



**Improving patient access to gene and cell therapies for rare diseases in Europe**

**A review of the challenges and proposals for improving patient access to advanced therapeutic medicinal products in Spain**

**V1**

**January 2020**

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**Reader notes:**

This document contains country-specific insights on challenges and potential solutions to patient access to advanced therapeutic medicinal products (ATMPs) for patients with rare diseases.

The purpose of the document is to provide a starting point for country-specific engagement and discussion within multi-stakeholder meetings.

The challenges and solutions were discussed and prioritised with members of the RARE IMPACT Working Group in meetings and WebEx's between September 2018 and September 2019. Country-specific challenges/solutions have drawn on global recommendations previously published by EUCOPE and ARM, both members of the Working Group.

The challenges and solutions contained within this document are those that have been proposed as priorities for discussion with local stakeholders by members of the Working Group – the report does not include all challenges identified during the secondary research or Working Group meetings.

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## **Executive Summary**

The RARE IMPACT initiative was launched at the European Conference on Rare Diseases and Orphan Products in 2018. It is a multi-stakeholder initiative working to improve patient access to gene and cell therapies (or advanced therapy medicinal products [ATMPs])<sup>1</sup>. This patient-focused initiative aims to both assess challenges and propose actionable solutions to concerns regarding patient access to these transformative rare disease treatments in Europe. Through engagement with health technology assessment (HTA) agencies, regulatory bodies, payers, patient groups, clinicians, manufacturers and other experts across Europe, RARE IMPACT partners have proposed ideas to provide better access to ATMPs in Europe.

A focus on cost-containment and affordability and the de-centralised nature of the pricing & reimbursement system has historically resulted in delays in patient access in Spain when compared with other EU5 countries. However, Spain has been actively addressing its approach to ATMPs and the National Strategy for Advanced Therapies has been put in place to improve access to these therapies. This has resulted in Kymriah and Yescarta being reimbursed much earlier than typically seen for orphan products in Spain.

P&R negotiations at the national and regional level have been focused on cost-containment and the near-term budget impact of the introduction of high-cost drugs. The assessment process in Spain is less rigorous than in other countries and there is no specific route for ATMPs. The opacity in assessment processes adds further to affordability challenges. Combined, these challenges make Spain a less attractive country for manufacturers to launch ATMPs, which is detrimental for patient access.

The model used to assess and grant reimbursement for CAR-Ts seeks to ensure equal access to high-cost medicines in all autonomous regions. The model requires monitoring of therapeutic effectiveness through a centralised procedure. The monitoring allows further information on the outcomes of the treatment to be collected to inform reimbursement discussions. This model could be a template for ATMPs in the future. Alongside providing equitable access, the model seeks to provide reimbursement at a national level for ATMPs. Innovative contractual agreements are not common in Spain, but they have been used for an ATMP in the past (ChondroCelect – payment-by-performance) and the finance models used for Yescarta and Kymriah also point to a willingness to engage in the development of innovative models.

A national level solution is important for ATMPs as otherwise, autonomous regions will conduct HTA processes and these can put greater emphasis on cost-effectiveness than those at the national level. It is likely that regional HTA will pose a major barrier to ATMP access given challenges associated with surrogate endpoints, outcomes, indirect treatment comparisons and evidence quality in rare diseases. Challenges concerning HTA requirements for ATMPs are common to orphan drug assessment generally. Small patient numbers in trials and limited duration of evaluation limits the efficacy and safety data that can be generated at the time of launch.





A focus on cost-containment in Spain could lead to use of hospital exemptions as a means to avoid reimbursement of commercially available products. The hospital exemption may pose a challenge to future patient access as it currently stands (although this issue tends to apply more to cell therapies), where products approved through the central authorisation process of the European Medicines Agency (EMA) may have to compete with products developed under a hospital exemption. This has implications for future product development and patient access to current and future products and undermines the stringent regulatory protocols products with Marketing Authorisation are required to undergo. To address this, the EU could issue guidelines defining more specifically the scope and requirements for hospital

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<sup>1</sup> Medicines for human use developed from genes, cells or tissues are classified as ATMPs by the EMA.

exemptions for ATMPs, stating clearly that when patients have access to an ATMP with a Marketing Authorisation, countries should not authorise hospital exemptions for the same medical indication.

