

ARM recommendations on cross-border and regional access to Advanced Therapy Medicinal Products (ATMPs) in Europe

Advanced Therapy Medicinal Products (ATMPs) include cell therapies, gene therapies and tissue engineered products. These highly complex treatments differ from traditional medicines, both in terms of how they are made, administered and work and the type of benefit they provide. ATMPs have an extraordinary potential to offer durable, life-changing solutions for patients with few or no therapeutic alternatives. Some gene therapies, for example, address the root cause of disease, offering the prospect of a cure after a single administration. Cell therapies and tissue-engineered products are sometimes manufactured specifically for an individual, creating a highly tailored medicine with potentially transformative benefits for the patient.

On 8 July 2019, The Alliance for Regenerative Medicine (ARM) published recommendations for timely access to ATMPs in Europe (see [here](#)). The consensus report recommended a number of key measures, including:

- A quick adoption of new payment models such as conditional reimbursement, pay-for-performance, and annuity-based payments
- ATMP-dedicated funds, allowing health systems to invest in ATMPs that offer the potential for long-term benefits
- Better-adapted health technology assessment (HTA) methods, including greater use of real-world evidence (RWE) and development of infrastructure required to collect and use high-quality RWE
- Expansion of opportunities for early dialogue between ATMP developers and payers, supported by increased EU funding
- Development of pan-European initiatives to ensure timely and effective access to cross-border healthcare for patients

This position paper focuses on and further elaborates on the recommendations for the timely and effective access to cross-border healthcare for patients. It represents the views of ARM membership and aims to stimulate debate and reach consensus on solutions to ensure all European patients can get access to ATMPs irrespective of the country or region they live in.

Background

Not all ATMPs are expected to be available in all countries in Europe or in all regions of a country:

Due to their specificities and the conditions they aim to address, not all approved ATMPs are expected to be made available to all countries in Europe or to all regions of a given country:

- Approximately half of the ATMPs in development address complex, rare or ultra-rare conditions. Rare conditions require diagnosis and treatment in specialized centers. Ultra-rare diseases affect only a few patients per year in Europe and require highly innovative treatments and a concentration of knowledge and resources that may not be available in all European countries. In some small Member States such as Malta, Luxembourg, Cyprus, but also some larger ones like Slovenia, Estonia, Denmark, the epidemiology of rare diseases may not support the maintenance of an expert ATMP treatment center. In these cases, patients would be treated abroad while the ATMP would not be available locally.
- In some cases, ATMPs need to be administered using special devices or surgical procedures, and/or may need to be administered by trained/certified healthcare providers or in highly specialized centers, not necessarily available in all countries. Regulatory authorities in Europe may require a qualification of the treatment centers by Marketing Authorisation Holders.
- A safe administration of ATMPs typically require experienced clinical teams, managing a large number of patients in order to develop and maintain their expertise, for instance in managing potentially severe side-effects.
- All the above is especially relevant for autologous therapies, that are short-lived and require a dedicated logistical setup.

For all these reasons, ATMPs can only be administered in specialized and qualified centers meaning that patients must relocate to a different region or even a different country to receive the treatment they need.

Legal frameworks granting the right to cross-border treatments for patients in Europe:

Patients in the European Union (EU) or in the European Economic Area (EEA) have the right to access medical diagnosis, treatment, or prescription in any other EU/EEA country or Switzerland¹ and be treated abroad. In theory, European patients should be eligible for treatment in any other EU/EEA country or Switzerland and be reimbursed for all or part of its cost if they were travelling to or working in these countries or if a given treatment was not available in their home country. The reality, however, is quite different and considerably more complex.

Two different routes exist for accessing healthcare abroad and enjoying assumption of costs by the national health service/health insurance provider under European law:

- 1) Social Security Regulations (EC) 883/2004 and 987/2009
- 2) Directive 2011/24/EU on patients' rights in cross-border healthcare

The range of covered healthcare services, the conditions to access medical treatment for planned treatments abroad, i.e. when healthcare is the reason for the travel abroad, as well as the financial implications differ under both routes:

¹ Cross-border healthcare in Switzerland is excluded from the Directive 2011/24/EU route. As a result, under EU law patients are only entitled to reimbursement for cross-border healthcare in Switzerland under the Social Security Regulations (EC) 883/2004 and 987/2009. Besides, in some cases patients may have additional rights and entitlements to treatment in Switzerland under national law.

