

Evaluating patient access to rare disease treatments

Insights from
the UK and beyond

November 2023



Foreword from BIA



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People living with rare diseases face many challenges, from difficulties in getting a diagnosis to the impact on their mental health. Treatments for rare diseases can alleviate many of these challenges, and in recent years we have seen some new rare disease treatments being made available to patients in the UK. Despite this progress, most rare diseases have no licensed treatment.

One of the challenges faced by developers of rare disease medicines is securing access for these treatments in different markets, including the UK. Because of the unique challenges associated with rare disease medicines, there are often obstacles to generating robust evidence of cost-effectiveness. The BIA's Rare Disease Industry Group (RDIG) has been making the case for many years for changes that would help to overcome these obstacles and secure broader and faster patient access to rare disease treatments in the UK.

In November 2020, the BIA and PwC published *A Rare Chance for Reform*,¹ which made the case for a new way forward for evaluating medicines for rare and ultra-rare diseases in England. The report was published following the announcement that NICE would be embarking on a wide-ranging review of its methods and processes for health technology assessments (HTAs).² Our report identified key areas where reform would help to lift the barriers faced by rare disease medicines.

While the NICE review has brought some positive changes, it failed to match the ambition set out at the start of the review, and the promise of a "high ambition" methods review that featured in the Government's Life Sciences Vision.³ In particular the specific challenge of rarity was not adequately resolved by the changes NICE introduced.⁴

The BIA and PwC have worked together to conduct a comprehensive assessment of the changes that have been made since the previous report was published. These include the changes introduced by NICE in the methods review, as well as other recent initiatives to improve access to medicines. Drawing on focus groups, interviews and extensive desk research, this report presents an analysis of the progress that has been made and the challenges that remain.

We also felt it would be valuable to explore whether there are lessons we can learn from how other countries approach access to rare disease treatments. We have taken a close look at the approaches taken by some of our nearest neighbours – France, Spain and Germany – as well as countries with comparable HTA systems – Canada and Australia. We also looked at the USA, as the country with the highest number of medicines available, despite the obvious differences in healthcare systems.

Recently, both NICE and the MHRA have announced new ways to increase their collaboration with other HTA bodies and regulators, including through the new International Recognition Procedure.^{5, 6} The BIA welcomes these developments and hopes that this report will provide some helpful context for these collaborations and highlight the potential opportunities for improving access to rare disease treatments. We look forward to continuing to engage with stakeholders as we develop our recommendations for change, informed by the evidence presented in this report.

¹ <https://www.bioindustry.org/static/875ae91a-1583-4544-9f5d3ca9bfe696b7/A-Rare-Chance-for-Reform.pdf>

² <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation>

³ <https://www.gov.uk/government/publications/life-sciences-vision>

⁴ <https://www.bioindustry.org/news-listing/bia-response-to-conclusion-of-nice-methods-and-processes-review.html>

⁵ <https://www.nice.org.uk/news/article/nice-partners-with-international-health-technology-assessment-bodies>

⁶ <https://www.gov.uk/government/publications/international-recognition-procedure>

Foreword from PwC



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We are pleased to be supporting the BIA on this important piece of research. We would like to thank the companies, industry bodies, the NHS and NICE, clinicians and patient associations who have provided their time and insight to help draw this research together and make this report possible.

Patients living with rare and ultra rare diseases, and their families, face an enormous challenge with respect to both the diagnosis and treatment of their conditions. Patients and their families can face lifelong hardship with respect to the financial burden, education and mental wellbeing challenges caused by these diseases. The inherent hurdles created by the individually low patient numbers of each disease, and the difficulties that this presents in terms of the understanding and diagnosis of these diseases, coupled with the uncertainty around the evidence base generated from clinical trials, leads to a systemic environment of unmet need.

While individually rare, collectively large numbers of rare disease patients globally are suffering, with many of the debilitating and often life-threatening diseases arising in the paediatric population.

The evolution of diagnostic testing and genomics, combined with a greater ability to understand the pathophysiology of disease, should mean that a wider population of rare disease patients are identified for treatment. Furthermore, with the level of breakthrough sciences and new advanced therapy medicinal products, great strides have been made in identifying potential treatment for some of these diseases.

However, globally, the inherent challenges continue to leave large populations of rare disease patients without an effective treatment. Recently, the UK Government's Rare Diseases Framework, published in 2021, recognised the importance of a multifaceted approach to improving the lives of those suffering from rare diseases, including faster diagnosis, building clinical awareness, coordination of care and improved access to treatment and medicines.

It is promising that delivering change across all these areas has been identified as a priority by all stakeholders in the UK's healthcare ecosystem. We are delighted to support the discussion in providing research in this report which focuses on access to rare disease medicines. Our report identifies and reviews some of the recent changes in the UK access environment and looks to some international comparisons for evidence of useful benchmarks in driving more effective access to medicines. Open dialogue and collaboration across all stakeholders, including patients and patients' families, are required to overcome these significant challenges to continue to make an impactful change.

Building on the positive momentum of the recent focus, as well as addressing the key priorities of the Framework will be critical if society is to address the level of unmet need in rare disease populations.

Contents

Executive summary	05
Introduction and background	08
Changes to the UK access environment since 2021	10
Comparison of UK access versus other OECD countries	27
Conclusion	36
Appendix	38

Executive summary

Rare diseases are classified as diseases that impact fewer than 1 in 2,000 of the population.

There are over 7,000 known rare diseases and whilst individually these diseases are rare, collectively they are common and are estimated to affect over 3.5m individuals in the UK and c.350m globally. For the majority of diseases, there are no approved medicines. Not only do these diseases impact patients directly, but they often place a significant burden on patients' families and their carers. Caring for these patients can be incredibly difficult, as patients can face significant delays in receiving an accurate and timely diagnosis due to the inherent complexities of rare diseases. As a result, patients, their families and their carers, can face lifelong hardship with respect to the financial burden, educational and mental wellbeing challenges caused by these diseases. Therefore, there is a need for greater education and awareness about rare diseases to support improved diagnosis of these conditions, as well as focus on supporting access to the medicines that treat them.

Fundamentally, supporting access to the drugs that treat rare diseases, termed orphan drugs, is challenging across all healthcare systems because of their unique characteristics, such as their smaller patient population, complex and difficult diagnosis, higher cost of development relative to revenue potential and uncertainty around the evidence base generated from clinical trials. All of these features make it hard for these drugs to demonstrate their cost-effectiveness and gain timely approvals from regulatory bodies. These are global challenges that are inherently linked to the nature of rare diseases and their treatments, and are faced by all countries and healthcare systems. The UK and other OECD countries have put in place a number of strategies in their market access ecosystems to attempt to address these challenges.

In the UK, the Rare Diseases Framework (the Framework), published in 2021, was a significant refresh of the UK's original rare diseases strategy from 2013, and recognised the importance of a holistic approach to improving the lives of those living with rare disease. Since 2021, there have also been i) a number of changes to existing market authorisation (MA) and pricing & reimbursement (P&R) processes; and ii) a number of new market access pathways launched, all of which should help to improve the UK access environment for orphan drugs.

This report aims to evaluate the progress and impact of the Framework, and the changes to the UK's access environment for orphan drugs since 2021. Alongside this, the report reviews some of the rare disease access environments in selected OECD countries to identify best practice in other systems which support access to orphan drugs.

Changes to the UK access environment since 2021

In the UK, the Framework identified four key priorities to improve the lives of those living with rare diseases: i) faster diagnosis, ii) building greater clinical awareness of rare diseases, iii) better coordination of care and iv) faster access to treatment and medicines. This fourth priority specifically addresses both the incentives and specialised pathways, and specific funding allocated to support access for orphan drugs – this fourth priority is the focus of this report. Following the publication of the Framework in 2021, some of the other key changes to improve access to orphan-drugs include:

- i. Revisions to NICE's Health Technology Assessment (HTA) methods as part of the NICE Methods Review, which has led to:
 - a) Greater acceptance of uncertain evidence bases, for example, including real world evidence (RWE)
 - b) Consideration of a broader range of Quality of Life (QoL) measures in both single technology appraisals (STA) and highly specialised technologies (HST)
 - c) Proportionate approach to drug assessments to increase capacity for more complex submissions (i.e. streamlined approach to lower risk therapies)
 - d) Changes from an "end of life" quality-adjusted life year (QALY) modifier to a "severity" based modifier for the STA
 - e) HST committees with appropriately skilled members starting to sit on STA committees to share experiences of assessing rare disease treatments, and;
 - f) Simpler and clearer entry criteria for HST assessment
- ii. Launch of the Innovation Licensing and Access Pathway (ILAP) and Innovative Medicines Fund (IMF) to improve access to innovative drugs in which many rare disease drugs may sit

Apart from revisions to the HST entry criteria, these changes do not exclusively impact orphan drugs, but the nature of many of them have the potential to support improved access to these treatments.

UK Rare Diseases Framework

The Framework was seen as a positive step forward, with a strategic national focus supported by significant senior stakeholder engagement to drive progress against the Framework's priorities, including the Deputy Chief Medical Officer for England co-chairing the Framework's Board, as well as other similarly senior stakeholders leading the Framework's Delivery Group and Forum. These mechanisms are supportive of measuring progress against the Framework and ensuring accountability amongst key stakeholders. The Framework is also underpinned by action plans from each Home Nation, which ensures a commitment to improve access across the UK.

NICE Methods Review and other HTA process changes

The Methods Review, along with the proportionate approach to assessment and HST committee members beginning to sit on STA committees, are a clear step forward to improve the reimbursement pathway for innovative drugs. Many of these changes, such as the introduction of the severity modifier, will directly benefit orphan drugs as well. However, orphan drugs and some ultra-orphan drugs will continue to be channelled through the STA process, which has an ICER threshold of £20-30k compared with £100-300k in the HST. As such, the bar to be recommended for reimbursement in the STA is higher than the HST and to date, there is limited evidence of the impact of the change in STA modifier on improving access to orphan or ultra-orphan drugs.

There are some promising examples of how some of these changes are working in practice however, there are challenges that still remain that need to be addressed going forward, such as the need for greater clarity over how new QoL measures will be considered and more flexibility and transparency in the application of the new severity based QALY modifier.

ILAP and IMF

The ILAP and the IMF, introduced in 2021 and 2022 respectively, have been designed with the intention of improving access to innovative drugs. In general, ILAP was found to be helpful in offering greater engagement between sponsors and regulatory bodies, and helping sponsors successfully navigate the MA and P&R process. However, stakeholders have reported that resource constraints at ILAP partners (e.g. MHRA, NICE, NHS) have limited the effectiveness of the scheme and given the similarity with existing market access schemes, the incremental benefit of ILAP has been questioned.

While the idea behind IMF as a specific £350m p.a. fund for innovative drugs is welcomed, there is a notable challenge within the structure of the fund. This has meant that to date, no drugs, whether orphan or non-orphan, have been funded via a managed access agreement by the IMF.

However, it is promising to see that there is a commitment from regulatory bodies to evaluate the effectiveness of these newer pathways where challenges have been identified. This evaluation (and any subsequent reviews) will be important to assess the impact of these pathways and support their subsequent evolution to ensure that they can appropriately support rare disease medication access.

Summary assessment of changes to the UK access environment

Overall, the changes in the UK have been promising, but a period of transition is underway as these revisions and new mechanisms are embedded into regular practice. Therefore, their full effect on improving access is yet to be seen given a number of these changes are still very recent. In addition to the evaluation of these schemes already planned as part of the 2023 action plan, there remains further work to be done to address remaining challenges, such as: i) the lack of consideration of the impact of familial or carer quality of life in the health economic evaluation of drugs as part of the HTA process; ii) limited clarity over the application of the higher severity modifier in the STA process; or iii) clarifying the incremental benefit of ILAP and addressing the resource constraints within ILAP partners which might be impacting the programme's effectiveness.



Comparison of UK access versus other OECD countries

Recent data from the European Federation of Pharmaceutical Industries and Associations has shown that, relative to other European counterparts of Spain and France, England and Scotland have a faster average time from MA to appearance on public reimbursement lists. There is, however, room for improvement on this metric relative to other close peers such as Germany, where speed is much faster. In reviewing how other OECD countries facilitate access to orphan drugs, this review has identified interesting examples of: i) MA and P&R pathways for all drugs that are supportive of access to orphan drugs; ii) specialised MA or P&R pathways dedicated to improve access to orphan drugs; and iii) dedicated funding to enable access to orphan drugs.

1. MA and P&R pathways applicable to all drugs

Germany and France operate a single HTA process that places greater weight on the incremental health benefit of the drug, which benefits orphan drugs in particular given they often have a higher price per patient relative to other drugs and have a more limited evidence base, which can make proving their cost-effectiveness more challenging. Most interestingly, Germany's six-month free pricing period, available to all drugs, is crucial in supporting faster access. Australia approaches HTAs in a similar way to NICE, since it uses a cost-effectiveness led approach. However, it does not make use of a formal ICER threshold when assessing drugs, which provides greater flexibility during the assessment but is perhaps at the expense of transparency of decisions. Additionally in Australia, as well as in Canada, all drugs can benefit from parallel processing of MA and P&R dossiers, which helps to accelerate the time to access.

2. Specialised pathways for orphan drugs

The USA has several innovative MA processes that aim to accelerate MA of orphan drugs either by increasing communication with the regulatory body (US Food and Drug Administration), allowing earlier MA approval through surrogate endpoints, or reducing the regulatory review timeline itself through the use of priority review vouchers, which can either be granted by the FDA or purchased from manufacturers which have received it. There are also examples of specialised pathways within the P&R process that will support access to orphan drugs. A key example of this is Australia's Life Saving Drugs Programme (LSDP), which provides access to selected ultra-orphan and lifesaving drugs that are not successfully approved through the normal P&R process for cost effectiveness reasons.

3. Dedicated funding to enable access to innovative and orphan drugs

The Liste-en-Sus in France is a key example of a dedicated reimbursement mechanism to support equal access to innovative and highly priced medicines that are used in hospitals. The scheme itself has demonstrated evidence of success in the form of providing access to a number of orphan drugs since launch. Although it was only announced in March 2023, the Canadian government has also committed up to CA\$1.4bn over three years to provinces and territories to help fund bilateral agreements and enable orphan drug access.

Conclusion

Overall, the UK has made positive progress in improving access to rare disease treatments in recent years, and a period of transition is underway. Whilst the recent changes to MA and P&R processes and new market access mechanisms are steps in the right direction, there have been challenges identified with them, which are important to address in order to reach the ambition set out in the Rare Diseases Framework. Separately, there are several useful takeaways from other OECD countries that demonstrate how these countries are facilitating access to orphan drugs, but each of these countries have their own challenges to address. What is clear is that a successful strategy for driving greater access to treatments and care for rare disease patients requires solutions across a multitude of areas while there is positive progress and action plans drawn up across these areas, there remain real challenges that are limiting access to rare disease medicines.

Ultimately, gaining faster and broader access to effective rare disease treatments will drive real clinical outcomes, and improve the lives of patients, families and carers, as well as provide significant benefits to society and the wider economy, while potentially generating greater efficiencies within the healthcare system.



Introduction and background

Rare diseases (also known as orphan diseases) are estimated to affect almost 1 in 17 individuals in at some point in their lifetime, equating to over 3.5m people overall in the UK and an estimated c.350m globally.^{7,8} While they may be individually rare, orphan diseases are collectively common. In the UK and most other countries, these diseases are defined as those that affect fewer than 1 in 2,000 in the population.⁷ The majority of these, (c.75%), will affect the paediatric population, which places a significant burden on individuals, their families and carers, and the wider healthcare system.⁷ A subset of rare diseases, which are extremely rare and affect fewer than 1 in 50,000 in the UK population, are called ultra-rare diseases.^{9, 10}

There are over 7,000 known rare diseases which are likely to increase as diagnostic techniques evolve and scientific breakthroughs are made, allowing new diseases and their causes to be identified.⁷ Rare diseases can be further segmented into those caused by cancer (oncology), those caused by infections, and the rest (non-oncology and non-infectious). The non-oncology rare diseases are the focus of this report. Some of the most well-known rare diseases include sickle cell disease, cystic fibrosis, Duchenne muscular dystrophy and haemophilia.¹¹ Medicines that treat these complex and rare conditions are termed orphan drugs.

These drugs have low patient numbers and often have high research and development (R&D) costs, which make it hard to incentivise drug developers to invest in them. As a result, they tend to require a higher price relative to other drugs, in order to recoup the high overall development investment. Given the relatively high price per patient, the provision of these drugs can lead to a high burden on healthcare systems, which creates a greater challenge for payors to evaluate the cost effectiveness of these drugs. Therefore, there is a need for developers to clearly demonstrate the value that these drugs offer to both patients and the healthcare system through clinical evidence. For rare diseases this is inherently more challenging due to low patient numbers involved in clinical trials.

