White Paper

LEAVING NO-ONE BEHIND: IMPROVING ACCESS TO MEDICINES FOR RARE DISEASES PATIENTS

An evidence-driven analysis of the UK rare disease landscape commissioned by Roche Products Limited, supported by IQVIA & Public Policy Projects

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ABOUT THIS PAPER

To explore the rare disease landscape in the UK, Roche Products Ltd. commissioned extensive research into the historical trends in access to rare disease medicines. The requirement for an evidence-driven narrative surrounding the rare disease space became clear, and using IQVIA data assets, a comprehensive database was compiled to determine the UK access environment for rare disease, and orphan drug medicines (medicinal products with Orphan Medicinal Product designation intended for the diagnosis, prevention or treatment of life-threatening, or very serious diseases or disorders that are rare). Public Policy Projects, an organisation Chaired by Rt Hon Stephen Dorrell, which provides practical policy analysis and development in health, care and other public policy areas were commissioned to author the following whitepaper.

The rare disease research was taken to an expert panel of key stakeholders in the UK to discuss, and act as the editorial board for the creation of this whitepaper led by Roche, and supported by IQVIA. Senior experts from the rare diseases policy community assessed the current state of public policy in their area of expertise, and provided confirmation and clarity on the research topics, identifying additional hurdles and opportunities to improve rare diseases policy in the future.

In summary, the research provides a foundation for this report, while the expert workshop provided the key pillars and recommendations for the whitepaper below. The resulting whitepaper draws on a comprehensive data set, aligns with key stakeholders, and offers solutions to reduce delays in access.

EDITORIAL ADVISORY BOARD:

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» Dr Brian Montgomery (Independent Healthcare Consultant, bwm.med)

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» Helen Taylor (Access Launch Lead)

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» Smita Sealey (Engagement Manager, IQVIA)
» Angela McFarlane (Market Development Director, IQVIA)
» Rt. Hon Stephen Dorrell (Chair, Public Policy Projects)

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EXECUTIVE SUMMARY

By Rt. Hon Stephen Dorrell
Chair, Public Policy Projects

Providing high quality care for people living with rare diseases is a significant challenge for health systems across the world. In the UK, it is estimated that 3.5 million people will be affected by a rare disease at some point in their lives,[1] this represents 1 in 17 people. It is also important to recognise the overall impact of rare diseases, rather than simply their incidence or prevalence. Many of these diseases are severe, chronic and life limiting. They can cause significant impact throughout life and have dramatic impacts on families. Despite the scale of the issue, many of these patients do not currently have access to the right care and treatment.

The UK is experiencing a period of significant political and economic change and there is an opportunity to shape the future for investment in medical research and development, as well as patient access to innovative medicines. There is a growing focus in government on ensuring the UK is a global leader in life sciences post-Brexit, as reflected in the agenda set out in the Life Sciences Industrial Strategy and Sector Deal. Improving rare diseases outcomes, needs to be a key part of this agenda.

It is widely acknowledged that a key strength of the National Health Service (NHS) is its access to a wide and diverse data set in terms of clinical trials and evaluations. Maximising economies of scale as represented in this data set is of vital importance for rare diseases. It is also an invaluable strength for the UK to build on, as the Government seeks to strengthen life sciences for a post Brexit economy. The good news is that thanks to recent scientific advances there are a growing number of new, innovative treatments being developed. We are already seeing more people with a rare disease living longer, something which will require significant changes to the services needed to provide care and support for people with rare diseases.

In recent years we have seen greater availability of effective treatments that alter the course of a disease, transforming many rare diseases from incurable, life-limiting, disorders to manageable conditions. The factors outlined above demonstrate that there is a unique opportunity to truly transform rare disease care in the UK. This document focuses on a major barrier to radical improvement in outcomes for people living with rare disease - namely poor access to new innovative medicines.

Research by the Office of Health Economics highlights that compared with many other EU countries, the UK typically takes longer to assess new orphan drugs and reimburses fewer.[2] The research commissioned by Roche Products Ltd. aims to explore in more detail the issues around access to rare disease medicines in the UK. The research paints a picture of a system for assessing new, innovative rare disease medicines which is not currently fit for purpose. In particular we found numerous routes to access. While there is a clear route for treatments of very rare conditions there is not a suitable evaluation method for the majority of 'orphan' medicines.

This situation is a source of considerable confusion for the pharmaceutical sector and patients alike. There are access routes via National Institute for Health and Care Excellence (NICE), NHS England (NHSE) and equivalent programmes for the devolved nations for assessing treatments, all of which work in different ways. Sometimes there are four separate decisions being made on the same treatment – not all of them reaching the same conclusion. Our analysis found that only nine rare disease medicines have reached the market through NHSE since 2010 whilst many more entered the NICE Health Technology Assessment process.[3] Our research also found that the English system in particular is not keeping pace with the scale of medicines being developed.

Some action has been taken which aims to improve care for people with rare disease and access to new medicines. The Government's 2013 UK Strategy for Rare Diseases contains proposals that represent a genuine advance in treatment and care. The respective Scottish, Welsh, Northern Irish, and (recently published) English, Implementation Plans for the UK Strategy for Rare Diseases, all follow with tangible opportunities to implement and embed change, benefitting patients. In addition, the Accelerated Access Review (AAR) and the subsequent creation of an Accelerated Access Pathway (AAP) was launched as an essential first step in ensuring that UK patients can access much needed new technologies at an affordable cost. However, the AAP only looks at five technologies a year and falls short of the more far reaching changes which need to be taken to improve access. The ability of patients with rare diseases to access new, innovative medicines must be at the heart of the implementation of the Life Science Industrial Strategy.

RECOMMENDATIONS

The current system needs to be re-designed to allow for the efficient evaluation of rare disease therapies, with proper focus given to the assessment and equitable patient access to new and effective orphan medicinal products. To this end we urge the Government to work with relevant stakeholders across the UK to implement the following recommended actions:

1. **Definition:** The criteria used by health technology assessment (HTA) bodies such as NICE to define rare diseases should be increased to include severe, chronic and life limiting conditions, as well as their potential to cause significant impact throughout life.

2. **Process:** The Government should support the International Rare Diseases Research Consortium's (IRDiRC) goal to ensure 1,000 new treatments for rare disease receive regulatory approval by 2027; encouraging payers to view rare diseases as long-term conditions, and also the standard practice of pharmaceutical companies working with stakeholders to ensure equitable access.

3. **Industrial Strategy:** The Life Sciences Industrial Strategy (LSIS) and Sector Deal must be fully implemented, with equitable access to drug treatment as a vital strand. This would reflect the vision for personalised medicine in '*Generation Genome'* and the potential innovations and increase in treatments for rare disease that could help the UK to become a world leader in science.

4. **Performance Management:** As NHS England develops the matrix to assess the Rare Diseases Implementation Plan for England through the Rare Disease Forum and Policy Board, it should include clear performance indicators, based on real-world evidence, to support effective monitoring and accountability for delivery.

5. **Brexit:** The Government should produce a full impact assessment of Brexit for the rare disease community.

6. **Assessment of Value in Reimbursement Decisions:** HTA bodies need to re-evaluate current assessments of quality of life to include the wider improvements to patients' lives and those of their families including a review of the use of Quality Adjusted Life Years (QALYs) as the major criterion in appraisals of rare disease therapies.

7. **Patient Voice:** The voice of the patient should also be strengthened in assessing the impact a treatment has and its cost effectiveness. Health technology assessment bodies must strengthen the opportunities given to patients and their families to input into evaluations of the value of treatments for rare diseases to ensure that what is important to the patient, is part of the evaluation.

8. **Reimbursement routes:** NICE and NHS England should work together to address the differing and confused reimbursement routes, to ensure the Highly Specialised Technology (HST) process is strengthened to meet the growing demand for appropriate treatment. Both bodies should also look to align HST evaluation processes across the UK to reduce duplication of assessment and conflicting evaluations.

9. **National Rare Diseases Implementation Plans:** The Rare Diseases Policy Board (RDPB) should continue to analyse devolved administration rare disease implementation plans as part of sharing best practice and greater coordination between nations. This will help avoid duplication and deliver improved transparency for pharmaceutical companies and patients.

At a glance:

Rare Disease and Orphan Medicines Research

Roche Products Ltd. and IQVIA methodology:

We recognised the emerging need for an evidence-driven narrative surrounding the rare disease space. Using IQVIA data assets, a comprehensive database was compiled to determine the UK access environment for rare disease medicines. We drew on the extensive expertise of our editorial panel; designing a workshop to review the analytical findings, brainstorm, and address the underlying issues faced in the rare disease community via a multi-stakeholder workshop.

THE TOP 5 TAKEAWAYS

90

Total indications, and their related medicinal products studied in-depth by IQVIA to support the whitepaper's evidence-driven recommendations

The expected number of orphan drugs with EMA marketing authorisation in 2020, compared to 19 in 2016

75

42% - 93%

Case study on product success rates in non-oncology area if reviewed by NHS England or NICE highlighting disparity in access dependent on route

Previously assessed HST products that achieve the possible ICER of £300k per QALY gained within the new NICE Highly Specialised Technologies (HST) weighting system

0

-77%

Percentage reduction in Individual Funding Route (IFR) decisions made between 2013 and 2017

WHY RARE DISEASES MATTER

With the fast pace of medical and scientific discovery, everyone in the UK will be affected by a rare disease at some stage in their life – either directly or through friends or family members with a rare disease. The word rare might be misleading, as it could generate a perception that "it won't happen to me". By contrast, the statistic that 1 in 17 people will be affected by a rare disease equates to approximately 3.5 million people in the UK and 30 million people across Europe[1]. As recognised in the 2013 UK Strategy for Rare Diseases the total number of rare diseases is steadily increasing because genetic research is beginning to explain disease patterns we did not understand before.

