APPENDIX

Background material

Existing cross-border legislation and frameworks

Contents

1. Overview

Two European legislations are related to planned cross-border healthcare: Social Security Regulations (EC) 883/2004 and 987/2009; and the Directive 2011/24/EU. One parallel procedure was identified in Belgium that could be addressed for ATMP treatment abroad (the Special Solidary Fund). In addition, two existing parallel procedures in Belgium were identified that currently exist outside the context of ATMPs. They could however serve as an example for regulating cross-border healthcare in the context of ATMPs: a specific national regulation was developed for hadron therapy and bilateral agreements were made for patients living in cross-border areas.

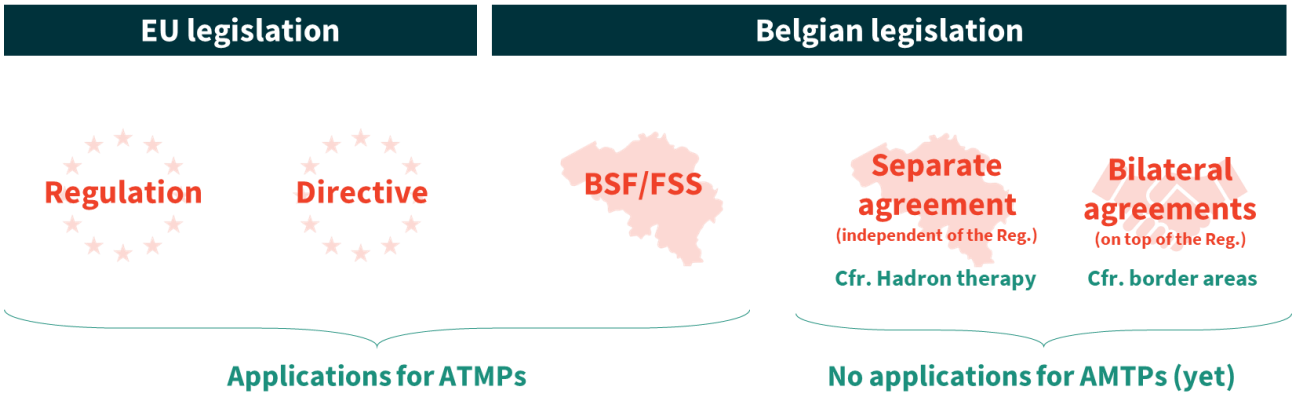

Figure 1. Overview of the existing legislation in Belgium, incl. EU legislation that also apply.

Note that these different legislations complement each other, thus can be combined when seeking treatment abroad in the context of ATMPs. However, for the sake of clarity, the different routes are first discussed separately in the appendix.

In short, we can conclude that seeking authorization and reimbursement in the context of ATMP treatments abroad via **the Directive route** appears to be inoperable, due to:

- the lack of predefined conditions for which authorization must be granted, as is the case in the Regulation;
- the required patient prepayment.

The Directive route could however be applied for reimbursement of concomitant treatment, of which it is feasible for the patient to pay the costs upfront and receive reimbursement afterwards.

Hence, of the two European legislations currently in place, **the Regulation seem to be the most feasible backbone** in the context of ATMP treatments abroad. When a patient seeks reimbursement for his treatment abroad via the Regulation:

- Tariffs from the guest country will be applied;
- Prior authorization is always required, based on two main preconditions:
  - Treatment is among the benefits provided in Belgium,
  - Treatment cannot be provided in Belgium within a medically justifiable time.
- In the context of ATMPs, a third condition must be fulfilled, namely that the patient must be found eligible for this treatment, based on the reimbursement criteria.

The **Special Solidary Fund** is an additional safety net on top of the regular health insurance system in Belgium, making it – by default – **not a structural solution** to seek reimbursement for cross-border healthcare. It can however be addressed to cover travel- and accommodation costs, but this implies that patients need to file a separate request.

Two national parallel procedures could be relevant to further explore in the context of cross-border healthcare for ATMPs:

- Establishing bilateral agreements between countries function ***on top of* existing *European legislation*** and can facilitate the use of it. Currently identified agreements in Belgium are focused on patients living in border areas.
- Specific national legislation can be created, **independent from European legislation**, to regulate treatment abroad for a particular treatment. This has been done for hadron therapy.

Different legislation and frameworks for cross-border healthcare, both on the European and national levels, create a complex reality for patients, healthcare providers, industry, and payers. In addition, each route comes with different remaining issues, summarized in Table 1.

Table 1. Main issues of the identified routes in Belgium. "×" indicates that the issue exists under that route.