The UK Government published its first 'Strategy for Rare Diseases' in 2013, and more recently has refreshed this in 2021, with the publication of the UK Rare Diseases Framework ('the Framework'), which outlines a holistic approach to delivering better health outcomes and improving the lives of those affected by rare diseases.^{7, 12} It outlines four key priorities, one of which is focused specifically on improving "access to specialist care, treatments and drugs". These priorities are further detailed in the following section. It is recognised by all stakeholders that, despite this refreshed strategic focus and explicit priority of improving access, there remains a significant access challenge to overcome. This is not isolated to the UK. It is a global problem. Only 5% of known rare diseases have at least one approved treatment globally.¹³ There are a number of reasons for this, such as: i) the lack of a specific drug development programme to treat the disease; ii) a drug being in the development pipeline; or iii) a drug having completed development but not yet received a marketing authorisation (MA) or receiving reimbursement approval.

Rare diseases are often severely debilitating and can be life-threatening, so improving access to medicines can significantly improve the quality of life (QoL) for patients and may be life-saving. In the case of paediatric patients, where more than 30% of children die before their fifth birthday, the life-saving benefits accruing to patients, families, and carers, as well as wider benefits to society, in the form of contributions to GDP, are material. Despite this, improving access to rare disease treatments remains challenging across all healthcare systems as these treatments:

- 1 target a small patient population (often targeting paediatric populations)
- 2 have a high cost of development relative to their revenue potential (due to their smaller target patient populations)
- 3 present a more limited evidence base as clinical trials recruit fewer patients and are often single arm open label trials (as opposed to a randomised double-blind placebo-controlled trial – the gold standard for clinical research)

These impediments mean most rare disease patient populations are tragically underserved by medicines. In this report, we highlight some of the approaches and strategies adopted by the UK and other OECD countries to support access to rare disease medicines.

⁷ DHSC: The UK Rare Diseases Framework (2021)

⁸ <https://www.ucl.ac.uk/news/2023/feb/feature-why-rare-diseases-are-key-scientific-discovery>

⁹ <https://err.ersjournals.com/content/29/156/200195.short>

¹⁰ <https://doi.org/10.1093/qjmed/hci128>

¹¹ <https://www.rarebeacon.org/rare-diseases/what-are-rare-diseases/>

¹² Department of Health: The UK Strategy for Rare Diseases (2013)

¹³ <https://www.pfizer.com/science/focus-areas/rare-disease>

Each country places varying degrees of importance on different elements of a pricing and reimbursement (P&R) submission, which can be categorised based on the centralisation of decision-making and the focus of the assessment:

Centralised decision-making

- Cost-effectiveness prioritised by calculating incremental health benefit per unit of spend (compared to a standard of care, per patient) – UK, Canada, and Australia
- Incremental therapeutic benefit prioritised – Germany and France

Decentralised decision-making

- Overall budget-impact prioritised – Spain
- Free market access prioritised (access determined by formulary tiers and positioning in the therapeutic paradigm) – the USA

Given the number of people affected by rare diseases in the UK, and the overall patient and societal benefits, it is critical to understand how to improve access to effective orphan drugs and assess the success of recent policy changes that were designed either directly or indirectly to improve access to rare disease medicines. These changes include:

- UK Rare Diseases Framework 2021⁷
- National Institute for Health and Care Excellence's (NICE) review of the approach to health technology assessment (HTA) in 2022¹⁴ (Methods Review)
- Innovative Licensing and Access Pathway (ILAP) launched in 2021¹⁵
- Innovative Medicines Fund (IMF) launched in 2022¹⁶

The Framework builds on the UK Strategy for Rare Diseases 2013.¹⁷ While ILAP and the IMF were created to improve access to innovative medicines, that should, in theory, also benefit orphan drugs, as many orphan diseases are innovative first-in-class treatments. Outside the UK, other OECD countries have also published their own rare disease strategies in recognition of the challenges around access to orphan treatments – see exhibit 1.^{18, 19, 20, 21, 22, 23}

This report aims to evaluate the progress and impact of the Framework, and other recent changes (since its publication) to the UK's access environment for orphan drugs.

Alongside this, it reviews the rare disease access initiatives in selected OECD countries to identify best practice in other systems to support access to orphan drugs and benchmark the UK's performance against them.

Our research has been developed through a desktop review of key ecosystems, as well as interviews with industry participants, market access and rare disease experts, and regulatory and clinical stakeholders.

This research has been complemented by:

i) roundtable discussions with industry participants, patient group representatives and regulatory stakeholders; and ii) a review of available literature examining the performance of different ecosystems.

Exhibit 1 – Key rare disease strategies across selected OECD countries



¹⁴ <https://www.nice.org.uk/news/article/nice-publishes-new-combined-methods-and-processes-manual-and-topic-selection-manual-for-its-health-technology-evaluation-programmes>

¹⁵ <https://www.gov.uk/guidance/innovative-licensing-and-access-pathway>

¹⁶ NHS England: The Innovative Medicines Fund Principles (2022)

¹⁷ Department of Health: The UK Strategy for Rare Diseases (2013)

¹⁸ Australian Government, Department of Health: National Strategic Action Plan for Rare Diseases (2020)

¹⁹ <https://www.canada.ca/en/health-canada/news/2023/03/government-of-canada-improves-access-to-affordable-and-effective-drugs-for-rare-diseases.html>

²⁰ Ministry of Solidarity and Health: French National Plan For Rare Diseases 2018-2022 (2018)

²¹ NAMSE: National Plan of Action for People with Rare Diseases (2013)

²² Rare Diseases Strategy of the Spanish National Health System

²³ U.S. Government: Rare Diseases Act of 2002 (2002)

Changes to the UK access environment since 2021

In the UK, the access environment for orphan drugs is complex and has evolved in recent years. The Medicines and Healthcare products Regulatory Agency (MHRA), the Department of Health and Social Care (DHSC), NICE and the Scottish Medicines Consortium (SMC) have implemented changes to existing systems and introduced new pathways, schemes, and funds to support access to drugs in the UK. Some have targeted orphan drugs specifically, others have targeted severe/life-threatening conditions or innovative drugs.

The publication of the Framework in 2021 has driven greater awareness and coordination between key stakeholders in the UK market access ecosystem supported by the Rare Disease Framework Board, Delivery Group and Forum.²⁴

In addition, there have been other key changes to improve access, which include:

i. Revisions to NICE's HTA methods, which has led to:

- a. Greater acceptance of uncertain evidence bases (e.g., real world evidence (RWE))
- b. Consideration of a broader range of QoL measures in both single technology appraisal (STA) and highly specialised technologies (HST)
- c. Proportionate approach to drug assessments (i.e., streamlined approach to lower risk therapies) to increase capacity for more complex submissions
- d. Changes from an “end of life” quality-adjusted life year (QALY) modifier to a “severity” based modifier for the STA
- e. HST committees with appropriately skilled members starting to sit on STA committees to share experiences of assessing rare disease treatments
- f. Simpler and clearer entry criteria for HST assessment

ii. Launch of ILAP and IMF intended to accelerate and improve access to innovative drugs (in which many rare disease drugs may sit) and address some of the access issues observed in the system

Background

In 2013, the Government published its first UK Strategy for Rare Diseases, followed by the development of nation-specific implementation plans.

The key objective of the strategy was “to ensure that people living with a rare disease have the best quality of evidence-based care and treatment that our health and social care systems, working with charities and other organisations, our researchers and industry, can provide”.

Following this 2013 strategy, several pathways/schemes were set up by Nations across the UK to support access, such as the: i) launch of the HST NICE assessment process in 2013; ii) launch of the Early Access Medicines Scheme (EAMS) in 2014; iii) SMC's introduction of the Patient and Clinician Engagement (PACE) scheme in 2014; iv) introduction of the New Treatment Fund in Wales in 2017; and v) introduction of the ultra-orphan pathway in Scotland in 2018.



²⁴ <https://www.gov.uk/government/publications/uk-rare-diseases-framework/the-uk-rare-diseases-framework>

Overview of the UK Rare Diseases Framework 2021

Building on the first UK Strategy for Rare Diseases, the Government published the UK Rare Diseases Framework in 2021. Its four priority areas are:

- 1** **Helping patients get a final diagnosis faster**, timely access to treatment, provide possible prognosis and offer options for family planning
- 2** **Increasing awareness of rare diseases among healthcare professionals (HCPs)**, including use of genomic testing and digital tools to support faster diagnosis and better care
- 3** **Better coordination of care** throughout a rare disease patient's journey
- 4** Improving access to specialist care, treatment, and drugs
Focus of this report

Priorities 1, 2 and 3 address the infrastructure and systems that support rare disease diagnosis, HCP awareness, and broader coordination of care. Priority 4 addresses both the incentives and specialised pathways, and specific funding allocated to support access for orphan drugs – this priority forms the focus of this report.

The Framework provides a five-year strategic direction for the UK, with each of the constituent Nations obliged to develop their own specific action plans to drive progress against these priorities, each with specific and measurable actions and outcomes. Three key groups have been set up to coordinate rare disease stakeholders, drive policy, set action plans as well as monitor progress against them. These are all chaired by senior stakeholders from Government, DHSC and the NHS to ensure experienced oversight.

The key groups, their purpose and their chairs include:

- **UK Rare Diseases Framework Board**
Ensures alignment and co-ordination of rare disease policy and action plans across Nations – co-chaired by Deputy Chief Medical Officer (DCMO) for England and rotates between individuals of equivalent seniority from the devolved governments
- **Rare Disease Framework Delivery Group**
Responsible for producing and monitoring progress of Nation-specific action plans – England's Group is chaired by Deputy Director, NHS Quality, Safety, Investigations directorate in the DHSC
- **UK Rare Diseases Forum**
Supports engagement between the Framework Board, Nation-specific delivery groups and the rare disease community (e.g., patient groups, clinicians) – chaired by Alastair Kent, previously co-chair of the UK Rare Disease Policy Board

England published its action plan in February 2022, with an update and progress report released in February 2023,^{25, 26} Northern Ireland (NI) published its action plan in March 2022 with a progress report in September 2023. Wales and Scotland also published their own action plans in 2022 with progress updates still pending.^{27, 28, 29, 30}

England's action plan is highly detailed and sets out 29 action points to date, which were developed in conjunction with patient groups, clinicians, and industry. Similar actions against the four priorities were outlined in the action plans for Scotland, Wales, and NI. The impacts of actions relating to priority 4 are detailed on the following page.



²⁵ <https://www.gov.uk/government/publications/england-rare-diseases-action-plan-2022/england-rare-diseases-action-plan-2022>

²⁶ <https://www.gov.uk/government/publications/england-rare-diseases-action-plan-2023/england-rare-diseases-action-plan-2023-main-report>

²⁷ Northern Ireland Department of Health: Northern Ireland Rare Diseases Action Plan 2022/23 (2022)

²⁸ Northern Ireland Department of Health: Northern Ireland's Rare Diseases Action Plan Progress Report Year 1 (2023)

²⁹ <https://executive.nhs.wales/networks/implementation-groups/rare-diseases/wales-rare-diseases-action-plan-2022-2026>

³⁰ <https://www.gov.scot/publications/rare-disease-action-plan/>

Priority 4 – Improving access to specialist care, treatment, and drugs

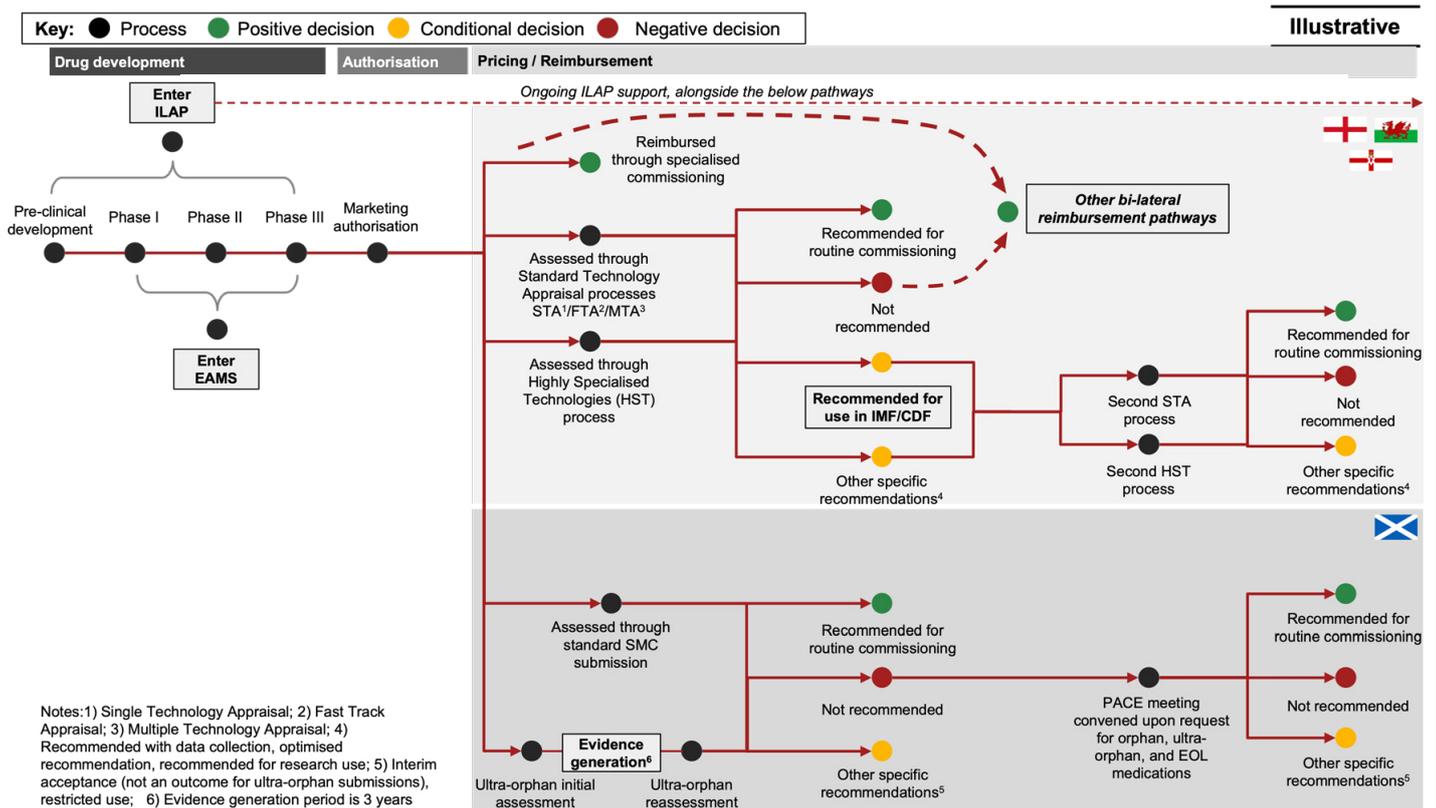
Providing timely access to specialist expertise and treatments can be challenging as rare diseases are more complex and may be less well understood relative to other types of diseases. The UK has an existing foundation of specialist NHS centres and clinicians which enable rare disease patients to receive expert care and innovative treatments. Priority 4 has a clear aim to “improve the pathway for rare diseases treatments reaching patients on the frontlines of clinical care”.

There has been some progress against this, with changes to: i) the HTA methods for all drugs through the Methods Review; and ii) initiatives to improve access to innovative therapies, which will include orphan drugs. These have been summarised in table 1 and their position in the overall access landscape in the UK has been outlined in exhibit 2.