## An overview of challenges and proposals for improving patient access to ATMPs in Spain

Impact	Challenge	Proposed solution	Feasibility
<b>Assessment</b> 	<b>AS1.</b> Regional (de-centralised) reimbursement processes are inconsistent and lack transparency	<b>AS1.</b> Utilise the centralised procedures for assessing gene and cell therapies, rare diseases drugs and oncology drugs	+++
	<b>AS2.</b> Assessment process is not accommodating of data that is generated in trials for ATMPs (e.g., surrogate endpoints, synthetic control arms, indirect treatment comparisons)	<b>AS2a.</b> Utilise managed entry agreements (MEAs) to manage uncertainty in data	++
		<b>AS2b.</b> Involve patients in the assessment process	++
		<b>AS2c.</b> Multi-stakeholder early dialogue to establish expectations for data generation	++
<b>Affordability</b> 	<b>AF1.</b> Spain's focus on near-term budget impact does not capture long-term value of ATMPs	<b>AF1a.</b> Utilise Spain's financing model for high-cost medicines	+++
		<b>AF1b.</b> In absence of an ATMP inclusion in high cost medicines model, use early dialogue to identify the likelihood of reimbursement in regions	+++
<b>Availability</b> 	<b>AV1.</b> Cross-border access is legislated for in Spain; however, the applicability of legislation for ATMPs is unclear	<b>AV1.</b> AEMPS should develop a cross-border access plan for ATMPs	+++
	<b>AV2.</b> Interpretation of the hospital exemption legislation means approved ATMPs may have to compete with products developed under hospital exemption	<b>AV2.</b> EU should be pressed to provide guidelines to prevent marketed products from competing with products with hospital exemptions for the same medical indication	+
<b>Accessibility</b> 	<b>AC1.</b> If not reimbursed centrally, there are inequalities between regions in terms of budget, resource and population size that can impact access	<b>AC1.</b> Cross-regional initiatives may reduce inequalities in patient access	++
	<b>AC2.</b> Regional variation in timelines, criteria and transparency can delay access	<b>AC2.</b> The national agreement used to provide access to Yescarta and Kymriah should be leveraged to avoid delays at the regional level	++
	<b>AC3.</b> Establishing registries can delay adoption	<b>AC3.</b> Early dialogue with the treatment centre, regional and national level administrators	++

**Notes:** \*The working group assessment of the relative impact of the challenge of each domain on patient access is represented by Harvey balls from highest (represented by a full blue Harvey ball) to lowest (represented by an empty, white Harvey ball); \*\*Feasibility: Working Group assessment of feasibility of solutions to be implemented. + low feasibility, ++ medium feasibility, +++ high feasibility.

## **The collaboration**

RARE IMPACT is a collaboration of three not-for-profit organisations, two trade associations and 18 manufacturers of ATMPs brought together by EURORDIS, a non-governmental patient-driven alliance of patient organisations. The overarching objective of the collaboration is to ensure European patients with rare diseases obtain quick access to gene and cell therapies and to create a sustainable model for manufacturers and payers to maintain patient access and innovation. To achieve this objective, the collaboration has established the following goals:

- Identify challenges that are preventing rare disease patients accessing ATMPs
- Propose actionable solutions to address these challenges
- Utilise these ideas within multi-stakeholder discussions within individual countries and in pan-regional forums

## **The approach**

A framework for categorising barriers to patient access was developed and validated by the collaboration. The framework includes four categories, described in Table 1 below.

**Table 1. Framework applied to structuring identified challenges**

Category	Description
Assessment (magnitude of benefit)	Challenges related to the assessment of the benefit of ATMPs within pricing and reimbursement processes. This includes topics such as evidence uncertainty, generating comparative data, use of surrogate endpoints and assessment pathways
Affordability (price, cost and funding)	Challenges concerning the pricing, funding and affordability of ATMPs, including the application of innovative payment models
Availability (legally available)	Non-regulatory challenges to the product being available within countries, such as those related to cross-border healthcare and hospital exemptions
Accessibility (accessible by patients)	Administrative, service capacity and geographic challenges that delay or prevent patient access to ATMPs

## **Identification of challenges and proposals for improving patient access**

Primary and secondary research was conducted to identify challenges to patient access to ATMPs and potential solutions. Secondary research was conducted to create a database of conceptual and country-specific challenges. This research included:

- A targeted literature search
- Reviewing outputs from other initiatives (e.g., ARM's "Recommendations for Timely Access to ATMPs in Europe" and EUCOPE's "Gene & Cell Therapy – Pioneering Access for Ground-Breaking Treatments")
- Assessing pathways through which patients access ATMPs in the countries of interest
- Reviewing HTA and P&R decisions for existing ATMPs

Challenges and potential solutions were supplemented, assessed and prioritised through a review process including:

- Members of the Working Group (including EURORDIS, trade associations, affiliated NGOs, and 18 member companies)
- Country-specific patient associations
- Country level decision makers, such as policymakers, HTA bodies and budget holders
- Experts and advisors, such as healthcare professionals, patient representatives, P&R system experts, ATMP technical experts, economists and academics

In Spain, stakeholders engaged included policy and health economic experts and a representative from CIPM.

Following stakeholder engagement, the challenges and solutions were refined and prioritised to reflect the perceived importance in improving patient access and feasibility of implementation. Therefore, the challenges in this report are not exhaustive of all identified through primary and secondary research but represent the most important issues as determined by stakeholders.

The outputs from this process have been summarised in this report as a basis for discussion within multi-stakeholder meetings in each country and at European level.

