EQUITY AND ACCESS:

MAKING THE UK A RARE DISEASE LEADER

This report was commissioned and funded by Shire and developed in collaboration with an external steering group.
ABOUT THIS REPORT

The EU Regulation on Orphan Medicines (EC/141/2000) established a centralised procedure for the designation of orphan medicinal products (OMPs) and put in place incentives for the research, marketing and development of medicines for rare diseases in 1999. This paved the way for a centralised EU wide approval by the European Medicines Agency (EMA) for orphan drugs. To review the impact of these changes, Shire commissioned OHE Consulting Ltd to undertake a data analysis of access to orphan medicines across the UK, France, Germany, Italy and Spain (EU5) and convened a Steering Group of Experts to produce a report on the barriers to patient access and identify recommendations for policymakers. While OHE Consulting Ltd’s data analysis included specific data for each of England, Scotland and Wales, due to the complex differences between the health systems in each of the four UK nations, the focus of the report is on steps that could be taken to improving OMP access in England relative to the EU5. Further work will be undertaken to consider improvements that can be made across the whole of the UK.

This report was developed by an expert steering group and was facilitated by Hanover Communications. The project was commissioned and funded by Shire. Shire were not part of the expert steering group and did not participate in writing the report. Shire has reviewed the report for factual accuracy and compliance with the ABPI Code of Practice for the Pharmaceutical Industry.

The results of the OHE Consulting Ltd study ‘Comparing Access to Orphan Medicinal Products (OMPs) in the United Kingdom (UK) and other European countries’ are presented and analysed in detail in an OHE Consulting Ltd report. A summary of the methodology used by OHE Consulting Ltd can be found in the appendix of this report.

ABOUT SHIRE

Shire is the leading global biotechnology company focused on serving people with rare diseases and other highly specialised conditions. We strive to develop best-in-class products, many of which are available in more than 100 countries, across core therapeutic areas including Haematology, Immunology, Neuroscience, Ophthalmics, Lysosomal Storage Disorders, Gastrointestinal / Internal Medicine / Endocrine and Hereditary Angioedema; and a growing franchise in Oncology.

www.shirepharmaceuticals.co.uk
The Steering Group was convened by Shire, to consider the findings of the OHE Consulting Ltd report, and to agree on a series of recommendations to the Government and NHS which would help patients to access rare disease medicines. The Steering Group, who were not paid, met in November 2016, and all of the members, listed below, have stated their support for the findings in this report:

- Professor Bobby Gaspar, Professor of Paediatrics and Immunology at the University College of London Institute of Child Health, Director Designate of the Zayed Centre for Research
- Alistair Kent, Chair, Rare Disease UK and Director, Genetic Alliance UK
- Laura Szutowicz, CEO, Hereditary Angioedema Association
- Tanya Collin-Histed, CEO, Gauchers Association
- Dr Paul Brennan, Clinical Director, Northern Genetics Service
- Baroness Masham, House of Lords
- Professor David Taylor, Emeritus Professor of Pharmaceutical and Public Health Policy, University College London
- Josie Godfrey, regulatory consultant, former Associate Director at NICE responsible for the Highly-Specialised Technologies programme
- Martina Garau, Principal Economist, OHE Consulting Ltd
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very definition, orphan medicines are often the only medicines available for a particular group of patients, addressing high levels of unmet need. As such, not to confront and solve the issue of slow and low access to these medicines is to deny many patients a life-changing opportunity. Regrettably, instead of addressing this issue appropriately, the NHS in England is currently focused on introducing cost-containment measures which may create additional barriers for rare disease patients.

However, the work of the Life Sciences Industrial Strategy Board, in the context of the Government’s ongoing development of a new Industrial Strategy, provides an opportunity to take forward the recommendations outlined in this report.

At this critical time for the future of the UK and the NHS, it is imperative that these recommendations are taken forward by Government and its arm’s length bodies to improve the lives of rare disease patients. Working together the rare disease community, physicians, industry and policymakers can ensure that the NHS is able to deliver on its values of equity and access for all patients.

Sebastian Stachowiak
Head of UK & Ireland Country Cluster/
General Manager, UK

FOREWORD FROM SHIRE

Shire has a strong heritage of working to improve the lives of people with rare diseases; researching, developing, and marketing novel products that enhance the quality of life of those impacted by conditions which might otherwise be ignored.