	Regulation	Directive	Special Solidarity Fund	Hadron therapy	Bilateral agreements	Comparator: treatment in BE
Authorization process						
Difficult to identify the most optimal route		Yes		No	?	N.A.
The patient must be the initiator for requesting authorization.	Yes	Yes	Yes	No	?	No
Lack of support and uniformity in the authorization process	Yes	Yes	No	No	?	No
Room for discretionary decisions in the handling of authorization requests	No	Yes	?	No	No	No
Private institutions are included.	No	Yes	Yes	N.A.	Yes	Yes
Budgetary concerns for the patient						
(Drug) cost possibly only partially covered *(e.g., when list price guest country > list price Belgium)*	No	Yes	Yes	No	No	No
Coverage of travel- and accommodation costs	No	No	Yes	Yes	(No)	N.A.
Payment upfront by the patient is required	(No)	Yes	No	No	?	No
Budgetary concerns for the health system						
Limited by a relatively small fixed yearly budget	No	No	Yes	(Yes)	No	No
Payers might need to pay higher prices than agreed upon on the national level. *(e.g., when list price guest country > list price Belgium)*	Yes	No	No	No	(Yes)	No
MEA is agreed on a national level	Yes	Yes	N.A.	N.A.	(Yes)	N.A.
Feasibility of the route in the context of ATMP for rare diseases	✓	✗	✗	✓	✓	

2. Detailed descriptions of the existing routes

Different cross-border healthcare pathways are identified from desk research that address the specific context of cross-border healthcare for ATMPs. It compares their practical implementation to the path typically followed for an orphan ATMP with (temporary) reimbursement available in Belgium. This comparison stems from the underlying premise that:

- For patients, in as many ways as possible, the path they follow to get access to treatment should be no different for a product that requires them to cross borders than for a product that does not require them to cross borders.
- Access to cross-border healthcare for products that have been accepted for reimbursement in Belgium should not be hampered by underlying barriers (e.g., budgetary or payment concerns) for any of the stakeholders involved.

For the reference situation as well as each route, two aspects are considered:

- The **practical process steps** a patient and their treating physician take to request and receive reimbursement.
- The **flow of funds** between patient, healthcare provider, and RIZIV/INAMI.

2.1. Reference situation

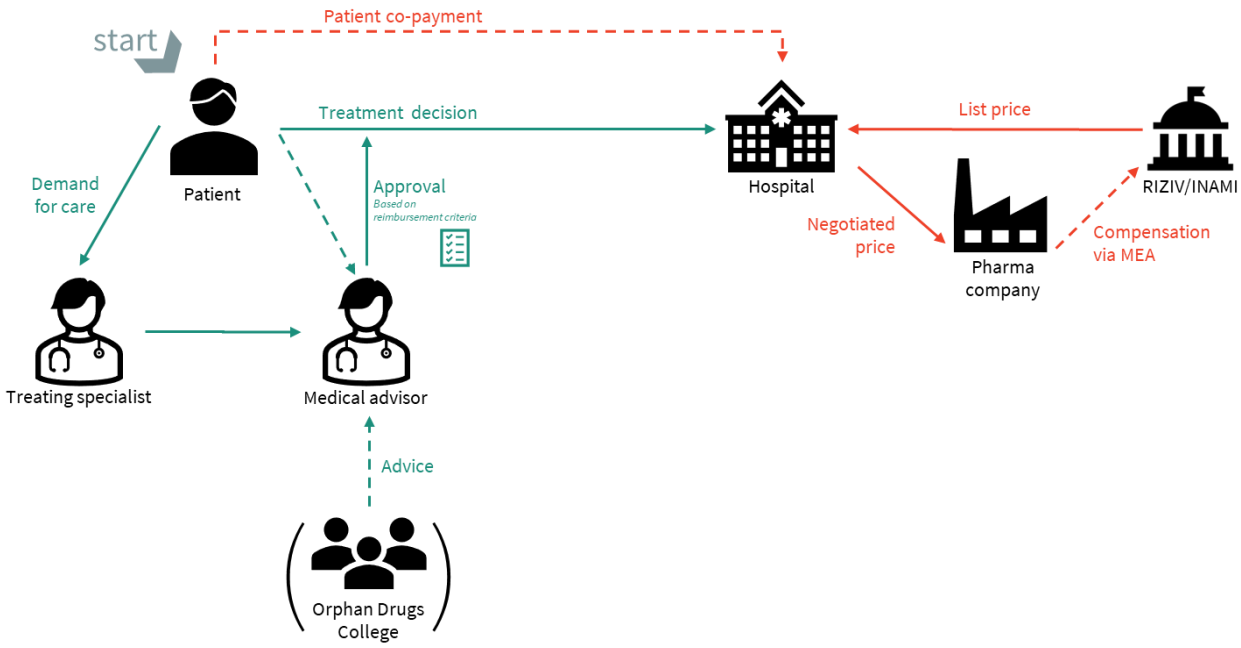

Figure 2. Reference situation: treatment pathway (blue arrows) and financial streams (red arrows) for a reimbursed orphan ATMP available in Belgium.