Table 1 – Key initiatives to UK improve the access to innovative therapies since 2021 (not specific to orphan drugs)

Initiative	Stakeholders	Date	Objective
ILAP	<ul style="list-style-type: none"> MHRA NICE / SMC / All Wales Therapeutics and Toxicology Centre (AWTTC) NHS England / NHS Improvement 	2021	Facilitating access to innovative and novel treatments by offering support through the development, regulatory and reimbursement process
Methods Review for health technology evaluation	<ul style="list-style-type: none"> NICE 	2022	Create fairer, faster, and more consistent HTAs
IMF	<ul style="list-style-type: none"> NHS England NICE 	2022	Allocate £340m per year to fund access to innovative non-oncology drugs ‘recommended with managed access via the IMF’ through the NICE HTA process

Exhibit 2 – Current pathways in the UK for orphan drugs, including specific pathways for ultra-orphan drugs



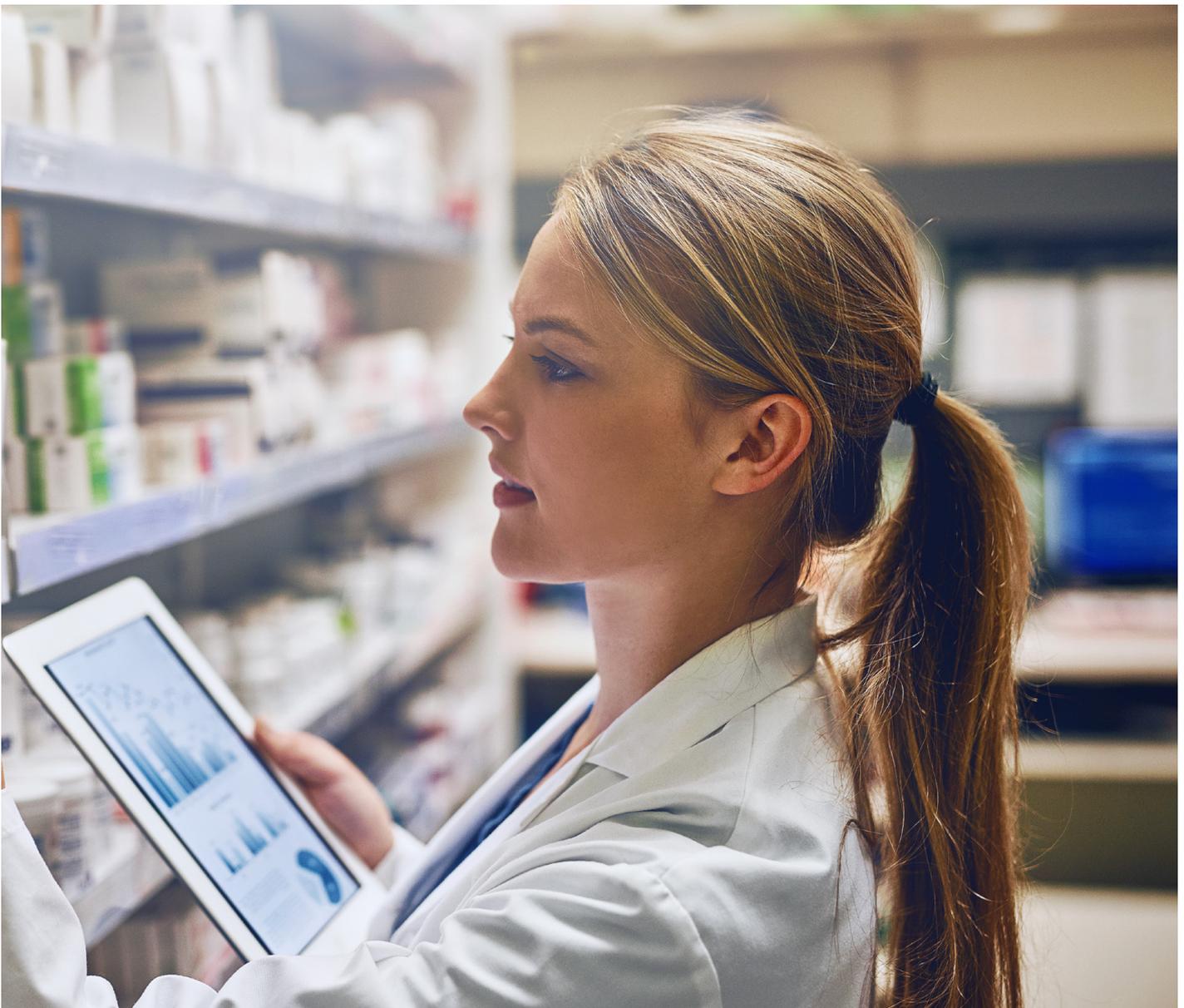
Assessment of the Framework

From the desk-based research, interview programme and roundtable discussions conducted as part of this report, there were some positive views of the Framework from industry participants, with a number of benefits cited such as: i) increasing the awareness of rare diseases amongst regulatory stakeholders, clinicians and the broader public; ii) the creation of detailed national action plans; and iii) encouraging greater system coordination, all of which is supported by senior stakeholder ownership. However, given the relative recent development of the Framework, it is still too soon to measure its full impact.

The Framework has raised awareness of the challenges faced by rare disease patients, carers, and the healthcare system itself. It has also highlighted the challenges in accessing rare disease treatments faced by patients and their families, several of which have been noted in the introduction. It is important to continue to highlight these challenges and keep the priorities of the framework in focus, particularly given other healthcare system pressures.

The Framework is also underpinned by action plans from each Home Nation; England's action plan identifies specific owners for each action and clearly states the approaches used to assess progress against each action. Furthermore, there has been a commitment made in England's 2023 action plan to evaluate the effectiveness of some of the pathways created to facilitate access to orphan drugs, which includes EAMS, ILAP, and the IMF.

Finally, the Framework has encouraged greater coordination amongst stakeholders within the rare disease community (such as patients, carers, and clinicians), ensuring the priorities that have been developed are aligned to patient needs. The Rare Disease Framework Board, Forum and Delivery Group are key groups that have been set up to drive governance and progress and are led by senior stakeholders from government, NHS executive members and experienced civil servants. This level of engagement should help to ensure that there are material improvements against the four priorities, even if there are no direct changes to local-level NHS operational plans.



Review of existing and new access initiatives

EXPLAINER

EQ-5D

- The EQ-5D is an approach to measuring the quality of life of an individual
- It consists of a series of questions that asks the respondent to rate their health across 5 dimensions: i) mobility, ii) self-care, iii) usual activities, iv) pain / discomfort, v) anxiety / depression

<https://euroqol.org/eq-5d-instruments/>

Quality Adjusted Life Years (QALY)

- A QALY is a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life
- One quality-adjusted life year (QALY) is equal to 1 year of life in perfect health

<https://www.nice.org.uk/glossary?letter=q>

NICE Methods Review

Background

NICE is responsible for assessing the cost-effectiveness of a drug and determining whether it can be recommended for routine commissioning and reimbursement in the NHS. NICE typically conducts its evaluations for orphan drugs through one of two key pathways:

i) Single Technology Appraisal (STA)

- Covers a single technology for a single indication

ii) Highly Specialised Technologies (HST)

- Covers drugs for ultra-rare diseases

Each evaluation process is overseen by separate committees, which include health and social care professionals, along with therapeutic area experts, health economic experts, patients, and carers.

In January 2022, NICE concluded its Methods Review and introduced: i) a revised HTA evaluation process and updated guidance for the evaluation of diagnostic tools, drugs and medical technologies; and ii) the simplification of the criteria used to determine whether a drug is assessed via the HST process. NICE has also stated that in the future, it will make more targeted updates to its HTA methods and processes (compared to the Methods Review, which was extensive) to allow it to adapt faster and be more flexible with its processes as newer technologies come to market.³¹

The main method changes introduced by NICE as a result of the Methods Review that impact orphan drugs were:

- Acceptance of greater uncertainty in evidence bases
- Provision of further guidance on the use of real-world evidence in HTAs
- Broader consideration of QoL measures when the existing standard, EQ-5D, is not appropriate
- Replacement of the end of life QALY modifier with a severity modifier, and;
- Reduction of the HST eligibility criteria from seven to four



³¹ <https://www.nice.org.uk/news/article/nice-signals-commitment-to-greater-flexibility-in-its-evaluation-of-promising-new-health-technologies-and-making-patient-access-fairer>

Background

1. Greater acceptance of uncertain evidence

Universally, randomised controlled trials are the gold standard for clinical evidence generation, whereby individuals are randomly assigned to one of two groups, one that receives the intervention being tested and the other that receives an alternative treatment (i.e., current standard of care or placebo).³² The two groups are followed up to identify any differences in outcome – it is considered to be the most robust method of evaluating the effectiveness of an intervention.

However, in the case of rare disease treatments, there are circumstances where generating robust gold-standard evidence is challenging and further data collection to resolve this is not feasible, most often due to very small patient populations and associated recruitment challenges. In these circumstances, where the evidence is sparse and relatively uncertain, NICE has stated that committees can have greater flexibility when considering this data and evidence base during the assessment for new drugs.

2. Further guidance on use of RWE

RWE is a type of clinical data gathered when a drug is administered to a patient outside a controlled trial setting. One of the other key outcomes of the Methods Review was NICE's commitment to allow greater consideration of RWE in drug HTA evaluations. Part of this commitment has included the publication of an RWE assessment framework to upskill and guide committees when assessing this evidence, by: i) helping them identify when they can use real-world data to reduce uncertainties and improve guidance; and ii) describing best-practices for planning, conducting, and reporting RWE studies.³³

Impact of accepting greater uncertainty and use of RWE

These two changes are relatively recent, but there are emerging case studies of how this might work in practice. One such case study details NICE's review of Takeda's mobocertinib for non-small cell lung cancer (NSCLC) in 2022.³⁴ In this review Takeda presented data comparing the impact of its intervention in a single arm trial against RWE from the use of alternative treatment options in the USA and Germany. These two data sources had been combined to create a single blended comparator, demonstrating the impact across all the other available options. The use of RWE from other countries and the blended comparator defined in the study created uncertainty for the committee evaluating the drug, because some of the treatments that were compared against mobocertinib are rarely used in NHS practice, so the comparability of the findings were questioned.

In this case, NICE's RWE framework helped guide Takeda in the development of an alternative comparator that excluded drugs that were rarely used in the NHS and worked with them to reduce any potential for confounding due to differences in the underlying patient characteristics in the RWE data. Ultimately, the drug was approved for routine commissioning in January 2022.³⁵

Assessment

These changes are welcome and are potentially beneficial for rare disease drugs. These will typically target small, paediatric patient populations, where there can be significant uncertainty in clinical trial data, and it may not always be possible to conduct randomised controlled trials, resulting in pharmaceutical companies relying on other types of clinical evidence to support the HTA.

While the case study of mobocertinib is a useful example to show how this can work in practice, this remains a very recent change and it will be important to monitor how these changes are implemented in order to assess their full benefit and impact.



³² <https://www.nice.org.uk/process/pmg4/chapter/determining-the-evidence-for-review-and-consideration#-types-of-evidence>

³³ <https://www.nice.org.uk/corporate/ecd9/chapter/overview>

³⁴ <https://indepth.nice.org.uk/use-of-a-real-world-data-external-control-arm/index.html>

³⁵ <https://indepth.nice.org.uk/use-of-a-real-world-data-external-control-arm/index.html>

3. Broader consideration of QoL measures

Background

As noted earlier, the EQ-5D has been the traditionally preferred QoL measure used by NICE in its HTAs.³⁶ Following the Methods Review, NICE has committed to consider a broader range of QoL measures, by publishing a hierarchy of different types of measures (including condition-specific measures) and when/where they can be considered – see exhibit 3.³⁷

Evidence of the impact

The use of condition-specific QoL measures is particularly beneficial for rare disease populations, where conditions can be highly complex and specific to a particular cohort of patients. There is some evidence currently of other QoL measures being considered and accepted by NICE, as seen in the assessment of ataluren for Duchenne muscular dystrophy (DMD) in 2023³⁸. This assessment used a tailored health economic model that used a DMD-specific QoL measure that better captured the impact of DMD on patients (relative to EQ-5D). This is a direct outcome of Project HERCULES, which was a concerted effort involving Duchenne's patients, patient groups and manufacturers working together to produce a more suitable approach to modelling and capturing the impact of disease on this patient population³⁹. The Duchenne's QoL measure is one of the few examples of well-developed alternatives to the EQ-5D that has been accepted in practice.

Assessment

Overall, this is a positive shift to support access to orphan drugs, as the EQ-5D measure is often less suitable for them, given that they often impact paediatric populations, their symptoms can be complex, and they will also impact patient's families and carers. The EQ-5D does not currently capture the impact of the disease on families and carers. Furthermore, as these paediatric patients grow up and develop, the severity of impact may often change for the worse.

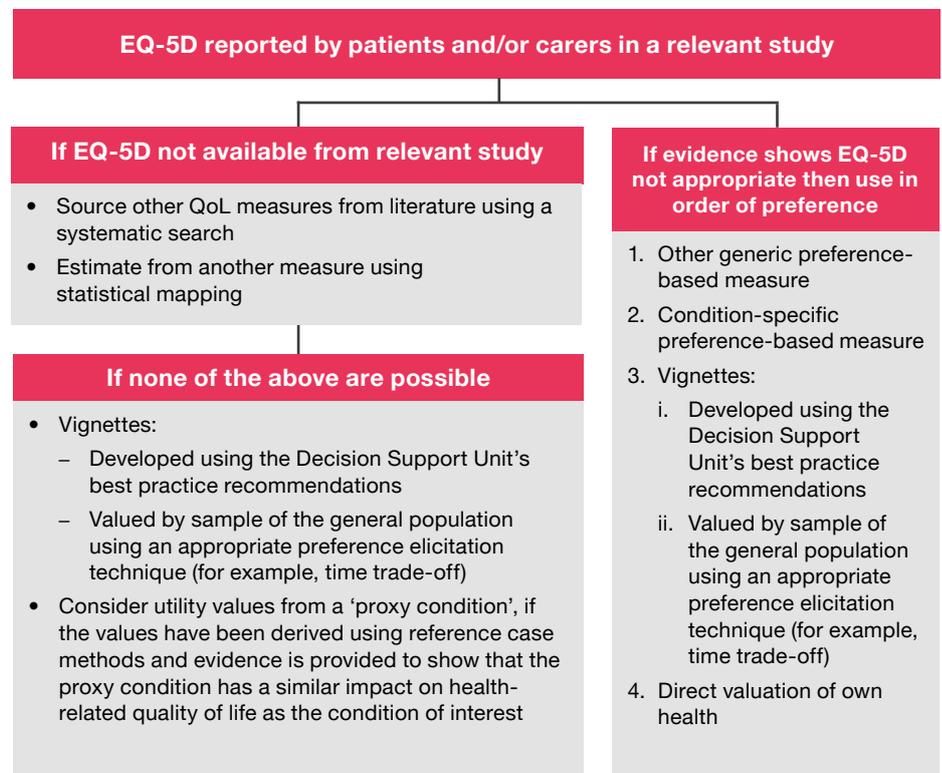
Therefore, this shift should support evaluations of orphan drugs, by enabling manufacturers to better demonstrate the impact of these diseases through more appropriate measures.

Some stakeholders have noted that whilst a broader range of QoL measures will be considered when the EQ-5D is inappropriate, there is a need for pragmatism as having specific measures for each disease may not be feasible. This is due to the large number of diseases that exist, with each individual measure needing to be validated for use in evaluations, which may not be practical.

Nevertheless, this is a step in the right direction and further engagement between patient groups, academics, clinicians and regulators would support the development of broader range of acceptable QoL measures for future use. While more time is required to better understand when and how the new approach will work in practice, as well as what type of other QoL measures would be acceptable to NICE committees, there is a clear need to use other QoL measures to support faster access.