## ASSESSMENT

Impact:



Challenge	Proposed solution	Feasibility
<b>AS1.</b> Regional (de-centralised) reimbursement processes are inconsistent and lack transparency	<b>AS1.</b> Utilise the centralised procedures for assessing gene and cell therapies, rare diseases drugs and oncology drugs	+++
<b>AS2.</b> Assessment process is not accommodating of data that is generated in trials for ATMPs (e.g., surrogate endpoints, synthetic control arms, indirect treatment comparisons)	<b>AS2a.</b> Utilise managed entry agreements (MEAs) to manage uncertainty in data	++
	<b>AS2b.</b> Involve patients in the assessment process	++
	<b>AS2c.</b> Multi-stakeholder early dialogue to establish expectations for data generation	++

The Working Group assessment of the **impact** relate to all challenges in each domain. The Working Group assessment of **feasibility** relates to the individual or groups of proposed solutions.

### Working Group identified assessment challenges

#### Challenge AS1.

#### ***Regional (de-centralised) reimbursement processes are inconsistent and lack transparency.***

In Spain, while pricing decisions are taken nationally, reimbursement decisions are normally based on assessments conducted at the regional level. The assessment protocols vary from one region to another which is likely to challenge patient access to ATMPs across Spain. In general, drugs developed for rare diseases undergo the same assessment as drugs for non-rare conditions. However, some regions have evolved their own rare disease plans.

In recognition of the regional variation in assessment procedures the Spanish Society for Hospital Pharmacy (SEFH) has established the GENESIS project. The objective of this project is to provide a standard methodology to hospitals conducting evaluations of new medicines in an effort to standardise an evaluation approach nationally. However, hospital participation is not mandatory and there remains no standardisation between regions on an assessment approach.

#### Proposed solution AS1.

#### ***Utilise the centralised procedures for assessing gene and cell therapies, rare diseases drugs and oncology drugs.***

Due to the rising number of gene and cell therapies, rare diseases drugs and oncology drugs, the Spanish Agency of Medicines and Medical Devices (AEMPs) initiated and launched a new model for high-cost medicines that goes beyond financing. The approach calls for the incorporation of patients in clinical trials, preparation for a pharmaco-clinical protocol for equal access in all autonomous regions and standards for the measurement of therapeutic effectiveness. The pharmaco-clinical protocol also establishes homogenous treatment criteria, coordinated by the General Directorate of the Basic Portfolio of Services of the SNS, with the collaboration of experts from the autonomous regions, AEMPS and disease experts. This model involves monitoring the therapeutic effectiveness of new treatments through a centralised procedure to attain improved insight into treatment outcomes. This procedure has provisions for additional registry data collection to inform reimbursement discussions.

Registries and real-world evidence (RWE) data collection requirements could be agreed during early dialogue so they can be established at the time of marketing authorisation. This additional data collection could help in managing evidence uncertainty and help in making better informed pricing and reimbursement decisions. This is supported by EUCOPE's positioning on data collection to address long-term uncertainty and questions on evidence quality.

Yescarta and Kymriah were both assessed and are now reimbursed in Spain under a risk-sharing agreement that is part of National Strategy for Advanced Therapies. If the pilot scheme for the CAR-Ts is not expanded further, variation in regional assessment will remain for future ATMPs.

While utilising the national-level initiatives for high-cost medicines would be preferable for ATMPs, if these are not expanded for ATMPs there are additional solutions that can be proposed to overcome regional variability. In this case, early dialogue with regions could enable manufacturers to identify the clinical cost-effectiveness criteria required to satisfy the cost-effectiveness analysis which can be considered in their data generation activities. Within this dialogue the methodological and procedural challenges associated with the assessment of ATMPs in rare diseases should be addressed. Proposals could be brought forward on:

1. Specific technical solutions for extrapolating short-term data to inform decisions on the potential long-term benefit
2. Incorporation of data from ITCs
3. Incorporating data generated following initial assessment

This is aligned with the Alliance for Regenerative Medicine's (ARM's) recommendation that HTA frameworks need to be better adapted to ATMPs, by improving extrapolation methods, allowing validated surrogate endpoints, incorporate indirect costs and lower the discount rates for health in health economic models.

**Feasibility: +++**

**Stakeholders:** AEMPS, SEFH, SNS, clinical experts, patient associations, trade associations

**Timeframe:** 6–18 months

### **Challenge AS2.**

***Assessment process is not accommodating of data that is generated in trials for ATMPs (e.g., surrogate endpoints, synthetic control arms, indirect treatment comparisons).***

Challenges concerning HTA requirements for ATMPs in rare diseases share similarities with those faced by orphan drugs in general. Small numbers of patients and relatively short duration of trials limits the efficacy and safety data that can be generated at the time of launch. There are also difficulties in capturing the long-term benefit within the timeframes of the clinical trials.

### **Proposed solution AS2a.**

***Utilise managed entry agreements (MEAs) to manage uncertainty in data.***

Managing financial uncertainty will likely address challenges to evidential uncertainty, which are addressed in proposed solution AS1. The introduction of managed entry agreements (MEAs) and payment-by-results at a national level can help reduce the uncertainties associated with ATMPs. To effectively administer MEAs, national-level coordination is required to give a large enough sample size to inform decisions. To avoid regional-level negotiation requirements, manufacturers should propose outcomes-based deals at the national level, with regional involvement in their design.