Treatment pathway for patients with a rare disease that can be treated in Belgium.

The patient consults a specialist with a demand for care. If, after diagnosis, the treating physician believes the patient fulfills the reimbursement criteria, as defined by Royal Decree, the specialist will initiate the reimbursement request. In the case of an orphan drug, the product will most likely be a Chapter IV product (1), implying that prior authorization is needed to receive reimbursement.

The request will be evaluated by a medical advisor affiliated with a sickness fund. An Orphan Drug college may be in place to support the medical advisor. Based on the advice of the Orphan Drug college, the medical advisor is responsible for the authorization of reimbursement.

Financial streams for orphan drugs in Belgium

The hospital pharmacy pays for the product at a price negotiated between the hospital and the pharmaceutical company (the negotiated price cannot exceed the maximum price as determined by the Federal Public Service (FPS) Economy). When authorization for reimbursement is granted, the hospital pharmacy delivers the product to the patient and receives the reimbursed price of the product from RIZIV/INAMI. The patient possibly pays co-payment, although, in this context, it would concern vitally important (reimbursement category A/Fa) or essential therapeutic products (reimbursement category B/Fb) with no or limited co-payment.

To close the financial stream, the pharmaceutical company might be bound to financial compensations towards RIZIV/INAMI, defined in a managed entry agreement (MEA). MEAs are agreements between the pharmaceutical company and the payer aiming to bring meaningful innovation to the market as quickly as possible, even though there might be uncertainty about the performance of technologies. This way, the adoption of technologies can be more strictly managed to maximize effective use or limit their budget impact (2). Most MEAs in Belgium are price-volume agreements, such as a partial refund of the realized revenue if eventual sales exceed the agreed threshold (3).

2.2. European legislation: Social Security Regulations (EC) 883/2004 and 987/2009

A summary of this route

A regulation is a binding legislative act, meaning that it must be applied in its entirety across the EU (4). As stated by Article 20 of Regulation (EC) No 883/2004 on the coordination of social security systems (from now on referred to as "the Regulation"), **the patient needs prior authorization to receive treatment outside the Member State of residence**. Authorization by the competent institution should be given when two conditions are fulfilled:

1. The treatment is covered by (included in) the benefits provided for by the legislation in the Member State where the person concerned resides (i.e., the home country of the patient)

2. The treatment cannot be provided in the home country within a medically justifiable time.

In the context of ATMPs, a third condition must be fulfilled, namely that the patient must be found eligible for this treatment, based on the reimbursement criteria.

Via this route, prior authorization is based on two clearly defined preconditions (in combination with additional administrative conditions). This should theoretically leave little room for discretionary decisions if these conditions are fulfilled. Note that it is possible to receive authorization when the conditions are not fulfilled. After authorization, the patient will be considered as though he were insured in the guest country. In other words, tariffs of the guest country will be applied.

Authorizations for planned healthcare under the Regulation are arranged using the S2 form. In 2019, Belgium received 550 requests via S2 forms, of which 342 (62%) were refused. This refusal rate is exceptionally high compared to other countries (5).

- About half of the refusals were based on the two preconditions mentioned above (treatment not included in the Belgian services (12.9%); therapy can be delivered within a medically justifiable period in Belgium (29.8%)). Other reasons for refusal were: insufficiently documented requests, treatment not proven beneficial for the patient, care in question already provided without prior authorization, or treatment provided at private institutions (5).

- Despite the preconditions as formulated in the Regulation, Belgium issued four authorizations in 2019 for care not included in the services provided in Belgium.

The 208 (38%) authorizations granted by Belgium (i.e., 550 received, minus 342 refused) are primarily directed to a specific set of treating member states: France (43.3%), Germany (29.8%), The Netherlands (13.5%), UK (6.7%), Switzerland (3.8%), and Luxembourg (2.9%). This is in line with the general use of the Regulation in Europe, where planned cross-border healthcare is mainly sought in neighboring countries, focusing on West-European countries (France, Belgium, Luxemburg, Germany, Austria, and Switzerland) (5). This is facilitated by parallel procedures such as bilateral agreements in border areas (see infra).

Implications for rare diseases

In cross-border healthcare for rare diseases, where treatment is only available in specialized centers, the condition of treatment not being available in Belgium within a medically justifiable time is likely to be fulfilled.

Given the recent change in law (see Introduction of the report), ATMPs do not need to become available in Belgium, so pharmaceutical companies can now go through the national reimbursement procedure. Hence, both conditions of the S2 route can be met, making this route available for patients seeking cross-border ATMP treatment. The expected reimbursement and financial streams for this route are depicted in Figure 3.

