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CROSS-BORDER HEALTHCARE FOR RARE DISEASES PATIENTS

WHAT CAN BE DONE?

A Position Paper developed by the EUCOPE Gene & Cell Therapies Working Group

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2. EXECUTIVE SUMMARY

The complexities related to delivering some Advanced Therapy Medicinal Products (ATMPs) most likely will require highly specialized clinical expertise and infrastructures, which currently do not exist in all EU counties. Therefore, relocating or **crossing borders often represent the only solution for many patients**.

A well-developed and highly functioning cross-border healthcare framework at the EU level is essential to provide patients with access to needed life-saving and life-transforming therapies.

In theory, all EU citizens have the right to access healthcare in any EU country and to be reimbursed for care abroad by their home country[1], as per the *European Commission Directive 2011/24 on patients' rights in cross-border healthcare* (the Directive). In practice, this is not the case, and 10 years after its adoption, it is fair to say **the Directive has fallen short of its primary objective**.

[1] https://ec.europa.eu/health/cross_border_care/overview_en, accessed 3 March 2021.

The Directive foresees a **pre-payment for treatment by patients**, which is not an equitable viable option in the case of ATMPs, where both the treatment's and related costs can be high and **represent an obstacle for patients and carers**.

This **system of prior authorisation**, when the Member States of origin can decide which planned treatment is required/available for their patients seeking care abroad, **creates an unequal situation between Member States, and eventually between patients in Europe**.

This is why, today, most patients seeking treatment for ATMPs abroad use the provisions of the EC Social Security Regulations 883/2004 and 987/2009[2] (the S2). However, this route is far from ideal.

Patients seeking treatment under the S2 pathway will **face a complex approval process with variable timelines**. Time delays can be **a major obstacle to potentially life-saving and life-transforming treatments**, with potentially significant consequences for patients.

Together with our members, EUCOPE calls for far greater collaboration between **the EU institutions, Member States and all related stakeholders to come with practical solutions to facilitate cross-border healthcare for patients in need of an ATMP treatment**.

This paper provides a set of recommendations, targeting the S2 Route and the Directive, with a long-term and sustainable approach to **ensure the cross-border framework finally becomes suitable for patients with rare and ultra-rare conditions**.

3. INTRODUCTION

Advanced Therapy Medicinal Products (ATMPs) are medicines for human use that are based on genes, tissues or cells. They offer ground-breaking new opportunities for the treatment of disease and injury[3], bringing with them the promise not only of treatment to manage the symptoms of severe, disabling or life-limiting conditions but also the promise of one-time disease-modifying and potentially curative treatments, in addressing the underlying genetic cause of a disease.

Due to their specificities, the technology used and the conditions they aim to address, some ATMPs may require specialist manufacturing and patient treatment processes and not all can be administered in all hospital settings. Highly specialised or qualified treatment centres are most likely needed, and administration by specialist doctors and nurses with specific training will be required.

ONLY A SMALL NUMBER OF SPECIALISED CENTERS

[2] https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32009R0987, accessed 3 March 2021.
[3] https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview, accessed 18 March 2020.

The complexities related to delivering some ATMPs most likely will require highly specialized clinical expertise and treatment centre infrastructures, which currently do not exist in all EU counties. For countries without such expertise, patients likely need to be treated in another country. Relocating or crossing borders often represent the only solution for many patients, whether they live in a country where the conditions' prevalence is low, or in a country where the treatment is not (currently) available.

A well-developed and highly functioning cross-border healthcare framework at the EU level is therefore essential to provide patients with access to needed life-saving and life-transforming therapies.

4. THE CURRENT EU FRAMEWORK NOT FIT FOR ATMPS

In theory, all EU citizens have the right to access healthcare in any EU country and to be reimbursed for care abroad by their home country[4]. This was the aim of the *European Commission Directive 2011/24 on patients' rights in cross-border healthcare* (the Directive). In practice, this is sadly not the case, and 10 years after its adoption by the European Parliament and Council, it is fair to say the Directive has fallen short of its primary objective. We strongly encourage the Commission to use the ongoing evaluation of the Directive to assess the current and future needs of patients in cross-border healthcare in all relevant pathways and to develop and propose concrete solutions that will improve the efficiency of the framework in order to meet its primary objective.

DIFFERENT ROUTES

Today, patients seeking treatment for ATMPs abroad use the provisions of the EC Social Security Regulations 883/2004 and 987/2009[5] (commonly known as the S2 Route). However, as described further below, this route or pathway for accessing medicines across borders is far from ideal. Moreover, while bilateral agreements between countries are possible to allow for cross-border patient access, they occur on a case-by-case basis and usually only offer short-term solutions to patients in need.

