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 England

V1

January 2020

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.

Contents

Executive Summary

The RARE IMPACT initiative was launched at the European Conference on Rare Diseases and Orphan Products (ECRD) 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 patient access to ATMPs in Europe.

To date, patient access to ATMPs in England has been relatively good, with largely positive decisions from the National Institute for Health and Care Excellence (NICE) on both gene and cell therapies appraised in the last 18 months. This may reflect a particularly supportive political environment for ATMPs currently. Despite these positive precedents, there are systemic challenges that bring into question the sustainability of access to ATMPs in the UK (particularly if political enthusiasm wanes). The Medicines and Medical Devices Bill was reintroduced in the Queens Speech in December 2019, putting it on the agenda for the current government. The bill is part of a strategy to promote growth in the life sciences sector and will look to remove barriers to access to innovative therapies. The primary challenges relate to HTA assessment methods, the willingness to pay for innovation (especially in small populations), and accessibility challenges where clinical services are not currently aligned with ATMP requirements.

Assessment challenges for ATMPs reflect a misalignment between HTA methodology and evidence generation for potentially curative treatments in small populations. For example, while NICE allows the extrapolation of short-term data to long-term outcomes, this is very difficult in practice, particularly for diseases in which there is an absence of natural history data. Similarly, where the comparator in the pivotal trial is not the standard of care (SoC) in England, NICE will allow indirect comparisons, yet in the absence of common control arms this may not be possible. This challenge was observed in the NICE appraisal of Kymriah in relapsed/remitting diffuse large B-cell lymphoma (R/R DLBCL). NICE is currently revisiting its HTA methods, which represents an opportunity to refine approaches to the assessment of ATMPs. Consideration should be given to providing guidance on a standardised approach to extrapolating short-term data, incorporation of data from single-arm trials and methods for indirect treatment comparisons (ITC) for ATMPs. More clarity should be given on the evidence that is required to address data uncertainty within patient access schemes and managed access agreements for ATMPs.

Adaptive assessment processes can also reduce evidential uncertainty. While NICE and NHSE have multiple mechanisms that allow for evidence generation and adaptive assessment, there is currently no appropriate routine option for ATMPs. Existing approaches, particularly managed access agreements and Cancer Drug Fund mechanisms, should be further developed to allow ATMPs to be routinely assessed through adaptive processes that reflect the value of the innovation while reducing the clinical uncertainty for the NHS.

A related challenge concerns the multiplicity of reimbursement pathways for orphan ATMPs in England and Wales. These include NICE Single Technology Appraisal (STA), NICE Cancer Drug Fund (CDF), NICE Highly Specialised Technology (HST) Programme, the Clinical Priorities Advisory Group and direct commissioning from NHSE. Incremental cost-effectiveness ratio (ICER) thresholds vary according to pathway, from £20K to £300K per quality-adjusted life year (QALY). There is considerable uncertainty about the route through which any particular ATMP is likely to be assessed. A single sustainable

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

pathway for the assessment of ATMPs for rare diseases in England and Wales would provide greater certainty and allow for more tailored assessment methods.

Affordability (willingness to pay) is potentially a major impediment to future orphan ATMP access in England and Wales, as it has been for orphan drugs in general. Flexible commercial arrangements have been identified as a potential solution. NHSE is currently seeking consultation on a proposed Commercial Framework that provides more guidance on how it intends to negotiate commercial agreements in future. It is important that this framework is appropriate for ATMPs. In particular, it should create the option for staggered (annuity) payments, ensure sufficient flexibility in deal structures to reflect the specificities of individual ATMPs, and simplify and expedite the process of negotiating commercial agreements. Given the particular challenges associated with ATMPs, it will also be important to further build ATMP expertise and infrastructure within the NHS commissioning process, to allow for better informed discussion on payment models.

Accessibility is also a major consideration as the delivery of ATMPs is complicated due to their personalised nature. Accessibility challenges exist in the NHS in situations where clinical services are not currently aligned with ATMP requirements. Although NHSE has moved quickly to adapt processes where needed, change to service provision inevitably takes time and represents a barrier to adoption. A systematic analysis of the number of future ATMPs, the typical support services required, and the geographic dispersion is necessary to inform health service planning. At the individual ATMP level, considerations of the health service impact of a new treatment should be addressed as early as possible through horizon scanning to better prepare providers and reduce the time to patient access.