'A rare disease is defined by the European Union as one that affects less than 5 in 10,000 of the general population. There are between 6,000 and 8,000 known rare diseases and around five new rare diseases are described in medical literature each week.[1,4]

In the UK, a single rare disease may affect up to about 30,000 people[1]. The vast majority of rare diseases will affect far fewer than this – some will affect only a handful, or even a single person in the whole of the UK. 80% of rare diseases have a genetic component[1]. Often, they are chronic and life-threatening. Rare diseases can be single gene, multifactorial, chromosomal or non-genetic.

A key factor in the development of rare disease policy is the recognition that 75% of rare diseases affect children[1] – with half of new cases arising in childhood – and as scientific knowledge increases, this number is set to rise. Many of these diseases are severe, chronic and life limiting thus causing significant impact throughout life. The existing classification of diseases as being *rare* is based on the epidemiological assessment of less than 5 in 10,000,[4] and does not include the level of unmet need, this should be included as a differentiation. More importantly this distinction must be better reflected in methods for evaluating rare disease medicines. The question for this paper is how that unmet need can be addressed in part or whole by increased access to new medicines.

Rare diseases represent a significant cause of illness and the overall number of patients with a rare disease poses a high healthcare cost to the system, including medical consultations, psychological assistance, rehabilitation programmes – making considerable demands on the resources and capacity of the NHS and other care services.

Rare diseases are a growing component of directly commissioned NHS expenditure, but although it is centrally commissioned there is scant evidence that its effectiveness is monitored. Transparency and accountability measures have not kept up with the pace of comparable conditions. Furthermore, no significant attempt has been made to monitor the contribution of rare diseases to locally commissioned services.

Given the impact of rare diseases on both patient wellbeing and NHS expenditure, systems should be established to ensure that these funds are used effectively – particularly as many patients will require long-term care.

In the case of rare cancers, treatments might be expensive in the short term, but may not be needed over the long-term: any response is likely to be measured in terms of weeks or months, rather than years. By contrast, treatments for conditions such as enzyme deficiency disorders are likely to be required throughout life. Such rare diseases should therefore be regarded, from a payer's perspective, as long-term conditions, but this is not always the case.

SUMMARY RECOMMENDATION:

1. The criteria used by HTA bodies such as NICE to define ***rare diseases*** should be increased to include severe, chronic and life limiting conditions, as well as their potential to cause significant impact throughout life.

A REVOLUTION IN THE MAKING – RARE DISEASES DRUG DISCOVERY AND DEVELOPMENT

The rare disease landscape is evolving rapidly as scientific advances provide valuable molecular insights into how diseases develop and act upon the body. There is growing availability of effective treatments that alter the course of a disease. This is transforming many rare diseases from incurable, life-limiting, disorders to manageable conditions. The use of gene therapies in patients with severe combined immunodeficiency syndrome is a good example of this. The potential benefits of these treatments in terms of improving outcomes, is significant.

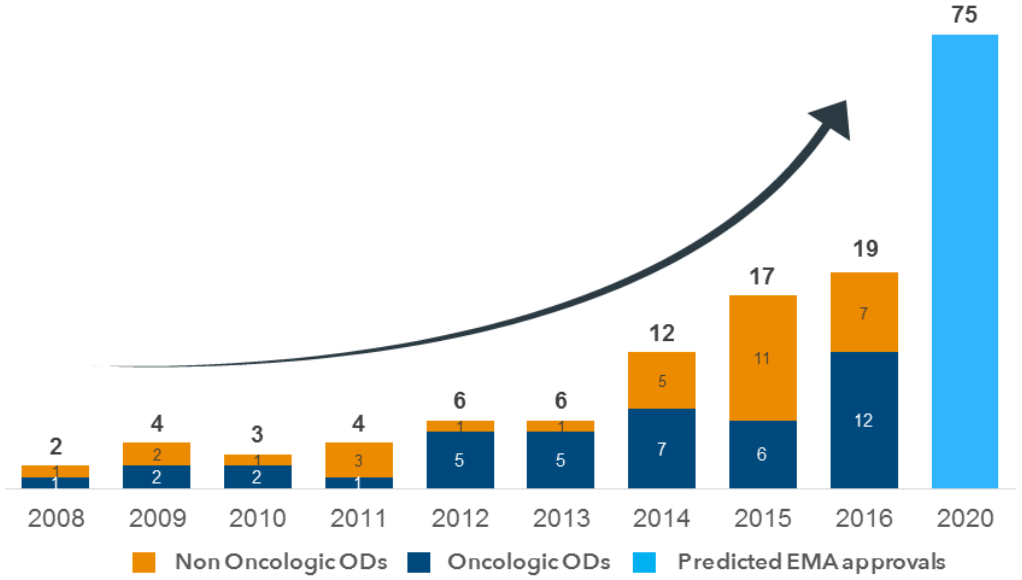
There is now strong data to show the long-term effectiveness of treatments such as Glivec® (imatinib) in previously untreatable conditions. Furthermore, due to greater understanding of disease processes, we are on the brink of an opportunity to intervene. This is through both a combination of scientific advancement and opportunities to access orphan drug approval pathways that did not exist a decade ago.

There have been numerous breakthroughs and transformative developments to care for patients with rare/orphan diseases in the last 7-10 years in the UK, and there are several examples of innovative therapeutic interventions for conditions where best supportive care had previously been the only available option.

As seen in figure 1, previous work by IQVIA shows the growth in the orphan drug development space: 33% of all new chemical entities (NCEs) launched in 2014-2015 were orphan drugs, and it is anticipated that 75 new drugs will receive European Medicines Agency (EMA) regulatory approval by 2020.[5] In context, since 2000, only 143 orphan medicines have been authorised for the benefit of patients suffering from rare diseases.[2] Data from IQVIA suggests that the size of the rare disease market will reach €22 billion by 2020.[6] It is important to recognise, however, that this growth will not be exponential: it will be essential to manage misconceptions of an uncontrolled increase in costs.

The diagnosis of rare diseases is moving away from a symptom-only approach to one which combines symptoms and the molecular testing of cells and their behaviour. Rare diseases may have similar symptoms but can be very diverse at the molecular level. This presents as many current obstacles, as long-term opportunities. For the pharmaceutical sector, understanding this transition is critical for long-term business development. For those patients with a rare disease, molecular level discovery will produce long-term benefits, giving greater insight into their particular condition. However, the demand for orphan medicine access has never been greater and more targeted treatment will only increase this demand.

Figure 1: Growth in EMA approvals for orphan drugs (ODs) to 2020 is predicted to increase four-fold[5]



WIDER POLICY CONTEXT – ALIGNMENT WITH UK PRIORITIES

The combination of unmet health need and rapid progress in treatment for rare diseases has led to a response from the international scientific community. In February 2017 the Paris summit of the International Rare Diseases Research Consortium (IRDiRC) celebrated the early achievement of its goal to deliver 200 new therapies.[7] Yet, it also hopes to ensure that 1,000 new treatments for rare disease receive regulatory approval by 2027, the majority of which should be for conditions without already approved treatment options.[7] This agreement - by a global consortium of private and public sector research funders, patient advocacy groups and scientific advisers - provides a strong basis for the work of the 2013 UK Strategy for Rare Diseases and for the implementation of faster policy changes for the rare diseases community. This is a valuable target to aim for and one that should be supported by efforts in the UK, particularly if the UK wishes to be an international leader in the rare diseases public policy arena.

International definitions for orphan diseases have been published, and the European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL) has published nine guiding principles to help improve the consistency of pricing and reimbursement decision-making in this setting.[8]

The UK is going through a period of significant political and economic change and there is an opportunity to shape the future for investment in medical research and development as well as patient access to innovative medicines. As with similar healthcare systems worldwide, the NHS is facing a combination of financial challenges and increasing numbers of new and effective treatments for rare diseases. Obstacles to equity of access to treatments and research must be removed, whilst recognising the context of an overstretched health service.

In 2013 the UK Government published its UK Strategy for Rare Diseases to join up services with patients, industry and the NHS. It was welcomed by the rare diseases community as a major opportunity to deliver real change in the rare diseases public policy arena. Following a sustained two-year campaign by the All-Party Parliamentary Group (APPG) for Rare, Genetic and Undiagnosed Conditions, Rare Disease UK and the wider rare disease community, NHSE agreed to publish a Rare Diseases Strategy Implementation Plan by the end of 2017, confirmed by the Minister in Parliament in March 2017.[9] Rare Disease UK welcomed the news and agreed to a constructive dialogue as the implementation plan developed through the Clinical Reference Groups. The completed implementation plans were published by NHSE, and the Department of Health and Social Care on 29th January 2018.[10, 11]

In his Life Sciences Industrial Strategy (LSIS) report for the Government, Sir John Bell recognised life sciences as one of the dominant economic sectors in the UK. There is little coincidence that the Government chose to publish the LSIS ahead of other sector strategies, given the long-term importance to the UK economy and its place in the world. The report acknowledges that although enormous gains in health outcomes and life expectancy have been achieved over the last thirty years, it is likely the UK's ability to continue these improvements will depend on both existing innovation platforms for drug and device discovery and a host of new scientific platforms including gene therapy, nucleic acid based therapies and cell therapy – all of which are highly relevant to the treatment of rare conditions.

> *"Enhancing the UK's capabilities for discovery and development of new medicines, creating new diagnostics and medtech capabilities and…new areas of medical innovation using data analytics… will also provide the tools for transforming our healthcare system."*[12]

The LSIS report also highlighted that Genomics England has set the global standard for genomic healthcare data in rare disease. Sir John suggested the strategy can significantly contribute to sustaining the UK as the global genomics leader by capturing the data generated by a commissioned whole genome sequencing service in the NHS in England.