**Feasibility: ++**

**Stakeholders:** AEMPS, SEFH, SNS, clinical experts, individual companies, autonomous regions

**Timeframe:** 6–18 months

**Proposed solution AS2b.**

***Involve patients in the assessment process.***

The routine inclusion of patient groups in the assessment of ATMPs should be confirmed in guidance from AEMPS. Patient groups have a potentially important role in assessing orphan products in Spain. Early dialogue between manufacturers, patients and payers may highlight the unmet need in specific indications. For example, advocacy groups were involved in the assessment of Spinraza (a treatment for spinal muscular atrophy [SMA], but not an ATMP). The patient groups helped autonomous regions and healthcare professionals establish protocols for access, so that the economic model ultimately could be accepted by the pharmacy commission.

There is no legislation mandating the involvement of patients in the assessment process. Doing so would strengthen the position of patients in the assessment process.

**Feasibility:** ++

**Stakeholders:** AEMPS, SEFH, SNS, patient associations

**Timeframe:** 6–18 months

**Proposed solution AS2c.**

***Multi-stakeholder early dialogue to establish expectations for data generation.***

Early dialogue at both national and regional level regarding evidence requirements may prepare for data generation requirements for regulators and HTAs. If the challenges can be identified in advance, manufacturers are better able to tailor their evidence package in order to satisfy requirements. This is supported by a report from ARM who suggest early dialogue activities to give manufacturers insights on how they can mitigate uncertainty. This dialogue should include multiple stakeholders including patients and administrators.

Additionally, this dialogue could occur simultaneously to dialogue with EUnetHTA, the collaboration of HTA agencies that seek to define and implement scientific and technical cooperation on HTA across Europe. Advice can be gathered on data that should be collected on patient-reported outcomes (PROs) or other data generation activities that can be conducted to satisfy HTA requirements. As interaction with EUnetHTA is currently a voluntary process, it is a decision to be made by manufacturers whether this pathway would be optimal to identify data generation activities, which subsequently could assist assessment at a country-level.

**Feasibility:** ++

**Stakeholders:** AEMPS, SNS, EUnetHTA, individual companies, autonomous regions

**Timeframe:** 6–18 months

## **AFFORDABILITY**

Impact:



Challenge	Proposed solution	Feasibility
<b>AF1.</b> Spain's focus on near-term budget impact does not capture long-term value of ATMPs	<b>AF1a.</b> Utilise Spain's financing model for high-cost medicines	+++
	<b>AF1b.</b> In absence of inclusion in high cost medicines model, use early dialogue to identify the likelihood of reimbursement in regions	+++

The Working Group assessment of the **impact** of the challenge relate to all challenges in each domain. The Working Group assessment of **feasibility** relates to the individual or groups of proposed solutions.

### **Working Group identified affordability challenges**

#### **Challenge AF1**

##### ***Spain's focus on near-term budget impact does not capture long-term value of ATMPs.***

As Spain has a heavy focus on cost-containment, near-term budget impact (often over 3 years) is of particular importance. This means the long-term value of ATMPs is not captured and a large part of the value proposition is not considered. Consequently, up-front payment will be problematic for ATMPs. The focus of budget impact analysis is usually with only the healthcare budget in mind, so the assessment of benefits inadequately captures the benefits in terms of savings in the social care budget (e.g., rehabilitation or long-term social care).

#### **Proposed solution AF1a.**

##### ***Utilise Spain's financing model for high-cost medicines.***

The experience of treatments that have been reimbursed through the high-cost medicines financing model could be leverage for future ATMPs. As the intention is to expand this model, this is likely to benefit orphan medicines in the future. The criteria for inclusion in this framework are:

1. Treatments with a high economic impact
2. With a high unmet need
3. With a small subset of patients

The model was agreed between the autonomous regions, patients and manufacturers. The benefit of this model for ATMPs is that it allows reimbursement while further data are generated.

With Spinraza, the payment model used was an outcomes-based, managed-entry agreement. Half of the treatment costs is paid over the first year of treatment as the manufacturer further collects data on efficacy and safety. There is no clawback if the medication is not effective. Instead, administered medication will be paid for even if not effective, and will subsequently be withdrawn. If effective, it will be maintained and fully paid for. This provided a positive outcome for patients and it has been stated that the regions supported this national initiative. This is a model that could be replicated for ATMPs in future. Yescarta and Kymriah have been made available using a risk-sharing scheme. Details of this deal are unclear at present. The duration of this scheme is important as the outcomes of an ATMPs may not be fully realised over a short time frame. A 5-year time horizon may be more appropriate to adequately capture the benefit of the product.