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

Domain (Impact)*	Challenge		Proposed solution		Feasibility**
Assessment 	**AS1.**	It is difficult to estimate long-term outcomes and QALYs vs comparators for ATMPs.	**AS1a.**	Review NICE HTA methods, including: • Updated specific solutions for standardised methods of extrapolating short-term data • More regulated approaches for incorporating ITC data • Regular use of real-world evidence post launch to gather better long-term efficacy data over time **AS1b.** Adaptive assessment processes to manage uncertainty around estimates of long-term effects.	+++
	AS2.	Cost-effectiveness assessments can be especially challenging for ATMPs due to sensitivity to discount rates and calculation of potential long-term outcomes and cost savings.	**AS2.**	Apply a greater use of existing flexibility in discount rates and introduce new modifiers (beyond end-of-life and HST) for ATMPs.	++
Affordability 	**AF1.**	Multiple P&R pathways with variable ICER thresholds and limited willingness to pay.	**AF1.**	Alignment with NICE and NHS on a sustainable pathway for assessment of ATMPs.	++
	AF2.	Uncertainty about NHS flexibility and capability to negotiate innovative payment models.	**AF2.**	Build ATMP expertise in the NHS commissioning process to better align product value and expenditure.	++
	AF3.	Annual budget impact threshold of £20m affects ATMPs greater than continuous treatments.	**AF3.**	Budget impact assessments should account for the distribution of costs over time.	++
Availability 	**AV1.**	Treatment via cross-border initiatives is deemed a route of last resort within the NHS.	**AV1.**	Education on the benefit of cross-border healthcare in concentrating clinical and technical expertise in order to avoid delays to patient access at the time of marketing approval.	++

Domain (Impact)*	Challenge	Proposed solution	Feasibility**
Accessibility 	**AC1.** Uncertainty about capacity and reconfiguration of associated clinical services (e.g., apheresis units, inpatient beds and intensive care units).	**AC1.** Analysis of clinical services requirements for future ATMP use incorporated into NHS planning process. More in-depth horizon scanning to identify service requirements at the individual ATMP level.	+

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 England, stakeholders engaged included representatives from:

- NICE
- NHSE
- Scottish Medicines Consortium (SMC)
- Genetic Alliance
- UK Thalassaemia Society

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 the European level.

ASSESSMENT

Impact: 

Challenge		Proposed solution		Feasibility
AS1.	It is difficult to estimate long-term outcomes and QALYs vs comparators for ATMPs.	**AS1a.**	Review NICE HTA methods, including: • Updated specific solutions for standardised methods of extrapolating short-term data • More regulated approaches for incorporating ITC data • Regular use of real-world evidence post launch to gather better long-term efficacy data over time	**+++**
		AS1b.	Adaptive assessment processes to manage uncertainty around estimates of long-term effects.	
AS2.	Cost-effectiveness assessments can be especially challenging for ATMPs due to sensitivity to discount rates and calculation of potential long-term outcomes and cost savings.	**AS2.**	Apply a greater use of existing flexibility in discount rates and introduce new modifiers (beyond end-of-life and HST) for ATMPs.	**++**

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.

It is difficult to estimate long-term outcomes and QALYs vs comparators for ATMPs.

NICE undertakes cost-effectiveness assessments of new products using a structured, data driven, modelling approach. Estimation of lifetime QALY gains is central to the assessment process and a major driver of the recommendation decision. ATMPs for rare diseases face significant challenges within this quantitative assessment process due to the nature of the interventions and the type of evidence available at the time of appraisal. Some of these challenges exist for all orphan medicines, such as small sample sizes in trials, data derived from single arm studies, surrogate endpoints and lack of information on the disease course. For ATMPs these issues can be exacerbated by the need to extrapolate data over very long time-horizons (possibly in excess of 60 years in the case of treatments for paediatric diseases) due to the potentially curative effect of treatment.