Under the Social Security Regulations (EC) 883/2004 and 987/2009, patients are entitled to assumption of costs for the treatment in another EU/EEA country or Switzerland as though they were insured under the social security system of that country. In order to be entitled to reimbursement, patients receiving planned care abroad will need prior approval from their national health service/ statutory health insurance provider. Prior authorisation is granted on issuance of the European S2 form (old E112 form).

Under Directive 2011/24/EU on patients' rights in cross-border healthcare, patients are entitled to assumption of costs for treatment in any EU/EEA country² as though the treatment was provided in their home country. For some planned treatments abroad Member States have the possibility to install a system of **prior authorisation**. In particular, for healthcare involving an overnight hospital stay and healthcare involving highly specialised and cost-intensive medical infrastructure or equipment. Member States decide, at their discretion, which specific treatments they subject to prior authorisation, resulting in a different set of rules in each Member State. Upon prior-authorisation, patients³ initially pay all medical costs upfront. Upon return home, patients may file for reimbursement with their national health service/ health insurance provider who will reimburse them according to the domestic tariffs applied for the same treatment at home.

The main differences for planned medical treatment (i.e. when healthcare is the reason for the travel abroad) between both frameworks are summarized in the table below:

	Social Security Regulations (EC) 883/04 and 987/09	Directive 2011/24/EU on patients' rights in cross-border healthcare
General principles	Direct assistance - The health services are paid directly as if the patient is insured by social security system of that country.	Indirect assistance - The patients have to pay for treatments and then to request reimbursement in the form of a refund in their home country upon submission of proof of payment. The refund will be assessed as though the treatment were provided in the patients' home country
Variability by country	Regulations impose the same process, requirements, and conditions in all countries.	The national implementations may be different, with additional rules specific to countries
Need for prior authorization?	Yes, prior authorisation from home country required (S2 Form). Cannot be refused if treatment in the home country cannot take place within a time limit medically justifiable	No, for a wide range of treatments. Prior authorisation should be an exception, not the rule, however it may be required before travelling for healthcare involving an overnight hospital stay and healthcare involving highly specialised and cost-intensive medical infrastructure or equipment (like in the ATMP case)
Costs covered & tariffs	The S2 form covers treatment costs (i.e. drugs) + clinical costs (i.e. DRG if hospitalised/clinical	Costs covered are based on home country tariffs, with country to country variations.

² Directive 2011/24/EU does not apply to cross-border healthcare in Switzerland

³ For reference, please see MANUAL FOR PATIENTS released in March'19 by the EC

	services). Costs are based on tariffs in the treatment country Logistics (i.e., travel & lodging) are not covered and are managed case by case by the insurance, social assistance, etc.	Travel and lodging are typically not covered, as well as long term care, organ transplantation, and public vaccination programmes.
Eligible healthcare providers	Covers only public providers. Private providers are usually not covered except if contracted or affiliated to the social security scheme and entitled to provide services covered under the social security legislation	Covers all healthcare providers in the EU, public or private

National Contact Points (NCPs) are country organizations advising patients and interested parties on both legal paths, since these two legal frameworks may have specific applications in the State where the patient is insured and they can be supplemented.

In both frameworks, the national authorities may not refuse to reimburse costs if the patient is entitled to this treatment in his/her home country and the treatment cannot be provided on its territory within a time limit which is medically justifiable.

However, as noted in the Manual for Patients published by the European Commission, as national health services or health insurance providers decide, at their discretion, whether or not authorisation for treatment abroad is granted, patients with rare diseases may be offered the possibility under the Social Security Regulations (EC) 883/2004 and 987/2009 to seek treatment in another EU/EEA Member State or Switzerland even for diagnosis and treatments which are not available in the patient's home country. As long as the treatment concerned is covered in the country of treatment prior authorisation may be granted.

Applicability to ATMP treatments:

Due to the upfront payments imposed by the Cross-border Healthcare Directive, cross-border treatment regulated by the Social Security Regulations (EC) 883/04 and 987/09 is currently the only practical option for cross-border treatment with ATMPs. Indeed, it would not be feasible for patients to bear the total costs of their treatment and then only subsequently seek reimbursement. Yet, this model also presents some flaws. First, travel and accommodation costs incurred by patients and their families are not reimbursed. In addition, the need for payer of origin's prior authorization can potentially slow-down or even prevent access to life-saving and other urgent healthcare treatments. In particular, there may be difficulties when the ATMP is not included in the basket of care in the home country despite being in the basket of care in the treatment country, even in the case of rare diseases. In some cases, health technology assessment and reimbursement decisions cannot take place if the product is not available in the home country.