**Feasibility:** +++

**Stakeholders:** AEMPS, patient associations, trade associations, individual companies, autonomous regions

**Timeframe:** Immediate –18 months

**Proposed solution AF1b.**

***In absence of inclusion in high cost medicines model, use early dialogue to identify the likelihood of reimbursement in regions.***

If a national level agreement is not established, early dialogue between regions and manufacturers would establish the criteria for reimbursement in each region. Subsequently, these discussions could be used to identify opportunities for collaboration across regions on reimbursement for ATMPs. However, if the cross-regional pooling of resources is not feasible, a national initiative enabling access and resources could be discussed. EUCOPE's position on ATMPs also suggests that collaboration is needed to identify approaches to funding, reimbursement and payment mechanisms.

**Feasibility:** +++

**Stakeholders:** Patient associations, trade associations, individual companies, autonomous regions

**Timeframe:** Immediate –18 months

## **AVAILABILITY**

**Impact:**



Challenge		Proposed solution	Feasibility
<b>AV1.</b>	Cross-border access is legislated for in Spain; however, the applicability of legislation for ATMPs is unclear	<b>AV1.</b> AEMPS should develop a cross-border access plan for ATMPs	+++
<b>AV2.</b>	Interpretation of the hospital exemption legislation means approved ATMPs may have to compete with products developed under hospital exemption	<b>AV2.</b> EU should be pressed to provide guidelines to prevent marketed products from competing with products with hospital exemptions for the same medical indication	+

The Working Group assessment of the **impact** of the challenge relate to all challenges in each domain. The Working Group assessment of **feasibility** relates to the individual or groups of proposed solutions.

### **Working Group identified affordability challenges**

#### **Challenge AV1.**

***Cross-border access is legislated for in Spain; however, the applicability of legislation for ATMPs is unclear.***

In Spain, there is a regulation (Royal Decree 1015/2009) that enables reimbursement of products that are only available outside of Spain for conditions with high unmet need. The criteria stipulate that there can be no other authorised or available therapeutic alternative for the patient in Spain before authorising reimbursement in another country.

This legislation has been used previously for high-cost products for rare disease. Such products have been imported from countries where they are reimbursed, rather than the patient travelling cross-border to receive treatment. The sustainability of this route for patient access is uncertain. For ATMPs, there are technical and regulatory barriers that make the applicability of the route less clear.

#### **Proposed solution AV1.**

***AEMPS should develop a cross-border access plan for ATMPs.***

The EU directive on cross-border access provides a framework for access but authorisation is required from AEMPS before patients can use this route. In order to ensure Spanish patients can access ATMPs in cross-border scenarios, the Royal Decree 1015/2009 could be amended to include provisions for such scenarios.

**Feasibility: +++**

**Stakeholders:** AEMPS, patient associations

**Timeframe:** Immediate–18 months

#### **Challenge AV2.**

***Interpretation of the hospital exemption legislation means approved ATMPs may have to compete with products developed under hospital exemption.***

The article 28 (2) of the ATMP Regulation 1 modified the Directive 2001/83/EC2 by adding the article 3(7), referred to as the 'hospital exemption' (HE). According to the legislation, it is permitted to use an

ATMP without a Marketing Authorisation under certain circumstances. The purpose of this legislation is to provide unauthorised ATMPs to individual patients on a non-routine basis.

The varying interpretation of this EU legislation means it could be used as a way to circumvent the applicable legal instruments for the marketing of safe and effective ATMPs. This could act as a disincentive for manufacturers to develop ATMPs to regulatory and manufacturing standards as the commercial opportunity could be challenged by unauthorised, individual products with no requirement to undergo the regulatory rigour to achieve Marketing Authorisation. In Spain, the focus on cost-containment could encourage the use of hospital exemptions to avoid reimbursing commercially available products.

### **Proposed solution AV2.**

***EU should be pressed to provide guidelines to prevent marketed products from competing with products with hospital exemptions for the same medical indication.***

The EU should be pressed into issuing guidelines defining more specifically the scope and requirements for hospital exemptions for ATMPs, stating clearly that when patients have access to an ATMP with a Marketing Authorisation, countries should not authorise hospital exemptions for the same medical indication. The guidelines should also address the possible interference of hospital exemption with recruitment of patients in clinical trials for the same indication. This echoes the ARM position on hospital exemptions.

**Feasibility: +**

**Stakeholders:** Patient association (EURORDIS), trade associations, EU parliament

**Timeline:** 6–18 months

## ACCESSIBILITY

Impact:



Challenge	Proposed solution	Feasibility
<b>AC1.</b> If not reimbursed centrally, there are inequalities between regions in terms of budget, resource and population size that can impact access	<b>AC1.</b> Utilise national initiatives to reduce inequalities in patient access at regional level	++
<b>AC2.</b> Regional variation in timelines, criteria and transparency can delay access	<b>AC2.</b> The national agreement used to provide access to Yescarta and Kymriah should be leveraged to avoid delays at the regional level	++
<b>AC3.</b> Establishing registries can delay adoption	<b>AC3.</b> Early dialogue with the treatment centre, regional and national level administrators	++

The Working Group assessment of the **impact** of the challenge relate to all challenges in each domain. The Working Group assessment of **feasibility** relates to the individual or groups of proposed solutions.