NICE allows the use of statistical methodologies to account for lack of direct within-trial comparisons and extrapolation of surrogate data, but this is particularly difficult for ATMPs in rare diseases where there is often an absence of natural history data. Furthermore, while NICE allows indirect comparison if the trial comparator is not standard of care, this is difficult to implement in the absence of a common control arm (this was a challenge for Kymriah in R/R DLBCL).

For these reasons, ATMPs in rare diseases, while having a high potential for life-changing benefits for patients, also have higher uncertainty around the QALY gain estimates than for less innovative therapies. When faced with such uncertainty, Appraisal Committees are more inclined to focus on scenarios based on conservative assumptions about treatment benefit.

Proposed solution AS1a.

Review NICE HTA methods, including:

- ***Updated specific solutions for standardised methods of extrapolating short-term data***
- ***More regulated approaches for incorporating ITC data***
- ***Regular use of real-world evidence post launch to gather better long-term efficacy data over time***

The Association of the British Pharmaceutical Industry (ABPI) and UK government recently agreed the 2019 Voluntary Scheme for Branded Medicines Pricing and Access (voluntary scheme), part of which allows proposals for changes to the assessment of new products. NICE has subsequently agreed to review its HTA methods. A broad set of topics relevant to ATMPs have been published for consultation, including:

- How uncertainty is managed (e.g., evidence available at assessment or assumptions made in economic modelling)
- How quality of life is incorporated into economic analysis
- How to address the challenges of evaluating technology-specific issues

Within this consultation, there is an opportunity to address the methodological and procedural challenges associated with the assessment of ATMPs in rare diseases. These should include proposals on:

1. Updated specific technical solutions for extrapolating short-term data to inform decisions on the potential long-term benefit. NICE provides guidance on extrapolation data in its Technical Support Document from 2011, which could be updated to include more recent methods. NICE has also recommended being involved in scientific advice discussions on the extrapolation of survival data and the appropriate sensitivity analysis to conduct for a cost-effectiveness analysis.
2. An update to DSU TSD #18 (developed in 2016 on “Methods for population-adjusted indirect comparisons in submissions to NICE”) to give guidance on the more systematic use of ITC data for ATMPs to reconsider the more conservative approach currently taken.
3. Incorporating data generated following initial NICE assessment. This would reduce the uncertainty in the clinical effectiveness assessment of the product by placing requirements on the manufacturer to generate additional real-world data. Given the small sample sizes in rare diseases, data requirements would ideally be uniform across European countries to allow for aggregation of data and enhanced understanding of real-world clinical effect. Given that the costs of ATMPs are usually incurred as a one-off at the time of treatment, adaptive assessment and payment processes would be necessary to make use of post-approval data collection (See solution AS1b).

Feasibility: +++
Stakeholders: ABPI, individual manufacturers, NICE
Timeframe: 0–12 months

Proposed solution AS1b.

Adaptive assessment processes to manage uncertainty around estimates of long-term effects.

Adaptive assessment processes have been identified as an important part of the solution to evidential uncertainty in rare diseases, and for ATMPs in particular. Where long-term extrapolation of short-term data is necessary, modelling assumptions about the shape of survival curves and other outcomes can be revisited on a more frequent basis as clinical trial data matures and real-world data are collected. Models can be incrementally adjusted to reflect the changing balance of data and implications incorporated into contractual agreements (a form of ‘mark to market’ reimbursement).

Currently, NICE already has several mechanisms to allow appraisals to be more adaptive. Patient Access Schemes (PAS) have been used extensively for medicines assessed through the STA pathway, and complex PAS can incorporate outcomes-based payments. However, most PAS are simple discounts and there has been reluctance to accept proposals for more complex schemes.

Managed Access Agreements (MAA) have been used for medicines assessed through the HST pathway and have been seen to be very flexible, incorporating evidence generation requirements, outcomes-based payments, start-stop rules, population-specific pricing and other financial components. However, the creation of MAA schemes requires multi-stakeholder involvement and is resource intensive for NICE and NHSE. Accordingly, there has been some reluctance to use these sorts of agreements routinely for HST-assessed medicines and the same flexibility does not exist for STA drugs.

The Cancer Drugs Fund (CDF) is also an existing approach for managing evidential uncertainty while allowing patient access. Kymriah has been granted access via this route. While an ATMP-specific fund may not provide a solution, a mechanism similar to that in the CDF may provide a route to reducing evidential uncertainty.

