited 2023 Aug 14]. Advanced therapy medicinal products: Overview. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview

2. Farkas AM, Mariz S, Stoyanova-Beninska V, Celis P, Vamvakas S, Larsson K, et al. Advanced Therapy Medicinal Products for Rare Diseases: State of Play of Incentives Supporting Development in Europe. Frontiers in Medicine. 2017;4.

3. Frederiksen SD, Avramović V, Maroilley T, Lehman A, Arbour L, Tarailo-Graovac M. Rare disorders have many faces: in silico characterization of rare disorder spectrum. Orphanet Journal of Rare Diseases. 2022 Feb 22;17(1):76.

4. Van De Voorde C, Van den Heede K, Beguin C, Bouckaert N, Camberlin C, de Bekker P, et al. Required hospital capacity in 2025 and criteria for rationalisation of complex cancer surgery, radiotherapy and maternity services. 2017 p. 544. Report No.: KCE report 289.

5. Hict. Cross-border healthcare in ATMPs: A Belgian cross-stakeholder perspective [Internet]. 2022 [cited 2023 Aug 14]. Available from: https://hict.com/volumes/whitepaper/CBHC-Report-20221208.pdf

6. Art.72 bis, KB van 3 juli 1996 tot uitvoering van de wet betreffende de verplichte verzekering voor geneeskundige verzorging en uitkeringen. 72 bis.

7. De Wispelaere F, De Smedt L, Pacolet J. Cross-border healthcare in the EU under social security coordination. Reference year 2020. HIVA-KU Leuven; 2022.

8. Talarico R, Cannizzo S, Lorenzoni V, Marinello D, Palla I, Pirri S, et al. RarERN Path: a methodology towards the optimisation of patients' care pathways in rare and complex diseases developed within the European Reference Networks. Orphanet Journal of Rare Diseases. 2020 Dec 14;15(1):347.

9. Marwaha S, Knowles JW, Ashley EA. A guide for the diagnosis of rare and undiagnosed disease: beyond the exome. Genome Medicine. 2022 Feb 28;14(1):23.

10. UMD [Internet]. [cited 2023 Aug 29]. Available from: https://www.unitedformetabolicdiseases.nl/

11. European Commission. European Reference Networks: Overview [Internet]. 2023 [cited 2023 Aug 14]. Available from: https://health.ec.europa.eu/european-reference-networks/overview_en

12. EMA. European Medicines Agency. 2018 [cited 2023 Aug 29]. Guideline on safety and efficacy follow-up risk management of advanced therapy medicinal products - Scientific guideline. Available from: https://www.ema.europa.eu/en/guideline-safety-efficacy-follow-risk-management-advanced-therapy-medicinal-products-scientific

13. Whittal A, Jommi C, Pouvourville GD, Taylor D, Annemans L, Schoonaert L, et al. Facilitating More Efficient Negotiations for Innovative Therapies: A Value-Based Negotiation Framework. International Journal of Technology Assessment in Health Care. 2022 Jan;38(1):e23.

14. République Française. Accord préalable de l'Assurance maladie [Internet]. [cited 2023 Aug 18]. Available from: https://www.service-public.fr/particuliers/vosdroits/F168

15. VGZ. Machtiging aanvragen voor medicijnen [Internet]. [cited 2023 Aug 18]. Available from: https://www.vgz.nl/vergoedingen/machtiging/machtiging-medicijnen

16. UMC Zorgverzekering. Machtiging aanvragen voor geneesmiddelen [Internet]. [cited 2023 Aug 18]. Available from: https://www.umczorgverzekering.nl/vergoedingen/machtigingen/machtiging-geneesmiddelen

17. Sarepta Therapeutics, Inc. A Phase 3 Multinational, Randomized, Double-Blind, Placebo-Controlled Systemic Gene Delivery Study to Evaluate the Safety and Efficacy of SRP-9001 in Subjects With Duchenne Muscular Dystrophy (EMBARK) [Internet]. clinicaltrials.gov; 2023 Jul [cited 2023 Aug 27]. Report No.: NCT05096221. Available from: https://clinicaltrials.gov/study/NCT05096221

18. Horgan C, Watts K, Ram D, Rust S, Hutton R, Jones S, et al. A retrospective cohort study of Libmeldy (atidarsagene autotemcel) for MLD: What we have accomplished and what opportunities lie ahead. JIMD Reports [Internet]. [cited 2023 Aug 29];n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jmd2.12378

19. European Commission. Exchange of electronic health records across the EU | Shaping Europe's digital future [Internet]. 2023 [cited 2023 Aug 18]. Available from: https://digital-strategy.ec.europa.eu/en/policies/electronic-health-records

20. Hict. Cross-border healthcare in ATMPs: A Belgian cross-stakeholder perspective. Background material [Internet]. 2022 [cited 2023 Aug 14]. Available from: https://hict.com/volumes/whitepaper/CBHC-Appendix-20221208.pdf

21. Kolnikova M, Rybanska B, Fumagalli F, Calbi V, Gallo V, Recupero S, et al. Treatment of metachromatic leukodystrophy with atidarsagene autotemcel - autologous lentiviral hematopoietic stem-cell gene therapy - in the EU: A case report. In: 15th European Paediatric Neurology Society Congress [Internet]. 2023. Available from: https://www.epns.info/wp-content/uploads/2023/06/EPNS23_Abstract_Book.pdf

22. Cancer: referral of patients to centres for hadron therapy [Internet]. [cited 2023 Aug 18]. Available from: https://www.inami.fgov.be/nl/professionals/verzorgingsinstellingen/ziekenhuizen/zorg/Paginas/Hadron-english.aspx

23. CLEISS. Vous partez sur le territoire d'un Etat membre de l'UE ou de l'Espace Economique Européen (Islande, Liechtenstein et Norvège) pour vous faire soigner [Internet]. [cited 2023 Aug 18]. Available from: https://www.cleiss.fr/particuliers/partir/soins/ue/soins-programmes-ue-eee.html#autorisation