"Capturing the data generated by a commissioned whole genome sequencing service in NHS England will rapidly accumulate large numbers of relevant variants and produce the richest dataset for rare diseases in the world."[12]

Furthermore, in highlighting the risk of not pursuing the access, adoption and diffusion agenda more effectively, the UK has become a challenging market to operate in. To Sir John, the risk is that this will ultimately lead to less clinical development taking place in the UK. It is unethical to commence clinical studies unless there is a willingness to maintain therapy with effective products. The challenge for the NHS and industry is to work together to define an optimum access route for rare diseases.[12]

The LSIS Sector Deal published late-2017 highlights the need to move at pace with the implementation of LSIS. Covering five key foundations of productivity, ideas, people, infrastructure, business environment and places, rapid delivery of this deal will help to improve outcomes for patients with a rare disease.[13]

Given the omission of the LSIS Report's 'access to medicines' recommendations in the Sector Deal, there is an urgent requirement to establish a fair mechanism for pricing and appraisal of all drugs – including orphan drugs. The Association of the British Pharmaceutical Industry (ABPI) and others have also pointed to the trend towards developing 'personalised' drugs, which are only suitable for small groups of patients, and suggests there is a need to develop new thinking about how to pay for such treatments. There is also a need to understand if the processes are sustainable for the long-term.

The next Pharmaceutical Pricing Regulation Scheme (PPRS) is currently being negotiated between government and industry and needs to be agreed by the end of 2018. The negotiations are a significant opportunity to ensure patients can access new innovative, medicines including rare disease therapies.

To ensure the UK is a leader in life science, the next PPRS should propose a growth rate that recognises advances in medicine and which will help improve outcomes for both a growing population and for the UK economy. This will send a signal to the global business community that the UK is a place where life sciences innovation can thrive post-Brexit, despite growing global competition for investment.

In July 2017 Dame Sally Davies, Chief Medical Officer for England, launched the *'Annual report of the Chief Medical Officer 2016: Generation Genome'* – promoting the potential of this existing branch of medicine.[14] The objective is to save costs and improve the quality of care by targeting treatment, maximising benefit and reducing side effects. For patients with rare diseases, this would shorten their 'diagnostic odyssey' by helping to identify therapeutic options faster and improving outcomes for screening and the possibilities for prevention. As the focus on 'personalised' medicines increases, including initiatives from industry such as the partnership between Roche Products Ltd. and oncology genomic diagnostics company Foundation Medicine, it will be important to ensure that the impact of these developments is reflected in rare disease policy.

Given the UK's leading place in genome research, the opportunity also exists to apply advancements in genomic research to pharmaceutical research and development, and it may be anticipated that funding and uptake of new therapies should follow as a result. There is therefore a clear opportunity to support the objectives of Dame Sally Davies' *'Generation Genome'* report. Developing new treatments for rare diseases is challenging:

"Drug development costs are expensive, and treatments for rare conditions may not be financially appealing to pharmaceutical companies. Recruitment to clinical trials can be difficult for rare disorders, many sites may need to be involved, and there will be set-up costs and local approval requirements for studies." [14]

Every patient with a rare disease should be offered the opportunity to participate in clinical research aimed at developing new treatments for their disease and research assessments should be incorporated into the routine clinical follow-up of patients. This can be achieved by following the guidance in the 2013 Rare Diseases Strategy. The '*Generation Genome'* report suggests that this data and analysis will underpin the development of new treatments in collaboration with global academic and industry partners.

Lastly the UK's withdrawal from the European Union is likely to have an impact on the development of drug treatments and their access to market and the operation of NICE guidelines within the UK healthcare system.[15] As NICE identified in 2017, the UK Government must decide upon regulatory divergence/ convergence on medicine approval processes following the decision to leave the European Union.

It is vital for UK patients that there is regulatory certainty and clarity on the future trading relationship post-Brexit. Combating rare disease is a global challenge and the UK government will need to ensure UK institutions can continue to work with international partners and look at consistency with global definitions and standards. However, we are optimistic about the UK's prospects and believe that Brexit provides an opportunity to address current challenges, despite aspects of the current UK environment that frustrate scientific discovery or limit its contribution to improving the care received by UK patients.

One opportunity post-Brexit could be greater flexibility in the conduct of clinical trials, particularly early-stage trials. Evidence has been presented both for and against the EU Clinical Trials Directive, yet there has been no assessment using real world evidence. It is hard, however, to present a case against continuing with the same regulatory system when average clinical trial length in the UK is 2 years, compared with 90 days in the USA.

SUMMARY RECOMMENDATION:

2. The Goverment should support the International Rare Diseases Research Consortium's (IRDiRC) goal to ensure 1,000 new treatments for rare disease recieve regulatory approval by 2027, encouraging payers to view rare diseases as long-term conditions, and also the standard practise of pharmaceutical companies working with stakeholders to ensure equitable access.
3. The LSIS and Sector Deal must be fully implemented, with equitable access to drug treatment as a vital strand. This would reflect the vision for personalised medicine in 'Generation Genome' and the potential innovations and increase in treatments for rare disease, that could help the UK to become a world leader in science.
4. As NHS England develops the matrix to assess the Rare Diseases Implementation Plan for England through the Rare Disease Forum and Policy Board, it should include clear performance indicators, based on real-world evidence, to support effective monitoring and accountability for delivery.
5. The Government should produce a full impact assessment of Brexit for the rare disease community.

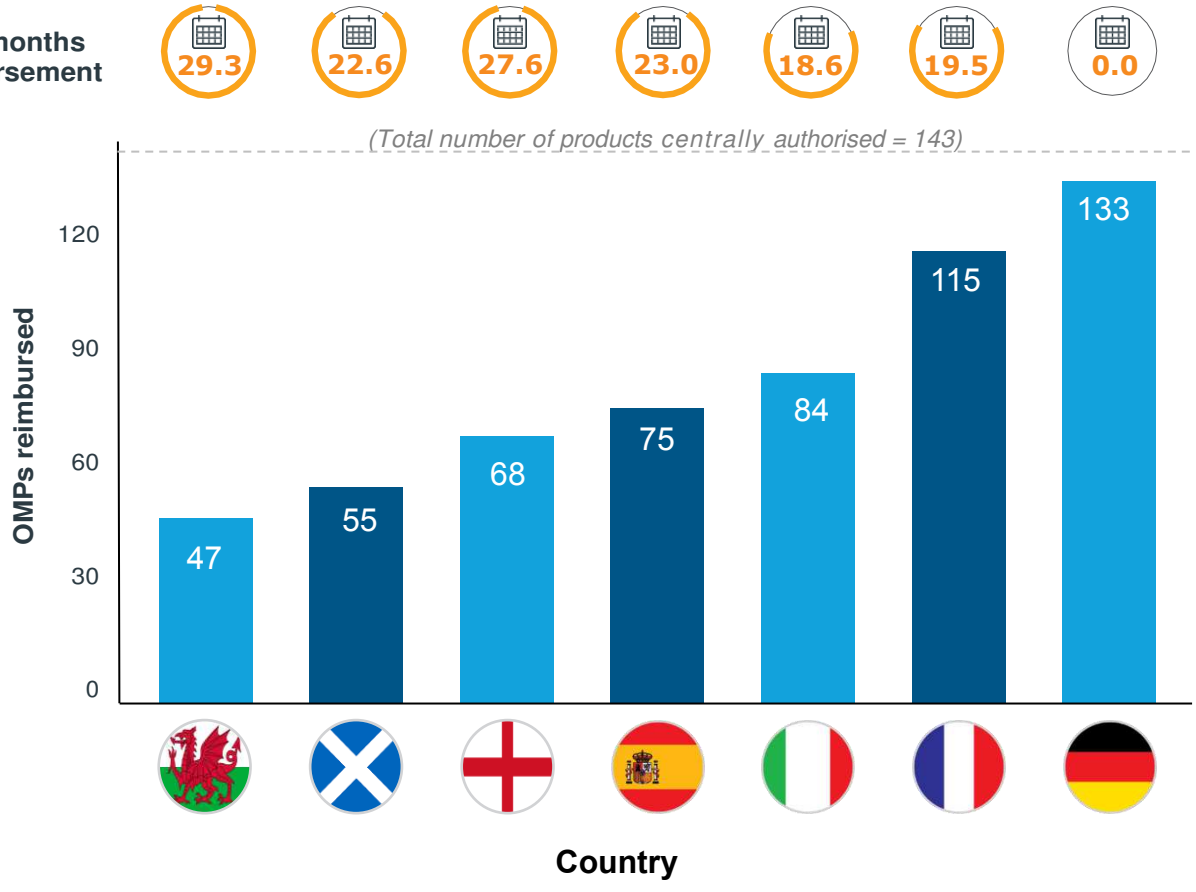
THE CURRENT POSITION OF ACCESS TO DRUG THERAPIES IN THE UK

Recognising the need for evidence driven discussion around this issue, Roche Products Ltd commissioned IQVIA to develop a comprehensive database to establish the current position of access to rare disease medicines in the UK.