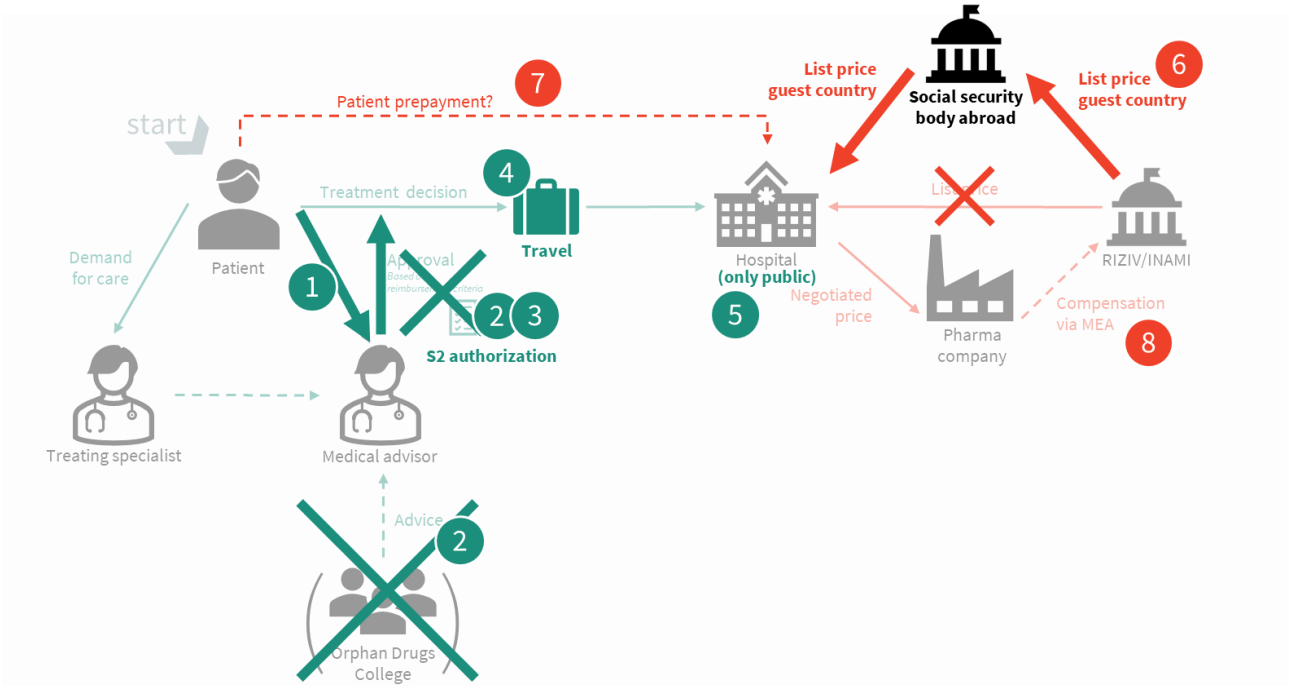

Figure 3. Treatment pathway (green arrows) and financial streams (red arrows) for cross-border healthcare via the Regulations (in comparison with a situation where treatment would be provided in Belgium).

When this procedure is compared to our reference situation (i.e., treatment for rare diseases in Belgium), several potential issues are apparent:

1. In a regular approval procedure for receiving specialized care in Belgium, the treating specialist is responsible for submitting authorization requests. In the S2 route, the patient is responsible for submitting the request to the medical advisor (affiliated with the sickness fund). This shifts responsibility to initiate the process to the patient and can create a first barrier toward equitable access to healthcare.

2. The S2 authorization criteria differ from a regular approval procedure. Moreover, the medical advisor responsible for evaluating the request is not supported in their evaluation by a designated college or committee. Although the legal preconditions for receiving authorization via the Regulation route appear to be well-defined, this procedure is more prone to variations between individual decisions.

3. Belgian law stipulates that an authorization request must be handled within 45 days to avoid extensive delays. Prior authorization is automatically granted when this period is exceeded. However, this maximum period is no longer valid when the medical advisor requests additional information.

4. Travel and accommodation costs are not covered. These costs could be substantial, for example, when a patient needs to stay abroad for a long time or when the patient needs to be accompanied (e.g., by a parent or informal caregiver).

5. The S2 authorization system only concerns those seeking care with public health care providers, as this system does not cover treatment in private institutions.

6. According to the Regulation, RIZIV/INAMI is bound to pay the list price of the guest country, which could differ from the list price in Belgium. In other words, the Belgian reimbursement procedure includes a price negotiation for a list price that will eventually not be used within this route.