Much progress has been made since the introduction of European Regulation of Orphan Medicine in 2000 which, together with industry striving for innovation, has significantly improved the number of treatment options developed and authorised for rare conditions. Despite this, patient access to these medicines across European health systems remains variable. Too many patients in England are unable to access innovations which might help them, and those who can access rare disease treatments often have to wait longer than those in comparative European countries.

This report, delivered independently by a steering group of experts in the field of rare diseases, makes a significant contribution to the policy debate about the future of rare diseases. Such debate must build on the recognition from all four UK health departments in the UK Strategy for Rare Diseases that patients with rare diseases should not be “left behind just because they have a rare disease”. At Shire, we are committed to work with patient groups, clinicians and policymakers to make the UK a world-leading country for the treatment of rare diseases in order to deliver equity and access for rare disease patients.

As the Steering Group has identified, one of the major challenges facing rare disease patients in accessing treatments in England is the lack of a dedicated evaluation pathway for orphan medicines that recognises the full value, as well as the societal benefits, of treating rare diseases. Unfortunately, this problem is not new. The NHS therefore needs to focus on tackling this inequality now, rather than waiting for the problem to get worse. By their
The UK has made progress in recognising the importance of providing care for people with rare diseases in recent years, with an increased focus on early diagnosis, better care and information sharing. This culminated in the UK Strategy for Rare Diseases in 2012, which brought a welcome focus, from all administrations in the UK, to an area that has too often been neglected due to its small patient base.

Yet there remains some way to go. The Rare Disease Strategy did not, in any concerted way, address the failure of the UK to bring through the benefits of medical research and innovation to patients on the ground. As the comprehensive analysis by the Office of Health Economics shows, the UK has lagged behind other European countries in developing the right systems for bringing these treatments through to patients.

In England, there have been attempts to close this gap through the development of more appropriate methods of evaluating promising treatments for ultra-rare diseases. The Advisory Group for National Specialised Services (AGNSS) process and the Highly-Specialised Technology (HST) programme rightly looked beyond a narrow attempt to quantify the cost-effectiveness of these medicines, and sought to recognise the value of patient experience, carers and wider families. Yet the process has not delivered the gains many in the rare disease community had hoped. There have only been three positive HST indications since the programme was launched. This has left NHS England as the main evaluation body, which too often fails to prioritise treatment for rare diseases, and fails to look at wider considerations of value and long term benefit, with too much emphasis on cost. Unlike more common diseases where a number of treatment options exist, rare disease patients often have limited or no specific treatments and the need to make new orphan medicines available is ever more pressing. The system is too often fragmented and lacks transparency, which leads to inconsistency in the availability of these treatments.

On top of that, recent reforms proposed by NHS England to the HST process risk unpicking the consensus on a more tailored evaluation criteria, with the introduction of a Quality Adjusted Life Years (QALY) threshold for the first time in the HST process. There is another set of patients, whose conditions are rare but not rare enough to qualify for the HST route, where there is still no appropriate mechanism to evaluate these treatments.

That is why this report comes at such a crucial time for the rare disease community. There is a clear challenge to address – we are too slow to evaluate these treatments, we fail to properly recognise the wider benefits of treating patients with rare diseases, and we are now falling behind our European counterparts. This report sets out some clear, deliverable recommendations to change that.

I passionately believe that people with rare diseases deserve the same equity and access as the health system provides for more common conditions, and these recommendations will go some way to deliver that. I hope that the NHS, NICE and all bodies will reflect on these proposals, and consider carefully what they can take forward.

**Professor Bobby Gaspar,**

*Chair of The Steering Group, Professor of Paediatrics and Immunology at the UCL Institute of Child Health, Director Designate of the Zayed Centre for Research*
The UK Strategy for Rare Diseases 2012 set out the ambition for equity of access and to “ensure no one gets left behind just because they have a rare disease”. However, for many patients with a rare disease across the UK, access to care and treatment is still more challenging than for patients with common conditions. Since 2000, patients with a rare disease in the UK have benefited from the impact of a Europe wide initiative to improve the availability of rare disease treatments. The EU Regulation on Orphan Medicinal Products (OMPs) introduced a range of incentives to encourage industry to develop medicines for rare diseases, including extending the period of marketing exclusivity. These reforms have led to a significant increase in the number of treatments for rare diseases that have been developed and subsequently authorised by the European Medicines Agency (EMA).

