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 France

V1

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Chaired by:

Secretariat support by:

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])[1]. 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.

France has begun granting access to ATMPs while maintaining existing processes of HAS. ATMPs that have launched in France recently have achieved ASMR levels (a determination of the medical benefit a product offers over current standard of care) that allow for central reimbursement via inclusion on the *liste en sus*. Maintaining national-level reimbursement for future ATMPs via the existing assessment processes pose the biggest barrier to sustainable patient access.

How a product is funded is dependent on the ASMR level granted by HAS – those with an ASMR of I–III are included on the *liste en sus.* Those with an ASMR IV or V can also be on the *liste en sus* if the relevant comparator is already listed on the *liste en sus*, however, products with an ASMR IV or V usually require funding through hospital budgets. Both reimbursement routes could pose challenges for ATMPs where costs are loaded upfront.

An ASMR level is granted based on a very structured assessment of evidence presented by the manufacturer. The challenge for ATMPs is similar to assessment challenges seen in other countries, meeting evidence requirements for positive reimbursement in a process not designed to assess ATMPs. Under the assessment criteria, achieving an ASMR I–III without survival data versus the standard of care treatment in France and with single-arm trial data is difficult. Yescarta and Luxturna did achieve this, highlighting the willingness in France to be flexible for innovative products. Even though there is a lack of long-term data, the efficacy level and unmet need motivated the Transparency Committee (TC) decision. Kymriah, on the other hand, only achieved an ASMR IV for one of its two indications. For a more sustainable and transparent approach, the assessment and awarding of ASMR levels for ATMPs should be evolved.

There seems to be recognition from HAS that the current assessment process can be challenging for ATMPs, which may provide an opportunity to explore solutions to address these challenges. These could include guidance on acceptance of data from single arm trials, indirect treatment comparisons (ITC), surrogate endpoints and real-world evidence (RWE), which would provide ATMP manufacturers with greater certainty.

Historically, payers in France have been reluctant to engage in more complex managed-entry agreements (MEAs), such as outcomes-based schemes, which could help in managing evidential and financial uncertainty. However, recent negotiations of CAR-T have included such arrangements. Additional proposals to manage affordability challenges include linking RWE data collection with outcomes-based rebates and the removal of barriers to annuity payments to address skewed upfront costs.

Despite reimbursement and assessment barriers, patients in France can currently gain access to ATMPs in cross-border specialist treatment centres in certain circumstances. The sustainability of this type of availability is uncertain as there is no standard approach for ensuring access for future ATMPs. Given the importance of the French market and the high priority put on treating rare diseases, it is relatively unlikely that this scenario will play out regularly. However, a policy on providing patient access to

[1] Medicines for human use developed from genes, cells or tissues are classified as advanced therapy medicinal products (ATMPs) by the European Medicines Agency (EMA)

treatment centres in cross-border scenarios would provide clarity to patients and treating physicians on the protocols for ensuring patients can get access when a treatment is not available in a specialist centre in France.

Early dialogue with the Ministry of Health (MoH) could further identify the resource needs for ATMPs in advance so that patient access is not delayed at the time of launch. With regard to certification of treatment centres, a requirement for CAR-T delivery, France is well prepared and aiming to have 15-20 certified centres by the end of 2019. Leveraging this experience will be important for preparing for delivery of future ATMPs.