Commissioning through evaluation (CtE) is another theoretical option for adaptive assessment. It enables a small number of patients to have funded access to treatments within a protocol-driven assessment of real-world effectiveness. This approach has been used mostly by non-pharmaceutical treatments, such as medical devices. It is not currently considered to be a viable route through which ATMPs could be routinely funded and assessed.

While NICE and NHSE have multiple mechanisms that allow for evidence generation and adaptive assessment, there is currently no appropriate routine option for ATMPs. Existing approaches, particularly MAA and CDF mechanisms, should be further developed to allow ATMPs to be routinely assessed through adaptive processes that reflect the value of the innovation while reducing the clinical uncertainty for the NHS.

In addition, resources and infrastructure are required to capture outcomes data to inform discussions on outcomes-based agreements. The existing UK data collection infrastructure in the indications most likely to see launches of cell and gene therapies over the next five years needs upgrading to facilitate routine outcomes-based reimbursement agreements.

Feasibility: **++**
Stakeholders: NHSE, NICE, ABPI, patient associations
Timeframe: 0–24 months

Challenge AS2.

Cost-effectiveness assessments can be especially challenging for ATMPs due to sensitivity to discount rates and calculation of potential long-term outcomes and cost savings.

Estimation of QALY gains are a major challenge for ATMPs (AS1), but other aspects of cost-effectiveness analysis (CEA) can also present problems.

One important technical challenge relates to discount rates. NICE's default is to discount all costs and benefits at 3.5% and in special circumstances this can be reduced to 1.5%. ATMPs are particularly sensitive to discount rates due to the potential benefit being accrued over many decades while the cost of treatment is all incurred in the present. ATMP costs are therefore not discounted, while chronic comparator costs (if they exist) are discounted at 3.5%, and lifetime QALY gains from treatment are greatly reduced through discounting at 3.5%. Accordingly, the combined effect of discounting diminishes the perceived cost effectiveness of ATMPs – this was a finding from NICE's own assessment of the suitability of its methods for ATMPs. The 1.5% discount rate exception, while potentially helpful, has

rarely been applied in practice and not for any ATMP to date. The correct discounting rates are essential for successful evaluation.

A second economic challenge relates to estimating the cost savings from ATMPs in rare diseases. Often in rare diseases there is no effective existing treatment and supportive care costs are poorly understood. Where existing high-cost treatments are SoC, cost-effectiveness can often be demonstrated. For example, in the NICE appraisal of Strimvelis, savings from reduced use of enzyme replacement therapy and immunoglobulins helped offset the cost of the new treatment. Where SoC is low-cost (often in rare diseases), estimating cost savings over a patient lifetime is difficult and demonstrating cost-effectiveness is challenging.

Proposed solution AS2.

Apply a greater use of existing flexibility in discount rates and introduce new modifiers (beyond end-of-life and HST) for ATMPs.

An ATMP pilot/mock assessment has been conducted that highlighted the sensitivity of cost-effectiveness analyses to discount rates. Greater flexibility is required for ATMPs. For instance, NICE currently has a curative threshold of benefits for >30 years, where a 1.5% discount rate may be applied – this would exclude products that demonstrate benefits up to 29 years. The threshold is one factor that could be modified. In addition, NICE is looking to introduce new modifiers for ATMPs over and above the existing end-of-life and HST. These could be time limited and kept under constant review.

Feasibility: **++**
Stakeholders: NICE, ABPI
Timeframe: 0–12 months

AFFORDABILITY

Impact: 

Challenge		Proposed solution		Feasibility
AF1.	Multiple P&R pathways with variable ICER thresholds and limited willingness to pay.	**AF1.**	Alignment with NICE and NHS on a sustainable pathway for assessment of ATMPs.	++
AF2.	Uncertainty about NHS flexibility and capability to negotiate innovative payment models.	**AF2.**	Build ATMP expertise in the NHS commissioning process to better align product value and expenditure.	++
AF3.	Annual budget impact threshold of £20m affects ATMPs greater than continuous treatments.	**AF3.**	Budget impact assessments should account for the distribution of costs over time.	++

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.

Multiple P&R pathways with variable ICER thresholds and limited willingness to pay.