Data collected by OHE Consulting Ltd for this report commissioned and funded by Shire shows that between 2001 and June 2016 1,360 medicines were designated as ‘orphan treatments’ by the European Union’s Committee on Orphan Medicinal Products. Of these, 143 were identified as part of this study as obtaining a marketing authorisation from the EMA. While the EMA’s marketing authorisation applies to all European health systems, there is considerable variation in the ability of different health systems to make these treatments available to patients. Since 2000, different health systems across Europe have introduced a range of policies to regulate and reimburse OMPs.

EXECUTIVE SUMMARY

The UK Strategy for Rare Diseases 2012 set out the ambition for equity of access and to “ensure no one gets left behind just because they have a rare disease”. However, for many patients with a rare disease across the UK, access to care and treatment is still more challenging than for patients with common conditions. Since 2000, patients with a rare disease in the UK have benefited from the impact of a Europe wide initiative to improve the availability of rare disease treatments. The EU Regulation on Orphan Medicinal Products (OMPs) introduced a range of incentives to encourage industry to develop medicines for rare diseases, including extending the period of marketing exclusivity. These reforms have led to a significant increase in the number of treatments for rare diseases that have been developed and subsequently authorised by the European Medicines Agency (EMA).

New data collected by OHE Consulting Ltd shows that of the EU5 countries (France, Germany, Italy, Spain and the UK), Germany and France routinely provide both the quickest and the broadest access to OMPs. By contrast England is, on average, slower than Germany, France, Spain and Italy in making OMPs available to patients. Of the 143 OMPs that are potentially available to patients, in England 120 have a decision on use, and only 68 are routinely funded, compared to 116 OMPs in France and 133 in Germany. The time taken for an OMP to receive funding in the English health system is considerably slower compared to other comparable countries. In England, the average time to the treatment being funded is 27.6 months, 4.6 months slower than Spain, 5 months slower than Scotland, 6.6 months slower than France, 8.6 months slower than Italy and over two years slower than Germany.

Since 2000, national regulatory and reimbursement systems in England have undergone continued evolution. However, while there has been growing recognition that processes and systems to assess non-orphan medicines are not appropriate for orphan medicines, English policymakers have been slow to introduce changes. Instead of improving patient access to OMPs in recent years, the direction of travel in commissioning and assessment policy has created more barriers to access.
All developed health systems face challenges in improving access to orphan medicines, such as the difficulty of undertaking technology assessments due to lack of data on clinical effectiveness and inappropriate use of Health Technology Appraisal processes. Yet while some systems in Europe have introduced specific protocols and processes to assess OMPs, the English health system does not have a dedicated pathway to evaluate orphan medicines. Following the Health and Social Care Act of 2012 the National Institute for Health and Care Excellence (NICE) developed a dedicated process, the Highly-Specialised Technologies (HST) programme, to assess ultra-orphan medicines, however to date only three medicines have had positive indications under this process. Without a specific NICE pathway to evaluate OMPs and with limited capacity for NICE to undertake regular HST evaluations, NHS England are increasingly undertaking their own assessments. However, NHS England’s approach fails to consider the wider societal benefits of treating rare diseases and uses cost and affordability as the overriding criteria for investment decisions.

This report, and the recommendations it puts forward, are particularly timely. As the UK prepares to leave the European Union, the Government has published a green paper ‘Building our Industrial Strategy’. The ten pillars on which the strategy will be built include ‘investing in science, research and innovation’, and work has also commenced on a ‘sector deal’ for the life sciences sector, led by the Life Sciences Industrial Board. This should enable the UK to meet the challenges and maximise the opportunities presented by leaving the European Union. As such, both the industrial and life sciences strategy provide a platform to help to improve the lives of people living with rare diseases. To help achieve this, the recommendations below must be considered within their development.

Prioritisation and leadership

• An annual inter-governmental summit or steering group is required to drive forward the aspirations of the UK Rare Disease Strategy.
• The summit should commit to refreshing the Rare Disease Strategy no later than 2018, with a dedicated implementation plan.
• The next version of the NHS Mandate should include a specific commitment to provide equity and access to rare disease patients.
• A member of the NHS England board, such as the Medical or Nursing Director, should be made accountable for rare diseases.
• A new National Director for Rare Diseases should be appointed to drive forward improvements and provide leadership to the rare disease community.
• The National Director should develop a Rare Disease Plan for England, along the lines of the Five Year Forward View for Primary Care or Mental Health.