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

Domain (Impact)*	Challenge	Proposed solution	Feasibility**
Assessment 	**AS1.** Unclear how flexible TC methodology is to account for specificities of ATMPs in rare diseases	**AS1.** Provide clarity on the flexibility afforded to ATMPs on evidence requirements at launch	++
	AS2. Long-term benefits cannot be captured within the timeframe of clinical trials and RCTs are not always possible	**AS2a.** Expansion of methods guidance regarding extrapolation of surrogates and indirect comparisons	++
		AS2b. Adaptive assessment processes and real-world evidence	++
Affordability 	**AF1.** There is an increasing emphasis on CEA assessment in price negotiation	**AF1.** Engage with CEESP on the development of specific guidance for ATMP CEA models	+
	AF2. MoH is focused on budget neutrality which is likely to result in increased scrutiny of high-priced products	**AF2.** Remove barriers to annuity payments schemes and therefore better allocate investment over patient life	++
	AF3. In the absence of inclusion on *liste en sus*, funding is required from hospital budgets	**AF3.** Revision of the *liste en sus* methods to reduce burden on individual hospitals	+
Availability 	**AV1.** Uptake/willingness to use cross-border initiatives is uncertain in France	**AV1.** Clarity on MoH policy on patient access in cross-border scenarios	++
Accessibility 	**AC1.** Health service organisations 'readiness' to adopt novel technologies, or ability to adapt existing infrastructure and care delivery can pose hurdles to adoption	**AC1.** Early dialogue with MoH to identify resource needs	+

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 two trade associations, three not-for-profit organisations 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 France, stakeholders engaged included representatives from:

- AFM-telethon
- Institut du Cerveau et de la Moelle épinière
- The Economic Committee for Health Products (CEPS)

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
AS1.	Unclear how flexible TC methodology is to account for specificities of ATMPs in rare diseases	**AS1.**	Provide clarity on the flexibility afforded to ATMPs on evidence requirements at launch	++
AS2.	Long-term benefits cannot be captured within the timeframe of clinical trials and RCTs are not always possible	**AS2a.**	Expansion of methods guidance regarding extrapolation of surrogates and indirect comparisons	++
		AS2b.	Adaptive assessment processes and real-world evidence	++

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 assessment challenges

Challenge AS1.

Unclear how flexible TC methodology is to account for specificities of ATMPs in rare diseases.

The Transparency Committee (TC) takes a rigorous, structured approach to assessing treatment benefit, with emphasis on the quality of data available at the time of launch. For instance, it is difficult to achieve ASMR levels I, II or III (an ASMR of I–III secures access to *liste en sus*) without having a head-to-head randomised controlled trial (RCT) using the designated clinical comparator and a well-established outcome-based endpoint. Pivotal study results drive decisions on additional benefit. Real-world evidence, whilst submissible, is less influential at the time of initial assessment.

Historically there has been less acceptance of data from single arm trials with smaller numbers of patients, surrogate endpoints, projection of survival data or lack of comparators, which represents a significant challenge for many ATMPs due to ethical considerations, impossibility of blinding, and ATMPs being novel therapies. Disease rarity or orphan designation does not confer any different assessment approach within the TC process, yet flexibility has been seen in the assessment of recent ATMPs. In the assessments of Yescarta and Kymriah, for instance, historical control cohorts were permitted to inform comparisons to standard of care, and ASMR III was awarded for each (and mandated collection of RWE). In the case of Luxturna, less clinically established endpoints in RCT were accepted.

There is some variation between the methods guidance on acceptable evidence versus what has been accepted in recent ATMP assessments. This has created uncertainty for manufacturers with regard to the extent of methodological flexibility for ATMPs in rare diseases, the situations in which it might be applied, and the likelihood of such flexibility being applied to ATMPs in future.

Proposed Solution AS1.

Provide clarity on the flexibility afforded to ATMPs on evidence requirements at launch.

As seen in recent assessments, there is a recognition by HAS that additional flexibility in methods is necessary for ATMPs in rare diseases. There is thus an opportunity to provide further clarity to manufacturers on how ATMPs will be assessed, the circumstances in which flexibility will be accorded, and methodological recommendations for dealing with challenges associated with one-off use, potentially curative treatments in rare diseases.

It is expected that the degree of flexibility on evidence requirements will reflect the characteristics of the treatment and the disease under assessment. For example, greater flexibility might be given in diseases that are more rare, where less observational data exists, and where the standard of care is more heterogeneous.

Importantly, given that most ATMPs will be provided in hospitals, clarity needs to be provided on how such products can achieve ASMR III (and thus inclusion on *liste en sus*). Now that a number of ATMPs have been assessed in France, HAS could provide information to manufacturers on learnings from these assessments and implications for future ATMPs. In particular, further clarity on methods for indirect comparisons, data extrapolation and real-world evidence generation (see Challenge AS2).