7. It is possible that patients need to pay the treatment costs upfront (6). It is unclear if this can be arranged differently for these types of treatments, where its costs easily exceed the financial capabilities of an individual.

8. Practical implementation of MEA is agreed upon on the Belgian level. The translation to a cross-border healthcare context of MEA practicalities is not clear.

2.3. European legislation: Directive 2011/24/EU and subsequent Belgian law

A summary of this route

As described in the first Article of Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare (from now on referred to as "the Directive"), its goal is to facilitate access to safe and high-quality cross-border healthcare and to promote cooperation on healthcare between the Member States.

Contrary to European regulations, a directive is a legislative act that sets out a goal that all EU countries must achieve (4). To reach these goals, individual countries are expected to transpose the Directive into national laws, regulations, and administrative provisions. In Belgium, the regulatory base of healthcare is the Law on compulsory insurance health care and benefits, coordinated on 14 July 1994 (replacing the Law of 9 August 1963), and the Royal Decree of 3 July 1996, implementing that Law. The Directive is transposed to Belgian law without any significant changes or further specifications for Belgium.

In comparison with the Regulation, the main advantage of the Directive is that no prior authorization is required. However, several exceptions are made, such as treatment that requires overnight hospital accommodation or highly specialized and cost-intensive medical infrastructure or medical equipment. Under the Directive, authorizations for planned healthcare are arranged using the 'ad-hoc' form. In contrast to the Regulation, the Directive and subsequent Belgian law do not provide specific preconditions that need to be met for authorization to be granted. Hence, this leaves more room for the decision-maker to refuse requests at their discretion.

Art. 294 of the Royal Decree of 3 July 1996 further stipulates that the Belgian healthcare system can only reimburse healthcare services after the patient prepays the costs. Reimbursement of the healthcare services will be according to the Belgian tariffs (i.e., similar to when treatment would have been provided in Belgium) but cannot exceed the actual expenditures made.

Implications for rare diseases

One of the Directive's goals was to facilitate cooperation between national health authorities through the European reference networks, which should – among other things – tackle treatments for rare diseases. The Directive treatment pathway and financial streams are visualized in Figure 4.

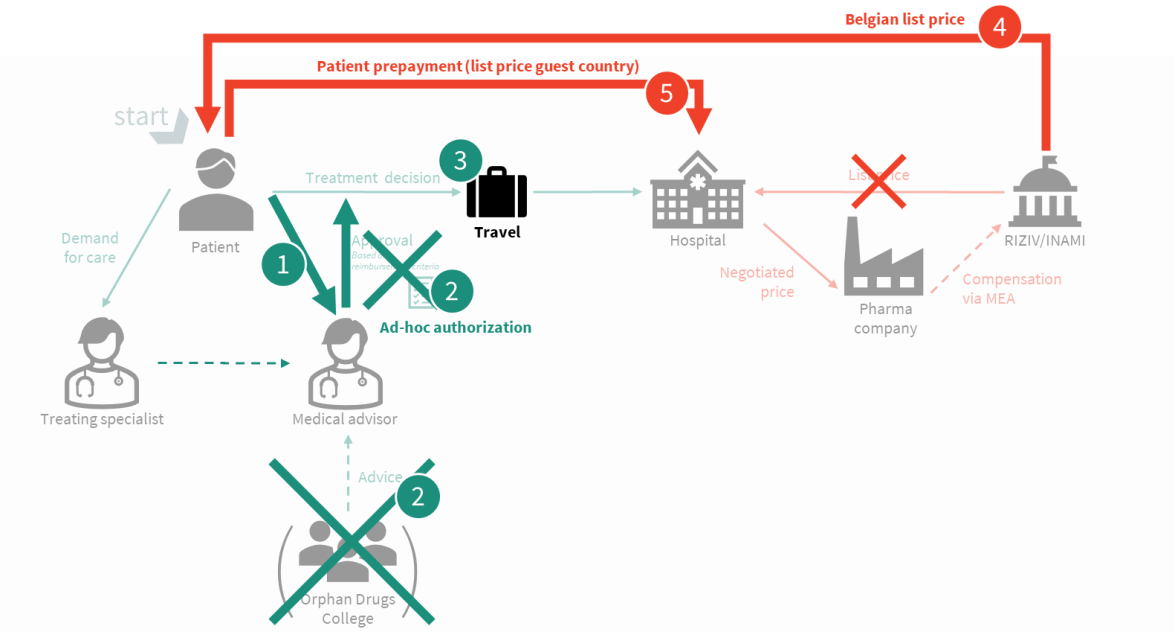

Figure 4. Treatment pathway (blue arrows) and financial streams (red arrows) for cross-border healthcare via the Directive (in comparison with a situation where treatment would be provided in Belgium).