5. THE DIRECTIVE: INAPPROPRIATE FOR GENE AND CELL THERAPIES

The Directive foresees a ***pre-payment for treatment by patients***, which is not an equitable viable option in the case of ATMPs, where both the treatment and related costs (covering travel, accommodation, multiple visits to the centre of treatment on a case-by-case basis based on the social assistance provided in each country) can be high and represent an obstacle for patients and carers. As highlighted in the 2019 Special

[4] https://ec.europa.eu/health/cross_border_care/overview_en, accessed 3 March 2021.
[5] https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32009R0987, accessed 3 March 2021.

Report of the European Court of Auditors on EU actions for cross-border healthcare[6], it would not be reasonable to ask patients for an upfront payment and then subsequently ask for a reimbursement.

This system of ***prior authorisation***, as designed by the Directive, when the Member States of origin can decide, at their discretion, which planned treatment (involving an overnight hospital stay[7] and highly specialised equipment) is required/available for their patients seeking care abroad, creates an unequal situation between Member States, and eventually between patients in Europe.

In addition, and despite demonstrating significant added value to patient diagnosis and research on rare diseases in the EU, the ***European Reference Networks (ERNs) are under-utilized*** when it comes to accelerating patient access to care. This has been highlighted in EURORDIS's recent Policy Brief on ERNs, identifying the need for clearly defined cross-border referral and patient pathways connecting each Network with the EU27 healthcare systems[8]. These ERNs should also have a mechanism in place which allows them to be connected and work with specialised treatment centres, administering the ATMPs.

Each Member State has a so-called National Contact Point (NCP). In theory, these NCPs are there to assist patients with creating further understanding of the cross-border pathway. In practice, these NCPs, which are often placed in larger national organisations with very different responsibilities, are not well known and difficult to reach.

Finally, another critical shortcoming in the implementation of the Directive is the level of awareness of the relevant stakeholders, in particular patients and physicians. As shown by a 2018 Commission study[9], patients' awareness of their rights and possibilities to access health services abroad and of the existence of National Contact Points is still low, hindering the use of cross-border healthcare in the EU. Patients often have to rely on the work of patient organisations or other stakeholders to relay the necessary information.

6. THE S2 ROUTE IS CURRENTLY THE ONLY VIABLE PATHWAY BUT HAS ITS SHORTCOMINGS

[6] https://www.eca.europa.eu/en/Pages/DocItem.aspx?did=49945 , accessed 3 March 2021.
[7] In case of overnight stay or highly specialized equipment use, the Regulation should anyway be considered first, before looking at the Directive.
[8] https://www.eurordis.org/maturevisionern, accessed 3 March 2021.
[9] Study on cross-border health services: enhancing information provision to patients, June 2018, https://ec.europa.eu/health/sites/health/files/cross_border_care/docs/2018_crossborder_frep_en.pdf, accessed 11 March 2021.

The S2 pathway[10] provided by Regulation 883/2004 and implemented by Regulation 987/2009 is currently the only viable framework to enable patient access to ATMPs in Europe since the home Member State reimburses the treating Member State directly at the cost level of the treating Member State.

Patients seeking treatment under the S2 pathway will, however, face a ***complex approval process*** as they seek prior authorisation for treatment from their home country through an S2 Form. This process has ***variable timelines*** as patient access depends on local approval timelines, which vary by country ranging from a few weeks to several months. Such time delays can be a major obstacle to potentially life-saving and life-transforming treatments, in which even the slightest delay in access can have significant consequences for patients.

In addition, the ***discretionary nature of the approval process*** if the treatment is not directly available in the patient's home country leads to unequal patient access around Europe. Obtaining authorisation will often be dependent on the inclusion of the therapy in the home country's basket of care[11]. This is often not the case for cell and gene therapies and other ATMPs as HTA and pricing/ reimbursement decisions cannot take place if the product is not available locally[12].

Finally, the lack of clarity or awareness on how to obtain/request reimbursement results in some stakeholders putting the responsibility of reimbursement onto manufacturers or hospitals/providers in the treating country, involving additional administrative burden, financial constraints, and likely delays in patient care.

7. RECOMMENDATIONS

As underlined by a couple of initiatives[13],[14], the use and scalability of both the Directive and the S2 Route for planned ATMP treatments abroad, the lack of incentives from healthcare professionals/hospitals to send their patients abroad in addition to the low awareness of patients, impede the effectiveness and practicality of the EU's legislative framework for cross-border healthcare. Each pathway presents important hurdles and obstacles preventing patient organisations, healthcare professionals and companies to prepare for their use; improvements must be made to assist with patient access and further resources should be given to the NCPs for them to play the critical role of advising patients on the best route.