Exhibit 3 – NICE hierarchy of preferred QoL methods



Notes: 1) Vignettes are used to describe the health states associated with a disease or condition; 2) The Decision Support Unit provides advice and supports NICE with i) technical support, ii) methodological development, iii) analytics, iv) education and v) quality assurance of economic models

³⁶ <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l>

³⁷ NICE: NICE health technology evaluations: the manual (2022)

³⁸ <https://www.nice.org.uk/guidance/hst22/chapter/3-Committee-discussion>

³⁹ <https://www.duchenneuk.org/duchenne-uk-and-project-hercules-announce-new-patient-centred-quality-of-life-tool-for-duchenne-muscular-dystrophy>

4. Change from an End of Life to a severity based QALY modifier

Background

NICE utilises a cost-effectiveness approach to determine the circumstances in which a drug can be approved for routine reimbursement. This approach calculates the value of an incremental cost-effectiveness ratio (ICER), which compares the incremental cost to the incremental gain in health (measured as a QALY) of a new drug, relative to a chosen comparator therapy. NICE sets a separate threshold for the STA and HST processes, and a drug must demonstrate an ICER of below this to be recommended for reimbursement – in the STA this is £20-30k, whereas in the HST this is £100-300k.⁴⁰

In certain circumstances during the STA process, NICE can apply a quantitative modifier to the QALY, to better reflect the value of the added health benefit of providing a drug to patients, over and above the calculated QALY. The benefit of this is that it increases the QALY value, which reduces the ICER that is calculated and increases the likelihood that a drug will meet NICE's thresholds for reimbursement. Historically, this modifier could only be applied to drugs which benefitted patients at the end of their life, an end of life (EOL) modifier, and NICE had the ability to apply a modifier of 1.7x to a QALY, where the treatment is for patients with a short life expectancy or where there is significant evidence to show the life-extending benefits of a drug.⁴¹

Following the Methods Review, NICE replaced this EOL modifier with a severity-based modifier, which: i) shifts the criteria for eligibility for this modifier away from patients nearing the EOL to patients with a severe disease; and ii) provided a broader range of modifiers of 1.2x and 1.7x, depending on the severity of the condition.⁴²

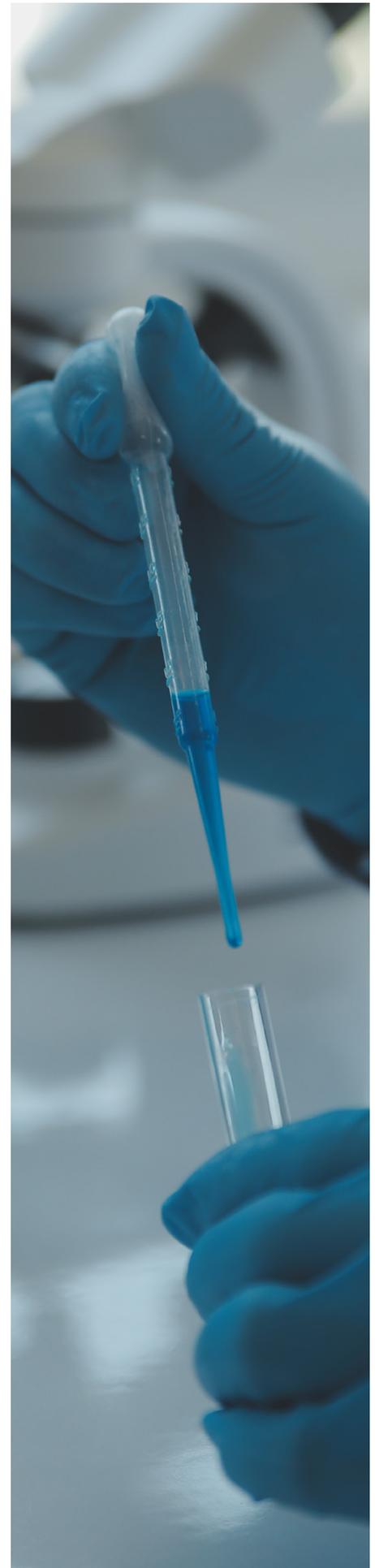
Review of the impact

The shift from EOL to a severity-based modifier could benefit many rare disease drugs, as the diseases they target are more likely to be severe in nature. Additionally, not all orphan drugs will be targeted for EOL patients, and therefore this broader modifier could benefit more orphan drugs overall. Stakeholders also noted that the previous modifier tended to benefit oncology drugs over rare disease drugs specifically.

However, industry stakeholders have reported that the application of the severity modifier is unclear and may benefit from greater flexibility and transparency in how it can be applied for severe conditions. The new modifier was designed to be "opportunity cost neutral" compared with the EOL modifier, meaning the overall financial impact on payors is similar to the EOL modifier.⁴³ Furthermore, an independent assessment from the Office of Health Economics has noted that NICE's threshold to benefit from the higher severity modifier of 1.7x is higher relative to the thresholds for similar modifiers taken in other countries such as Netherlands or Norway.⁴⁴ Interviewee feedback on this change also highlighted that this approach does not consider the severity of impact on families and carers, albeit we understand that this is considered qualitatively during the committee discussions instead.

Ultimately, the change to a severity modifier better captures the nature of the impact of many rare diseases, but the crucial factor is how it is applied. For rare disease treatments routed to STA, modifiers can provide an important opportunity to help meet the STA's cost-effectiveness thresholds.

For many drugs, the lower 1.2x modifier may not provide a sufficient increase in the QALY to meet the ICER thresholds and could result in a negative decision from NICE.



⁴⁰ <https://pharmaphorum.com/market-access-2/how-does-rare-disease-prevalence-impact-drug-pricing-england>

⁴¹ NICE: Guide to the methods of technology appraisal 2013 (2013)

⁴² NICE: NICE health technology evaluations: the manual (2022)

⁴³ <https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/technology-appraisals/methods-processes-and-topic-selection-review-board-paper-appendix.docx>

⁴⁴ <https://www.ohe.org/insight/nices-severity-modifier-step-right-direction-still-long-way-go/>

5. Reduction in the number of the eligibility criteria for HST

Background

The HST process is a separate HTA pathway for ultra-rare diseases, and benefits from a higher cost-effectiveness threshold compared to the STA. NICE decides whether drugs are eligible for the STA or HST process and will route drugs accordingly. Before the Methods Review, there were seven qualitative criteria used to assess eligibility for HST, which were:⁴⁵

1. **Target patient group is so small** that treatment is usually concentrated in very few NHS centres
2. The target patient group is **distinct for clinical reasons**
3. **Chronic and severely disabling** conditions
4. Expected to be used exclusively in the **context of a highly specialised service**
5. Likely to have a very **high acquisition cost**
6. Potential for **life-long use**
7. **Significant need** for national commissioning

Following the Methods Review, the number of eligibility criteria for a drug to be routed through HST was reduced from seven to four.⁴⁶ These are:

1. Disease is **very rare** – prevalence less than 1 in 50,000 people
2. No more than **300 people** eligible for the technology in its licensed indication and no more than 500 across all indications
3. Disease for which the technology is indicated **significantly shortens life or severely impairs QoL**
4. No **other satisfactory treatment options**, or there is **significant additional benefit over existing treatments**

Review of the impact

It is still early to gather data on the impact of the change of this routing criteria. However, it is worth noting, from stakeholder interviews, the intention behind this change was not to increase the number of drugs going through HST, rather it was to make the criteria clearer for manufacturers.

More broadly, the HST process itself appears to be working well, particularly as a dedicated route to support access to ultra-orphan drugs. The effectiveness of the pathway was demonstrated in a 2021 study comparing the types of recommendations provided via the HST to orphan drug outcomes from the STA process between 2015-2020.⁴⁷

Of 12 outcomes from the HST process in this period, 100% received a normal positive recommendation, compared to 63% for orphan drugs in the STA pathway.

Of the remaining 37%, the vast majority received an optimised recommendation (see callout opposite) as opposed to being rejected but this narrows the eligible patient population.

This demonstrates the effectiveness of the HST process, with its higher thresholds for cost-effectiveness supporting access to drugs that may perhaps have otherwise not been recommended or optimised.

NICE process outcomes for a HTA (non-exhaustive)

- Recommend - case for adoption for applied indication is fully supported by evidence presented
- Optimised - case for adoption is partially supported, so the technology is recommended in specific patient populations or circumstances
- Managed access use in the CDF or IMF - case is not currently supported but the technology has the potential to be cost effective and has potential to provide significant patient or healthcare system benefits if uncertainties in the evidence are addressed
- Not recommended - case for adoption is not supported

<https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance#technology-appraisal-decisions>

<https://www.nice.org.uk/process/pmg36/chapter/committee-recommendations#recommending-a-technology>



⁴⁵ <https://source-he.com/the-nice-hst-process-2-3-differences-in-assessment-of-cost-effectiveness-between-the-hst-and-sta/>

⁴⁶ <https://www.nice.org.uk/process/pmg37/chapter/highly-specialised-technologies>

⁴⁷ <https://ojrd.biomedcentral.com/articles/10.1186/s13023-021-01845-x>

Assessment

Manufacturers and patient groups welcomed the intention to make the criteria simpler and clearer. From our stakeholder discussions, routing criteria 1 and 2 were seen to be beneficial in providing greater simplicity and clarity over the prevalence and patient number thresholds. These were previously undefined and open to interpretation. Additionally, criteria 3 and 4, the qualitative criteria for severity and presence/effectiveness of other treatment options, are helpful in providing a degree of flexibility when deciding how to route drugs that are close to the quantitative criteria. However, concerns were raised about the new routing criteria. Routing criteria 1 and 2, relating to prevalence and patient numbers, while clearer, were felt to be highly selective given the requirement to meet a high bar for both prevalence and eligibility criteria.

Effectively only treatments for ultra-rare diseases can be eligible because of the 1 in 50,000 limit on prevalence. Stakeholders also noted that there was insufficient clarity on how precisely conditions were defined for the purposes of routing (e.g., for criteria 1 or 2, it is unclear if the sub-type of a disease is considered, if a group of sub-types is considered together, or if the broader disease is considered instead).

On the qualitative criterion for severity, stakeholders felt that the approach to decision-making when this criterion is used could benefit from greater transparency and consistency.

In combination, these factors were felt to make the HST process more challenging to enter, with the result being that many orphan drugs end up being routed through STA, where the cost-effectiveness thresholds are much lower and orphan drugs were more likely to receive a negative reimbursement outcome.

The HST process itself is seen to be effective for the ultra-orphan drugs which meet the entry criteria, in that it is a dedicated route to support access for drugs which target an unmet need. The HST committee, which oversees HST drug evaluations, was considered to be more experienced given its focus on evaluating rare disease treatments.



On evaluations, the committee also places greater weighting (relative to the STA) on the patient and clinical voice given the greater uncertainty in the evidence. Finally, and perhaps most importantly, drugs routed through HST benefitted from a higher cost-effectiveness threshold (relative to the STA) of £100k-£300k/QALY, which should benefit orphan drugs.

Overall, the changes will go some way to help provide manufacturers with more clarity over the entry criteria for HST. When accessed, the pathway appears to be working well, with no drugs receiving a 'not recommended' outcome. Drugs instead tended to receive a normal, non-optimised, outcome. There are some concerns that remain around the changes to the criteria, particularly with criteria 1 and 2, but NICE seems to be aware of these concerns and notes in its HST manual that these highly selective criteria are required because it is a "deliberate departure from the standard technology appraisal process" and the criteria "intentionally do not seek to capture every case".⁴⁸

Other recent HTA process changes

Although not directly related to the Methods Review, there have been some other changes made to NICE's processes that should help to either increase capacity for more complex drug evaluations such as orphan drugs through a more proportionate approach or increase experience of rare diseases in STA evaluations to evaluate them in a more informed way. Separately, as part of the Methods Review, NICE reviewed its reference case discount rate of 3.5% on health gains and costs and agreed that there is a case for change to a lower rate of 1.5%, which would benefit many orphan drugs. However, due to factors outside the scope this review, this discount rate was maintained at 3.5% - the impact of this is discussed in further detail below.

⁴⁸ <https://www.nice.org.uk/process/pmg37/chapter/highly-specialised-technologies>

1. Proportionate approach to drug evaluations

In recognition of the increasing number of complex therapies in the pipeline, NICE piloted and introduced the proportionate approach to technology appraisals in 2022, to increase NICE's capacity for publishing appraisals by 20% from 2023-24.^{49, 50} In theory, this change will enable faster evaluations for low-risk, low-complexity treatments with the aim of increasing capacity for more complex orphan drug appraisals. While it is still too early to see the full beneficial impact of this change in approach, there are several emerging examples of how this would help speed up some evaluations, as seen in the case studies provided by NICE below:⁵¹

Somatagron for treating growth disturbance

7 weeks

faster than standard processes

Vutrisiran for treating amyloidosis

20 weeks

faster than standard processes

Nivolumab for resectable non-small cell lung cancer

9 weeks

faster than standard processes

2. Building experience of rare diseases in STA evaluations

NICE is aware of the need to build more experience of orphan drug HTAs, particularly within STA committees. In response to this, NICE HST committee members, who are experienced in dealing with complex drugs, uncertain evidence bases and RWE as part of their HST experience, are beginning to sit on STA committees to share their insights and learnings.

This change will benefit orphan drugs that are going through the STA, and the more informed committees should be better able to deal with complex drug evaluations alongside a fairer and more informed review of their evidence base. In doing so, this should enable more consistent evaluations and support STA committees who deal with orphan drug submissions.

Stakeholders have noted that there remains scope to minimise the variability in interpretation of evidence from the external assessment groups (EAGs), which both consider the evidence submitted by manufacturers and build economic models to support committees' decision making. Furthermore, there is a need for more consistent reviews and greater transparency of assessment outcomes from across different EAGs, particularly with orphan drug assessments.

Nevertheless, this change would be welcomed by industry and these changes are likely to improve access to orphan drugs, many of which will end up going through the STA process.

3. Reference discount rate

During the Methods Review, NICE assessed the case for changing the reference-case discount rate used in health economic evaluations from 3.5% to 1.5%. Discounting is an economic method used to assess the costs and benefits of an intervention over time, and results in outcomes accrued today being valued more highly than outcomes accrued in the future. The HM Treasury Green Book outlines a differential discount rate of 1.5% for health outcomes and 3.5% for costs as most appropriate.⁵² However, NICE uses a discount rate of 3.5% for both health outcomes and costs. After the Methods Review, NICE concluded that there is an evidence-based case for changing the reference-case discount rate to 1.5%. Despite this, NICE has been unable to make this change due to "wider policy and fiscal implications and interdependencies" that were deemed to be beyond the scope of the Methods Review.⁵³

The discount rate of 3.5% used in health economic evaluations has previously been cited as a barrier to access, as this rate makes it more challenging to demonstrate the cost-effectiveness of high-cost one-off orphan drugs where health benefits are realised over a longer period of time. Furthermore, the health economic models used in HTA processes do not typically capture the lost productivity among the carers and parents looking after patients with rare diseases. While there is a non-reference discount rate of 1.5% that can be applied and support the evaluation of certain orphan drugs, NICE has stated that this is to be only used in exceptional circumstances, given the need to be cognisant of broader budgetary pressures. This is seen in practice, with very limited use and with limited transparency over its application, making it difficult for companies to understand when it might be applied.



⁴⁹ <https://www.nice.org.uk/about/what-we-do/proportionate-approach-to-technology-appraisals>

⁵⁰ NICE: Proportionate approach to technology appraisals: final report 2022-23 (2023)

⁵¹ <https://www.nice.org.uk/about/what-we-do/proportionate-approach-to-technology-appraisals>

⁵² <https://www.gov.uk/government/publications/the-green-book-appraisal-and-evaluation-in-central-government/the-green-book-2020>

⁵³ <https://www.nice.org.uk/Media/Default/Get-involved/Meetings-In-Public/Public-board-meetings/nov-22-pbm-CHTE-methods-process-and-topic-selection.docx>

Overall conclusion on Methods Review and recent HTA process changes

The Methods Review, along with more recent changes, such as the proportionate approach to assessment and HST committee members beginning to sit on STA committees, are a clear step forward to improve the reimbursement pathway for innovative drugs. Many of these changes will directly benefit orphan drugs as well. However, orphan drugs and some ultra-orphan drugs will continue to go through the STA process, where they must demonstrate a much lower ICER in order to be recommended for reimbursement and there is limited evidence of the impact of recent changes.

There are some promising examples of how some of these changes are working in practice, such as the way RWE and uncertain evidence are being considered in evaluations, and how the proportionate approach to assessment is helping speed up the assessment of lower complexity drugs. However, there are challenges that still remain that need to be addressed going forward.



Innovative Medicines Fund

Background

The IMF was set up in June 2022 by NHS England and NICE with the aim of providing a consistent and transparent process for managed access agreements (MAAs) for non-oncology drugs at a “responsible price”.¹⁶

Prior to the IMF, a number of MAAs had been agreed to support access to non-oncology drugs but these were not delivered through a specific fund or process. The IMF defined principles for faster patient access to non-oncology treatments, whilst allowing for a further data collection period of five years to build the evidence-base to be recommended for routine commissioning.

Drugs can be recommended for use via the IMF when they do not meet the cost-effectiveness thresholds of the STA or HST, but they have the potential to demonstrate cost-effectiveness with this additional data collection.

The IMF has been modelled on the Cancer Drugs Fund (CDF), which was set up in 2010 and modified in 2016. The CDF has been successful, as judged by increasing access to therapies. The most recent statistics from July 2022 shows that more than 80,000 patients have benefitted from being able to access life-extending/saving drugs who might not have been able to if the therapies had gone through routine commissioning.⁵⁴ Similar to the CDF, the IMF has an annual budget of £340m.

Evidence of the impact

The objectives of the IMF have been welcomed across the rare disease community, from patients, patient advocacy groups, manufacturers, and clinicians. While targeted at all types of innovative therapies, the fund provides a particular opportunity to support access to rare disease treatments, particularly where there is a limited evidence base.

However, since it was launched in June 2022, no MAAs for drugs, rare disease or otherwise, have been agreed through the IMF.