The need to go abroad for an ATMP treatment originates from the need for specialized and complex procedures and devices, so, likely, prior authorization would always be necessary. Hence, the most significant advantage of the Directive route, being that prior approval is not required in most situations, does not apply to the context of ATMPs. This also implies that difficulties related to prior approval that were previously identified remain:

1. The patient is the initiator of the authorization request
2. There is no support from a designated college or committee. Moreover, there are no distinct criteria for which authorization must be granted, leaving more room for discretionary decisions.
3. Travel and accommodation are not covered.

Additionally:

4. Via this route, RIZIV/INAMI no longer needs to agree to pay the list price of the guest country, as the reimbursement will be according to the Belgian list price. However, if the list price in the guest country is higher, the patient will need to cover the difference between the Belgian list price and the list price in the guest country. Especially in the case of ATMPs, this cost might be unrealistically high for the patient.
5. The patient will always have to pay the costs upfront and receive reimbursement upon return to Belgium. In ATMP for rare diseases, this will likely be a blocking barrier.

The lack of predefined conditions for which authorization must be granted, as is the case in the Regulation, and the required patient prepayment make the Directive route inoperable in the context of ATMP treatments abroad.

2.4. Belgian parallel procedures: Special Solidarity Fund

A summary of this route

Belgium introduced the Special Solidary Fund (SSF) in 1990 as an additional safety net on top of the regular health insurance system. The Solidarity Fund has a separate annual budget to provide financial compensation for medical treatments of severe conditions. You can apply for the SSF in specific instances, including the need for treatment abroad.

As described in Art. 25sexies of the coordinated Law of 14 July 1994, a SSF application must simultaneously meet a list of criteria to receive a grant. Treatment must be expensive, proven to be effective, beyond an experimental stage, the only acceptable alternative (within a medically acceptable timeframe), prescribed by a specialist (and possibly confirmed by a second specialist), and be required for a life-threatening condition.

Use of this route and implications in rare diseases

It seems feasible to meet the abovementioned criteria in ATMPs for rare diseases. It is not required for a product to be reimbursed in Belgium to qualify for financial compensation through the Solidarity Fund. Figure 5 shows the treatment pathway for this route.

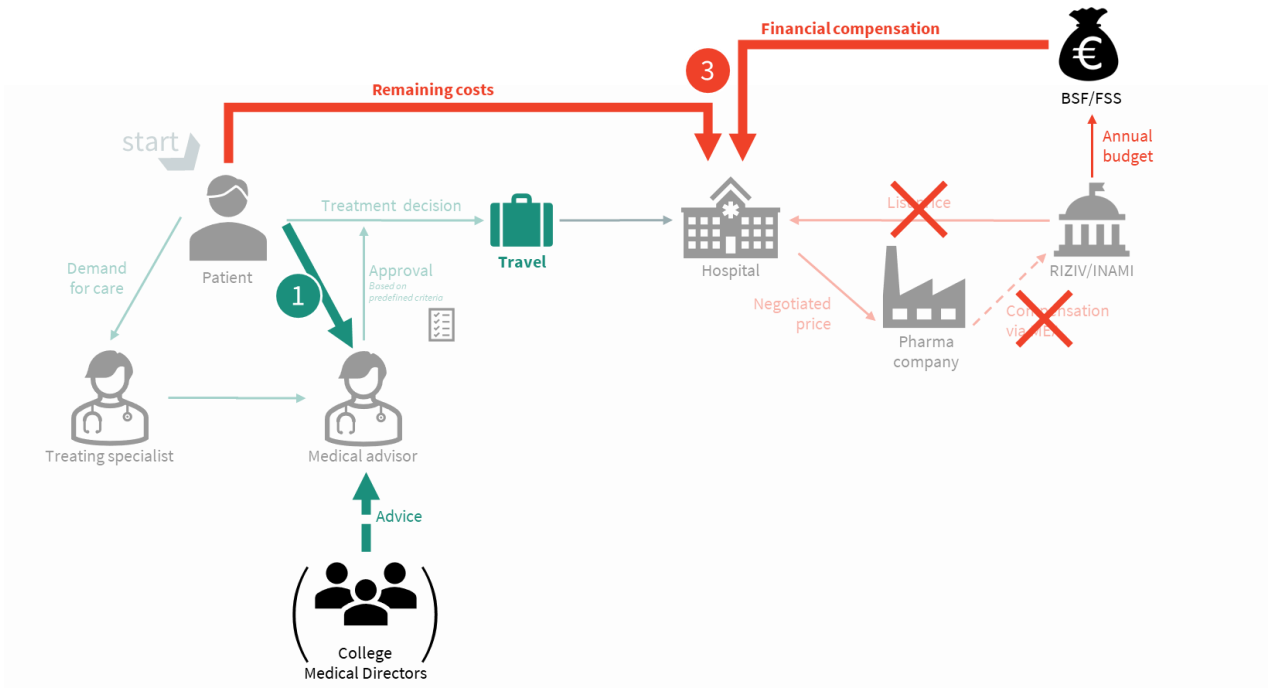

Figure 5. Treatment pathway (blue arrows) and financial streams (red arrows) for cross-border healthcare via the Special Solidary Fund (in comparison with a situation where treatment would be provided in Belgium).