Any revision of methods guidance should involve ATMP specialists, including physician experts who can validate and rationalise trial designs for ATMPs, and patients who understand the burden of the disease and can interpret the relevance of novel endpoints.

This is aligned with the Alliance for Regenerative Medicines (ARM) recommendation to better adapt evidence requirements and HTA frameworks and develop RWE infrastructure that will allow timely and efficient collection of real-world data to be used by HTAs and payers. This need was acknowledged, and infrastructure was developed in the case of CAR-Ts. Now HAS has the opportunity to further develop, establish and communicate on this evolving process.

Feasibility: ++
Stakeholders: HAS, TC, individual companies, clinical experts, trade associations, patient associations
Timeframe: 6–24 months

Challenge AS2.

Long-term benefits cannot be captured within the timeframe of clinical trials and RCTs are not always possible.

Long-term benefits cannot be captured within the timeframe of clinical trials for ATMPs, given the potentially curative benefits and frequent use in paediatric populations. Currently the assessment process in France does not allow modelling to extrapolate clinical data to predict long-term benefit, instead putting the focus on additional data collection post launch. Surrogate endpoints are not accepted if there is insufficient data to demonstrate the relationships with outcomes to a high level of statistical proof. The requirement for surrogate endpoints is higher for ATMPs because the duration of benefit is longer. In such situations, it is not possible to collect outcomes data in time for initial payer assessment.

It is also difficult to obtain a positive outcome at TC based on single-arm or unblinded studies. These are more common for ATMPs in rare diseases, because regulators are often reluctant to permit controlled trials in highly morbid populations with no other effective treatment options, and blinding is extremely difficult given the nature of the intervention for cell and gene therapies.

Proposed solution AS2a.

Expansion of methods guidance regarding extrapolation of surrogates and indirect comparisons.

In situations where it is not possible to collect outcomes data in studies, there should be more opportunity to use modelling methods to extrapolate to long-term benefits. Guidance should be provided to ATMP manufacturers on the situations in which surrogate endpoints are acceptable and the requirements for validating the link to outcomes in small populations. There should be acceptance that the level of statistical uncertainty around the correlation of surrogates to outcomes will be greater in ATMPs in rare diseases, especially in diseases in which little observational data has been historically captured, or where study endpoints are not standardised. Extrapolated estimates of clinical benefit should incorporate RWE (see

Solution AS2b) and be updated on an ongoing basis as new data becomes available (both clinical data and observational data).

For ATMPs that are supported by data from single-arm trials, further clarity should be provided on the methods of indirect treatment comparison (ITC). The TC process allows for the incorporation of ITC data, but further advice tailored to ATMP challenges would be helpful. Current HAS guidelines on methodology for ITCs were published in 2009, but methods have advanced since that time, particularly in relation to patient matching and the creation of synthetic control arms. These issues were very pertinent to the assessment of Yescarta and Kymriah, which could provide valuable case studies. Given the need for existing observational or RCT data for comparator treatments, early advice on ITC requirements is necessary early in the development process to help manufacturers optimise the data available at launch.

Feasibility: ++
Stakeholders: HAS, TC, individual companies, trade associations,
Timeframe: 6–18 months

Proposed AS2b.

Adaptive assessment processes and real-world evidence.

Adaptive payer processes involve undertaking repeated HTA assessments over time and incorporating RWE generated since launch. Such adaptive processes are necessary for ATMPs in rare diseases given the uncertainty of long-term benefit at the time of initial assessment. In France, TC assessments are already revisited five years after first assessment, but for ATMPs where initial assessments are based on estimates of long-term benefits, re-assessments timelines should reflect the generation of RWE.

Liaising with the TC on the methodology for RWE data collection and analysis will ensure the data package for ATMPs can be assessed appropriately. Aligning these evidence requirements with the EMA post-approval evidence generation requirements would be an effective method of maximising the value of the collected data. Pre-approval ATU data should also be given sufficient emphasis in the TC assessment. Data collected from ATUs should be structured so as to be aligned with post-approval evidence collection, maximising the amount and duration of data. In the assessments of Luxturna, Yescarta and Kymriah, the TC requested follow-up data and data from the nominative and cohort ATUs, indicating that the TC can show flexibility in their approach for ATMPs with RWE.