Assessment

The failure to agree any MAA may be in part due to:

- i. the relative newness of the fund
- ii. drugs are being appropriately appraised via the STA or HST pathway with no need for IMF funding, as has been suggested by some policymakers
- iii. how the IMF is structured

The IMF was modelled on the CDF. As a result, the same obligations are placed on drug manufacturers in the IMF, as they are in the CDF. From our research, drug manufacturers are finding these restrictions overly punitive. For example:

- i. in the event of a negative NICE recommendation after the five-year MAA period, companies are required to continue to fund, at their own cost, treatment for patients who have already received the drug
 - given that rare diseases disproportionately affect children, this could mean funding a lifetime of treatment, without the prospect of reimbursement. This would in most cases likely be commercially unsustainable. While the CDF has the same mechanism, the total length of treatment is typically shorter
- ii. the MAA allows a long time for data generation of up to five years, but there may be certain instances where orphan drugs would benefit from a longer period of data collection (e.g., drugs for paediatric populations where the benefit may only be evidenced when they are adults, or drugs for ‘nearly’ ultra-rare diseases that may narrowly miss qualifying for HST assessment, yet still require more time to evidence their cost-effectiveness due to their smaller patient populations)

The counter argument to the idea that the duration of The MAA period should be longer, is that payors should not have an obligation to continue to fund drugs if they have not proven their cost-effectiveness.

Additionally, a five-year period may be viewed as sufficient time to generate further evidence, particularly given a longer funding period may limit funding for other potential treatments that could be eligible for the IMF.



¹⁶ NHS England: The Innovative Medicines Fund Principles (2022)

⁵⁴ <https://www.england.nhs.uk/2022/07/thousands-of-patients-to-benefit-as-nhs-marks-100th-fast-tracked-cancer-drug/>



Conclusions on IMF

Despite these perceived challenges, the IMF represents an attempt to facilitate a more consistent and transparent process for faster patient access to orphan drugs.

The fact that no drugs have yet been funded through the IMF, in our view, is most likely due to the structure and mechanisms of the fund being modelled on the CDF, and the relatively onerous disincentives in relation to non-oncology medicines. Given the lack of funds deployed for MAAs to date, the review of the IMF as part of England's 2023 action plan will be an important step in refining the parameters of the fund, so that it can meet its stated objectives.

Innovative Licensing and Access Pathway

Background

The Innovative Licensing and Access Pathway (ILAP) aims to reduce the time to market for innovative medicines by facilitating engagement between manufacturers and regulators to improve timeliness of the approval, market access and reimbursement processes. Successful applicants receive an innovation passport, which allows sponsors to access a Target Development Profile (TDP) that supports drug development activities, such as compliance inspections, regulatory reviews, and evaluation of the evidence and data needed to expedite the approval process.⁵⁵

Direct engagement is provided with experts from ILAP's partner organisations – MHRA, NICE, SMC and the All Wales Therapeutics and Toxicology Centre. This access helps manufacturers design an efficient and "regulation and access ready" development programme.⁵⁶ Patient involvement is also prioritised, by connecting sponsors to the MHRA Patient Group Consultative Forum, which provides sponsors with the opportunity to engage with patients from clinical design through to real world data generation.



Eligibility criteria

To be eligible for ILAP, the medicine must either treat life-threatening or seriously debilitating conditions or address a significant patient or public health need. The medicine must also be one or more of the following: i) innovative; ii) targeted at a clinically significant new indication; iii) for a special population (includes rare disease patients as well as neonates and children, elderly and pregnant women); or iv) aligned with UK public health priorities (e.g., tackling smoking, obesity and harmful use of alcohol and drugs).⁵⁷

Typically, the ILAP is applicable for sponsors at the pre-clinical stage to phase II, with application during later stage trials being less common. It is likely to be most beneficial at early-stage development, especially for small start-ups with a lack of in-house resources. There is no clear trend for the type of medicines or the type of companies being awarded the passport, with both oncology and non-oncology drugs benefitting from this as well as pharmaceutical companies of a range of sizes.

The MHRA has indicated that the "next phase" for ILAP may include narrowing ILAP's entry criteria.⁵⁸ This would bring ILAP's definition of innovation more in line with schemes launched by other regulators to improve access to innovative treatments, including the European Medicines Agency (EMA)'s priority medicines (PRIME) scheme and the US Food and Drug Administration (FDA)'s Breakthrough Therapy Designation (BTD).⁵⁹

Assessment of ILAP in practice

There have been 129 innovation passports awarded as of October 2023 in less than two years, indicating strong uptake by pharmaceutical companies.⁵⁸ There have also been some examples of drugs with an innovation passport receiving market authorisation and a positive reimbursement outcome. In England, these include Amicus' Pombiliti/Opfolda combination treatment for late-onset Pompe disease and Merck's Belzutifan, a treatment for adults with von Hippel-Lindau disease, which is currently being appraised via STA, with publication expected at the beginning of 2024.^{60, 61, 62} In Scotland, Gilead's Trodelvy for breast cancer, Amgen's Lumykras for lung cancer, and Pfizer's Lorviqua for lymphoma, have all received an innovation passport and were recommended for reimbursement by the SMC.⁶³ It should be noted that, with the exception of Amicus' Pombiliti/Opfolda for Pompe disease, all of these products were approved under Project Orbis, a dedicated programme for oncology products which provides a framework for concurrent submission and review among international partners, which helps to speed up approvals and patient access.⁶⁴

In general, the feedback from market stakeholders highlighted several benefits of the ILAP such as: i) its rare disease applicability; ii) offering earlier engagement between developers and regulatory bodies; iii) helping developers understand the appropriate type of evidence needed to support a successful MA and P&R process; and iv) gaining access to expert input as detailed above. In particular, it can be helpful for manufacturers with early-stage products and smaller biotechs which may not have the in-house resources or expertise to appropriately engage with regulators without ILAP.

⁵⁵ <https://www.gov.uk/guidance/the-target-development-profile-toolkit>

⁵⁶ <https://www.ecmcnetwork.org.uk/regulatory-routes-cancer-treatment-britain-innovative-licensing-and-access-pathway-ilap>

⁵⁷ <https://www.gov.uk/government/organisations/office-for-health-improvement-and-disparities/about#priorities>

⁵⁸ MHRA: Future of UK Regulation, MHRA – from Design to Delivery (2023)

⁵⁹ <https://pink.citeline.com/PS149037/UK-MHRA-Says-Time-For-Tough-Decisions-On-Entry-To-Innovative-Pathway>

⁶⁰ <https://pink.citeline.com/PS148717/Amicus-Wins-English-Funding-For-PombilitiOpfolda-Immunocore-To-Appeal-Kimmtrak-Rejection>

⁶¹ <https://www.gov.uk/government/news/first-innovation-passport-awarded-to-help-support-development-and-access-to-cutting-edge-medicines>

⁶² <https://www.nice.org.uk/guidance/indevelopment/gid-ta10817>

⁶³ <https://pink.citeline.com/PS145823/Scotland-Okays-First-ILAP-Drugs-For-Reimbursement>

⁶⁴ <https://www.gov.uk/guidance/guidance-on-project-orbis>

However, some stakeholders have also reported that resource constraints within ILAP partners have limited the effectiveness of the scheme.

Additionally, some developers noted that there was some overlap with existing schemes to support access such as NICE's Preliminary Independent Model Advice (PRIMA) and the Office for Market Access (OMA).^{65, 66}

Stakeholders have noted that it is too soon to prove the true benefit of ILAP, especially since most of the approved products with an innovation passport were also part of Project Orbis and it is challenging to disaggregate the benefit of ILAP from the benefit of Project Orbis, as well as any other market access schemes.

Furthermore, these products have so far been from larger pharmaceutical companies, which are more likely to have access to dedicated in-house resource, expertise, or funds and may have received a positive reimbursement outcome without ILAP.



PRIMA

NICE-administered programme, designed to support manufacturers review their health economic model structure, computation, coding, usability and transparency

OMA

NICE-administered programme, that helps manufacturers with market access by:

- Identifying the best people in the healthcare system for manufacturers to engage with
- Organising and facilitating confidential discussions with relevant stakeholders

Conclusions on ILAP

Overall, ILAP is an innovative new scheme that has many potential benefits and through its objectives should support rare disease populations, by helping manufacturers through the development and market access process. It is viewed as being especially useful for smaller biotechs and products at an early stage of development. Stakeholders have suggested many of the benefits of the ILAP already exist, for example manufacturers are still able to engage with regulators without the ILAP.

Therefore, the incremental benefit of the scheme has been questioned. Resource constraints within ILAP partners has also been raised a factor that has limited the effectiveness of the scheme so far. Ultimately, the process is still relatively new and its full impact on speed and likelihood of access is yet to be seen.

⁶⁵ <https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/prima>

⁶⁶ <https://www.nice.org.uk/about/what-we-do/life-sciences/office-for-market-access>

Additional change relating to the MHRA's priority review

Immediately prior to the publication of the UK Rare Diseases Framework in January 2021, the MHRA published guidance on a new 'priority review' MA timeline in December 2020.⁶⁷ This mechanism allows for a faster, 150-day assessment of MA applications, relative to the normal 210-day assessment timeline.⁶⁸

This process is open to 'high-quality' MA applications for new active substances, biosimilars and new uses of an existing active substance. Whilst not rare disease specific, there is an opportunity for orphan drugs to be eligible for this expedited review timeline. However, the criteria for what constitutes a 'high-quality' application is unclear and would benefit from further clarity.

Biosimilar medicine

A biosimilar medicine (known as a 'biosimilar') contains a version of an active substance of an approved biological medicinal product, known as the reference product.

A biological medicine is a complex medicine made or derived from a biological source.

<https://www.england.nhs.uk/long-read/what-is-a-biosimilar-medicine/>

Summary of impact of changes to UK access environment since 2021

In summary, there have been a number of changes to existing process and new initiatives introduced in the UK since the Framework was launched in 2021. Given the how recent these changes are, there is period of transition underway as these changes are embedded into regular practice. There is significant senior stakeholder engagement in the key mechanisms that have been set up to drive progress against the Framework's priorities, namely the Framework's Board, Delivery Group and Forum.

Importantly, the Framework takes a holistic approach to improving the UK access landscape to rare disease treatments, considering diagnostic improvements, better education of HCPs, coordination of patient care as well as specific initiatives to improve access to drugs, which is the focus of this report.

The intention behind the changes is positive and they have the potential to improve access. In some areas it is too early to see the results of these changes. For ILAP, while not specific only to rare disease treatments, the early signs are positive with significant uptake of the innovation passports and evidence that some ILAP drugs have received positive reimbursement. Some questions remain around whether these drugs would have received this outcome without ILAP and there is limited data on whether this is increasing the speed or likelihood of access, but the intention behind the scheme is creditable and there is an upcoming review of the scheme, which should help identify areas for improvement.

HST is a positively regarded HTA process and is seen to be working well for those ultra-orphan drugs that enter it. However, a large number of orphan and ultra-orphan drugs are still unable to benefit from the HST's higher cost-effectiveness thresholds and are instead routed to STA.

The Methods Review has implemented a number of changes that will help to improve the ability of the STA to appropriately evaluate orphan drug submissions. HST committee members are beginning to sit on STA committees and share their experiences of assessing ultra-orphan drug submissions, which are typically more complex in nature. This will also be supported by new guidance to accept greater uncertainty in the evidence base and clearer guidance when considering RWE as part of a submission. NICE has also indicated a willingness to accept other types of QoL measures when the EQ-5D is inappropriate. As with ILAP, these changes are still new and there are few case studies that show how this works in practice. Therefore, the full impact of these changes is yet to be seen, particularly with regards to understanding the impact on orphan drug evaluations specifically.

The IMF, launched in 2022, was set up with the aim of improving access to innovative drugs, which will include non-oncology orphan drugs. The structure and mechanisms of the IMF, modelled on the CDF, are not entirely appropriate for rare diseases and some of the obligations on drug manufacturers may be challenging to overcome, particularly in the event a drug is not recommended following the five-year MAA, where companies could have to fund a lengthy period of treatment at cost. While some may view the five-year data collection period as insufficient for rare diseases, the counterpoint to this is that the NHS should not necessarily continue to fund drugs that do not prove their cost-effectiveness after a five-year period. It is encouraging that this is going to be reviewed, but currently there is a sense that this is not helping rare diseases specifically and there is limited evidence to support the view that drugs are being successfully routed through STA instead.

Overall, the UK has made positive progress in improving access to rare disease treatments in recent years, and a period of transition is underway. It is important that remaining challenges are addressed in order to reach the ambition set out in the Rare Diseases Framework.

⁶⁷ <https://www.gov.uk/guidance/guidance-on-150-day-assessment-for-national-applications-for-medicines>

⁶⁸ <https://questions-statements.parliament.uk/written-questions/detail/2023-06-12/188920/>

Comparison of UK access versus other OECD countries

Introduction and rationale

Beyond assessing recent changes to the UK's access environment for orphan drugs, it is also useful to compare performance against other OECD countries and look for best practice that might be considered to improve the UK environment. Some countries have a dedicated access pathway for orphan drugs (similar to NICE's HST process for ultra-orphan drugs), whereas others may have no dedicated processes to assess orphan drugs separately. This could be because the 'normal' process supports sufficient orphan drug access. This may be due to the nature of HTA assessment undertaken, or due to the existence of a specialised fund to support access to these drugs. Reviewing other systems may provide valuable learnings for the UK to consider as it evolves its access environment.

Both the MHRA and NICE have announced that they are looking to actively collaborate with other regulatory bodies for MAs and HTAs, respectively. The aim of this collaboration is to increase capacity for new drug assessments and increase the speed of market access for all drugs, including orphan drugs.

Some examples of recent collaborative efforts include:

1. MHRA joining the Access Consortium (2020) – greater MA collaboration by sharing resources across regulatory agencies in Australia, Canada, Switzerland and Singapore, and allows manufacturers to submit a single dossier for review across multiple MA agencies.^{69, 70}

1

Aim: To increase each agency's MA review capacity and limit duplication of effort across regulatory agencies

2. NICE's active collaboration on HTAs (2022) – collaboration between NICE and other HTA bodies that take a similar approach to HTAs, including Canada and Australia.

2

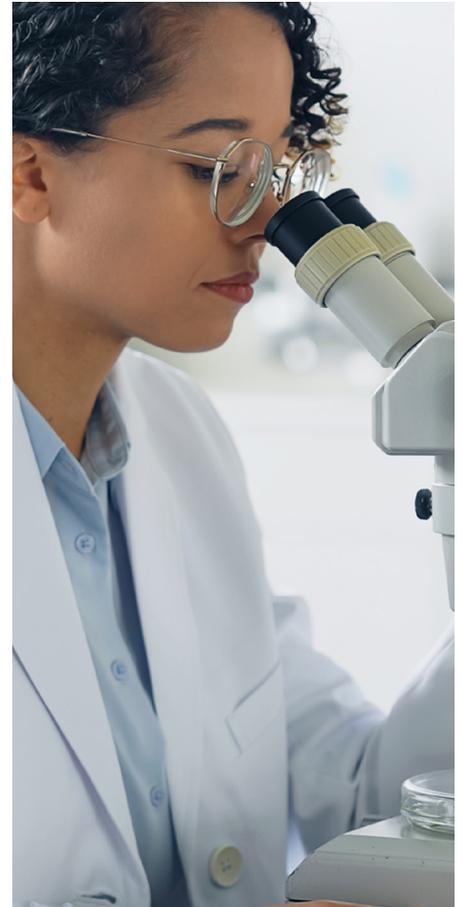
Aim: To increase speed of access by exploring the feasibility of mutually recognising decisions or using HTA information generated in other countries²⁷

3. MHRA's recognition of international MAs (2024) – recognition of MAs granted in other healthcare systems of Australia, Canada, Switzerland, Singapore, Japan, United States and European Union (the final decision on MA approval in the UK would remain with the MHRA).⁷²

3

Aim: To increase the speed of access to all drugs

This report considers six OECD countries for comparison, namely: i) Germany; ii) France; iii) Spain; iv) Australia; v) Canada; and vi) the USA. Germany, France and Spain are large European counterparts and their geographic proximity and similarity in size serve as useful points of comparison for the UK. Australia and Canada, while more distant, are comparable to the UK in that they place a similar importance on cost-effectiveness in their HTA. Finally, the USA has been considered for its high levels of innovation and market size, which make it an attractive launch country. Additionally, we note that regulatory bodies in the UK are increasingly collaborating with other international agencies and therefore this review is both timely and valuable.



