European Alliance for Transformative Therapies

POLITICAL PRIORITIES FOR CELL AND GENE THERAPIES IN THE CONTEXT OF THE PHARMACEUTICAL STRATEGY

CONSENSUS STATEMENT

List of supporting organisations:

Thank you to all stakeholders who contributed to the drafting of this document, in particular Professor Maurizio Scarpa, Director of Regional Coordinating Center for Rare Diseases at Udine University Hospital and Coordinator of European Reference Network for Hereditary Metabolic Diseases (MetabERN), and Mr. Tadej Korosec, President of the European Alliance of Neuromuscular Disorders Associations.

About the European Alliance for Transformative Therapies

The European Alliance for Transformative Therapies is an informal interest group that aims to foster effective dialogue around cell and gene therapies and provide evidence-based policy recommendations to enable patient access. This multi-stakeholder Alliance connects Members of the European Parliament with patient groups, medical experts and associations, healthcare and non-healthcare specialists, scientists, researchers, industry actors and other relevant stakeholders.

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About this Consensus Statement

This Consensus Statement was developed by the European Alliance for Transformative Therapies. Through its Policy Secretariat, the Alliance has gathered multi-stakeholder input to create this political Statement, aiming to highlight the opportunities and challenges around cell and gene therapies. The contents were edited by Yordan Aleksandrov, Bonifac Makkai and Kit Greenop from RPP Group. It includes a Call to Action putting forward high-level recommendations on how initiatives stemming from the Pharmaceutical Strategy and other EU-level instruments should promote access to these transformative treatment options.

A MESSAGE FROM MEMBERS OF THE EUROPEAN PARLIAMENT

Growing innovation in the field of healthcare has fundamental implications for patients across Europe. Transformative cell and gene therapies hold the promise to transform the lives not only of patients who suffer from debilitating and life-threatening genetic disorders, but also their families and friends. This phenomenon is highlighted in the European Commission's Pharmaceutical Strategy, which specifies how advanced medicinal products, such as cell-based and gene therapies offer major therapeutic promise to patients.[1] These therapies, however, face a number of barriers to ultimately reach patients, which range from the lack of adequate healthcare centre capacities to the need for adapted policies, legislative frameworks and appropriate payment models.

The European Union (EU) has a tremendous added value in the field of healthcare, as shown amid the COVID-19 pandemic, and the next several years will be crucial for European healthcare systems to effectively prepare to provide these transformative therapies to patients. In this context, there is a political window of opportunity to rethink the current policy framework:

- The European Commission's Pharmaceutical Strategy offers the possibility for a series of actions cascaded across EU Member States.
- The review of legislation on medicines for children and rare diseases (Orphan Medicinal Products Regulation and the Paediatric Regulation)[2] provide opportunities to improve the therapeutic landscape and address unmet medical needs through strengthened incentives.
- The evaluation of the Cross-Border Healthcare Directive offers an opportunity to address shortcomings in its implementation.[3]

Prompt actions are needed to ensure that patients can benefit from these medical advances and the EU has an important position in this regard. We can help to support and facilitate access to medical innovation through effective policy changes.

Developing and implementing effective policies must also be a collaborative effort of all relevant stakeholders. The formation of the European Alliance for Transformative Therapies and this Consensus Statement are a vital starting point from which to develop the right environment for cell and gene therapies to reach patients as soon as possible.

MEP Claudia Gamon (Renew, Austria)
MEP Ondřej Knotek (Renew, Czech Republic)

Transformative cell and gene therapies represent a new frontier of medicine. They offer hope for many patients, particularly those affected by rare diseases. Gene therapies are a success story of the 21st century, with exciting treatment options in the pipeline for many diseases, such as rare bleeding disorders or different forms of neuromuscular disorders.[4] Likewise, cell-based products are offering new hope for several conditions (e.g. CAR-Ts for certain blood cancers).[5]

Despite this potential, important work remains to ensure that patients benefit from this progress. Patients, many of whom suffer from life threatening disorders with no other real treatment options, worry that access to these therapies may be hindered. New strategies and improved policies are needed to ensure rapid patient access to these transformative therapies.

This document aims to outline the current policy framework for cell and gene therapies, key areas which may act as barriers to patient access, and offer recommendations on how to ensure these treatments reach patients where their life-transforming potential can be realised.