### Working Group identified affordability challenges

#### Challenge AC1.

***If not reimbursed centrally, there are inequalities between regions in terms of budget, resource and population size that can impact access.***

There are existing inequalities between regions in budget, resource and population size, which may manifest as inequality in terms of access to ATMPs. Cross-regional mobility may be required, which adds an administrative hurdle when pre-authorisation and payment is required in advance. This challenge will arise if ATMPs are not reimbursed centrally.

#### Proposed solution AC1.

***Utilise national initiatives to reduce inequalities in patient access at regional level.***

Utilising the financing model for high-cost medicines or the National CAR-T strategy initiatives, may prepare Spain for providing equal access to ATMPs across regions. Autonomous regions have been involved in the development of these initiatives and as seen with the model for Spinraza, there appears to be a willingness to support access from regions. The expansion of these programmes to future ATMPs will reduce inequalities in patient access. In addition to finance and access, these initiatives should identify how cross-regional mobility will be approached to ensure equal access across regions.

**Feasibility:** ++

**Stakeholders:** AEMPS, patient associations, trade associations, individual companies, autonomous regions

**Timeline:** 6–18 months

#### Challenge AC2.

***Regional variation in timelines, criteria and transparency can delay access.***

While there is a perception that access in Spain is protracted due to the need to negotiate at a regional level, expert opinion is that delays are as a result of the place of Spain in traditional launch sequence of new products. As the decision-making criteria are uncertain in regions, this also contributes to a delay in

time to access. Furthermore, regions restrict the use of products until the evaluations have been conducted, regardless of the national level decision.

### **Proposed solution AC2.**

***The national agreement used to provide access to Yescarta and Kymriah should be leveraged to avoid delays at the regional level.***

If delay is a consequence of national-regional duality, it is important that the solution is a reflection of the actual problem. Therefore, addressing the duality could diminish the delay of access, regardless of Spain's place in the traditional launch sequence. For ATMPs, the national agreement used to provide access to Yescarta and Kymriah should be leveraged to avoid delays at the regional level. It should be noted that for orphan products, the average time from the Committee for Medicinal Products for Human Use (CHMP) decision to reimbursement is 23 months in Spain. For Yescarta and Kymriah the time from decision to reimbursement was approximately 12 months.

If the delay in access is as a result of the place of Spain in the launch sequence, removing the international reference component of the pricing system may address this. This component currently incentivises companies to launch in Spain after countries that traditionally have high prices.

**Feasibility: ++**

**Stakeholders:** AEMPS, trade associations, autonomous regions

**Timeline:** 6–18 months

### **Challenge AC3.**

***Establishing registries can delay adoption.***

Establishing post-approval registries for a new product can be a hurdle and can delay patient access. Delays can be caused in agreeing how data will be collected and how registries will be maintained and funded.

### **Proposed solution AC3.**

***Early dialogue with the treatment centre, regional and national level administrators.***

Early dialogue with the treatment centre, regional and national level administrators to define reimbursement flow, treatment codes and registry set-up requirements will expedite access at time of the reimbursement decision. Patient groups can support the establishment of registries and could be included in early dialogue

**Feasibility: ++**

**Stakeholders:** AEMPS, patients associations, autonomous regions

**Timeline:** 6–18 months

## **Bibliography:**

AEMPS. ChondroCelect. Available from: <https://www.aemps.gob.es/cima/publico/lista.html>

AEMPS. Glybera. Available from: <https://www.aemps.gob.es/cima/publico/lista.html>

AEMPS. Holoclar. Available from:

<https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-celulas-epiteliales-Holoclar-deficiencia-celulas-limbaires.pdf>

AEMPS. Imlygic. Available from:

<https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-talimogen-laheparepvec-Imlygic-melanoma.pdf>

AEMPS. Zalmoxis. Available from: <https://www.aemps.gob.es/cima/publico/lista.html>

AEMPS. Advanced therapies in the national health system. Available from:

[https://www.mscbs.gob.es/profesionales/farmacia/Terapias\\_Avanzadas.htm](https://www.mscbs.gob.es/profesionales/farmacia/Terapias_Avanzadas.htm)

Diariofarma. Cruz inaugura, con Spinraza, una nueva era en financiación de fármacos. Available from: <https://www.diariofarma.com/2018/02/06/cruz-inaugura-spinraza-una-nueva-financiacion-farmacos>

Gaceta Medica. Sanidad materializa un nuevo modelo de financiación. Available from:

<https://www.gacetamedica.com/politica/sanidad-materializa-un-nuevo-modelo-de-financiacion-BX1404641>

GENESIS Spanish Society for Hospital Drugs. 2019. Available from:

[http://gruposdetrabajo.sefh.es/genesis/genesis/Enlaces/InformesHosp\\_abc.htm?ml=1](http://gruposdetrabajo.sefh.es/genesis/genesis/Enlaces/InformesHosp_abc.htm?ml=1). Retrieved 12 July 2019

Genetic alliance. The Westminster All Party Parliamentary Group on Rare, Genetic and Undiagnosed Conditions. Available from: <https://www.geneticalliance.org.uk/appg/>

Hettle R., Corbett M., Hinde S., et al. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. *Health Technol Assess.* 2017;21(7):1-204.