⁶⁹ <https://healthbusinessuk.net/news/19052022/uk-regulator-approves-first-access-consortium-treatment>

⁷⁰ <https://www.gov.uk/guidance/access-new-active-substance-nas-work-sharing-initiative>

⁷¹ <https://www.nice.org.uk/news/article/nice-partners-with-international-health-technology-assessment-bodies>

⁷² <https://www.gov.uk/government/publications/international-recognition-procedure/international-recognition-procedure>

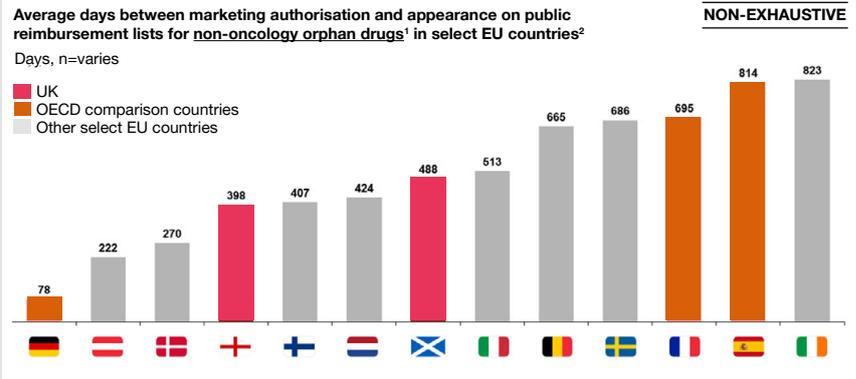
In order to compare the time to reimbursement following MA approval, and the degree of availability of medicines on reimbursement lists, the European Federation of Pharmaceutical Industries and Associations (EFPIA) publishes an annual 'Waiting to Access Innovative Therapies' (W.A.I.T.) report.⁷³ As part of the 2023 W.A.I.T. report, 44 non-oncology, orphan drugs that were granted MA between 2018-2021 by the European Medicines Agency (EMA), were analysed for their speed of access and degree of availability. On speed of access, drugs in England and Scotland took 398 and 488 days (see exhibit 4) on average respectively to appear on the reimbursement list following MA. Whilst this is faster than many other comparators, including France and Spain, it is slower than the average in Germany (78 days).

In addition to speed, the degree of availability is crucial. In the EFPIA report, the degree of availability is measured by the proportion of drugs with an MA that are either fully reimbursed through a national reimbursement system or through hospital budgets for all the patient populations targeted by a drug, or fully reimbursed for specific populations of a drug (limited availability) – see exhibit 5. Across a combination of these measures, both England and Scotland appear to be behind other markets, with fewer non-oncology orphan drugs approved on reimbursement lists (59% and 55% respectively of drugs with an MA were on reimbursement lists) compared to Germany (86%) and France (77%), albeit more than Spain (52%).

The EFPIA report also provides a breakdown of this figure, to assess the proportion of medicines available to the full patient population, versus those with limited availability – see exhibit 6. When specifically comparing the rates of full availability in England against others, the EFPIA report found that, in England, 69% of approved non-oncology orphan drugs were made available to the full patient population (the rest having limited availability), while the equivalent figure for Scotland was 71%. These figures are, however, lower than Germany (100%) and France (76%), but higher than Spain (57%).

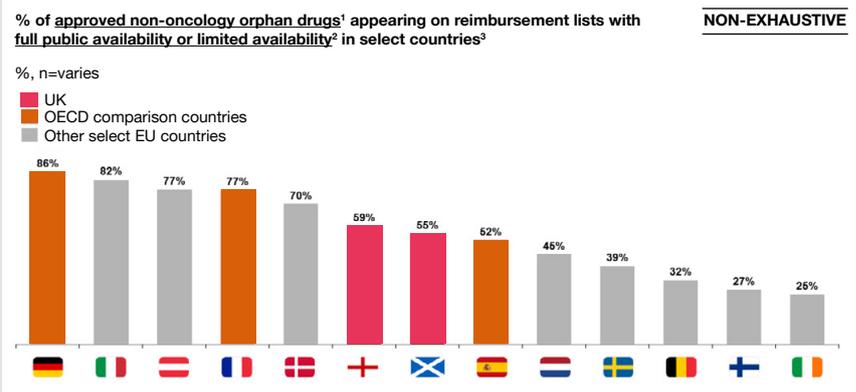
Some of these differences in speed and degree of availability can be understood by assessing the UK's access environment for orphan drugs against other OECD countries, by assessing: i) the MA and P&R process for all drugs that supports access to orphan drugs; ii) innovative or specialised pathways for orphan drugs; and iii) specialised funding to support orphan drug access.

Exhibit 4 – 2022 EFPIA W.A.I.T. indicator results for time to availability for non-oncology orphan drugs



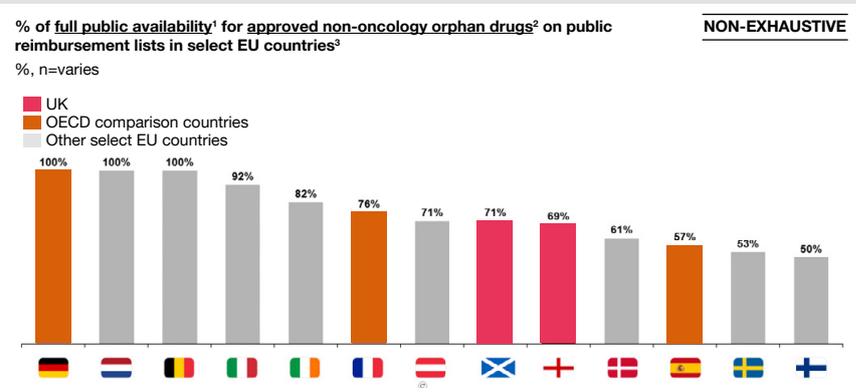
Notes: 1) From a sample of 44 non-oncology orphan drugs receiving EMA marketing authorisation between 2018-2021; 2) Countries chosen based on those selected for OECD comparison as well as those in the top 10 for GDP per capita in the EU based on latest World Bank data (exc. Luxembourg) | Source: EFPIA W.A.I.T. Report 2023, PwC Strategy& Analysis

Exhibit 5 – 2022 EFPIA W.A.I.T. indicator results for degree of full public availability and limited availability for non-oncology orphan drugs



Notes: 1) From a sample of 44 non-oncology orphan drugs receiving EMA marketing authorisation between 2018-2021; 2) Full public availability includes full reimbursement through a national reimbursement system or full automatic reimbursement by a hospital budget for all of the approved indications of a drug; limited availability includes limited reimbursement to specific subpopulations of approved indications, or on a national named patient basis, or while a decision is pending, or through a special programme (e.g. managed entry agreements); 3) Countries chosen based on those selected for OECD comparison as well as those in the top 10 for GDP per capita in the EU based on latest World Bank data (exc. Luxembourg); 3) | Source: EFPIA W.A.I.T. Report 2023, PwC Strategy& Analysis

Exhibit 6 – 2022 EFPIA W.A.I.T. indicator results for degree of full public availability for non-oncology orphan drugs



Notes: 1) Full public availability includes full reimbursement through a national reimbursement system or full automatic reimbursement by a hospital budget for all of the approved indications of a drug; 2) From a sample of 44 non-oncology orphan drugs receiving EMA marketing authorisation between 2018-2021; 3) Countries chosen based on those selected for OECD comparison as well as those in the top 10 for GDP per capita in the EU based on latest World Bank data (exc. Luxembourg) | Source: EFPIA W.A.I.T. Report 2023, PwC Strategy& Analysis

⁷³ EFPIA: EFPIA Patients W.A.I.T. Indicator 2022 Survey (2023)

Deep dive into OECD ecosystem comparisons

The OECD countries we have reviewed provide access to orphan drugs through one, or a combination of, the following:

i) MA or P&R processes that are applicable to all drugs, where there may be elements of these processes that are particularly supportive of orphan drug access, such as in:

a. Germany

- Free pricing period for all drugs and prioritisation of incremental health benefit in HTAs

b. France

- Prioritisation of incremental health benefit in HTAs

c. Australia

- Lack of a formal cost-effectiveness threshold in HTAs

d. Australia and Canada

- Parallel review of MA and HTA dossiers

ii) Specialised pathways for orphan drugs

a. USA

- Multiple mechanisms to accelerate orphan drug MA approval

b. Australia

- Life Saving Drugs Programme

c. France

- Direct access period post MA approval

d. Germany

- Abbreviated HTA pathway for orphan drugs

iii) Dedicated funding to enable access to orphan drugs

a. France

- Liste-en-Sus (supplemental reimbursement mechanism for innovative medicines)

b. Canada

- Committed funding for orphan drugs

The ways in which these pathways or funding mechanisms specifically support access to orphan drugs are discussed adjacent.

i) MA and P&R processes applicable to all drugs

The MA and P&R processes are the key regulatory and access steps that can substantially impact both the likelihood and the time for drugs to reach patients. This review has found that the MA process is broadly similar across the countries assessed.

The standard P&R process applicable to all drugs does, however, appear to vary across countries. It has been noted that there are certain mechanisms that can help support orphan drug access and these are discussed in detail below.

a) Germany – free pricing period for all drugs and prioritisation of incremental health benefit in HTAs

Perhaps the most notable example of a mechanism within the P&R process that supports rapid market access for all drugs, including orphan drugs, is in Germany. Manufacturers benefit from a 6-month free pricing period for all new drugs launched while the HTA and pricing negotiation process takes place (c.12-15 months in total).⁷⁴ This free pricing period is critical in supporting the fastest access to orphan drugs seen in the EFPIA data (78 days on average for non-oncology orphan drugs – see exhibit 4).

During the free pricing period, manufacturers are reimbursed fully through the German statutory health insurance plans. Once a price is determined, sponsors must pay a rebate reflecting any differences between the free price and final agreed price for sales from month seven onwards post-launch – effectively resulting in six months of free pricing overall.⁷⁵ Whilst this supports rapid patient access to orphan drugs and makes Germany an attractive market to launch in, it also creates a short-term burden on the healthcare system. This is evidenced by the fact that the 6-month free pricing period was reduced from 12 months in November 2022 as part of the German Financial Stabilisation Act in an attempt to limit the budget impact of this approach.⁷⁶

Unlike the UK, Germany adopts an HTA process that prioritises the incremental health benefit of a drug rather than its cost-effectiveness. This approach can support access to orphan drugs in particular given that they often have a higher price per patient relative to other drugs and have a more limited evidence base, which can make proving their cost-effectiveness more challenging. This approach may also explain the greater proportion of drugs available on reimbursement lists as per the most recent EFPIA data (exhibit 5), with 86% of approved drugs being available on reimbursement lists in Germany compared to 59% in England and 55% in Scotland.



⁷⁴ <https://www.iqwig.de/en/presse/in-the-focus/new-drugs-approval-benefit-assessment-coverage/1-drug-approval-and-early-benefit-assessment-in-germany/>

⁷⁵ <https://www.simon-kucher.com/en/insights/germany-how-gkv-finstg-law-transforming-pharma-pr-landscape>

⁷⁶ <https://www.insideeulifesciences.com/2023/07/05/germany-to-enact-new-law-with-significant-changes-to-drug-pricing-and-reimbursement-rules/>

b) France – prioritisation of incremental health benefit in HTAs

Similarly to Germany, in France the HTA process places a greater emphasis on the therapeutic benefit of a drug as opposed to its cost-effectiveness. This is measured in two ways,

i) the absolute health benefit of a drug and, ii) the health benefit relative to a comparator or standard of care. The body responsible for this process is the Haute Autorité de Santé, and it assesses these elements separately to determine pricing and reimbursement outcomes – see table 2 for a further explanation of these metrics.

Although the implication of the different scores is clear, research suggests that this process lacks transparency, and there is little guidance for sponsors to understand how each score may be achieved.

Measuring the health benefit separately, in both absolute and relative terms, perhaps adds a degree of complexity to the process. Stakeholder feedback suggests that the length of the pricing negotiation step in France, in particular, is a key factor impacting the speed of access.

These negotiations are often extensive, despite the stated policy around how the ASMR should determine the pricing of a drug. As a result, France's performance on speed of access is poorer relative to Germany, as well as England and Scotland (see exhibit 4), likely due to the additional level of complexity involved.

Table 2 – Overview of France's HTA framework⁷⁷

Type of therapeutic benefit	Metric	Use case	Scoring
Absolute health benefit	Service Médical Rendu (SMR)	Determines the proportion of public reimbursement	Extent of actual clinical benefit I – Irreplaceable – 100% II – Important – 65% III – Moderate – 30% IV – Mild – 15% V – Insufficient – not included
Relative health benefit (vs. existing therapies or current standard of care)	Amélioration du Service Médical Rendu (ASMR)	Determines the reimbursement price achievable	Extent of therapeutic advancement I – Major II – Important III – Moderate IV – Minor V – None Pricing approach depending on score I-III – European Reference Price IV – Greater than price of existing therapy V – Only reimbursed if lower than price of existing therapy

c) Australia – lack of a formal cost-effectiveness threshold in HTAs

Australia's HTA body, the Pharmaceutical Benefits Advisory Committee (PBAC), adopts a cost-effectiveness-led approach to HTA evaluations, as in the UK. The PBAC prioritises the health economic assessment of a drug, over the clinical evaluation of the drug against an identified comparator (or the current standard of care in the event of no direct comparator).

In contrast to the UK, however, where there is a defined cost-effectiveness threshold within the STA process, there is no defined threshold in Australia below which drugs are deemed to be cost-effective. This may help support orphan drug access, given these drugs typically have a higher price per patient compared to other drugs and demonstrating cost-effectiveness can be more challenging.

The benefit of the lack of a clear threshold is that evaluation committees have a greater degree of flexibility when recommending a drug for reimbursement.

However, this approach also makes it more challenging for sponsors to understand the drivers of reimbursement decisions and what level of cost-effectiveness is required to receive a positive reimbursement recommendation.

⁷⁷ https://www.has-sante.fr/jcms/r_1506267/fr/le-service-medical-rendu-smr-et-l-amelioration-du-service-medical-rendu-asmr

d) Australia and Canada – parallel review of MA and HTA dossiers

In the UK, the MA review and HTA processes are sequential, which means the HTA process can only begin following approval of an MA. However, in Australia and Canada, MAs and HTAs can occur in parallel, which means companies can submit an HTA dossier for review in advance of receiving their MA to help accelerate market access.

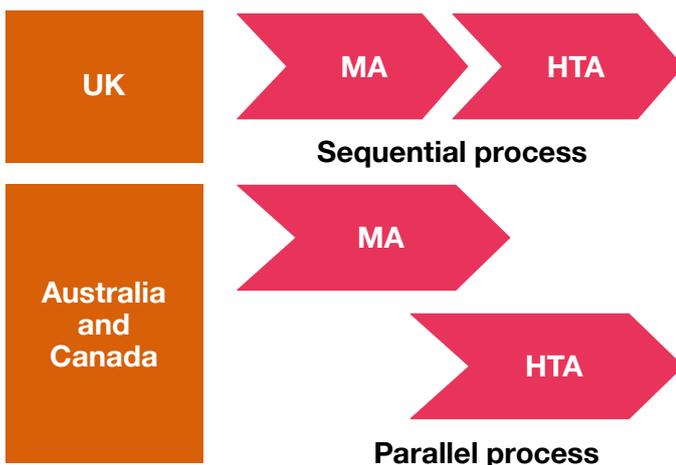
In Australia, orphan drugs can benefit from parallel processing, which is available for all new drug applications and applications for a new indication extension for an existing drug.^{78, 79} The HTA assessment commences once an indication of a positive MA review (called the positive TGA delegate's overview) is received by the manufacturer and the dossier is sent to the PBAC, which can be up to four months in advance of an PBAC assessment committee meeting. Although this process is not orphan drug specific, this process does appear to support faster access to these types of drugs relative to England and Scotland, as the average time from market authorisation to the appearance on reimbursement lists is 267 days (see exhibit 11 in the appendix) vs. 398 days for England and 488 days in Scotland (see exhibit 4).⁸⁰

In Canada, parallel processing is open to all drugs, and companies can submit their HTA dossier to the Canadian Agency for Drugs and Technologies in Health (CADTH, main HTA body in Canada) or the Institut national d'excellence en santé et services sociaux (HTA body for Quebec) up to 180 days before the anticipated date of receiving their MA. Analysis of data in Canada suggests that the parallel review process can significantly reduce the time between receiving MA approval and reaching an agreed price point to enable reimbursement (456 days if submission to CADTH occurred before MA approval vs. 791 days for submissions after MA approval). When comparing this Canadian data to the EFPIA data however, the overall speed of access to these orphan drugs in Canada is still slower than that in England and Scotland (see exhibit 4), as there is considerable complexity in the Canadian system driven by multiple sequential pricing and reimbursement steps, and final reimbursement decisions resting with individual provinces, which can involve further negotiation and complexity.⁸¹

EXPLAINER

In Canada, the P&R process for drugs to be listed on publicly-funded healthcare plans is sequential, which means drugs need to be first recommended for reimbursement before their price can be negotiated. The subsequent decision to reimburse then rests with individual provinces and may involve further negotiation between provinces and manufacturers.