What are cell and gene therapies and how do they work?

Cell and gene therapies have fundamentally different properties than medicines and surgery in that they treat the core underlying genetic causes of a disease rather than treating symptoms.

Cell therapy is the transfer of intact, live cells into a patient to help lessen or cure a disease. The cells may originate from the patient (autologous cells) or a donor (allogeneic cells). The cells used in cell therapy can be classified by their potential to transform into different cell types. Pluripotent cells can transform into any cell type in the body and multipotent cells can transform into other cell types, but their repertoire is more limited than that of pluripotent cells.[6]

Gene therapy is the use of genetic material to treat genetic diseases. This may involve adding or replacing a wild type copy of the gene (gene addition or gene replacement) or altering a gene with mutation to the wild type gene (gene editing). The treatment may take place outside of the body (ex vivo) or inside the body (in vivo).[7]

What is the current legislative/regulatory framework applicable to cell and gene therapies?

Cell and gene therapies are classified by the European Medicines Agency (EMA) as Advanced Therapy Medicinal Products (ATMPs). ATMPs is a large category also comprising tissue-engineered medicines, in addition to cell and gene therapies.

All advanced therapy medicines are authorised via the EMA. They benefit from a single evaluation and authorisation procedure.

The overall **legislative** framework for cell and gene therapies is provided by the Regulation 1394/2007 on Advanced Therapy Medicinal Products.

The European Directive 2009/120/EC (amending Directive 2001/83/EC) updated the definitions and detailed scientific and technical requirements for gene therapy medicinal products and somatic cell therapy medicinal products.

If an ATMP is also an Orphan Medicinal Product (OMP), then the EU Regulation 141/2000 on OMPs applies.[8] Furthermore, the Blood, Tissues and Cells Directives[9] as well as the Genetically Modified Organisms Directives[10] must also be taken into account during the development and manufacturing of certain cell and gene therapies.

What potential barriers do cell and gene therapies face and what can European and national policymakers do to ensure that transformative therapies reach patients?

The European Commission's Pharmaceutical Strategy recognised that cell-based and gene therapy products offer major therapeutic potential to patients. Despite this, there is a growing realisation that health systems may not be prepared for these treatments. In the context of the Pharmaceutical Strategy and developments relating to other EU-level policies (such as the Orphan Medicinal Products revision and the Cross-Border Healthcare Directive evaluation), certain actions should be taken to promote the uptake of and access to transformative treatment options. The following six points represent a **Call to Action to European decision-makers**.

Clinical Trials

Need:
Reinforce a competitive clinical trials framework in Europe for cell and gene therapies

Recommendations:
- Facilitate effective discussions between national authorities and stakeholders involved in clinical trials of advanced therapeutic medicinal products (ATMP) to reduce regulatory burden and safeguard Europe's innovative competitiveness.
- Reduce burdens on clinical trials of ATMPs containing or consisting of Genetically Modified Organisms (GMOs) by exempting them from GMO requirements.

Innovative payment models

Need:
Disseminate best practices on innovative payment models that can support national governments to increase patient access to transformative therapies

Recommendations:
- Identify where innovative payment models have already been successfully implemented securing access to these therapies.
- Share information on innovative payment models such as outcome-based agreements which can play an important role in providing payers with the needed confidence to invest in transformative therapies.

Infrastructure

Need:
Enhance the infrastructure for the provision of cell and gene therapies in Europe

Recommendations:
- Launch funding opportunities within existing programmes, such as Horizon Europe or the European Regional Development Fund, to adapt infrastructures to enable the provision of cell and gene therapies.
- Set-up or tailor European funding programmes to promote cross-disciplinary and patient-centred education for healthcare professionals on cell and gene therapies.

Cross-border patient access to therapies

Need:
Enable cross-border patient access to transformative therapies

Recommendations:
- Address shortcomings (e.g. upfront payments) of the Cross-Border Healthcare Directive in its foreseen evaluation.
- Address the challenges of the S2 Regulations[11] (such as the variability of timeline approvals between countries), which negatively impact patient access.