There are multiple reimbursement pathways for medicines in England and Wales, with differing assessments methods and variable ICER thresholds. These include the STA, HST and CDF pathways at NICE, along with Clinical Priorities Advisory Group and direct commissioning pathways from NHSE. NICE ICER thresholds can vary between £20K per QALY gained to £50K if end-of life criteria are met in the STA pathway, to £300K per QALY in the HST pathway. There is uncertainty as to which path any particular ATMP will be assigned. ATMPs for rare diseases are likely to be potential candidates for the HST pathway, but the criteria that determines assessment route is opaque and the capacity for HST assessments is limited. NHSE pathways have less transparency around both the process and the implicit cost effectiveness threshold. Consequently, manufacturers considering investment in ATMPs lack clarity on the willingness to pay for such specialist medicines in England and Wales.

This uncertainty is compounded by a perception of a declining willingness to pay for biopharmaceutical innovation in England and Wales over the last 20 years, symbolised by the lack of adjustment to ICER thresholds to reflect inflation since the introduction of NICE.

Proposed solution AF1.

Alignment with NICE and NHS on a sustainable pathway for assessment of ATMPs.

There needs to be a single sustainable pathway for the assessment of ATMPs for rare diseases in England and Wales. This topic has been explicitly recognised within the scope of the NICE methods review and there is currently an opportunity to establish greater clarity for manufacturers of ATMPs. Two options might be considered.

The first is a reduction in the number of pathways across NICE and NHSE and the development of a single pathway that incorporates sufficient flexibility in ICER thresholds and methodology to be able to appropriately assess a broad range of medicines and interventions, including ATMPs. In this scenario,

the Appraisal Committees would have latitude to accept higher ICERs and greater uncertainty associated with disease/drug characteristics that are currently recognised implicitly through the different pathways (e.g., end of life medicines, highly specialised medicines, etc.). However, rather than creating large steps in ICER thresholds between programmes, the relationship between characteristic and acceptable ICER would be more continuous in nature. This approach is closer to that of the TLV in Sweden.

The second option could be the creation of a new programme for ATMPs that is based on the reconfiguration of existing pathways and methods, such as the HST, or the creation of a standalone pathway for ATMPs. Specific criteria have been applied for paediatric and end-of-life indications in the past. NICE could also consider restructuring cost per QALY thresholds for ATMPs to better reflect the value they may provide, particularly in the context of diseases with high unmet need where no SoC exists. While increasing cost-per-QALY thresholds may be a difficult proposition for NICE and NHSE, adaptation of methods to calculate cost-effectiveness could be applied for ATMPs to better meet these thresholds. This relates to updated solutions for extrapolating short-term data to inform decisions on potential long-term benefit, more systematic incorporation of data from ITC and single-arm studies, more standardised acceptance of surrogate endpoints, incorporation of data generated following initial assessment and revision of discount rates.

The review of HTA methods provides an opportunity for proposals to be brought forward. The reconsideration of the NICE methods is also an opportunity for the Department of Health and the NHS to reassess the wider level of funding for medicines in England and Wales at the end of a decade of austerity and a new era of proactive industrial policy.

Feasibility: ++
Stakeholders: NICE, NHSE, Department of Health and Social Care
Timeframe: 0–12 months

Challenge AF2.

Uncertainty about NHS flexibility and capability to negotiate innovative payment models.

Affordability is a major impediment to patient access to ATMPs for rare diseases in England, as it has been for orphan drugs in general (there is relatively slow access compared with other major European countries). Flexible commercial arrangements have been identified as a solution to the affordability challenge for ATMPs. Outcomes-based agreements have previously been used in England, annuity payments have been proposed in the literature to increase patient access and other innovative funding options are in practice in for ATMPs in other countries (e.g., an outcome-based agreement for reimbursement of Strimvelis in Italy). However, there is uncertainty about NHS flexibility in negotiating innovative payment models and historically there has been limited capacity (and appetite) for complex commercial agreements. NHSE is currently seeking consultation on a proposed Commercial Framework (promised within the voluntary scheme) that provides more guidance on how NHSE intends to negotiate commercial agreements in future.