There are a small number of licensed medicines for rare diseases in England and many patients are unable to access support and treatment for their condition. The UK lags behind other countries in uptake of 'orphan' drug treatments; patients are seven times more likely to get a newly launched medicine in countries like Germany or France, while Scotland and Wales are both making strides to improve the use of new medicines.[2]

The Office of Health Economics (OHE) Consulting Report, published in early 2017,[2] illustrated this point for orphan drugs. Their analysis found that since the implementation of the Orphan Medicinal Product Regulation in 2000, 143 orphan drugs have obtained marketing authorisation in the EU[2]. These orphan medicines are most widely accessible in Germany and France. In comparison to the key EU markets, the UK takes an additional 6 months, with average time to reimbursement of around 2 years for orphan medicines from the point of marketing authorisation.[2] In the other countries between 30% and 60% of orphan medicines are reimbursed. In England, less than 50% of orphan medicines are routinely funded by the NHS, with one-third of these recommended by NICE. Scotland, Wales and Northern Ireland have already established their rare disease implementation plans and have focused their attention on drug access.

Figure 2: Comparative Access to Orphan Drugs in the UK versus European Countries, in terms of total number of products authorised centrally by EMA, and average months to reimbursement[2]



There are currently nine access routes through which licensed medicines for rare conditions can be evaluated and/or commissioned to enable publicly-funded patient access managed by either NICE or NHSE (see Appendix), and NICE is currently developing a tenth access route, the Abbreviated Technology Appraisal (ATA) process. There is anecdotal evidence from the expert panel workshop led by Roche to suggest that patients, pharmaceutical companies developing orphan medicines, and clinicians are struggling to navigate the current evaluation processes, preventing many rare disease patients from gaining access to new medicines.

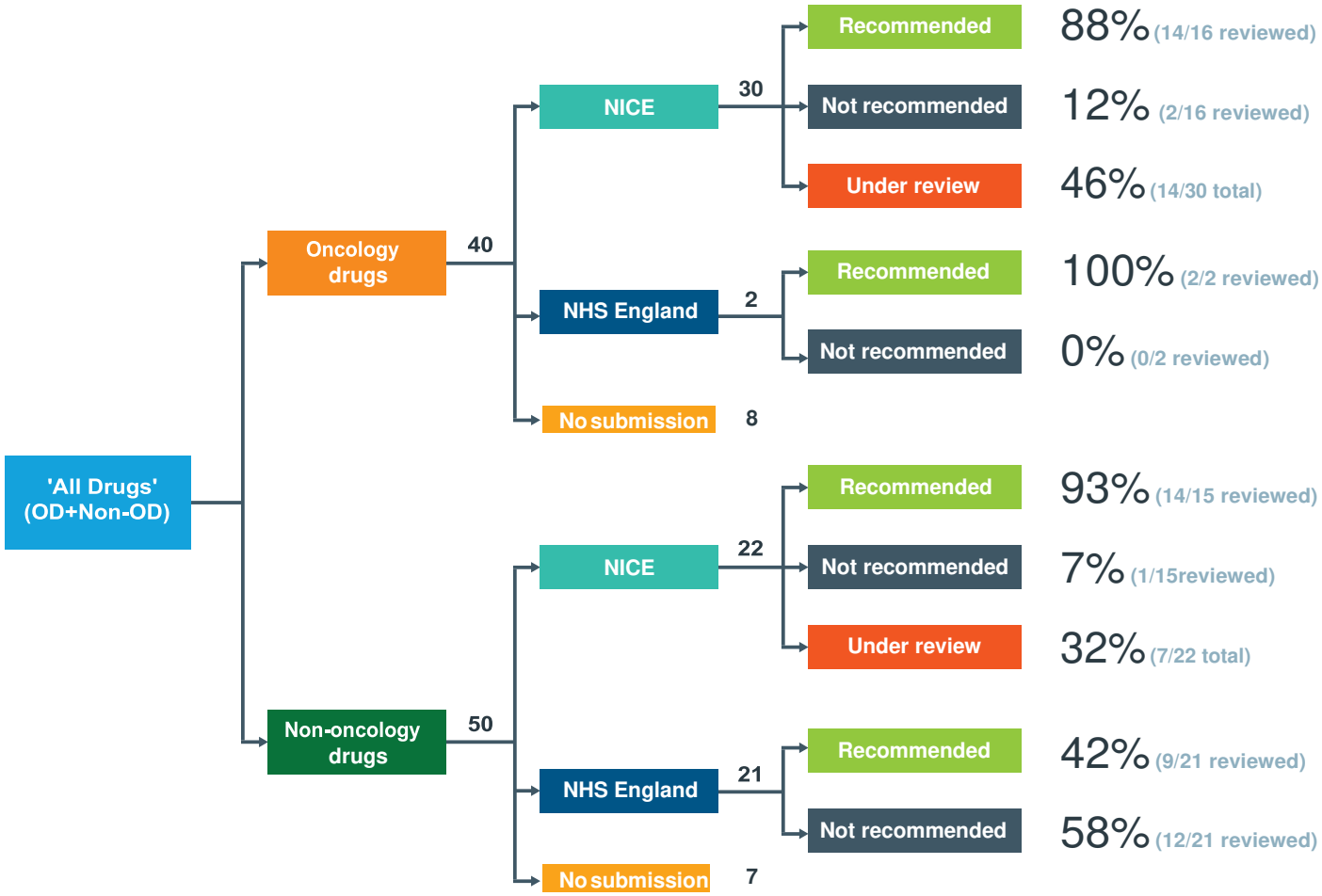
The lack of a single clear route of medicines assessment is of significant concern. Often pharmaceutical companies find approval processes difficult to navigate and feedback is that the processes lack transparency and clear guidance. Unlike generic and large cohort medicines, small patient numbers present additional difficulties, given the often inherent lack of clinical evidence for rare diseases. Of those nine processes, it is particularly important that the interaction between NHSE and NICE HTA routes work effectively for rare diseases. The difference in how orphan drugs are handled by the two bodies presents significant difficulties for pharmaceutical companies, clinicians, and patients as they seek more effective treatments for individual conditions.

For many patients in small cohorts, comparative clinical evidence does not exist, thus forcing patients into an Individual Funding Request (IFR) or for a Clinically Critically Urgent (CCU) request. Both routes often result in failure and appeal, thus creating further burdens to the patient as well as to the NHS administrative system. One solution is international collaboration, which is often essential to accrue enough patients to provide outcomes data to inform reimbursement decisions. This could, potentially, be more difficult after Brexit.

NICE'S ROLE IN RARE DISEASE MEDICINE APPRAISAL

NICE only appraises a small number of medicines for rare diseases. Between August 2012 and January 2017, 23 orphan drugs were considered through single technology appraisal (STA) by NICE. Of these, only five were non-oncology products, which is equivalent to 14% of the non-oncology orphan medicines that the European Medicines Agency (EMA) licensed in the same period;[3] and on average, NICE only appraises three products a year for ultra-orphan conditions (defined as having a prevalence of less than 1 in 50,000). According to a recent study by the OHE of historical decisions by NICE, the best predictor of whether a treatment will receive a positive recommendation is the incremental cost per Quality Adjusted Life Year (QALY) (or incremental cost effectiveness ratio – ICER).[16] The authors note that cost-effectiveness alone correctly predicted 82% of decisions; few other variables were significant and alternative model specifications lead to very small variations in economic model performance.[16] While cost per QALY measures provide a useful indicator of an individual's anticipated health gain following a particular course of treatment, surgery or care package, they do not fully capture the benefit a treatment can offer to patients and families, particularly if they are affected by a rare condition.

Figure 3: Breakdown orphan medicines, and rare disease medicines overall success rate through available routes[3]



Note: 'All drugs' includes all orphan drugs (OD), and non-OD (non-orphan drugs) i.e. those which are indicated for a rare disease. Products under review were calculated as a percentage on the total submissions

NICE aims to evaluate three ultra-orphan drugs a year through the Highly Specialised Technology (HST) process, despite it being likely that the EMA will license over four times that many in the same period (per annum). Meanwhile, the HST appraisal system has also been changed with the introduction of a new 'QALY modifier'. The HST Evaluation Committee will consider the size of the QALY gain in relation to the additional weight that would need to be assigned to the QALY benefits for the cost-effectiveness of the technology to fall within the HST £100,000 QALY limit. Depending on the number of QALYs gained over the lifetime of patients, when comparing the new technology with its relevant comparator(s), the committee will apply a weight of between 1 and 3, using equal increments, for a range between 10 and 30 QALYs gained. This results in the ICER threshold increasing up to £300k per QALY if 30 incremental QALYs are gained.[17] However, in reality it is increasingly difficult to demonstrate the QALY gains due to a number of factors including sub-optimal patient numbers, lengthy trials, and diseases that do not start until later in life as shown in figure 4 by the 'potential ICER threshold based on the new HST weighting'.

Greater transparency in the HST/NICE prioritisation process would be helpful to enable enhanced patient access to the most effective orphan medicines, as it is unclear how the three products allocated for HST appraisal each year are selected. Given this restriction in how many products are appraised and the opaqueness of which are chosen for appraisal, current NICE commissioning processes will not be fit for purpose as the number of emerging therapies continues to increase. The history of HST decisions illustrates this well as it shows a backlog, three per year over-running, and the reduction in positive responses.