Health Technology Assessment

Need:
Promote the development of appropriate Health Technology Assessments (HTA)

Recommendations:
- Call on Member States to re-assess their current HTA methods to ensure that they are appropriate for the specificities of cell and gene therapies – including for rare diseases – and consider new methods for evidence generation and assessment.
- Increase stakeholder collaboration, including patient groups, to agree on core data requirements and support policy action to produce high-quality data including Real World Evidence, a critical factor for the approval of cell and gene therapies.
- Strengthen and harmonise patient registries for cell and gene therapies through effective policies.

Innovative ecosystem

Need:
Promote a modern innovation ecosystem with effective incentives

Recommendations:
- Recognise the progress of transformative therapies in the rare disease space and further strengthening incentives that may increase innovation for the benefit of European patients.

Recommendations

- Facilitate effective discussions between national authorities and stakeholders involved in clinical trials of advanced therapeutic medicinal products (ATMP) to reduce regulatory burden and safeguard Europe's innovative competitiveness.
- Reduce burdens on clinical trials of ATMPs containing or consisting of Genetically Modified Organisms (GMOs) by exempting them from GMO requirements.

One key indicator of Europe's competitiveness in medical innovation is the extent to which the EU attracts clinical trials for Advanced Therapeutic Medicinal Products (ATMPs), including cell and gene therapies. While Europe was the first region to adopt specific regulation for the development and approval of ATMPs, in recent years the EU's attractiveness has declined compared to the US and Asia. The US initiated three times as many ATMP clinical trials as the EU between 2014 and 2019 which is due – in part – to the legislative framework of the Clinical Trial Directive, which entered into force almost 20 years ago[12] , as well as the GMO Directives[13], which disincentivises ATMP clinical trials in Europe.

The primary challenge is that the currently applicable Clinical Trials Directive gives Members States a certain amount of freedom in how they implement it, which results in discordance in how countries conduct ATMP clinical trials. This is a key challenge for cross-country trials and has decreased Europe's attractiveness in the field. The EU Clinical Trials Regulation[14], which was adopted and entered into force in 2014, will provide common and harmonised rules for conducting clinical trials to test the safety and efficacy of medicines in the EU[15]. The European Commission has clarified that the Regulation will be applied once an adequately robust IT system has been put in place. This is in line with the European Commission's Pharmaceutical Strategy, which will strive to support innovative trial designs, improve multidisciplinary coordination by also including patients to a greater degree, and ensure regulatory adaptability through an agile system of assessment.

Europe's attractiveness for conducting gene therapy clinical trials is further constrained by the Genetically Modified Organisms (GMO) Directives 2001/18/EC and 2009/41/EC. These Directives require that gene therapies containing or consisting of GMOs must conform to complex rules that vary greatly across Member States as they have certain leeway as to how Directives are transposed into national law. Therefore, despite the Clinical Trials Regulation's aim to harmonise and centralise clinical trial processes, the GMO Directives hinder the fulfilment of these aims, especially in the case of multicentre trials spanning across countries. The EU needs to ensure that the GMO Directives do not put additional burden on clinical trials and allow innovation to be pursued unhindered across EU borders. ATMPs that contain or consist of GMOs should be exempted from GMO requirements.

Recommendations

- Identify where innovative payment models have already been successfully implemented securing access to these therapies.
- Share information on innovative payment models such as outcome-based agreements which can play an important role in providing payers with the needed confidence to invest in transformative therapies.

Although EMA authorisation is necessary to market cell and gene therapies in the EU, negotiating adequate reimbursement and pricing mechanisms falls on national level payers to manage bilaterally with companies before such a product becomes accessible to patients in that country.

Traditional payment models are based on cost-per-unit of product or per procedure. While this is a sufficient mechanism for medications that function as a recurring treatment, the novelty of cell and gene therapies lie in the fact that they possess long-term, potentially curative effects with only one or a few doses. These transformative therapies are inherently more costly upfront than traditional medicines due to the intensive research and development as well as manufacturing costs. Understandably, traditional payment models may be suboptimal to support cell and gene therapies as it is often difficult for payers to justify reimbursing such a high upfront cost.