NHS budgets are set over three years and committing to longer term agreements is difficult; however, as a large single payer, one-off costs are less of a barrier than in other countries, at least while the number of ATMPs is relatively low. As a single funding body within a unified system, NHSE is well positioned to engage in sophisticated commercial agreements to help address issues of accessibility.

Proposed solution AF2.

Build ATMP expertise in the NHS commissioning process to better align product value and expenditure.

Given the particular challenges associated with ATMPs, an important first step will be to further build ATMP expertise and infrastructure within the NHS commissioning process, to allow for better informed discussion on payment models. It may be beneficial to have a specialist ATMP team within the NHSE commissioning group to centralise expertise on these technologies. NHSE and NICE should also seek to engage with ATMP manufacturers outside of specific assessments to provide opportunities for mutual education on the nature and challenges of these technologies.

It will also be important that the Commercial Framework being developed by NHSE is appropriate for ATMPs. In particular:

- It should create the option for staggered (annuity) payments in situations where this is desirable for reasons of aligning payment with value demonstration or to smooth budget impact over multiple years.
- The framework should be sufficiently flexible to reflect the specificities of individual ATMPs, recognising the needs and challenges can vary considerably across different technologies.
- It should simplify and expedite the process of negotiating commercial agreements. Currently multiple different NHS groups are involved (e.g., NICE PASLU, NICE MAA group, NHSE) and external stakeholders are engaged within MAA development.
- It should provide clarity on where responsibility sits for collecting and analysing data relevant to the commercial agreement.

Feasibility: ++
Stakeholders: NICE (MAA Group; PASLU), NHSE (Commercial Development Team)
Timeframe: 0–12 months

Challenge AF3.

Annual budget impact threshold of £20m affects ATMPs greater than continuous treatments.

The annual net budget impact threshold of £20m for triggering commercial discussions has a greater impact on ATMPs than other products as the cost of treatment is likely to be highest in the first year of launch while treating the eligible prevalent population. As ATMPs are likely to be one-off treatments, expenditure will then be limited to incident cases.

Proposed solution AF3.

Budget impact assessments should account for the distribution of costs over time.

NHSE has stated that the threshold is not a cap, but a level that triggers commercial discussions. Within these discussions it should be explicitly recognised that budget impact for ATMPs may be skewed towards early years. The assessment of the budget impact for an ATMP should be considered as an average yearly expense over a sufficient period of time (e.g., 10 years) to account for lower future expenditure as only incident cases are treated. If the distribution of cost over time is not accounted for, the incentive for developing ATMPs will be diminished versus medicines with a more extended duration of expenditure over time (but potentially a greater total cost).

The commercial discussions for ATMPs should reflect the need for staggered payments and flexibility as discussed in AF2. Further clarity is required regarding the accounting constraints on staggered payments. There is some uncertainty as to whether NHSE can legally enter into a payment structure that exceeds established budget cycle durations.

Feasibility: ++
Stakeholders: NHSE (Commercial Development Team), individual companies, patient associations
Timeframe: 0–12 months

AVAILABILITY

Impact: 

Challenge		Potential solution		Feasibility
AV1.	Treatment via cross-border initiatives is deemed a route of last resort within the NHS.	**AV1.**	Education on the benefit of cross-border healthcare in concentrating clinical and technical expertise in order to avoid delays to patient access at the time of marketing approval.	**++**

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.

Treatment via cross-border initiatives is deemed a route of last resort within the NHS.

While the academic and clinical infrastructure exists for ATMPs in England and Wales, the level of adaptation to existing infrastructure required to accommodate ATMPs will vary depending on the specific ATMP. There is an (understandable) institutional preference for managing patients in treatment centres in England and Wales. However, in instances where ATMPs targets ultra-orphan indications, and where there is limited domestic experience of managing the disease, there needs to be recognition that cross-border healthcare might represent the best option for patients.

This issue has previously been seen with proton-beam therapy in England and Wales. Prior to 2018, no facilities existed within the UK, yet funding patients to receive treatment overseas was deemed to be a route of very last resort. It took a significant length of time before a commissioning pathway was formulated so that patients could travel for treatment. In the assessment of Strimvelis, NICE recognised the need for patients to travel to Milan for treatment and for the NHS to make arrangements for travel and accommodation costs.