Linking RWE generation with an outcomes-based agreement could further increase the likelihood of achieving sustainable access. This type of agreement removes the need for discounts that are required if the final price obtained by CEPS once the product is approved is less than the price charged by the manufacturers when the product is in the ATU/post-ATU period. Although pay-for-performance contracts have not been preferred in France, for ATMPs if an agreement cannot be reached on price following assessment, a conditional price can be proposed while further post-marketing data is collected. This has worked on a case-by-case basis. Establishing a framework for data collection for ATMPs for this purpose would expedite patient access by omitting protracted initial negotiations at launch and provide CEPs with security of further negotiation depending on outcomes. The possibility of a conditional price being moderate at the beginning and increasing with data showing efficacy could also be investigated.

Feasibility: ++
Stakeholders: TC, individual companies, trade associations,
Timeframe: 6–18 months

AFFORDABILITY

Impact: 

Challenge	Proposed solution	Feasibility
AF1. There is an increasing emphasis on CEA assessment in price negotiation	**AF1.** Engage with CEESP on the development of specific guidance for ATMP CEA models	+
AF2. MoH is focused on budget neutrality which is likely to result in increased scrutiny of high-priced products	**AF2.** Remove barriers to annuity payments schemes and therefore better allocate investment over patient life	++
AF3. In the absence of inclusion on *liste en sus*, funding is required from hospital budgets	**AF3.** Revision of the *liste en sus* methods to reduce burden on individual hospitals	+

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.

There is an increasing emphasis on CEA assessment in price negotiation.

There is an increasing emphasis on cost-effectiveness analysis (CEA) in price negotiations in France. The Commission d' évaluation économique et de santé publique (CEESP) was created to assess the cost-effectiveness of healthcare strategies. ATMPs that are targeting an ASMR of I–III and are likely to generate €20m in annual sales in the first two years on the market must submit a cost-effectiveness model to CEESP. The "Accord Cadre'' from January 2016 (framework agreement between the CEPS and the pharmaceutical industry) appears to give more weight to the CEESP. Article 9 of this agreement specifies that the 'European price' automatically granted to product with an ASMR I–III is now conditional on the results of the CEESP's assessment. Therefore, a product can be denied a European price if the CEESP concludes that the cost-effectiveness evaluation has major methodological weaknesses. Products with a dossier requesting ASMR IV and V are currently not required to submit a cost-effectiveness evaluation to the CEESP. However, the expansion of the CEESP assessment to include submissions requesting ASMR IV is being discussed as these drugs may have a considerable economic impact. Given the evidence criteria typically required for achieving an ASMR I–III are difficult to meet for ATMPs, they may be more likely to receive and ASMR IV, which may now also require a CEESP assessment.

The acceptability of CEESP methods for CEA of ATMPs is not differentiated. In the CEESP analysis of Yescarta (ASMR III), the methodology was deemed as acceptable, but reservations were expressed regarding the absence of a comparative trial, biases in the ITC, the extrapolation methods, utility data used and the cost offsets.

Proposed solution AF1.

Engage with CEESP on the development of specific guidance for ATMP CEA models.

CEESP should provide guidance for CEA for ATMPs. This guidance should include:

a) Clarity on ITC methodology to reduce concerns of bias in the absence of an RCT
b) Methods for extrapolation
c) Appropriate cost offsets to include in model
d) Appropriate discount rates for ATMPs where benefit is accrued over long time periods

a) As discussed, the nature of the diseases ATMPs often target make RCTs difficult to design. As such ITCs will often be required to generate comparative evidence. The acceptability of this data is limited at present. Guidance on CEESP-preferred methodology to use for ITCs for ATMPs should be provided to ensure better acceptance in the future.