The HST appraisal process is not well suited to therapies for rare diseases, such as the various molecular subtypes of cystic fibrosis (CF), because it is likely larger cohorts of patients will require access to highly specialised technology than are currently considered in the HST process by NICE. The process was designed approximately five years ago, set by the treatments that were being evaluated at that time. The HST selection criteria were intended

Figure 4: Estimated HST ICER thresholds following introduction of new ICER weighting system for previously approved, transformative products[3]

	APPROVAL UNDER OLD-HST	INCREMENTAL QALY GAIN	POTENTIAL ICER THRESHOLD BASED ON NEW HST WEIGHTING
SOLIRIS® (eculizumab) ALEXION	Recommended	+ 25.22 (Company) + 10.14 (ERG)	£101k ICER
VIMIZIM® (elosulfase alfa) BIOMARIN	Recommended	+ 18.18 (Company) + 10.03 (ERG)	£100k ICER
TRANSLARNA® (ataluaren) PTC THERAPEUTICS	Recommended	+ 11.75 (Company) + 4.01 (ERG)	£100k ICER
STRENSIQ® (asfotase alfa) ALEXION	Recommended (limited)	+ 25.04 (Company) + 14.13 (ERG)	£141k ICER
GALAFOLD® (migalastat) Amicus Therapeutics	Recommended	+ 0.98 (Company) + 0.34 (ERG)	£100k ICER

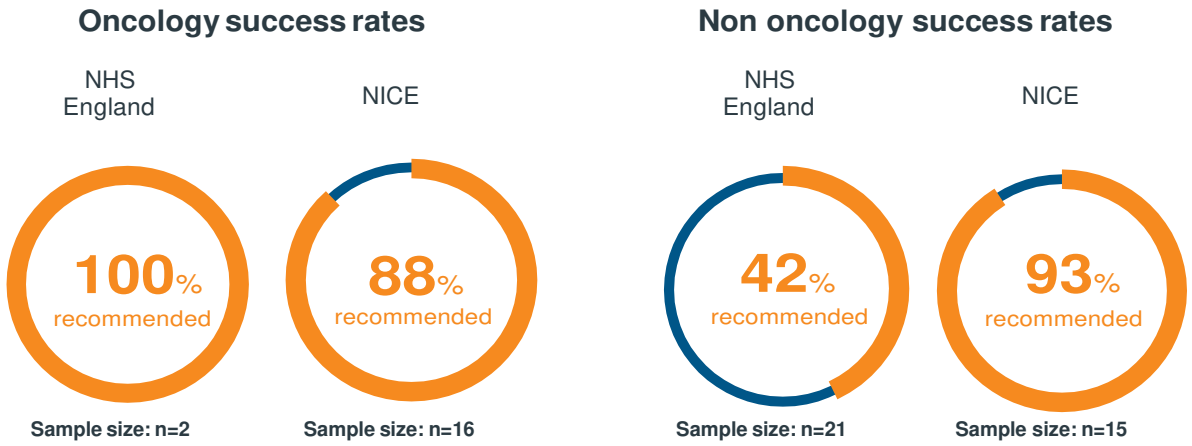
Figure 5: History of HST decisions[3]

PRODUCT	MANUFACTURER	DISEASE	PROGRESS OF DECISION
SOLIRIS® (eculizumab)	ALEXION	atypical hemolytic uremic syndrome (aHUS)	Recommended
VIMIZIM® (elosulfase alfa)	BIOMARIN	Morquio-A Syndrome	Recommended
TRANSLARNA® (ataluaren)	PTC THERAPEUTICS	Duchenne muscular dystrophy	Recommended
STRENSIQ® (asfotase alfa)	ALEXION	Perinatal/infantile- and juvenile-onset hypophosphatasia (HPP)	Recommended (limited)
GALAFOLD® (migalastat)	Amicus Therapeutics	Fabry Disease	Recommended
KANUMA® (sebelipase alfa)	ALEXION	Lysosomal acid lipase deficiency (LAL-D)	Not recommended*
CERDELGA® (eliglustat)	SANOFI genzyme	Gaucher›s Disease	Recommended
GLYBERA® (alipogene tiparvovec)	uniQure	Lipoprotein lipase deficiency (LPLD)	In progress
STRIMVELIS® (GSK2696273)	gsk	ADA-SCID	Recommended

**undergoing appeal*

by NICE to reflect those of the Advisory Group for National Specialised Services (AGNSS),[18] a group that came about as a result of a Department of Health consultation on ways to strengthen the national commissioning system, specifically with regards to review of high-cost, specialist technologies. As a result of the major and ongoing NHS reforms, from April 2013, AGNSS was dissolved and the framework was taken over by NICE. However, the criteria are neither evidence-based nor clear. Based upon the research, it is predicted that most orphan drugs will be evaluated through STAs, with a low probability of success dependant on route to access – as shown in figure 6 below.

Figure 6: Success rates in oncology and non-oncology, highlighting disparity between NICE and NHSE routes to access for orphan drugs and rare disease medicines[3]



In England, 63% of the new treatments were evaluated by NICE[3]; the highest approval rates were seen with products for enzyme deficiency disorders, despite the high ICERs associated with these products. ICERs were a key determinant of the time to market for oncology products, whereas for non-oncology products evaluated through STAs, clinical effectiveness was the principal determinant of time to access. This one example shows the need for variance reduction, where possible, and enabling the system to flow effectively thus freeing approval process time to focus on areas of high demand.

Figure 7: Variance in approval, and approach across England and the devolved nations within orphan designated and rare disease enzyme deficiency disorder products (2010-2018)[19]

Product	MA date	Funding route	Unmet need	England	N.I	Wales	Scotland
CERDELGA®	19-Jan-15	NICE	Very high	Recommended	Recommended	Recommended	Recommended
GALAFOLD®	26-May-16	NICE	Very high	Recommended	Recommended	Recommended	Recommended
KANUMA®	28-Aug-15	NICE	Very high (first in class)	Not recommended*	Not submitted	Not submitted	Not submitted
RAVICTI®	27-Nov-15	NHSE	Very high (high mortality)	Not recommended	Not submitted	Not submitted	In progress
RUCONEST®	28-Oct-10	NHSE	Very high (safety)	Recommended	Not submitted	Not submitted	In progress
STRENSIQ®	28-Aug-15	NICE	Very high (first in class)	Recommended	Recommended	Recommended	Not submitted
VIMIZIM®	28-Apr-14	NICE	Very high (first in class)	Recommended	Recommended	Recommended	Not recommended
VPRIV®	26-Aug-10	NHSE	Very high (first in class)	Recommended	Recommended	Recommended	Recommended

Key: MA = marketing authorisation; NI = Northern Ireland; *= undergoing appeal

VARIANCE IN NHS ENGLAND APPROVAL OUTCOMES

Though most medicines in England are assessed by NICE, a significant number are still assessed by NHSE, indicating that there is no direct appraisal route specific to products for rare diseases. Importantly there is a marked discrepancy between approval rates for oncology and non-oncology products reviewed by NHSE. The choice of evaluation mechanism will therefore be critical for rare disease treatments. As previously described, in England, the highest approval rates for rare disease therapies were seen with enzyme replacement therapies (ERTs), despite high ICERs.[3] For non-oncology products, clinical effectiveness is a key determinant of time to access, whereas for products evaluated by NHSE, a high unmet need is a key driver of access.[3]

It could be considered that high ICERs may be acceptable with treatments for rare diseases, given the potentially higher capacity for benefit; importantly, however, the rarity of the disease per se was not considered to add 'value'.

This raises the question of how to demonstrate the worth of life-changing treatments in rare diseases. Such conditions will often have immature data because of the low patient numbers and the life-limiting nature of the disease. For example, in the case of Strensiq® (asfotase alfa), which has recently been approved by NICE for the treatment of paediatric-onset hypophosphatasia,[20] a 5-year observational study was mandated to supplement the available data with real-world evidence.

Potential reasons for the high NHSE approval rates for ERTs include: a high unmet need; the pronounced impact of these treatments on quality of life, which may be greater than for other rare diseases; higher patient numbers, compared with some other rare diseases; the number of previous approvals of ERTs.

Assessing treatment benefit in rare diseases has become a distraction to the overall debate surrounding access to orphan medicines. However, to understand the effectiveness of one system above another, the Government ought to deliver a root and branch analysis of the effectiveness of the varying systems to ensure that pharmaceutical companies and patients gain improved transparency. This could form part of the ongoing review by the UK Rare Disease Policy Board (RDPB).

Research commissioned by Roche Products Ltd. shows that, for oncology products, high ICERs lead to delays in approval because of: additional committee meetings; disparity between pharmaceutical companies' submitted ICERs, and those from an Evidence Review Group (ERG) due to difficulties in providing strong clinical evidence in rare diseases due to low patient numbers. Whereas for non-oncology products, clinical effectiveness was a key determinant of speed of access. For products evaluated by NHS England, high unmet need was a key driver of access[3], and this allowed some leeway around other criteria. For example, Ruconest®(conestat alfa) for the treatment of hereditary angioedema (HAE) attacks was considered to meet a "very high" unmet need, and hence a high budget impact (£6.5 million - £26.3 million per annum) was regarded as acceptable.[21] It could be argued that a focus on budget impact per patient has little meaning: it is the total cost for a cohort of patients that is most relevant to payers.

Figure 8: NHS England product analysis for reimbursed products highlights a wide variety of different parameters with a correlation in unmet need as the key driver[3]

Product	Indication	Unmet need	Cost Utility Analysis	Budget Impact	Clinical effectiveness	Safety	Cost driver/ overall affordability	Patient Population
ADEMPAS®	Chronic thromboembolic pulmonary hypertension (CTEPH)	High	No	Unknown	High	High	Unknown	300
DEFITELIO®	Hepatic Veno-Occlusive Disease	High	Yes	Low (£0.3m)	High	High	High	78
DELTYBA®	Tuberculosis	Very high	No	Low (£0.45m)	Low	High	Medium	20-25
KALYDECO®	Cystic fibrosis	Very high	No	Very High	Very high	High	High	439
OPSUMIT®	Hypertension	Medium	No	Unknown	High	High	High (same cost as comparators)	Unknown
RUCONEST®	Blood disorders	Very high	No	High (£6.5m - £26.3m)	Medium	High	High	3800
SIGNIFOR®	Cushings disease	High	No	Unknown	High	High	Unknown	25
SIRTURO®	Tuberculosis	Very high	No	Low (£0.5m)	Low	High	Medium	20-25
VPRIV®	Gaucher's disease	Very high	Unknown	Unknown	Unknown	Unknown	Unknown	250

ROLE OF INDIVIDUAL FUNDING REQUESTS

Following a change in operating procedures for Individual Funding Requests (IFRs), approvals in England have decreased from 142 in 2015 to 46 in 2016, and fewer than 5 in the 2017 financial year.[22] It can be argued that this decline is due to a tightening of the eligibility criteria for IFRs, driven by economic, rather than clinical, criteria. However, the IFR mechanism is not well suited to drugs for rare diseases, because in this case a cohort of patients, rather than specific individuals, would be expected to benefit. In Scotland, access to treatments for rare diseases is determined through the Peer-Approved Clinical System (PACS), which ensures that funding from the New Medicines Fund will be available if clinically appropriate.