Exhibit 7 – Illustrative example of how parallel review works



⁷⁸ <https://www.pbs.gov.au/info/publication/factsheets/shared/tga-pbac-parallel-process>

⁷⁹ <https://www.pbs.gov.au/pbs/industry/listing/procedure-guidance/4-presubmission-requirements/4-1-types-of-submissions>

⁸⁰ Based on analysis of reimbursement recommendations for non-oncology orphan drugs in Australia from 2020-2022

⁸¹ Canadian analysis based on the same 44 non-oncology drugs considered in the 2023 EFPIA data



ii) Specialised pathways for orphan drugs

Specialised pathways for MA of orphan drugs

Separate to the typical MA or P&R processes described already, some countries will also have specialised market access routes, pathways, or incentive schemes to support orphan drug access.

Most countries will offer a faster review process for MA, where the eligibility for this is dependent on the nature of the drug being evaluated. These will typically be accessible to orphan drugs and can help to improve the speed of access. In the UK, this is the 'priority review' process offered by the MHRA, which offers an accelerated 150-day MA review. This period is in line with that of equivalent processes offered by the MA bodies in Australia (150 working days) and Europe (European Medicines Agency, 150 days). Separately in the USA, there are a variety of mechanisms to support accelerated MA of orphan drugs, which are detailed below.

a) USA – multiple mechanisms to accelerate orphan drug MA approval

In the USA, there are a number of mechanisms in place to accelerate the MA review process for new drugs which target an unmet need in the treatment of a serious or life-threatening condition.⁸² These mechanisms will therefore capture orphan drugs as well (see exhibit 8), and are termed:

- Fast track
- Breakthrough
- Accelerated approval
- Priority review

See table 3 to the right for more details on their benefits and eligibility criteria.

There are also other orphan drug-specific incentives that exist for drugs treating rare paediatric diseases, which are designed to incentivise their development. Drugs treating these types of diseases can be granted a Priority Review Voucher (PRV) by the FDA,

which enables these drugs to go through the FDA priority review process (see table 3) and reduces the MA review period from 10 months to 6 months. A PRV may be requested from the Rare Paediatric Designation Application stage up to and including the New Drug Application (the MA application). PRVs can also be sold to other sponsors, for use in any MA application, which can help the purchasers of the PRV drive faster access to their drugs.

Exhibit 8 – FDA – accelerated MA mechanisms and orphan drug uptake
of drugs going through mechanism, January 2020 to August 2023

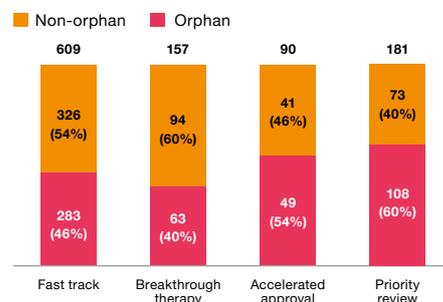


Table 3 – Overview of mechanisms to support MA of orphan drugs in the USA^{84, 85, 86, 87}

Mechanism	Benefit	Eligibility
Fast track	<ul style="list-style-type: none"> • More frequent meetings with FDA officials to discuss most suitable drug development plan and data required to support drug approval • More frequent written communication from FDA about clinical trial design and use of biomarkers • Grants eligibility for accelerated approval and priority review if criteria are met • Rolling review of New Drug Applications (NDA) or Biologics License Applications (BLA)⁸⁸ 	<ul style="list-style-type: none"> • Can be requested at any time during drug development • Drugs need to treat a 'serious condition' (FDA judgement) • Drugs need to target an unmet medical need
Breakthrough therapy	<ul style="list-style-type: none"> • All the benefits from the fast-track designation • Intensive guidance on a drug development programme • Ensures intensive involvement of senior managers from multi-disciplinary teams and input from experienced regulatory staff⁸⁹ 	<ul style="list-style-type: none"> • From Phase I onwards • Drugs need to treat a 'serious condition' (FDA judgement)⁹¹ • Data shows substantial improvement (FDA judgement) over available therapy on clinically significant endpoints (e.g. surrogate endpoints, biomarkers etc.)
Accelerated approval	<ul style="list-style-type: none"> • Faster MA approval process based on a 'surrogate or intermediate clinical endpoint' which grants early MA (on the condition that confirmatory trials are completed) • But, as trials still need to be completed, payors could still choose not to list a drug⁹⁰ 	<ul style="list-style-type: none"> • Drugs need to treat a 'serious condition' (FDA judgement) • Drugs need to target an unmet medical need • The endpoint chosen can predict the final therapeutic effectiveness of a drug (e.g., shrinkage of a tumour), but this need not be the final clinical measure itself (e.g., cure of a disease)
Priority review	<ul style="list-style-type: none"> • Faster MA approval process that allows BLAs and NDAs to be assessed within 6 months of submission (compared to 10 months under standard review) 	<ul style="list-style-type: none"> • Drugs that offer significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions

⁸² FDA: Guidance for Industry, Expedited Programs for Serious Conditions – Drugs and Biologics (2014)

⁸³ <https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs>

⁸⁴ Biomedtracker data and PwC Strategy& analysis, ⁸⁵ <https://www.propharmagroup.com/thought-leadership/fda-expedited-approvals>

⁸⁶ <https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review>

⁸⁷ FDA: Guidance for Industry, Expedited Programs for Serious Conditions – Drugs and Biologics (2014), ⁸⁸ MA application for a biologics drug

⁸⁹ Breakthrough Therapy Designation: Challenges and Opportunities for Innovative Drug Development – A Three-Year Review after PDUFA V (2016)

⁹⁰ <https://www.healthline.com/health-news/some-insurers-may-not-cover-new-fda-approved-alzheimers-disease-treatment-report-finds#Many-insurers-are-still-undecided-about-covering-Leqembi>, ⁹¹ <https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program>

Specialised pathways within the P&R process for orphan drugs

Aside from a faster MA process for orphan drugs, there are also examples of specialised pathways within the P&R process that will support access to orphan drugs. An example of this is the HST pathway in the UK, which is a dedicated pathway for ultra-orphan drugs and uses a higher cost-effectiveness threshold relative to the STA to support access to these drugs. The HST also involves rare disease experts in committee meetings to provide a more informed view when evaluating assessments that better considers the uncertain evidence base associated with orphan drugs.⁹²

There are several examples of mechanisms in other OECD countries to support orphan (and ultra-orphan) drug access specifically, such as the Life Saving Drugs Programme in Australia and the abbreviated early benefit assessment for orphan drugs in Germany.



b) Australia – Life Saving Drugs Programme

In Australia, the Life Saving Drugs Programme (LSDP) provides access to selected ultra-orphan and lifesaving drugs that are not successfully approved through the normal P&R process for cost effectiveness reasons. In this case, manufacturers can apply to the LSDP programme. However, the decision to list a drug on this programme rests with the Minister of Health as opposed to the HTA body, PBAC.⁹³ This approach provides a specialised pathway to support access to drugs which have the potential to significantly impact patients' lives but may not have demonstrated sufficient cost effectiveness as concluded by PBAC. As of September 2023, there were 18 drugs that were funded by the LSDP programme, which treat 11 rare diseases.⁹⁴ In the two-year period from 2020-2021, the LSDP benefited a total of 463 patients who would have otherwise not received these drugs.⁹⁵

c) Germany – abbreviated early benefit assessment for orphan drugs

In Germany, orphan drugs benefit from being routed through a separate HTA pathway, known as the abbreviated early benefit assessment pathway. In this pathway, manufacturers submit a shorter evidence dossier and do not have to compare clinical effectiveness of the orphan drug to a comparator therapy or standard of care (which may be required for the HTA in other countries). Instead, only the patient prevalence and absolute clinical effectiveness need to be evidenced.⁹⁶ In addition, orphan drugs are given a base-case HTA rating of a 'non-quantifiable benefit' – the 'no added benefit' outcome is not available in this route.⁹⁷ This has implications on the pricing negotiation process where this base-case outcome allows sponsors to achieve a higher, and more favourable, price relative to drugs which receive a 'no added benefit' outcome. Ultimately, this pathway for orphan drugs, which requires a shorter HTA dossier and may potentially provide manufacturers with a more favourable price relative to other launch markets, can help to improve access to these drugs for patients in Germany.

As with the free pricing period of 6 months, this abbreviated pathway can also place a greater financial burden on the healthcare system as it may enable orphan drugs to achieve a higher price than if they had been assessed via the non-orphan pathway. The German HTA body has tried to limit the costs of operating the abbreviated early benefit assessment pathway by requiring orphan drugs to go through the non-orphan HTA process once they generate over €30m in revenue in any 12-month period.⁹⁸ The revenue threshold was reduced from €50m at the same time as the free pricing period being reduced as part of the German Financial Stabilisation Act in November 2022.⁹⁹

The combination of Germany's free pricing period, combined with this abbreviated orphan drug pathway, appears to have allowed for both broad and rapid patient access for orphan drugs, evidenced by the fact that Germany had the fastest time from MA to placement on the reimbursement list in the latest EFPIA data (78 days), as well as having one of the highest percentages of reimbursed non-oncology orphan drugs compared to other OECD countries – see exhibit 4 and 5.

⁹² PwC Strategy & Interviews, ⁹³ <https://www.health.gov.au/our-work/life-saving-drugs-program/for-medicine-sponsors>

⁹⁴ <https://www.health.gov.au/our-work/life-saving-drugs-program/about-the-lsdp>

⁹⁵ https://www.aph.gov.au/About_Parliament/Parliamentary_departments/Parliamentary_Library/pubs/rp/rp2122/Quick_Guides/ThePharmaceuticalBenefitsScheme

⁹⁶ Gemeinsamer Bundesausschuss: Geschäftsordnung des Gemeinsamen Bundesausschusses (2023)

⁹⁷ <https://www.g-ba.de/themen/anzw/anzw-richtlinie-anlagen/nutzenbewertung-35a/zusatznutzen/>

⁹⁸ <https://www.simon-kucher.com/en/insights/germany-how-gkv-finstg-law-transforming-pharma-pr-landscape>

d) France – direct access period post MA approval

In France, orphan drug manufacturers can benefit from the Autorisation d'accès précoce (AAP) programme, which is designed to offer early access to drugs which meet the below criteria:^{99, 100}

1. drugs for patients suffering from a severe, rare or debilitating disease
2. drugs for which no authorised therapeutic alternatives are available
3. deferring treatment by preventing access to the drug would involve a serious and immediate risk to the patient's health
4. the drug is considered an innovative treatment

There are two elements to this programme, offering access both pre-MA and post-MA. There are potential lessons to be learnt from the post-MA AAP programme specifically, which offers one year of market access following the HTA whilst a price point is agreed with regulators. In addition to meeting the criteria outlined above, this programme is eligible for drugs that have received an SMR of I-II and ASMR of I-IV from the HTA (see table 2 for an explanation of these metrics and scores).¹⁰¹ This is intended to enable faster patient access however, the lengthy duration of the HTA process itself is likely to be why France's performance in the EFPIA data (see exhibit 4) lags behind Germany, England and Scotland for speed of access. During the period of market access, sponsors are fully reimbursed at a freely set price, with the caveat that they must pay back any difference to the final reimbursed price once it is agreed. Whilst the programme is aimed at supporting early access, this approach will have a higher upfront cost to the healthcare system, with a time lag to receiving a rebate from manufacturers once the reimbursement price has been agreed.



iii) Dedicated funding to enable access to innovative and orphan drugs

Some countries also have separate ringfenced funding, to support faster access to a core group of medicines. These funds can be targeted at either orphan drugs, ultra-orphan or innovative drugs. England's IMF, is an example of such a funding scheme, although as highlighted above no drugs have yet been funded by the IMF.

a) France – Liste-en-Sus

In France, the Ministry of Health operates the Liste-en-Sus (LES), which serves as a supplemental reimbursement mechanism to support equal access to innovative and highly priced medicines that are used in hospitals. All drugs receiving an ASMR of I-IV will be able to access this list, benefiting from direct reimbursement from the 'Assurance Maladie' – France's universal public health insurance plan that is available to anyone who works or resides in France and is distinct from other healthcare funding mechanisms.

Eligibility for the LES is determined by the pricing body within the Ministry of Health that negotiates drug prices (Comité économique des produits de santé). Drugs eligible for the LES include orphan drugs. There are currently 48 non-oncology orphan drugs on the LES, which represents 2.5% of the total number of drugs that are currently on the list. While a 2015 paper estimated €2.8bn was spent on this scheme in 2013, costs are managed by regularly reviewing the LES, and removing drugs when: i) the price of the drug is reduced; ii) MA is withdrawn or expires; iii) the drug is administered in the community; or iv) when insufficient clinical value is demonstrated.¹⁰²

b) Canada – committed funding for orphan drugs

In March 2023, the Canadian government announced that up to CA\$1.4bn would be made available over three years to provinces and territories to help fund bilateral agreements and enable orphan drug access.¹⁰³ This initiative aims to support Canada's first national strategy for rare diseases published in 2021, with the funds also being earmarked to support early diagnosis and screening tests for rare diseases. However, there has been limited information published to date on how use of the funds will be governed, and how it will operate in practice.

⁹⁹ <https://blue-reg.com/glossary/aap/>

¹⁰⁰ HAS: Authorisation for early access to medicinal products: HAS assessment doctrine (2021)

¹⁰¹ Evidera: Direct Market Access for Medicines: Analysis of Eligible Products in France and Comparison with Current German System (2022)

¹⁰² Value in Health Journal: Liste-en-sus reform in France – What are the consequences? (2015)

¹⁰³ <https://www.canada.ca/en/health-canada/news/2023/03/investments-to-support-access-to-drugs-for-rare-diseases.html>

Other important comparisons to the UK

While this report is focused on access to orphan drugs, there are other important comparisons for the UK related to improved diagnosis and HCP awareness of rare diseases which also became apparent during this review. These are summarised below.

Systems to support rare disease diagnosis and HCP awareness

Before individuals are able to receive an orphan drug, they need to be appropriately diagnosed. This requires access to suitable diagnostic testing and equipping HCPs with the knowledge and awareness of rare diseases to correctly identify symptoms. Accurately diagnosing more rare diseases increases the opportunity for patients to receive the most appropriate treatment. Some examples of such systems are provided below:

Newborn screening programmes

Newborn screening programmes offer one of the earliest opportunities to diagnose rare diseases. Testing for a wide range of diseases helps to support the early treatment and care of diseases, which often increases the clinical benefit of treatment. In the UK 9 diseases are part of routine newborn screening, including sickle cell disease and cystic fibrosis.^{104, 105}



A 2021 Charles River study compared a number of European countries' newborn screening programmes, and found that many countries offer a broader panel of tests than the UK.¹⁰⁶ Germany covers 21 diseases in its national newborn screening panel, while the panels offered in Spain and France vary significantly across regions, with Spain covering 40 diseases across all regions but only 7 at the national level, while France covers 15 diseases across all regions but only 6 at a national level.

Providing an answer to patients without a diagnosis

There are other initiatives in countries to support the diagnosis of patients who have a complex disease but are yet to receive a diagnosis. One of the initiatives that was a direct result of the UK Rare Diseases Framework, was the launch of a pilot clinic for patients with a 'syndrome without a name' (SWAN) launched in 2022. This initiative was

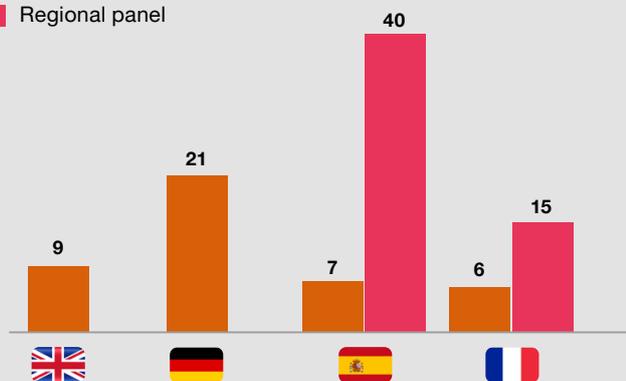
aimed at improving the diagnostic odyssey for patients with undiagnosed rare diseases by bringing together multidisciplinary teams from across the UK with expertise of rare diseases to assist in the diagnostic process.