b) Best practice for the methodology for extrapolation of efficacy outcomes for ATMPs should be provided. In the assessment of Yescarta, the methodology employed did not provide long-term extrapolation. Questions were raised on the PFS/OS coefficient ratio and the sensitivity analysis correction leading to reservations on the survival data. Providing methodological guidance for ATMPs where surrogates for survival will likely be used will aid manufacturers in the development of their model and CEESP in the interpretation of the data.

c) Guidance on the appropriate cost offsets should be provided. This could include guidance on current care pathways from HAS, incorporating expert clinical advice.

d) Discount rates result in greater weighting of clinical outcomes and costs in the short-term over those in the future. ATMPs are extremely sensitive to discount rates owing to the extended nature of the clinical benefit they offer to patients and the front-loading of cost. Lower discount rates should be applied to ATMPs that can demonstrate long-term benefit with acceptable extrapolation.

Feasibility: +
Stakeholders: HAS, CEESP
Timeframe: 6–18 months

Challenge AF2.

MoH is focused on budget neutrality which is likely to result in increased scrutiny of high-priced products.

There is a focus on budget neutrality in France which is likely to result in increased scrutiny of ATMPs, where the up-front costs associated with a single (very few) administration(s) may skew annual budget caps that are applied to innovative products.

Payers in France are more willing to adapt existing managed-entry agreements (MEA) models than introduce innovative funding options to address budget impact scrutiny or link outcomes with reimbursement over time. Existing options include a strong focus on national price-volume agreements, which are routinely negotiated for new medicine launches in France. The details of these models are strictly confidential and their applicability for ATMPs is uncertain. These agreements do not factor in the clinical value of drugs.

Proposed solution AF2.

Remove barriers to annuity payments schemes and therefore better allocate investment over patient life.

Barriers to annuity payments due to legislative or accounting standards need to be explored. It is currently understood that costs may need to be booked in the year of treatment even if payment is spread over subsequent years, meaning the financial benefit does not immediately translate to healthcare budgets. By addressing these barriers, it is easier for payers to allocate investment over a patient's life.

Modifying annuity payment models to account for evidential uncertainty could be part of a risk-sharing programme with manufacturers. Other innovative funding options that could address payer concerns include group purchase, where reimbursement for a group of ATMPs with similar modes of action/technical similarities would be negotiated at the same time.

Feasibility: ++
Stakeholders: CEESP, trade associations,
Timeframe: 6–18 months

Challenge AF3.

In the absence of inclusion on liste en sus, funding is required from hospital budgets.

For innovative, expensive drugs included in the *liste en sus*, companies negotiate a national price with the CEPS. Hospitals receive supplemental payments to cover products on the *liste en sus* (costs do not come from hospital budgets) as funding does not come from the DRG tariff but from the national health insurance. In the absence of inclusion on the *liste en sus* (if ATMPs receive an ASMR IV or V), funding is required from hospital budgets. As ATMP administration is often conducted in specialist centres, the burden of funding ATMPs with ASMR IV or V is placed on these hospitals alone in the absence of central funding.

Proposed solution AF3.

Revision of the liste en sus methods to reduce burden on individual hospitals.

Under current assessment procedures, with ATMPs often having single-arm trials, achieving an ASMR I–III is difficult, meaning they may be excluded from the *liste en sus* and central funding. A solution could be revision of the *liste en sus* methods to reduce the financial burden on individual hospitals. This funding could be linked RWE data collection and reassessment mentioned in the proposed solution AS1.

Authorities in France have been investigating alternative ways to fund innovative and costly drugs since August 2019, highlighting a willingness to address this issue.

Feasibility: +
Stakeholders: HAS
Timeframe: 6–18 months

AVAILABILITY

Impact: 

Challenge		Proposed solution		Feasibility
AV1.	Uptake/willingness to use cross-border initiatives is uncertain in France	**AV1.**	Clarity on MoH policy on patient access in cross-border scenarios	++

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 availability challenges:

Challenge AV1.

Uptake/willingness to use cross-border initiatives is uncertain in France.