Clearly there is considerable variation within England in IFR approval rates; IFR-approvals in 2017/2018 are at their lowest level since the system was created.

Freedom of Information Act requests allowed access to IFR data from NHSE, results showed that <10% of access came through IFRs for the period 2016/2017. Clinically Critically Urgent Requests (CCUs) are at an even lower level, only six were approved during the 2016/2017 period. A threshold limit to trigger a clinical commissioning policy by NHSE is no longer part of the newly published IFR framework (published November 2017).[23]

The complexity of the IFR process, averaging three days of a healthcare professional's time, above-and-beyond their daily duties, coupled with low success rates makes this route unfeasible, and unprofitable for developers. For patients looking to access the system, it is clear that the data shown in figures 9 and 10 highlights a system that is not working for the interests of patients.

Figure 9: 5-year progression of IFRs[22]

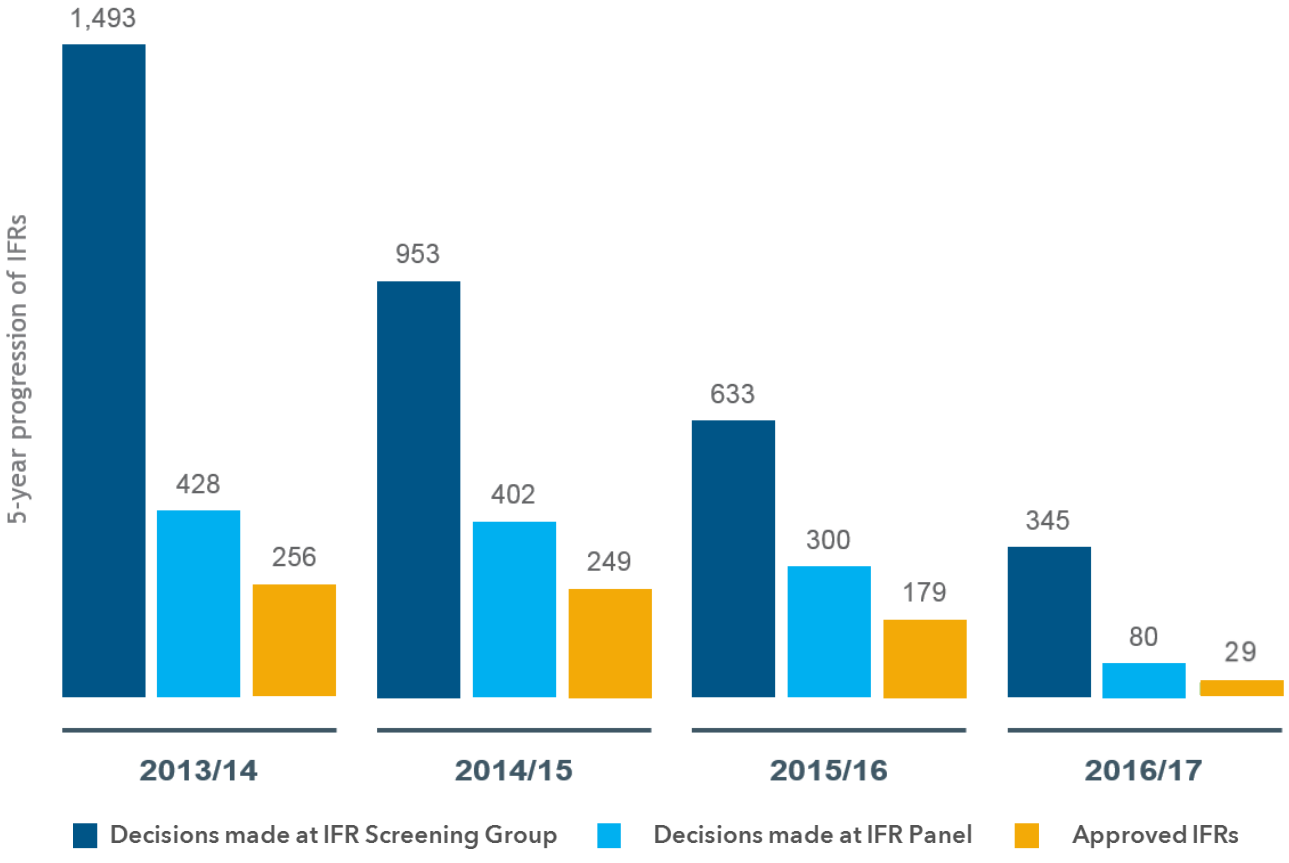
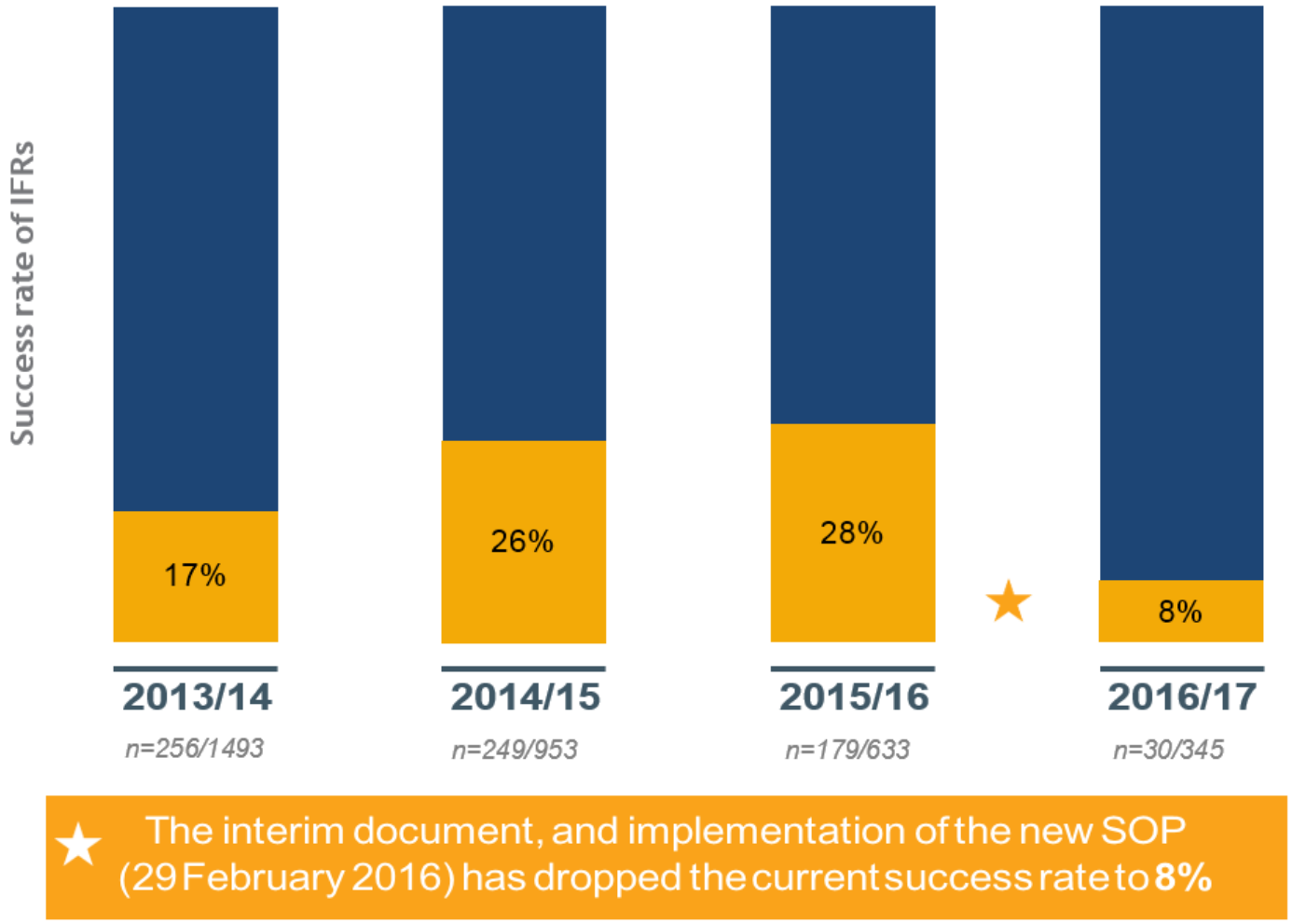


Figure 10: Success rate of IFRs have been in decline since the introduction of an updated standard operating procedure (SOP)[3]