Tackling the affordability issues for health systems should be based on the long-term perspectives of these transformative treatments. ATMPs have the potential to have an impact, not just in terms of improving patient outcomes and reducing burden on carers for example, but also through long-term savings in healthcare budgets and e.g. social security budgets. As such, the value of cell and gene therapy is accumulated over a long period of time[16]. The primary challenge comes from the difficulty of demonstrating long-term benefits and justifying the cost before long-term evidence is available, since many cell and gene therapies have gained EMA authorisation only recently. This is where innovative payment models show value: they facilitate patient access by allowing the necessary flexibility for payers and companies to find jointly acceptable reimbursement solutions. These models, such as most annuity payment models, outcomes-based payment models or risk-sharing agreements include conditionality clauses where reimbursement is tied to specific treatment performance or the company agrees to pay back if the promised outcome is not achieved.[17] [18]

Many patients worry that it may be difficult to access therapies[19]. Patient stand to benefit from the promise of transformative therapies and their perspectives must be taken into account when payers and industry collaboratively seek an adequate financing solution. Patient feedbacks represent an aspect of added value beyond by showcasing the value of potentially living a disease-free life.

Implementing best practices in innovative approaches to payments across Europe can ensure that patients access transformative therapies as soon as possible – which is essential for many who suffer from a disease with no current treatment options or which progresses very fast.

Recommendations

- Launch funding opportunities within existing programmes, such as Horizon Europe or the European Regional Development Fund, to adapt infrastructures to enable the provision of cell and gene therapies.
- Set-up or tailor European funding programmes to promote cross-disciplinary and patient-centred education for healthcare professionals on cell and gene therapies.

Due to the complexity of cell and gene therapies, both in terms of manufacturing and delivery, a certain degree of infrastructural capacity is required for their proper provision. For this reason, these therapies are delivered in certified centres with the necessary infrastructure[20] and specialist knowledge to provide treatment to patients with rare and complex conditions.

The expertise and infrastructure required to provide cell and gene therapies place requirements on healthcare providers. This includes site certification processes which are complex, time-consuming, and resource-intensive, and it may divert scarce resources away from providing care.[21 22 23]

Cell and gene therapies also often require formal training before healthcare professionals have the adequate information to convey the benefits and risks to them and can administer them[24 25] to patients .

Many institutions do not have yet these capabilities, which means further investment is needed to deliver these technologies.[26] This would address patients' concern about treatment centre availability for cell and gene therapies. In addition, many European healthcare systems struggle to secure adequate funds from governments for these investments. For this reason, EU funding initiatives may play a crucial role in preparing health systems to develop the necessary capacities to deliver cell and gene therapies to patients[l].

The current EU framework can provide opportunities to promote training of healthcare professionals - the Horizon 2020[27] and the Horizon Europe[28] programmes as well as the European References Networks (ERN) aim to provide focal points for medical training and research, especially in the field of rare diseases.[29] In addition, collaboration between industry actors (i.e. manufacturers) and non-governmental organisations in creating education pathways for the use and delivery of cell and gene therapies is crucial.[30]

Education efforts must also include collaboration with patients. Understanding rare diseases and the impact that cell and gene therapies will have on patients' life requires their close feedback and cooperation. Patients become experts of their condition over time and this should be welcomed by healthcare teams[31]. Their experiences with gene therapies could provide valuable insights to educate healthcare professionals and provide data for registries, safety and efficacy considerations and quality of life improvements as well as subsequent patient communication about these treatments

l This training is developed by the manufacturer and approved by the national-level authority.
Source: EURORDIS, Rare Impact (October 2020). Improving patient access to gene and cell therapies for rare diseases in Europe - Challenges and solutions for improving patient access to advanced therapies medicinal products at the European Union level.

Recommendations

- Address shortcomings (e.g. upfront payments) of the Cross-Border Healthcare Directive in its foreseen evaluation.
- Address the challenges of the S2 Regulations[32] (such as the variability of timeline approvals between countries), which negatively impact patient access.

Cell and gene therapies are highly personalised treatments with complex manufacturing and distribution processes.[33] Due to their complex nature, many of these therapies will be available in only a small number of treatment centres in Europe[34], as they require operational excellence and trained healthcare providers who adhere to the highest European standards. Consequently, many patients worry about the cross-border accessibility of treatments.