As before, specific issues are apparent, which again include:

1. The patient being the initiator,
2. Lack of support from a designated college.
3. The financial streams are pretty straightforward, although it should be borne in mind that the monetary compensation might only cover a part of the costs.

Following the SSF route, it looks like several issues might be resolved. For example, the SSF can (partially) cover travel and accommodation costs. However, the current yearly budgets appear insufficient to cover ATMP treatments. In 2018 the budget was set at 4.4 million euros, and actual expenditures amounted to 2.8 million euros. As shown in Figure 6. Expenditures of the Belgian Solidarity Fund for treatments abroad., there was already a substantial increase in the approved requests for cross-border healthcare between 2016 and 2018. In 2018 16 patients received financial compensation from the BSF for treatment abroad. The funding covered in total €74,384 (7). On average, this comes down to €4,649 per patient.

Hence, funding of ATMPs for rare diseases via the BSF would require a significantly increased budget, even if the number of cases remains low. And even with an increased yearly budget, this route might not provide a sustainable solution, given the nature of the BSF being an additional failsafe rather than a structural solution.

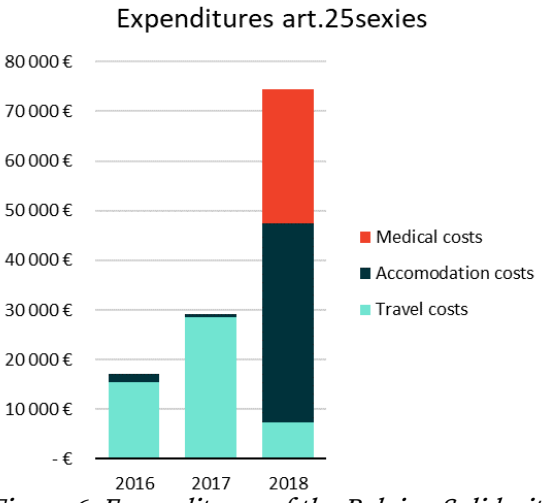

Figure 6. Expenditures of the Belgian Solidarity Fund for treatments abroad.

Belgian parallel procedures: Hadron therapy, a separate Royal Decree

A summary of this route

Proton beam therapy is a form of hadron therapy. It is an innovative radiation technique that delivers proton particles instead of the X-rays used in conventional photon radiotherapy. The main advantage of proton therapy is its precision, which results in almost no radiation of the normal (healthy) tissue surrounding the tumor. This could lead to reduced side effects (8).

Although this does not consider a pharmaceutical treatment, the example is relevant in cross-border healthcare and ATMPs for rare diseases. Proton therapy needs to be provided in a specialized center, of which only one is available in Belgium. Together with RIZIV/INAMI/NIHDI, there is a partnership between five specialized centers in Leuven (Belgium), Orsay (France), Heidelberg (Germany), Villigen (Switzerland), and Essen (Germany).

Hadron therapy is not included in the standard nomenclature. Instead, a Royal Decree was created to enable the compulsory Health Care Insurance in Belgium to grant financial contributions for proton therapy in one of these centers. Treatment-, travel- and accommodation costs are covered for patients that meet the predefined eligibility criteria and are referred by one of the certified radiotherapy centers following a fixed referral procedure. A fixed financial contribution is also foreseen for the referring radiotherapy center to cover administrative work related to the referral. Authorization decisions are handled by the Agreement Counsil.

The initial Royal Decree was in effect for three years (from October 2017 until September 2020). A new Royal Decree has been published, extending this regulation for another three years (until September 2023)[1]. The annual budget envelope used to be fixed at a maximum of €3.9 million, but the renewed Royal Decree no longer defines a yearly budget. Figure 7 provides a visual overview of this route.