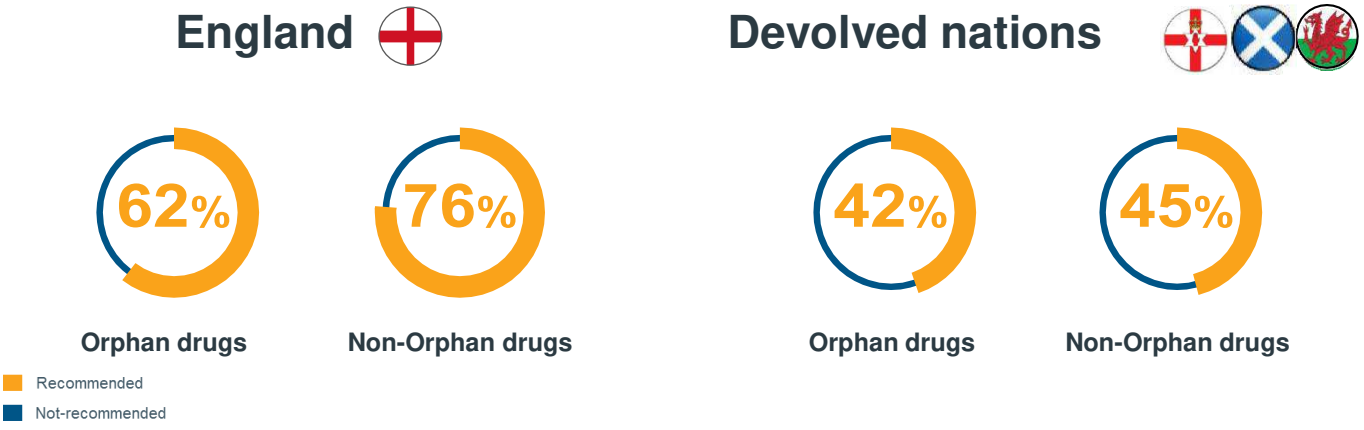
ENSURING EQUITABLE ACCESS ACROSS UK NATIONS

The different ways in which Scotland, Northern Ireland, England and Wales address care for those living with a rare disease was an issue which emerged from this research and the expert workshop that forms the basis of this white paper.

Specialised medicines account for a growing number of all new future product launches, a significant proportion of which constitutes therapies for rare diseases. Payers need to develop new methodologies more often, which in the UK differ by country and inevitably create wider variances within the overall system. Due to the discrepancies within the different systems, payers often find it difficult for a new system to embed effectively.

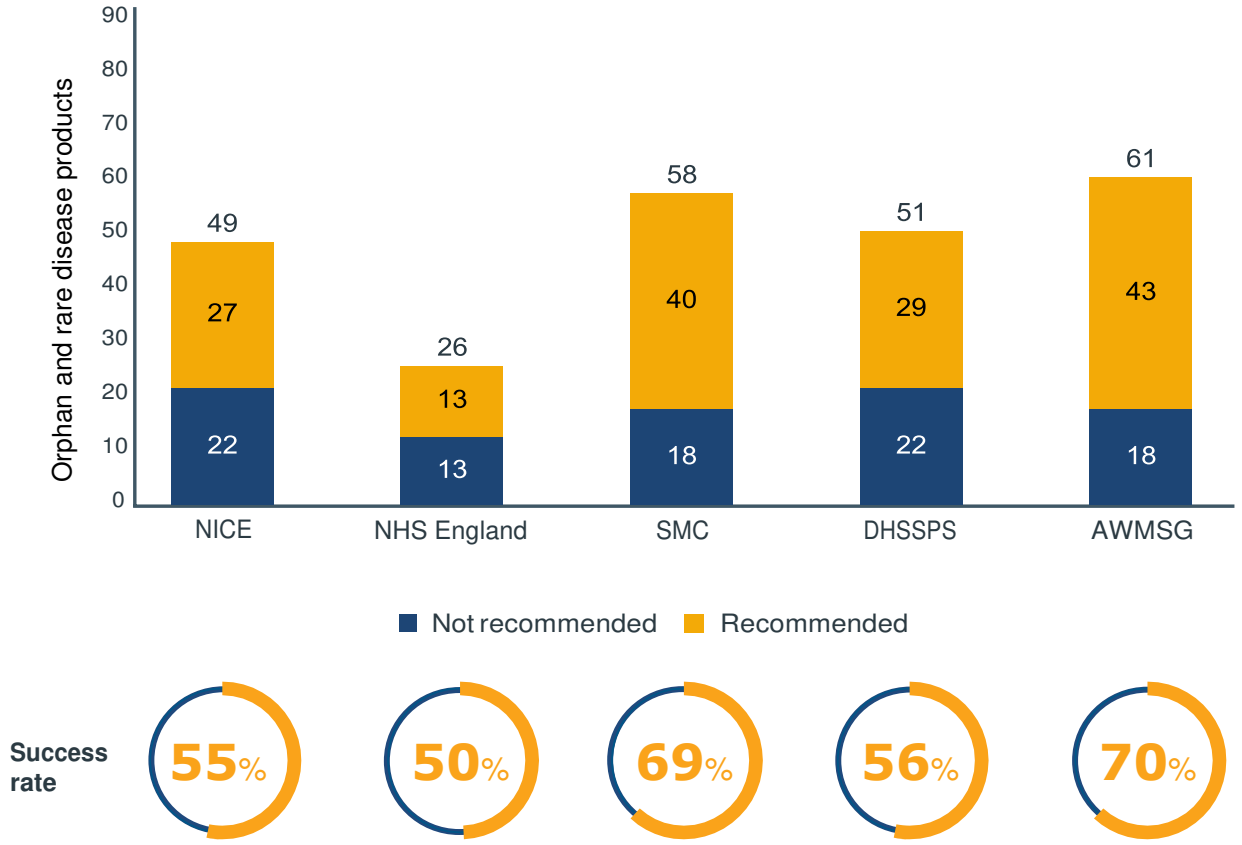
Across the UK, orphan designation itself was found to have neither a limiting, nor beneficial impact on the probability of success for either England or the Devolved Nations; however, when oncology and non-oncology products were considered separately, there was a nominal variability in reimbursement decisions within England as shown in figure 11. However, reviewing the overall success rates for products across the devolved nations, England has an overall success rate from its internal review organisations (NICE, and NHSE), lower than that of the respective bodies within: Scotland (Scottish Medicines Consortium, SMC), Wales (All Wales Medicines Strategy Group, AWMSG) and Northern Ireland (Department of Health, Social Services and Public Safety, DHSSPS), as shown in figure 12.

Figure 11: Orphan medicine designation for rare disease products has low overall impact on the probability of success in the UK[3]



Note: N=58 for orphan drugs, and n=32 for non-orphan drugs. Non-orphan drugs refers to products that treat a rare disease, but do not have an official orphan drug designation

Figure 12: Comparison of orphan and rare disease products success rates for England and the devolved nations[3]



Note: AWMSG = All Wales Medicines Strategy Group; DHSSPS = Department of Health, Social Services; NICE = National Institute for Health and Care Excellence; NHSE = NHS England; SMC = Scottish Medicines Consortium

There is a clear need to increase the capacity of NICE to review orphan medicines, not just ultra-orphan medicines, in HST. For rare diseases and orphan medicines, the UK has seen the lowest uptake compared to the rest of Europe.[2] New systems need to be considered to maximise efficiency and deliver the fastest possible access to new orphan drugs. Despite the system having been in place for several years, a systematic review of HST orphan medicines is yet to be forthcoming by the Government.

Other areas that have been highlighted include evidence gaps due to size and maturity. Policy makers need to understand how they fill in the evidence gaps between EMA fast-tracks and in relation to the overall maturity of the data produced. Policy makers must first identify gaps, provide evidence on how to address them and how to collaborate to provide solutions and then work alongside patients, payers, clinical trial developers and the pharmaceutical industry to provide solutions to the set of identified difficulties.

Due to the existing hurdles and variances in access, as well as funding of rare disease medicines, the UK often has little to no funding for EU and US medicines, which poses a significant problem for a generation of real world evidence insights. This must become a key priority for Simon Stevens as Chief Executive of NHSE and Rt. Hon Jeremy Hunt MP as Secretary of State.

In addition, inconsistencies in approach on HTA/HST evaluations across England and the devolved nations have been widely reported. This has caused a 'postcode lottery' across the UK for rare disease patient access to medicines. A wider debate needs to be held as to the appropriate scale of rare disease and orphan medicine commissioning in the UK – a debate that is both necessary and overdue. Central to this debate should be better coordination and alignment of HTA and reimbursement processes across the UK to reduce the duplication of assessment that takes place through different bodies and the conflicting evaluation criteria. This would also reduce the current 'lottery' around access to rare disease therapies across the UK and make it far easier for patients to make their voices heard in advocating for treatments that may make a huge impact on their quality of life.

There are certain inequalities in access to rare disease therapies across the UK. For example, SMC reviews more products than NICE, and its approval rate is higher[3] (as seen in figure 12). Moreover, the availability of patient-level funding through the New Medicines Fund means that most patients are likely to have access to treatment, whereas the same is not true in England. The effectiveness of the £80 million New Treatment Fund in Wales requires evaluation.

Although better alignment is likely to be difficult, it is potentially achievable: it is notable that AGNSS adopted a nationwide approach. This provides an interesting framework for policy makers to consider should they decide to integrate national rare disease plans. Importantly, there is a 'commonality of opportunity', in that all the constituent countries of the UK share the same vision of the NHS as a single, nationwide, healthcare system.

In addition to greater alignment of the HTA process and reimbursement decisions, harmonisation of rare disease implementation plans across the UK would also be beneficial. In developing their implementation plans, NHSE and the devolved administrations are already putting in place work streams to meet the objectives they have taken from the UK Strategy for Rare Diseases. As these work streams progress there will be valuable lessons which the devolved administrations should use to adapt and improve their approach. These should also be used by NHSE as they implement their plan. This presents a key opportunity to align the UK's approach to achieving the overall UK strategy, whilst recognising the structural differences that exist in each healthcare system.