Institute for Clinical and Economic Review (ICER) and Office and Health Economics (OHE). Gene Therapy: Understanding the science, assessing the evidence, and paying for value. White Paper.

Available from: <https://www.ohe.org/publications/gene-therapy-understanding-science-assessing-evidence-and-paying-value>.

Jørgensen J. and Kefalas P. Annuity payments can increase patient access to innovative cell and gene therapies under England's net budget impact test. *Journal of Market Access & Health Policy.* 2017.5:1, 1355203.

Jones Day. Compassionate Use in Europe: A Patchy Framework for Early Market Entry. Available from: <https://www.jonesday.com/compassionate-use-in-europe-a-patchy-frame-work-for-early-market-entry-08-20-2010/>

Josep Darbà. The Spanish Ministry of Health initiates a new financing model for high-cost medicines in the areas of rare diseases and oncology. Available from: <https://www.linkedin.com/pulse/spanish-ministry-health-initiates-new-financing-model-josep-darbà/?trackingId=%2FXuWOtgKD3ehU1%2B8LIWErw%3D%3D>

Kefalas P. Cell and gene therapy reimbursement: the CGC approach. 2016. Available from: <https://ct.catapult.org.uk/sites/default/files/The-Cell-and-Gene-Therapy-Catapult-approach-to-pricing-and-reimbursement-strategy-development.pdf>

Kefalas P. Opportunities and challenges with performance-based pricing schemes for ATMPs. 2017. Available from: [https://ct.catapult.org.uk/sites/default/files/publication/P\\_Kefalas\\_Performance%20Based%20Schemes\\_18102017.pdf](https://ct.catapult.org.uk/sites/default/files/publication/P_Kefalas_Performance%20Based%20Schemes_18102017.pdf)

Farmacia Hospitalria. Available from: <https://www.diariofarma.com/2018/02/06/cruz-inaugura-spinraza-una-nueva-financiacion-farmacos>

FundAME. Information. Available from: <https://wacean.com/registroame/>

Redaccion Medica. Sanidad estrena nuevo modelo de financiación para fármacos de alto impacto. Available from: <https://www.redaccionmedica.com/secciones/industria/sanidad-estrena-nuevo-modelo-financiacion-para-medicamentos-de-alto-impacto-2368>

Redaccion Medica. Spain, pioneer in CAR-T: approves the financing of Yescarta (Gilead). Available from: <https://www.redaccionmedica.com/secciones/industria/espana-pionera-en-cart-aprueba-la-financiacion-de-yescarta-gilead--2967>

Romar, R., et al. Un niño gallego, primero de España que será tratado contra la atrofia muscular. *La Voz de Galicia*. 2019. Available from: [https://www.lavozdeg Galicia.es/noticia/sociedad/2017/09/15/nino-gallego-primer-espana-sera-tratado-contra-atrofia-muscular/0003\\_201709G15P25991.htm](https://www.lavozdeg Galicia.es/noticia/sociedad/2017/09/15/nino-gallego-primer-espana-sera-tratado-contra-atrofia-muscular/0003_201709G15P25991.htm). Accessed July 17

Sampietro-Colom, L., Asua, J., Briones, E., & Gol, J. History of health technology assessment: Spain. *International Journal Of Technology Assessment In Health Care*. 2009. 25(S1), 163-173. doi: 10.1017/s026646230909059x. Available from: [https://www.researchgate.net/publication/26303639\\_History\\_of\\_health\\_technology\\_assessment\\_Spain](https://www.researchgate.net/publication/26303639_History_of_health_technology_assessment_Spain)

Sear, R., et al. European Health Technology Assessment exemptions and exceptions for orphan medicines. Presented at The 9th European Conference on Rare Disease and Orphan Products 2018, Vienna. 2018

The Economist Intelligence Unit. Value-based healthcare in Spain Regional experimentation in a shared governance setting. 2015. Available at: [https://eiuperspectives.economist.com/sites/default/files/ValuebasedhealthcareSpain\\_0.pdf](https://eiuperspectives.economist.com/sites/default/files/ValuebasedhealthcareSpain_0.pdf). Accessed July 17, 2019.