Dedicated funding

• Greater flexibility is needed in accounting for investment in innovation, potentially introducing multi-year budgets for commissioners, which would help the health system deliver the smoother introduction of innovation that will benefit patients and deliver value across the system.
• Consideration should be given to using the PPRS rebate to support innovation directly, as is the case in Scotland to fund rare disease medicines.
Harnessing data

- Adaptive and efficient processes need to be developed to optimise the use of real world data collected before and after an OMP value assessment.
- There should be greater flexibility around what data is used as part of an assessment, greater clarity from NHS England on the feasibility of these evidence requirements, and structures in place to support the sharing of data internationally, across borders.

Evaluation processes

- NICE, NHS England and the Department of Health should work together with patient groups and industry to establish a fair process of appraisal for orphan medicines, which reflects the wider societal benefits of investing in orphan treatments and recognises the scale of unmet need in rare diseases.
- Any future system of OMP appraisal should include safeguards or limitations on the use of cost effectiveness ratios.
- It is essential that NICE’s HST route for ultra-orphan medicines is maintained and not made subject to a £100,000 per QALY threshold, as suggested in the recent NICE/NHSE consultation.

ABOUT RARE DISEASES

A rare disease is defined by the European Union as a disease 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.8 One in 17 people will be affected by a rare disease at some point in their life, with 75 per cent of all rare diseases affecting children.9
OVERVIEW

OHE Consulting Ltd undertook a comprehensive analysis commissioned and funded by Shire of access to OMPs across the EU5 markets – Germany, France, Italy, Spain and the UK, as well as in England, Scotland and Wales. The analysis showed both the growing availability of orphan medicines since 2001 but also variable levels of access across Europe.

New data collected by OHE Consulting Ltd shows that of the EU5 countries, Germany and France routinely provide both the quickest and the broadest access to OMPs. By contrast the England is, on average, slower than Germany, France, Spain and Italy in making OMPs available to patients.

EU REGULATION ON ORPHAN MEDICINAL PRODUCTS

The EU Regulation on Orphan Medicinal Products was the first concerted attempt to improve the availability of treatments for patients with rare diseases in Europe. The EU regulation introduced a number of incentives to support development, including an extended period of market exclusivity for manufactures of OMPs. This was also tied to efforts to improve the approval process itself, with a centralised, EU-wide marketing authorisation system for OMPs.

### Table 1 - OMP Designations and Marketing Authorisations granted to OMPs since 2001

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<tbody>
<tr>
<td>Number of OMPs designated</td>
<td>173</td>
<td>355</td>
<td>86</td>
<td>118</td>
<td>124</td>
<td>182</td>
<td>185</td>
<td>137</td>
<td>1,360</td>
</tr>
<tr>
<td>Number of OMPs authorised</td>
<td>22</td>
<td>45</td>
<td>7</td>
<td>12</td>
<td>10</td>
<td>17</td>
<td>20</td>
<td>10</td>
<td>143</td>
</tr>
<tr>
<td>% OMPs Designations</td>
<td>12.70%</td>
<td>12.70%</td>
<td>8.10%</td>
<td>10.20%</td>
<td>8.10%</td>
<td>9.30%</td>
<td>10.80%</td>
<td>7.30%</td>
<td>10.50%</td>
</tr>
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</table>

Table 1 - OMP Designations and Marketing Authorisations for OMPs since 2001
Source: Zamorra, Maignen, Garau, O’Neill, Mestre-Ferrandiz (2017). Access to Orphan Medicinal Products (OMPs) in the United Kingdom and other European countries. OHE Consulting report. 11
Since 2001 there has been a substantial increase in the number of medicines designated as OMPs and the number authorised for use across European markets.

As Table 1 shows, there have been 1,360 medicines designated as “orphan treatments” since 2001. The “designation” makes these products eligible for the incentives and the extended market exclusivity that are offered by the regulation. Out of these 1,360 products, 143 (10.5 per cent) have obtained a marketing authorisation from the European Medicines Agency (EMA), which confirms that the treatment is efficacious in the indicated condition and generally well tolerated, and suitable for the manufacturer to promote across European markets.