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[10] Manual for Patients, Patient's right to accessing healthcare in any EU*/EEA* country, European Commission, https://ec.europa.eu/health/sites/health/files/cross_border_care/docs/2019_ncptoolbox_manualpatients_en.pdf, accessed 11 March 2021.
[11] Cross-border healthcare in the EU under social security coordination - Reference year 2018 https://ec.europa.eu/social/BlobServlet?docId=22295&langId=en
[12] For example, an ATMP for a very rare disease may not be offered to go through the formal HTA/P&R procedure of a country as there are either no patients or the No of patients is so small that it does not make sense to mount a whole HTA procedure.
[13] https://rareimpact.eu/challenges-solutions/european-level, accessed 3 March 2021.
[14] http://alliancerm.org/wp-content/uploads/2020/01/ARM-cross-border-final-230120.pdf, accessed 4 May 2021.

For the existing framework for cross-border healthcare to realise its full potential, it is paramount to address the low patient and physician awareness and the shortcomings in information provided to patients and physicians alike. To that end, we recommend the establishment of **a European one-stop-shop** and **unified single source of reliable, accessible information**, in coordination with the ERNs, to increase process transparency and help patients, their associations and other relevant stakeholders navigate the framework in place.

S2 ROUTE

- **European Commission guidelines** setting acceptable and harmonised review and approval timelines to expedite time-to-treatment in the EU;
- Support **harmonised HTA approach for ATMPs for rare / ultra-rare diseases** at the EU level that accounts for evidentiary uncertainties of ATMPs developed for small patient populations requiring qualified treatment centres, including limitations of clinical trial design and long-term data. Additionally, HTA assessors should have expertise in ATMPs, leveraging existing joint HTA assessment initiatives, such as EUnetHTA, to supplement S2 applications and to enable broader access to cross-border healthcare.

DIRECTIVE

- To address the issue of **upfront payment**, the Commission should consider encouraging Member States to implement the **Regulations' mechanism of financial compensation**, introducing direct billing between health institutions, removing the burden of upfront payments[15];
- As the COVID-19 pandemic taught us, closer cooperation between Member States can lead to substantial improvements for European citizens. We call for closer **collaboration between the ERNs** to set up simple and **standardised care pathways** and adequate support to navigate national and cross-border healthcare pathways. Such collaboration can be supported and funded by the European Commission.

LONG-TERM VISION

- Enable **innovative payment models** in a cross-border healthcare setting, especially in the context of bilateral and regional collaborative initiatives, including annuity-based payments and outcomes-based agreements for ATMPs that extend across borders.
- To **overcome delays at the national level** and ensure timely and easy patient access, EUCOPE strongly advocates for the Member States, the EU Institutions and stakeholders to get together and examine the opportunity and the mechanics to set up an **EU fund enabling cross-border**

[15] European Committee of the Regions Draft Opinion, Implementation and future perspectives for cross-border healthcare, 2020, https://webapi2016.cor.europa.eu/v1/documents/COR-2019-04597-00-00-PAC-TRA-EN.docx/pdf, accessed 11 March 2021.

treatment for ATMPs for severe rare and genetic diseases, possibly linked to some risk-sharing provisions - targeting countries with limited budget capacity.

- Develop **European-wide guidelines** on what treatments types[16] should be approved for CBHC to ensure equal access across countries;
- EU Institutions, stakeholders, including payers and insurers alongside patient communities define a clear set of criteria[17] for the applicability of cross-border healthcare to address inequalities in the management and care of the different rare diseases across Member States. In this context and for patient communities and cases that CBHC would be applicable and could offer value;
    - provision of financial and technical support to community initiatives aimed at improving system preparedness for ATMPs uptake (improving infrastructure and site readiness, certification/accreditation of centres) and provide united standards of treatment across EU[18] in order to increase equality and equity of care with ATMPs;
    - provision of EU financial and technical support to implement across countries multi-stakeholder/community-led fit for purpose (e.g. targeting specific rare conditions) pilots aimed at pressure-testing solutions to promote faster and broader access to ATMPs for (rare disease) patients.

EUCOPE – the European Confederation of Pharmaceutical Entrepreneurs

EUCOPE is Europe's trade body for small to medium-sized innovative companies working in the field of pharmaceuticals and medical technologies.

Based in Brussels, EUCOPE gives voice to more than 900 research-orientated innovative companies and associations active in research, development of pharmaceuticals, biotechnologies and medical devices. Many of its members are developing therapeutic solutions for persons living with a rare disease, who had little to no treatment available just a few years ago.

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[16] Conditional on patients pool size. Example: treatments for diseases affecting less than 1 in X patients in the EU get funded through the Special EU fund.
[17] For example: type/severity and prevalence of the rare disease; existence of adequate infrastructure – Centres of Excellence, certified/accredited/specialized centres - in place to support advanced management and care in all countries; level of complexity required for ATMP administration.
[18] See example in Haemophilia https://www.edqm.eu/en/news/haemophilia-new-standards-patient-care-council-europe-resolution