There is an example of a similar initiative in the form of the USA's Undiagnosed Disease Network (UDN).¹⁰⁷ The UDN is operated by the National Institutes of Health (NIH), which is part of the US Department of Health and Human Services. It is a government-funded programme launched in 2013 that aims to provide a diagnosis to patients with undiagnosed symptoms.¹⁰⁸ Patients must apply to join the programme and, if accepted, are admitted to one of 12 clinical sites across the USA for clinical assessment. The programme is not free to patients, although it aims to minimise out-of-pocket charges where possible. Although the number of applications is relatively low, the programme has demonstrated some evidence of success. As of 2023, 6,570 applications had been received, 2,612 of these had been accepted. The remainder were either under assessment or awaiting assessment and 2,220 of these had received an evaluation. Once assessed, c.30% of these patients received a diagnosis (n = 676), which demonstrates the benefit of this programme given these patients would not have otherwise been diagnosed.¹⁰⁹

Exhibit 9 – Comparison of diseases covered on national and regional newborn screening panels

of diseases, 2021

■ National panel ■ Regional panel



¹⁰⁴ <https://www.nhs.uk/conditions/baby/newborn-screening/overview/>

¹⁰⁵ <https://www.nhs.uk/conditions/baby/newborn-screening/blood-spot-test/>

¹⁰⁶ CRA Insights: A landscape assessment of newborn screening (NBS) in Europe (2021)

¹⁰⁷ <https://www.genome.gov/Current-NHGRI-Clinical-Studies/Undiagnosed-Diseases-Program-UDN>

¹⁰⁸ <https://www.ninds.nih.gov/current-research/focus-disorders/focus-undiagnosed-diseases-network>

¹⁰⁹ <https://undiagnosed.hms.harvard.edu/about-us/facts-and-figures/>

Conclusion

Improving access to orphan drugs for patients with rare diseases is inherently challenging, not just in the UK but in other countries examined too. There are shared challenges that are linked to the nature of these diseases and their treatments, such as the uncertain evidence base, small patient populations for clinical trial, and a lack of direct comparators against which sponsors can demonstrate clinical effectiveness. However, all stakeholders recognise that driving faster and broader access to orphan drugs is important, and the UK and other countries have put in place strategies in their market access ecosystems in an attempt to address the access challenges facing orphan drugs.

There have been recent changes to UK policy and regulation, resulting in updates to existing processes and the launch of new initiatives to improve its access environment for orphan drugs following the publication of the UK Rare Diseases Framework in 2021. The Framework itself was welcomed as a clear, comprehensive, action-backed strategy with significant senior stakeholder engagement in the key mechanisms that have been set up to drive progress against the Framework's priorities, namely the Framework's Board, Delivery Group and Forum. These mechanisms are supportive of both measuring progress against the Framework and ensuring accountability amongst key stakeholders. Importantly, the Framework takes a holistic approach to improving the UK access landscape to rare disease treatments, considering diagnostic improvements, better education of HCPs, coordination of patient care as well as specific initiatives to improve access to drugs.

The changes introduced following the NICE methods review have gone some way to make the HTA process more supportive of orphan drugs. In particular, the acceptance of greater uncertainty in evidence bases could help to address some of the inherent challenges with evaluating the cost-effectiveness of orphan drugs. The HST process is a positively regarded specialist pathway helping to improve access to ultra-orphan drugs specifically, although entry into the process itself is quite difficult given the presence of restrictive prevalence and incidence quantitative criteria, as well as qualitative criteria that lack transparency.

Newer systems, such as ILAP and IMF, have been designed with the intention of improving access to innovative drugs. In general, ILAP was found to be helpful in offering greater engagement between sponsors and regulatory bodies and helping sponsors successfully navigate the MA and P&R process. While the idea behind IMF as a specific fund for facilitating managed access to innovative drugs is welcomed, there are notable challenges within the structure and mechanisms of the fund. This has meant that to date, no drugs orphan or non-orphan have received funding from the IMF.

It is promising to see that there is a commitment from the authorities to evaluate the effectiveness of these newer regulatory and access pathways where there have been some challenges identified. This evaluation (and any further evaluations) will be important to assess the impact of these pathways on rare disease medication access, as well as support the evolution of these processes. Yet there remains further work to be done to address remaining challenges, such as: i) challenges noted with the lack of familial or carer quality of life impacts considered in the health economic evaluation of drugs as part of NICE's HTA process; ii) limited clarity over the application of the higher severity modifier in the STA process; or iii) resource constraints in ILAP which might be impacting its effectiveness. Overall, the changes in the UK have been promising, although their full effect on improving access is yet to be seen given a number of these changes are still very recent.

Recent data from EFPIA has shown that, relative to other European counterparts of Spain and France, England and Scotland have a faster average time from MA to appearance on public reimbursement lists. There is, however, room for improvement on this metric relative to other close peers such as Germany, where speed is much faster. In reviewing the way other OECD countries facilitate access to orphan drugs, there are potential learnings for the UK about how other countries are supporting access to orphan drugs. There are interesting examples of other MA processes, HTA approaches and specialised schemes that either help to facilitate orphan drug access or are specifically designed to do so. The USA is a particularly notable example of innovative MA processes, since there are a range of mechanisms in place to accelerate MA of orphan drugs either by increasing communication with the regulator (FDA), allowing earlier MA approval through surrogate endpoints, or reducing the regulatory review timeline itself through the use of priority review vouchers, which can either be granted by the FDA or purchased from manufacturers which have received it. However, given the MHRA's publicly stated resource constraints, the implementation of multiple programmes may be challenging.¹¹⁰

There are a range of approaches to HTAs as well. Although Australia approaches HTAs in a similar way to NICE, it does not make use of a formal ICER threshold. This provides greater flexibility during the assessment but is perhaps at the expense of transparency of decisions. On the other hand, Germany and France operate HTA processes that place greater weight on the incremental health benefit of the drug, which benefits orphan drugs in particular given they often have a higher price per patient relative to other drugs and have a more limited evidence base, which can make proving their cost-effectiveness more challenging. Most interestingly, the free pricing period in Germany, which is available to all drugs, has been crucial in supporting faster access.

¹¹⁰ MHRA: Annual Report and Accounts 2021/22 (2022)

Additionally, there are notable examples of dedicated funding mechanisms to support access to orphan drugs, such as the Liste-en-Sus in France and Life Saving Drug Programme in Australia, both of which have demonstrated evidence of success in the form of providing access to a number of orphan drugs since launch.

The OECD ecosystems we have assessed are not without their own challenges, but they provide useful context as ecosystems with elements that support access to orphan drugs. These learnings are especially important for the UK, where recent progress has been made and regulators are seeking to increasingly collaborate with other regulatory bodies. What is clear is that a successful strategy for driving greater access to treatments and care for rare disease patients, requires solutions across a multitude of areas, while there is positive progress and action plans drawn up across these areas, there remain real challenges that are limiting access to rare disease medicines.

Ultimately, gaining faster and broader access to effective rare disease treatments will drive real clinical outcomes, and improve the lives of patients, families and carers, as well as provide significant benefits to society and the wider economy, while potentially generating greater efficiencies within the healthcare system.

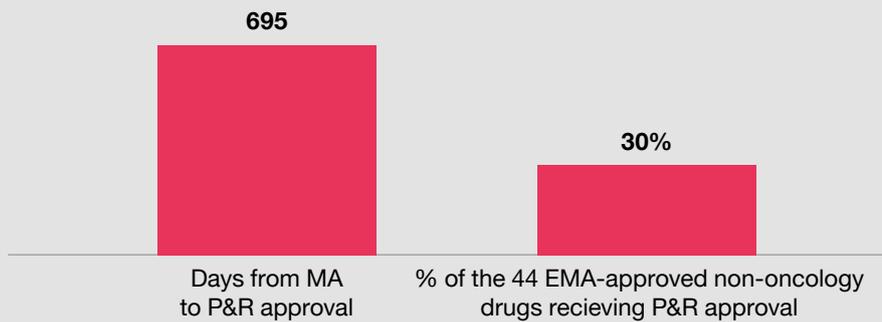


Appendix

Market access statistics in Canada

Exhibit 10 – Statistics on i) time from MA to P&R approval and ii) proportion of EMA-approved non-oncology orphan drugs on public reimbursement lists

Statistics for i) Days from Canadian MA to P&R approval and, ii) % of drugs receiving P&R approval, from 44 non-oncology orphan drugs obtaining EMA MA between 2018-2021



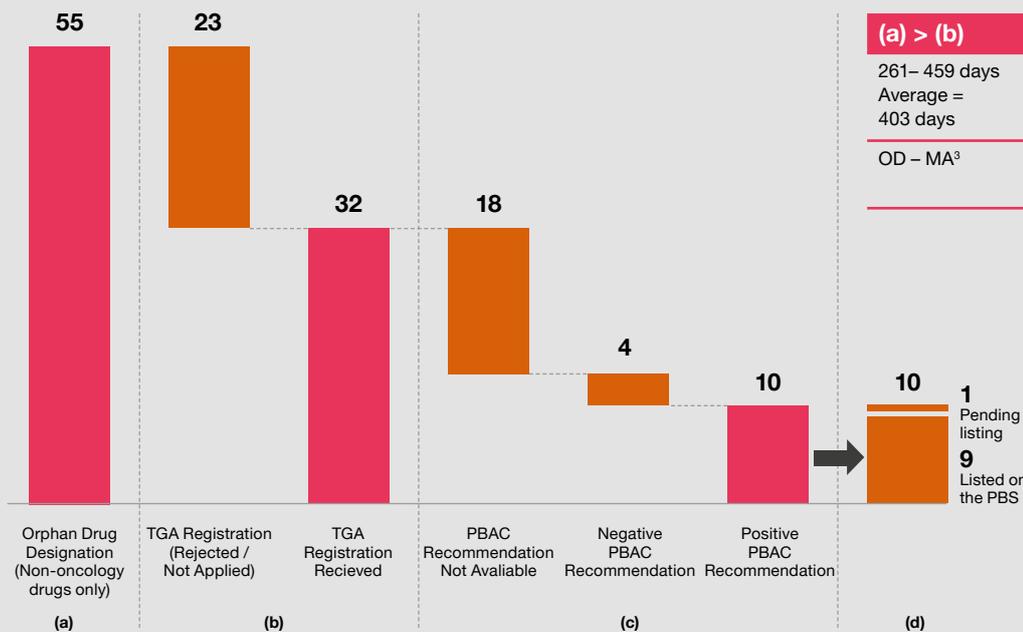
Source: CADTH, pCPA, Government of Canada, EFPIA Patients W.A.I.T. Indicator 2023, PwC Strategy& analysis

Market access statistics in Australia

Exhibit 11 – Statistics on number and time to appearance on a reimbursement list in Australia

Statistics on reimbursement recommendations for non-oncology orphan drugs in Australia

N=55 non-oncology drugs given orphan drug destination, 2020–22



Range, and average time to positive reimbursement listing from orphan designation

N=55 non-oncology drugs given orphan drug destination, 2020–22

(a) > (b)	(b) > (c)	(c) > (d)
261– 459 days	(-8) ⁶ – 282 days	62 – 244 days
Average = 403 days	Average = 124 days	Average = 133 days
OD – MA ³	MA – PR ⁴	PR – PBS Listing ⁵

- Parallel processing enables P&R recommendation to be issued shortly after MA is granted – average 124 days
- Ultimate P&R recommendation is not granted until the MA is confirmed
- Time taken from P&R recommendation to inclusion on the reimbursement list for takes on average of 133 days
- Average time from market authorisation to available on reimbursement list is 267 days

Notes: 1) TGA = Therapeutic Goods Administration, responsible for granting market authorisation; 2) PBAC = Pharmaceutical Benefits Advisory Committee, responsible for pricing & reimbursement recommendation; 3) OD = Orphan Designation, MA = Market Authorisation 4) PR = Positive Recommendation for reimbursement 5) PBS Listing = Inclusion on positive reimbursement list 6) Negative number of days between TGA Registration and positive PBAC Recommendation likely due to timing of PBAC meeting relative to TGA Registration Date. Positive delegate overview is likely to have been available for PBAC meeting prior to official TGA Registration Date | Source: PwC Strategy& analysis, PBAC, TGA

Methodology

To support our review, we conducted a programme of desktop research to support our assessment of the changes to the UK access environment since 2021, as well as our analysis of approaches in other OECD countries. Where relevant, we have also reviewed academic literature, independent analysis of the UK ecosystem and other OECD countries, as well as documents from regulatory bodies such as NICE, its international equivalents and the NHS.

Our research into the impact of changes to the UK access environment was supplemented by two roundtable discussions, which were attended by 19 stakeholders in total and elicited perspectives on these recent changes from industry participants, patient group representatives and regulatory stakeholders. In addition to these roundtable discussions, we have conducted a further 10 interviews with UK industry participants, market access and rare disease experts, and regulatory and clinical stakeholders. We have ensured that we have captured the perspectives of both regulatory body representatives (both current and recent formers) as well as industry stakeholders in order to build a balanced point of view.

For our OECD analysis, we considered six OECD countries for comparison, namely: i) Germany; ii) France; iii) Spain; iv) Australia; v) Canada; and vi) the USA. Germany, France and Spain are large European counterparts and their geographic proximity and similarity in size serve as useful points of comparison for the UK. Australia and Canada, while more distant, are comparable to the UK in that they place a similar importance on cost-effectiveness in their HTA. Finally, the USA was chosen for its high levels of innovation and market size, which make it an attractive launch country.

In addition to the desktop research we have conducted to examine the market access environment for orphan drugs in these OECD countries, we have conducted 22 interviews with key stakeholders across these six countries, including the types of stakeholders outlined above for the UK, as well as industry bodies such as EFPIA and Rare Voices Australia.

We are grateful for the contributions of representatives from the following organisations:

Pharmaceutical and biotech companies

- Alexion
- Alnylam
- Biogen
- Egetis Therapeutics
- Novartis
- Pfizer
- PTC Therapeutics
- Sanofi
- UCB
- Vertex

Patient organisations

- Genetic Alliance UK
- National Organisation for Rare Disorders

Rare disease specialists

- Cardiff and Vale University Health Board

Pharmaceutical and Life Sciences industry associations

- Alliance for Regenerative Medicine
- Association of the British Pharmaceutical Industry
- Biotechnology Innovation Organisation
- Cell and Gene Therapy Catapult
- European Confederation of Pharmaceutical Entrepreneurs
- European Federation of Pharmaceutical Industries and Associations
- Medicines Australia

Representatives from official bodies

- Conselleria de Sanitat de la Generalitat Valenciana
- Haute Autorite Sante
- NHS England
- NICE
- UK Rare Disease Forum
- Union Nationale des Organismes d'Assurance Maladie Complémentaire

Other industry participants

- Aetna

PwC Strategy&

- Global and UK rare disease policy subject matter experts
- Global and UK market access subject matter experts

Pharmaceutical and Life Sciences market access companies

- CRD Consulting
- JG Zebra Consulting
- MAP Patient Access
- N J Redfern Ltd
- Oxygen Strategy
- Partners4Access

Glossary of terms

AWTTC	All Wales Therapeutics and Toxicology Centre	ICER	Incremental Cost-Effectiveness Ratio	PRV	Priority Review Voucher
AAP	Autorisation d'accès précoce	ILAP	Innovative Licensing and Access Pathway	QALY	Quality Adjusted Life Year
ASMR	Amélioration du Service Médical Rendu	IMF	Innovative Medicines Fund	QoL	Quality of Life
BLA	Biologics License Application	LES	Liste-en-Sus	R&D	Research and development
BTD	Breakthrough Therapy Designation	LSDP	Life Saving Drugs Programme	RWE	Real World Evidence
CADTH	Canadian Agency for Drugs and Technologies in Health	MA	Marketing Authorisation	SMC	Scottish Medicines Consortium
CDF	Cancer Drugs Fund	MAA	Managed Access Agreement	SMR	Service Médical Rendu
CF	Cystic Fibrosis	MHRA	Medicines and Healthcare products Regulatory Agency	STA	Single Technology Appraisal
DCMO	Deputy Chief Medical Officer	NDA	New Drug Application	SWAN	Syndrome Without a Name
DHSC	Department of Health and Social Care	NI	Northern Ireland	TDP	Target Development Profile
EAGs	External Assessment Groups	NICE	National Institute of Health and Care Excellence	TGA	Therapeutic Goods Administration
EAMS	Early Access Medicines Scheme	NIH	National Institutes of Health	UDN	Undiagnosed Disease Network
EFPIA	European Federation of Pharmaceutical Industries and Associations	NSCLC	Non-Small Cell Lung Cancer	UK	United Kingdom
EMA	European Medicines Agency	OECD	Organisation for Economic Co-operation and Development	US	United States
FDA	US Food and Drug Administration	OMA	Office for Market Access	USA	United States of America
GDP	Gross Domestic Product	P&R	Pricing and Reimbursement	W.A.I.T	Waiting to Access Innovative Therapies
HCP	Healthcare Professionals	PACE	Patient and Clinician Engagement		
HST	Highly Specialised Technologies	PBAC	Pharmaceutical Benefits Advisory Committee		
HTA	Health Technology Assessment	PRIMA	Preliminary Independent Model Advice		
		PRIME	PRiority Medicines		

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