The increase in designations and authorisations reflects both an increase in R&D into these areas as a result of the incentives offered, but also changes in medical development, with more targeted medicines available as scientific understanding of these conditions has grown. That trend has led to the marked increase in OMP designations from 2006 to 2010, with the pace of innovation accelerating in the last 6 years.

While the number of OMPs available in European markets is increasing, as seen in the growth in designations and authorisations, the level of access to these medicines varies significantly across different health systems. Once OMPs have been granted a central marketing authorisation they typically undergo a further value assessment in individual markets. Despite receiving a marketing authorisation from the EMA, not all OMPs are launched in different markets. The data on the number of OMPs with a national decision on use is presented in Figure 1, alongside the time taken for an OMP to receive a national HTA assessment following EMA marketing authorisation. Of the 143 OMPs that have been granted a marketing authorisation by the EU, there are 120 (or 84 per cent) that have a decision on use in England while Germany has a decision on use for 134 (or 94 per cent).

The time it takes for each country’s health technology system to make a decision on use varies significantly. In the English health system, it takes on average 25.8 months for a decision to be made, compared to 13.4 months in France and 7.16 months in Germany.

Figure 1 - Comparison of time taken for availability across EU countries
Figure 2 – Comparison of reimbursement across EU countries


Note on figure 2: months to reimbursement indicates the time observed for OMPs to obtain a positive HTA decision.

There is an even greater difference in the number of medicines actually receiving funding. Following the regulatory process to approve a medicine for use, reimbursement is typically when a medicine is funded through the health system and becomes available for patients. Figure 2 captures both the number of OMPs receiving a positive HTA decision or being routinely commissioned (depending on the system) and the time taken from marketing authorisation to reimbursement. Germany has the broadest level of patient access, with 133 OMPs being reimbursed, second to France which has 116. In Germany, reimbursement is automatic so nearly all OMPs launched are available, while in France, more OMPs are reimbursed than those that have received a national HTA decision. While fewer OMPs have a decision on pricing and reimbursement in Spain (79), nearly 95 per cent of these are reimbursed.

In Italy and England, the proportion of OMPs receiving reimbursement is significantly lower. Of the 120 OMPs with a decision on use in England, only 68 have been routinely commissioned, or 46.9 per cent of all available OMPs. In Italy, slightly more OMPs are available to patients with 75 reimbursed, 52 per cent of all OMPs available. The lower levels of reimbursement are the consequence of negative decisions.

With the exception of Germany, where access is automatic following an EMA marketing authorisation, there is often a further delay in OMPs receiving reimbursement following a national assessment process. There is also considerable variation in the total time from marketing authorisation to reimbursed patient access. In England, the average time to reimbursement is 27.6 months, 4.6 months slower than Spain, 5 months slower than Scotland, 8.1 months slower than France, 9 months slower than Italy and over two years slower than Germany.
Table 2 - Access to OMPs in England, Scotland and Wales

Source: Zamorra, Maignen, Garau, O’Neill, Mestre-Ferrandiz (2017). Access to Orphan Medicinal Products (OMPs) in the United Kingdom and other European countries. OHE Consulting report.\textsuperscript{13}

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<th>England</th>
<th>Scotland</th>
<th>Wales</th>
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<tbody>
<tr>
<td>Number of OMPs centrally authorised</td>
<td>143(*)</td>
<td>143</td>
<td>143</td>
</tr>
<tr>
<td>No. of OMPs with a decision on use</td>
<td>120</td>
<td>96</td>
<td>84</td>
</tr>
<tr>
<td>% of OMPs centrally authorised</td>
<td>82.80%</td>
<td>67.10%</td>
<td>58.70%</td>
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<tr>
<td>No. of OMPs subject of a HTA Appraisal</td>
<td>53</td>
<td>96</td>
<td>84</td>
</tr>
<tr>
<td>% of OMPs centrally authorised</td>
<td>36.50%</td>
<td>67.10%</td>
<td>58.70%</td>
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<td>No. of OMPs Reimbursed, of which</td>
<td>68</td>
<td>55</td>
<td>47</td>
</tr>
<tr>
<td>No. of OMPs with HTA Decision Recommended</td>
<td>11</td>
<td>34</td>
<td>28</td>
</tr>
<tr>
<td>No. of OMPs with HTA Decision Optimised</td>
<td>12</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>No. of OMPs with NHS England Commissioning</td>
<td>32</td>
<td></td>
<td></td>
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<tr>
<td>No. of OMPs included in Cancer Drugs Fund</td>
<td>13</td>
<td></td>
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</tr>
<tr>
<td>% of authorised OMPs</td>
<td>46.90%</td>
<td>38.50%</td>
<td>32.90%</td>
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\textsuperscript{(*)} For these 143 orphan medicines, 145 different indications were appraised by NICE in England