The establishment of overseas programmes is associated with time delays. It is unclear if these programmes can be put in place routinely when single treatment centres are used for ATMPs across Europe. The S2/cross-border directives can be used in circumstances where the ATMP is for an ultra-orphan indication. NICE will not conduct an HTA assessment in these circumstances, but it is unclear what will happen if the ATMP is not for an ultra-orphan indication. There is added uncertainty over the terms of Brexit and the implications for granting patients access to ATMPs via cross-border initiatives.

Proposed solution AV1.

Education on the benefit of cross-border healthcare in concentrating clinical and technical expertise in order to avoid delays to patient access at the time of marketing approval.

Physicians, payers and policymakers need to be further educated about the benefits (and process) of cross-border healthcare, which allows for the concentration of clinical and technical expertise. By proactively engaging with health care services on the requirements for cross-border healthcare in terms of manufacturing standards, administration, follow-up and data collection, services can be prepared at time of launch.

Feasibility: ++
Stakeholders: ABPI, individual companies, NHSE
Timeframe: 0–6 months

ACCESSIBILITY

Impact: 

Challenge		Proposed solution		Feasibility
AC1.	Uncertainty about capacity and reconfiguration of associated clinical services (e.g., apheresis units, inpatient beds and intensive care units).	**AC1.**	Analysis of clinical services requirements for future ATMP use incorporated into NHS planning process. More in-depth horizon scanning to identify service requirements at the individual ATMP level.	**+**

The Working Group assessment of the **impact and importance** 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.

Uncertainty about capacity and reconfiguration of associated clinical services (e.g., apheresis units, inpatient beds and intensive care units).

Due to the technical aspects of ATMPs, many have short shelf-lives and this requires patients to be treated in centres with proximity to the Good Manufacturing Practice (GMP) facilities. These centres are required to have intensive care unit capacity and resources for any post-treatment observation and supportive care that may be part of the treatment programme. The level of readiness of the NHS to adopt novel technologies, or ability to adapt existing infrastructure and care delivery, could pose a barrier to adoption. There is a lack of capacity in clinical services such as apheresis units, inpatient beds and intensive care units to facilitate appropriate supportive care. This results in patient access being relatively slow, despite NHSE's efforts to quickly fund treatments.

Proposed solution AC1.

Analysis of clinical services requirements for future ATMP use incorporated into NHS planning process. More in-depth horizon scanning to identify service requirements at the individual ATMP level.

As more ATMPs come to market over the next ten years, the NHS will need to plan for the impact on associated services. This planning requires a thorough understanding of the likely number of ATMPs being developed, the typical support services required, and the geographical dispersion. The NHS could undertake a study to assess these factors, in collaboration with manufacturers, and build the resulting insights into the NHS planning process at the national and local levels. The planning process should include standardisation so that centres have a system that allows them to cope with new ATMPs.

In addition, at the individual ATMP level, considerations of the health service impact of a new treatment should be addressed as early as possible through horizon scanning to better prepare providers and reduce the time to patient access.

Feasibility: +
Stakeholders: ABPI, individual companies, NHSE
Timeframe: 0–12 months

Bibliography

CATAPULT. Can the existing data collection infrastructures for patient outcomes enable outcomes-based reimbursement in the UK? Available from: https://ct.catapult.org.uk/case-study/can-existing-data-collection-infrastructures-patient-outcomes-enable-outcomes-based

Department of Health and Social Care and Association of the British Pharmaceutical Industry. The 2019 Voluntary Scheme for Branded Medicines Pricing and Access. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/761834/voluntary-scheme-for-branded-medicines-pricing-and-access-chapters-and-glossary.pdf

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.

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

Kennedys Law. Queens Speech Assessment 2019. Available from: https://www.kennedyslaw.com/thought-leadership/article/the-queens-speech-the-medicines-and-medical-devices-bill.