Moreover, the European law does not address national issues in countries with regional budgets, such as Italy or Spain. In these countries, the budget of the region where treatment is provided may be unable to accommodate the costs for treating patients coming from other regions in the country.

Lastly, cross-border is today not compatible with some existing pricing models – such as clawbacks or annual rebates that are accounted for by payers in the treatment country, not taking into account that costs for cross-border patients are borne by payers in the home country.

ARM recommendations:

In order to ensure that patients across in Europe can access ATMP treatment, ARM recommends the following:

1) Creation of a one-stop shop coordination body at EU/EEA level

A one-stop shop coordination body could be established at EU/EEA level to act as a broker between the different stakeholders and facilitate cross-border patient treatment and funding. This body would perform assessments of cross-border treatments and determine if they are justified based on factors, including rarity of the condition, logistics issues, training or other qualifications for health practitioners, lack of other treatments providing similar benefit (based on pan-European assessment of the therapeutic benefit), etc. The coordination body would also help facilitating the conclusion of agreements between marketing authorisation holders, payers and treatment centres, detailing the potential market entry schemes and compensation mechanism in effect in the treatment center, potentially including considerations for the long-term follow-up. Such an entity would centralize and speed up the approval of S2 Forms to ensure patients can get timely access to their treatment. Finally, it could agree on the conditions and the compensation for the additional travel or accommodations for patients. Ultimately, this system would reduce financial uncertainty for treatment centers and eliminate payment delays.

2) Creation of one-stop shop in countries with regional funding or with multiple payers/insurers

Similarly to recommendation 1, in healthcare systems where funding is regional, rather than centrally-based, treatments could be managed via a one-stop shop, possibly leveraging the National Contact Point, to compensate authorities in the region of treatment for the costs of treating patients from other regions. This initiative would also reduce financial uncertainty for treatment centers and eliminate payment delays. One further measure would be to expand or/and leverage existing national funds, e.g. the innovation fund in Italy or cancer fund in the UK.

In a similar way, where multiple payers/insurers exist within a country, a single contact point, such as a body representing all payers/insurers within that country, would be helpful to anticipate potential difficulties when patients change from payer/insurer over time. This point is relevant for ATMPs due to their long-lasting, potentially life-long, effect.

3) More effective coordination of HTA activities

In order to ensure greater alignment within Europe on the product value assessment, it is proposed that Health Technology Assessments activities be coordinated in a more effective manner across countries. One proposal is to create a single clinical assessment with mandatory adoption by EU countries as foreseen in the original EC proposed HTA Regulation on health technology assessment and amending Directive 2011/24/EU (COM (2018) 51 final). ARM believes that the adoption of a joint clinical assessment, with no repetition of the assessment of aspects dealt with in the joint clinical assessment at national, regional or local levels, will build a common understanding on the product value across Europe, facilitating the decision to

have patients travelling to a different country to be treated with an ATMP not available in their home country.

Additionally, post-launch evidence requirements of the EMA and HTA bodies should be better aligned across the EU, bringing about greater harmonization across countries on the real-world-evidence and data to be collected post-launch. This is aligned with the consensus recommendation to develop pan-European initiatives to build real-world-evidence infrastructure, as detailed in the EU Market Access Report published in July 2019.

4) Additional measures

Opportunities for cross-country collaboration should be improved to deliver faster and broader access. Removing duplicative processes at national level and adopting policy principles to enhance cross-country collaboration would facilitate industry engagement in existing initiatives⁴.

Finally, cross-border treatments should be excluded from claw-back or other pay-back mechanisms that may be in place in the treatment country. Such pay-back mechanisms are indeed typically based on pharma expenses/sales in the country for 'national' patients. Additional transparency on the number and type of treatment provided for cross-border patients would therefore be warranted.

About the Alliance for Regenerative Medicine (ARM)

ARM is an international multi-stakeholder advocacy organization that promotes legislative and regulatory initiatives to facilitate access to life-giving advances in regenerative medicine worldwide. ARM comprises more than 350 leading life sciences companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapy community. ARM is the leader on the sector's most pressing and significant issues, fostering research, development, investment, and commercialization of transformational treatments and cures for patients worldwide.

To learn more about ARM, visit <http://www.alliancerm.org>.

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⁴ See also: [Efpia 'Policy Principles on Cross-country Collaborations on Medicines' Pricing and Access'](#)