The Cross-Border Healthcare Directive[35] offers the opportunity to address some regional inequalities across Europe. The Directive provides the conditions under which patients can travel to other EU countries to receive medical care, with patients needing authorisation from their home country to be treated abroad. Authorisations are often linked to the list of treatments that are available and reimbursed in the home country. The Directive also requires up-front payment from patients to the foreign healthcare provider[36]. These criteria pose particular challenges for cell and gene therapies (and more broadly for ATMPs) with up-front costs often impossible for patients to cover and limited centres able to provide these treatments. These requirements have also forced patients to seek healthcare abroad under the provisions of the Regulations on the coordination of social security systems (i.e. the S2 Regulations) where up-front payments are not required.[37] The Regulations, however, require bilateral agreements which can pose a number burdens as such agreements do not exist between all countries.

The upcoming evaluation of the Cross-Border Healthcare Directive[38] offers the chance to address some of its shortcomings. The evaluation needs to investigate the approaches implemented by Member States in practice, how effectively these are working and what areas still act as barriers to patients seeking healthcare abroad.

Recommendations

- Calling on Member States to re-assess their current HTA methods to ensure that they are appropriate for the specificities of cell and gene therapies – including for rare diseases – and consider new methods for evidence generation and assessment.
- Increasing stakeholder collaboration, including patient groups, to agree on core data requirements and support policy action to produce high-quality data including Real World Evidence, a critical factor for the approval of cell and gene therapies.
- Strengthening and harmonising patient registries for cell and gene therapies through effective policies.

In the EU, transformative therapies need to be examined through a national health technology assessment procedure, which informs subsequent price negotiations.

While cell and gene therapies have potential long-term (curative) benefits, data on clinical benefit for patients is often short-term and from relatively small trials due to the nature of these conditions.[39] For this reason, there is a need to rethink the current HTA approach and methods in order to assess the value of cell and gene therapies[40]. HTA processes fall short of their purpose especially for rare diseases and in cases where a disease does not have an existing treatment to use as a baseline comparator.

The inclusion of patients in the HTA process is crucial, as their input in the assessment and subsequent reporting leads to results that better meet patients' needs. To this end, documentation produced in HTA assessments needs to be adapted to and made accessible for patients. A better-informed patient is a better contributor.

Finally, patient registries play a key role in providing long-term evidence[II] as they are crucial in the continuous collection of data to underscore the safety and efficacy of treatments after market authorisation. However, healthcare professionals, regulators and companies face a number of challenges in using existing registries, in particular due to the scarcity of coordination in ongoing initiatives at national and international levels and the absence of harmonised protocols, methods and data structures. It is therefore essential that effective interconnectedness is established between the various patient registries, in order to harmonise European patient registries and ensure their benefit in advancing European medical innovation and patient access[41] [42].

II As per the definition of the European Medicines Agency, accessed through the EMA Official Website on 19 November 2020.

Recommendations

- Recognise the progress of transformative therapies in the rare disease space and further strengthening incentives that may increase innovation for the benefit of European patients.

The Orphan Medicinal Products (OMP) Regulation[43] was adopted in 2001 with the objective of improving treatment options for rare disease patients. It has positively stimulated research and development in rare conditions - a field of unmet medical needs.[III] The legal text of the Regulation introduces obligations, incentives, and rewards for the development of therapies for rare diseases.

Despite the positive contribution of the legislation, the European Commission has recognised that the legislative framework has shown a number of shortcomings[44] and needs to be revised to accommodate new transformative therapies. The Commission has decided to evaluate how to better adjust the system of incentives to further increase innovation in areas of unmet medical needs.

The Paediatric Regulation entered into force in 2007. Its objective is to improve the health of children in Europe by incentivizing research and development for paediatric medicines[45]. It has brought more attention to financial investment to paediatric development. This has led to an increase of paediatric research and an increase in the number of new products with paediatric indications. However, the European Commission has concluded that this improvement does not spread among all therapeutic areas but concentrate in areas linked with research priorities in adults[46]. It is precisely because of this reason that the European Commission undertook a joint evaluation of the OMP and Paediatric Regulations and is now looking into the improvement of the two files.

The foreseen revision of the Orphan Medicinal Products Regulation and the Paediatric Regulation[47] is an opportunity to further build on the success of the legislation and to ensure that the incentives framework is reinforced to encourage further research into therapies for conditions with unmet needs.

III Until December 2020, 188 orphan medicines for the benefit of patients suffering from rare diseases. Source: European Commission

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