Thomas Reuter Practical Law. Medicinal product regulation and product liability in Spain: overview. Available from: [https://uk.practicallaw.thomsonreuters.com/Document/Id4af42f21cb511e38578f7ccc38dcbee/View/FullText.html?navigationPath=Search%2Fv1%2Fresults%2Fnavigation%2Fi0ad6ad3e0000016c5219409afbd6f6fe7%3FNav%3DKNOWHOW\\_UK%26fragmentIdentifier%3DIId4af42f21cb511e38578f7ccc38dcbee%26parentRank%3D0%26startIndex%3D1%26contextData%3D%2528sc.Search%2529%26transitionType%3DSearchItem&listSource=Search&listPageSource=2afed81695bc0fd2b8c11340ece07abb&list=KNOWHOW\\_UK&rank=1&sessionScopelId=82d1233d074cb8ce0419f9590e92d391eb464c449a4d60f81d4d16c69bf01e38&originationContext=Search+Result&transitionType=SearchItem&contextData=%28sc.Search%29&comp=pluk](https://uk.practicallaw.thomsonreuters.com/Document/Id4af42f21cb511e38578f7ccc38dcbee/View/FullText.html?navigationPath=Search%2Fv1%2Fresults%2Fnavigation%2Fi0ad6ad3e0000016c5219409afbd6f6fe7%3FNav%3DKNOWHOW_UK%26fragmentIdentifier%3DIId4af42f21cb511e38578f7ccc38dcbee%26parentRank%3D0%26startIndex%3D1%26contextData%3D%2528sc.Search%2529%26transitionType%3DSearchItem&listSource=Search&listPageSource=2afed81695bc0fd2b8c11340ece07abb&list=KNOWHOW_UK&rank=1&sessionScopelId=82d1233d074cb8ce0419f9590e92d391eb464c449a4d60f81d4d16c69bf01e38&originationContext=Search+Result&transitionType=SearchItem&contextData=%28sc.Search%29&comp=pluk)

Touchet N., and Flume M. Early Insights from Commercialization of Gene Therapies in Europe. *Genes*. 2017. 8:78

Vadecum. Holoclar. Available from [https://www.vademecum.es/medicamento-holoclar+equivalente+de+tejido+vivo\\_46098](https://www.vademecum.es/medicamento-holoclar+equivalente+de+tejido+vivo_46098)

## Appendix

### Country profile:

Market type	Budget impact analysis
Position in launch sequence	Mid
Previous experience with ATMPs	Yes

	Status	Note
Strimvelis	Not assessed	
Holoclar	Not reimbursed	The General Directorate of the Basic Portfolio of Services of the SNS and Pharmacy has issued the resolution of non-financing <sup>1</sup>
Zalmoxis	Withdrawn	Authorised but not marketed <sup>2</sup>
Glybera	Withdrawn	Authorised but not marketed <sup>3</sup>
Imlygic	Assessed <sup>4</sup>	Authorised, Not included in financing of NHS – unknown regionally. The General Directorate of the Basic Portfolio of Services of the SNS and Pharmacy has issued the resolution of non-financing <sup>4</sup>
Provenge	Withdrawn	Not evaluated
MACI	Withdrawn	Not evaluated
ChondroCelect	Withdrawn	Revoked 28/11/2016. Previously authorised with a pay for performance scheme implemented <sup>5</sup>
Yescarta	Reimbursed	Authorised to follow guidelines established in the plan of ATMPs in the national system <sup>6</sup>
Kymriah	Reimbursed	Authorised for both indications, to follow guidelines established in the plan of ATMPs in the national system <sup>7</sup>
Alofisel	Reimbursed <sup>8</sup>	
Luxturna	Authorised	Authorised but not marketed <sup>9</sup>
Zolgensma	Not evaluated	
Zynteglo	Not evaluated	IPT underway <sup>10</sup>

<sup>1</sup> AEMPS. Holoclar. Available from: <https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-celulas-epiteliales-Holoclar-deficiencia-celulas-limbaires.pdf> & <https://cima.aemps.es/cima/publico/detalle.html?nregistro=114987001>

<sup>2</sup> AEMPS. Zalmoxis. Available from: <https://cima.aemps.es/cima/publico/detalle.html?nregistro=1161121001>

<sup>3</sup> AEMPS. Glybera. Available from: <https://cima.aemps.es/cima/publico/detalle.html?nregistro=112791001>

<sup>4</sup> AEMPS. Imlygic. Available from: <https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-talimogen-laherparepvec-lmlygic-melanoma.pdf>

<sup>5</sup> AEMPS. ChondroCelect. Available from: <https://cima.aemps.es/cima/publico/detalle.html?nregistro=09563001>

<sup>6</sup> AEMPS. Yescarta. Available from: <https://cima.aemps.es/cima/publico/detalle.html?nregistro=1181299001> & <https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-axicabtagen-ciloleucel-Yescarta-LDCGB-LPMCGB.pdf?x17133>

<sup>7</sup> AEMPS. Kymriah. Available from: <https://cima.aemps.es/cima/publico/detalle.html?nregistro=1181297001> & <https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-tisagenlecleucel-kymriah-LAL-LCGB.pdf>

<sup>8</sup> AEMPS. Alofisel. Available from: <https://cima.aemps.es/cima/publico/detalle.html?nregistro=1171261001>

<sup>9</sup> AEMPS. Luxturna. Available from: <https://cima.aemps.es/cima/publico/detalle.html?nregistro=1181331001>

<sup>10</sup> AEMPS. Zynteglo. Available from: <https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/grupo-coordinacion-posicionamiento-terapeutico/2019/docs/informa-reunion-GCPT-2-abril-2019.pdf>