ACCELERATED ACCESS REVIEW AND LIFE SCIENCE INDUSTRIAL STRATEGY

The Government has attempted to tackle some of the issues outlined in this paper. The Government's response to the AAR commits ministers to create Accelerated Access Pathways (AAPs) for "~5 products per annum". The full response published in November 2017,[24] makes clear the focus will be on those products that deliver the greatest benefit to patients and improve value for money. Whilst this is a step forward, the response document makes it clear that the Government's priority is the requirement that the proposed approach is cost neutral for the NHS.

There is a perception in the rare disease community of a disconnect with the AAR and Life Sciences Industrial Strategy, at the same time as new arrangements proposed by NHSE and NICE. Ministers statements have suggested that the AAR's focus has not been accelerated access, rather focus has been on larger patient cohorts. Patients with orphan and ultra-orphan conditions are smaller communities, and it is difficult to provide evidence for accelerated outcomes. Therefore, more thought needs to be given to applying an accelerated pathway to medicines in the context of the rare diseases public policy space. Furthermore, there has been wider criticism of rare disease trial design during HTA evaluations.

Despite the proposed AAPs due to be introduced in April 2018, the difficulty in securing sufficient clinical data on treatments for rare diseases to reach the levels required by mainstream evaluation criteria is not captured within the new process. The requirement of cost neutrality will also make it incredibly difficult to approve treatments for rare genetic conditions, because current methods cannot show the value for these treatments. This is particularly the case where costs are low because there is no disease modifying treatment currently available.

The Government's July 2017 announcement of investment in the AAR was an important and welcome step forward, with funding worth £86 million to be released, of which £6 million would be targeted towards helping small-to-medium enterprises (SMEs) to gain evidence from real world testing for innovative medicines and devices.[25] However, the funding announced falls considerably short of the AAR recommendation for £20 million to £30 million for SMEs and not-for-profits for the Early Access to Medicines Scheme (EAMS). Of note, the exact proportion of funding available for medicines from this £6 million is unclear. The funding covers medicines and devices, although devices are not currently available through EAMS.

The AAR was launched as an essential first step in ensuring that the UK 'builds a capability in life sciences that leads to strong economic growth and provides patients and the NHS with much needed tools and technologies at an affordable cost'.[26] While this is a laudable objective, it is hard to reconcile the Government's ambitions for an AAR that is 'as ambitious and transformative as possible'[26] and a wider healthcare system that supports the development of innovative treatment and medicines. It is hard to envisage how the development of AAPs would become cost neutral. More needs to be done to ensure the ability of patients with rare diseases to access new, innovative medicines is at the centre of the government's ongoing response to the Life Science Industrial Strategy.

SUMMARY RECOMMENDATION:

6. The Government/NHSE needs to re-evaluate current assessments of quality of life to include the wider improvements to patients' lives and those of their families including a review of the use of Quality Adjusted Life Years as the major criterion in appraisals of rare disease therapies;

7. The voice of the patient should also be strengthened in assessing the impact a treatment has and its cost effectiveness. HTA bodies must strengthen the opportunities given to patients and their families to input into evaluations of the value of treatments for rare diseases to ensure what is important to the patient is part of the evaluation.

8. NICE and NHS England should work together to address the differing and confused reimbursement routes, to ensure the Highly Specialised Technology (HST) process is strengthened to meet the growing demand for appropriate treatment. Both bodies should also look to align HST evaluation processes across the UK to reduce duplication of assessment and conflicting evaluations.

9. The Rare Diseases Policy Board (RDPB) should continue to analyse devolved administration rare disease implementation plans as part of sharing best practice and greater coordination between nations. This will help avoid duplication and deliver improved transparency for pharmaceutical companies and patients.

THE CASE FOR CHANGE

The research which forms the basis of this report clearly exposes the significant issues in the UK around patient access to rare disease medicines. The increase in new treatment options is a huge opportunity for the rare disease community as life-long treatments will be required. In addition, the methodologies employed in the UK need to change to ensure that UK patients benefit from this evolution.

Assessing treatment benefit in rare diseases has become a distraction to the overall debate surrounding access to orphan-medicines. However, to understand the effectiveness of one system above another, the Government ought to deliver a root and branch analysis of the effectiveness of the varying systems to ensure that developers and patients gain improved transparency.

Government must consider the holistic impact on carers, the family and those around the individual who is diagnosed with a rare disease. There is little evidence available that assesses the wider impact that rare diseases have on patient outputs and productivity. It is essential that economic modelling is conducted by Government/NHSE/NICE to understand the true impact of conditions and to evaluate the funding necessary to address the social impact of an individual's condition. As part of this process, it is essential that patient support groups and charities aligned to the rare disease community are involved given their impressive databases of qualitative data that can be used to enhance metrics.

While a developing scientific backdrop makes the determination of true patient numbers very challenging for the NHS, payers can have more confidence in the return on investment if treatment is offered to a small, well-defined, patient population. More evidence is therefore needed to understand the cost benefit of developing treatment that is more targeted – and thus more expensive per patient – but that is more effective at reducing the wider burden of a particular condition. Greater efforts should also be made to secure an economy of scale to increase the size and scope of the rare diseases cohort covering a wider geographical area.

The founding principles of the NHS were based on responding to need, rather than ability to pay. Against this background, equity of access to treatments for rare diseases should be as high a priority for the NHS across all four nations. Further assessment and patient feedback has shown there are marked differences in access across the UK, and hence there is a case for greater coordination between nations to evaluate treatments for rare diseases.

Action needs to be taken to ensure patients with rare diseases can benefit from the growing number of new, innovative treatments. As demonstrated in this document, this is a significant challenge for the UK health service – but also a huge opportunity for the UK to improve health outcomes and lead the way in rare disease care.

GLOSSARY OF TERMS

AAP	Accelerated Access Pathway
AAR	Accelerated Access Review
AGNSS	Advisory Group for National Specialised Services
APPG	All-Party Parliamentary Group
ATA	Abbreviated Technology Appraisal
AWMSG	All Wales Medicines Strategy Group
CCU	Clinically Critically Urgent
DHSSPS	Department of Health, Social Services and Public Safety
EAMS	Early Access to Medicines Scheme
EMA	European Medicines Agency
ERT	Enzyme-Replacement Therapy
EU	European Union
HAE	Hereditary Angioedema
HST	Highly Specialised Technology
HTA	Health Technology Appraisal
ICER	Incremental Cost-Effectiveness Ratio
IFR	Individual Funding Requests
IRDiRC	International Rare Diseases Research Consortium
LSIS	Life Sciences Industrial Strategy
MHRA	Medicines and Healthcare products Regulatory Authority
NCE	New Chemical Entities
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
OHE	Office of Health Economics
OMP	Orphan Medicinal Products: Medicinal products intended for the diagnosis, prevention, or treatment of life-threatening, or very serious diseases or disorders that are rare
ORPH-VAL	European Working Group for Value Assessment and Funding Processes in Rare Diseases
PACS	Peer Approved Clinical System
PPRS	Pharmaceutical Pricing Regulation Scheme
QALY	Quality-adjusted life years
RDAG	Rare Diseases Advisory Group
SMC	Scottish Medicines Consortium
SME	Small-to-medium enterprise
SOP	Standard Operating Procedure
STA	Single Technology Appraisal

APPENDIX

Nine routes to market access managed by NICE or NHS England:

1. **Single Technology Appraisal (STA) – NICE.** The Single Technology Appraisal Process is specifically designed to appraise a single product, device or other technology, with a single indication. The process normally covers new technologies (typically, new pharmaceutical products or licensed indications).
2. **Multiple Technology Appraisal (MTA) – NICE**. Designed to cover more than one technology, or one technology for more than one indication.
3. **Highly Specialised Technology (HST) Evaluation Programme – NICE**. HST evaluations are recommendations on the use of new and existing highly specialised medicines and treatments within the NHS in England and are used for very rare conditions.
4. **Cancer Drugs Fund (CDF) – NICE**. Amended in July 2016 to include a limited budget of £340 million, and the capacity to fund products during Real-World Evidence collection or trial maturation following review and recommendation by NICE.
5. **Fast Track Appraisl (FTA) – NICE.** The aims of the FTA process are to provide equally robust but less resource-intensive processes for appraising technologies than the STA and MTA processes, and will be appraised through the FTA process if the company's base-case incremental cost-effectiveness ratio (ICER) is less than £10,000 per quality-adjusted life year (QALY) gained.
6. **Individual Funding Requests (IFRs) – NHS England**. Individual Funding request is a procedure with the English and Welsh NHS for individuals who require treatments, drugs or therapies that are not normally funded. Since 2013 IFRs are managed according to the responsible commissioning service – either NHSE for specialised services or local clinical commissioning groups.
7. **Commissioning through Evaluation (CtE) – NHS England**. Enables a limited number of patients to access treatments that are not funded by the NHS, but nonetheless show significant promise for the future, while new clinical and patient experience data are collected within a formal evaluation programme.
8. **Specialised commissioning based on a recommendation by a Clinical Reference Group (CRG) – NHS England.**
9. **Clinically Critically Urgent (CCU) funding request – NHS England**. Clinically Critical Urgent request – this is a process intended for cases where no national clinical commissioning policy, policy statement or NICE Technology Appraisal exists, and where a patient is otherwise at risk of "imminent significant and irreversible clinical deterioration (life threatening or major loss of function) i.e. within the next 4 months".

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CONTACT US

welwyn.public_affairs@roche.com

LOCATION

Roche Products Limited
Hexagon Place
6 Falcon Way, Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom
(Company Registration Number 100674)