National Health Service. Appraisal and funding for cancer drugs from July 2016 (including the new Cancer Drugs Fund). Available from: https://www.england.nhs.uk/publication/cdf-sop-16/

NICE. Changes to new drug appraisals. Available from: https://www.nice.org.uk/news/feature/changes-to-nice-drug-appraisals-what-you-need-to-know

NICE. NICE announces details of health technology evaluation methods review. Available from: https://www.nice.org.uk/news/article/nice-announces-details-of-health-technology-evaluation-methods-review

NICE. Strimvelis. Available from: https://www.nice.org.uk/guidance/hst7/chapter/4-Consideration-of-the-evidence

NICE. Holoclar. Available form: https://www.nice.org.uk/guidance/ta467/chapter/4-Committee-discussion#cost-effectiveness

NICE. Yescarta. Available from: https://www.nice.org.uk/guidance/gid-ta10214/documents/final-appraisal-determination-document

NICE. Kymriah. Available from: https://www.nice.org.uk/guidance/gid-ta10270/documents/final-appraisal-determination-document

NICE. Alofisel. Available from: https://www.nice.org.uk/guidance/ta556/evidence/appraisal-consultation-document-committee-papers-pdf-665669790

NICE. Highly Specialised Technology. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-highly-specialised-technologies-guidance

NICE. Single Technology Appraisal. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance

SMC. Imlygic. Available from: https://www.scottishmedicines.org.uk/medicines-advice/talimogene-laherparepvec-imlygic-nonsubmission-124817/

SMC. Kymriah. Available from: https://www.scottishmedicines.org.uk/media/4132/tisagenlecleucel-kymriah-final-jan-2019-for-website.pdf

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

Appendix

Country profile

Market type	Cost-effectiveness analysis
Position in launch sequence	Mid
Previous experience with ATMPs	Yes

	Status	Note
Strimvelis	Recommended by NICE[1]	HST pathway
Holoclar	Recommended by NICE[2]	STA pathway
Zalmoxis	No NICE assessment	
Glybera	No NICE assessment	
Imlygic	Recommended by NICE[3a, 3b], not recommended by SMC[4]	In initial guidance, NICE concluded that Imlygic was not cost-effective and pointed out the lack of supporting evidence and the uncertainty of overall survival. However, the company provided additional evidence and agreed to a PAS with the Department of Health
Provenge	No NICE assessment	Withdrawn from EU market
MACI	No NICE assessment	Market authorisation suspended
ChondroCelect	No NICE assessment	Market authorisation withdrawn by TiGenix
Yescarta	Recommended by NICE[5]	'End of life' status granted
Kymriah	Recommended by NICE[6,7] Recommended by SMC[8]	'End of life' status not granted. ALL and R/R DLBCL indications funded through the CDF
Luxturna	Recommended by NICE[9]	
Alofisel	Not recommended by NICE[10]	
Zynteglo		Decision expected June 2020
Zolgensma	No NICE assessment	

[1]Strimvelis. NICE. Available from: https://www.nice.org.uk/guidance/hst7/chapter/4-Consideration-of-the-evidence
[2]Holoclar. NICE. Available from: https://www.nice.org.uk/guidance/ta467/chapter/4-Committee-discussion#cost-effectiveness
[3a]Touchet N., and Flume M. Early Insights from Commercialization of Gene Therapies in Europe. Genes. 2017. 8:78
[3b]Imlygic NICE. Available from: https://www.nice.org.uk/guidance/ta410/chapter/4-Committee-discussion
[4]Imlygic. SMC. Available from: https://www.scottishmedicines.org.uk/medicines-advice/talimogene-laherparepvec-imlygic-nonsubmission-124817/
[5]Yescarta. NICE. Available from: https://www.nice.org.uk/guidance/gid-ta10214/documents/final-appraisal-determination-document
[6]Kymriah. NICE. Available from: https://www.nice.org.uk/guidance/gid-ta10270/documents/final-appraisal-determination-document
[7]Kymriah. NICE. Available from: https://www.nice.org.uk/guidance/ta567/chapter/1-Recommendations
[8]Kymriah. Scottish Medicines Consortium. Available from: https://www.scottishmedicines.org.uk/media/4132/tisagenlecleucel-kymriah-final-jan-2019-for-website.pdf
[9]Luxturna. NICE. Available from: https://www.nice.org.uk/guidance/hst11/chapter/1-Recommendations

[10]Alofisel. NICE. Available from: https://www.nice.org.uk/guidance/ta556/evidence/appraisal-consultation-document-committee-papers-pdf-6656697901