In the current environment, patients usually have access to ATMPs in cross-border scenarios. However, cross-border legislation does not make it a statutory requirement for payers to cover treatment for patients in another EU country if it isn't available in France. If there are more ATMPs that require access via cross-border mechanisms, there is a risk of variation in access for patients. The sustainability of providing coverage in this manner for future ATMPs that require cross-border access is uncertain.

Proposed solution AV1.

Clarity on MoH policy on patient access in cross-border scenarios.

The Centre for European and International Social Security Liaisons (CLEISS) provide information on the support available to patients that need access to treatment in cross-border scenarios. A policy on providing patient access to treatment centres in cross-border scenarios would provide clarity to patients and treating physicians on the protocols for ensuring patients can get access. European Reference Networks (ERNs) can provide a template for how the coordination of healthcare across borders could work.

Feasibility: ++
Stakeholders: HAS, CLEISS
Timeframe: 6–18 months

ACCESSIBILITY

Impact: 

Challenge		Proposed solution		Feasibility
AC1.	Health service organisations 'readiness' to adopt novel technologies, or ability to adapt existing infrastructure and care delivery can pose hurdles to adoption	**AC1.**	Early dialogue with MoH to identify resource needs	+

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 accessibility challenges

Challenge AC1.

Health service organisations 'readiness' to adopt novel technologies, or ability to adapt existing infrastructure and care delivery can pose hurdles to adoption.

Due to the technical aspects of many ATMPs, many have short shelf-lives and this requires patients to be treated in centres with proximity to the Good Manufacturing Practice (GMP) facilities where these ATMPs are manufactured. Complex storage and pre-administration preparations as well as expertise with complex interventional procedures are also required. These centres are required to have intensive care unit (ICU) capacity and resources for any post-treatment observation and supportive care that may be part of the treatment programme. The adaptation of existing infrastructure and capital expenditure needed to reconfigure services may provide a barrier to access.

In the EPAR for Yescarta and Kymriah, manufacturers are required to certify centres that treat patients. There are no standard criteria for certification of centres and currently manufacturers are responsible for the management of certification.

Proposed solution AC1.

Early dialogue with MoH to identify resource needs.

Early dialogue with the MoH could identify the resource needs for ATMPs in advance so that patient access is not delayed at the time of launch. ERNs and manufacturers should play a role in identifying resource needs and location of services. An IT solution could be employed to identify clinical service availability.

With regard to certification of treating centres, France is aiming to have 15-20 certified centres by the end of 2019 and well placed for the delivery of CAR-Ts. In addition to the manufacturer-led certification, the National Cancer Institute and the Care Management body (DGOS) are developing their own approval criteria for healthcare centres in order to allow prescribing of CAR-Ts. While certification for delivery may be ATMP-specific, in future, France should leverage the learnings from certification process for CAR-Ts where possible.

Feasibility: +
Stakeholders: HAS, DGOS, individual companies
Timeframe: 6–18 months

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Appendix

Country profile

Market type	Comparative clinical effectiveness
Position in launch sequence	Early
Previous experience with ATMPs	Yes

	Status	Note
Strimvelis	Not assessed by TC	
Holoclar	Assessed by TC: ASMR IV[1]	Benefit is minor, only in bilateral forms with restrictions
Zalmoxis	Not recommended[2]	Insufficient clinical benefit to warrant reimbursement
Glybera	Not recommended[3]	Insufficient clinical benefit to warrant reimbursement
Imlygic	Not assessed by TC	
Provenge	Not assessed by TC	Withdrawn from EU market
MACI	Assessed in February 2005 by ANAES	Suspended for use in the EU
ChondroCelect	Not recommended[4]	Withdrawn from EU market
Yescarta	Assessed by TC: ASMR III[5]	Cohort ATU agreed
Kymriah	Assessed by TC:[6] ASMR III (ALL) ASMR IV (DLBCL)	Cohort ATU agreed
Luxturna	Assessed by TC: ASMR II[7]	
Alofisel	Assessed by TC: ASMR IV[8]	

[1]Holcolar. TC. Available from: https://www.has-sante.fr/portail/upload/docs/application/pdf/2017-05/dir71/holoclar_summary_ct15190.pdf
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