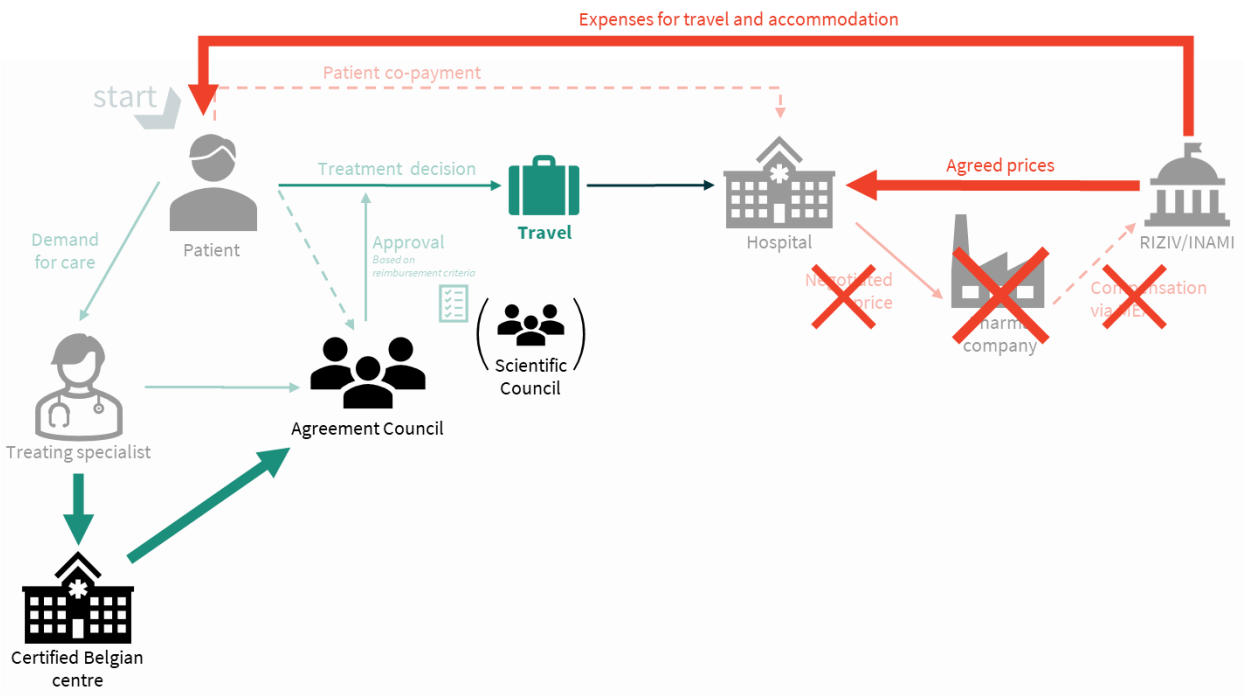

Figure 7. Treatment pathway (dark arrows) and financial streams (yellow arrows) for cross-border healthcare in the context of hadron therapy.

[1] https://www.asgb.be/node/17144

Use of this route and implications in rare diseases

This arrangement was put into effect because the therapy was unavailable in Belgium, although a treatment center was being built in Leuven starting in 2016. The first patients were treated in the proton therapy center in Leuven in 2020.

The specific national regulation continues to exist, as a small number of patients still need to be referred to the other centers. Examples are patients that need carbon ion therapy (another type of hadron therapy, not available in the Belgian center) or treatment of ocular melanoma that requires specific equipment.

The context of this legislative route slightly differs from the context of ATMPs, in a sense that its use would essentially diminish over time as the center in Belgium was under construction when the Decree was put into effect. For ATMPs, the need for treatment abroad is only expected to increase.

2.5. Belgian parallel procedures: (Bilateral) agreements

A summary of this route

There are several agreements between Belgium and its neighboring countries to facilitate healthcare access for patients living in border areas. Examples are ZOAST (Zone Organisée d'Accès aux Soins Transfrontaliers, a contract between Belgium, France, and Luxembourg) and the Ostbelgien-Regelung[2] (an agreement between Belgium and Germany).

These agreements further build upon the Regulation route (i.e., authorization via the S2 form) but impose additional conditions under which the administrative procedures can be simplified and thus accelerated. For ZOAST and the Ostbelgien-Regelung, conditions are mainly related to location (both the patients' residence and the location treatment is provided) and type of treatment (e.g., the Ostbelgien-Regelung only applies to specialist care).

Use of this route and implications in rare diseases

These agreements are significant, as the number of issued S2 forms for Belgium under these agreements is more than 30-fold that of S2 forms issued solely under the Regulation (7228 vs. 208 issued S2 forms in 2019).

The healthcare context for people living in border areas differs from ATMPs for rare diseases, where people will not necessarily receive treatment in a nearby center. However, previously identified issues under the Regulation could be addressed in a bilateral agreement between two or more countries, with or without an exhaustive list of participating centers. Although it has been argued that bilateral agreements do not bring long-term solutions, as they occur on a case-by-case basis (9), an agreement can be a viable approach to address short-term needs.

[2] https://ostbelgienlive.be/desktopdefault.aspx/tabid-6225/

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