Since 2000 there have been multiple routes to OMPs receiving reimbursement in England. Some of these routes are captured in Table 2, which also includes HTA decisions in Scotland and Wales. Of the 68 OMPs that are receiving reimbursement in England, only a third received a positive NICE appraisal. Of these positive appraisals half were for a select patient population determined by NICE (referred to as ‘optimised’ in Table 2). Nearly half of reimbursed OMPs are made available through NHS England’s specialised commissioning pathway. In recent years, the Cancer Drugs Fund has enabled patient access to 13 OMPs for rare cancers that may not have otherwise been reimbursed. While some patients have been able to access particular OMPs through Individual Funding Requests (IFRs) this data is not routinely available and was not considered in this analysis.
### Table 3. Availability and access to OMPs used in oncology in the England, Scotland and Wales

Source: Zamorra, Maiguen, Garau, O’Neill, Mestre-Ferrandiz (2017). Access to Orphan Medicinal Products (OMPs) in the United Kingdom and other European countries. OHE Consulting report 16

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<th>England</th>
<th>Scotland</th>
<th>Wales</th>
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<tbody>
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<td>Number of Oncology OMPs centrally authorised</td>
<td>56(*)</td>
<td>56</td>
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<tr>
<td>No. of Oncology OMPs with a decision on use</td>
<td>49</td>
<td>45</td>
<td>42</td>
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<tr>
<td>% of Oncology OMPs centrally authorised</td>
<td>84.50%</td>
<td>80.35%</td>
<td>75%</td>
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<tr>
<td>No. of Oncology OMPs with HTA Appraisals</td>
<td>39</td>
<td>45</td>
<td>42</td>
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<tr>
<td>% of Oncology OMPs centrally authorised</td>
<td>67.20%</td>
<td>80.35%</td>
<td>75%</td>
</tr>
<tr>
<td>No. of Oncology OMPs Reimbursed, of which</td>
<td>33</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>No. with HTA Decision Recommended</td>
<td>9</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>No. with HTA Decision Optimised</td>
<td>9</td>
<td>7</td>
<td>12</td>
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<tr>
<td>No. with NHS England Commissioning</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No. included in Cancer Drugs Fund</td>
<td>13</td>
<td></td>
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<tr>
<td>% of Oncology OMPs centrally authorised</td>
<td>56.90%</td>
<td>46.40%</td>
<td>37.50%</td>
</tr>
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(*) For these 56 OMPs, 58 different indications were appraised by NICE in England
Reported percentages for England were calculated over 145 indications.

### Table 4. Availability and access to non-oncology OMPs in the England, Scotland and Wales


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<td>87</td>
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<td>87</td>
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<tr>
<td>No. of Non-oncology OMPs with a decision on use</td>
<td>71</td>
<td>51</td>
<td>42</td>
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<tr>
<td>% of non-oncology OMPs centrally authorised</td>
<td>81.60%</td>
<td>58.60%</td>
<td>48.30%</td>
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<td>No. of Non-oncology OMPs with HTA Appraisals</td>
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<td>51</td>
<td>42</td>
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<tr>
<td>% of non-oncology OMPs centrally authorised</td>
<td>16.10%</td>
<td>58.60%</td>
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<tr>
<td>No. of Non-oncology OMPs Reimbursed, of which</td>
<td>35</td>
<td>29</td>
<td>26</td>
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<tr>
<td>No. with HTA Decision Recommended</td>
<td>2</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>No. with HTA Decision Optimised</td>
<td>3</td>
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<td>7</td>
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<tr>
<td>No. with NHS England Commissioning</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of OMPs centrally authorised</td>
<td>40.20%</td>
<td>33.30%</td>
<td>29.90%</td>
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Tables 4 and 5 show levels of access for orphan medicines for both oncology and non-oncology in England, Scotland and Wales. Of the 143 OMPs analysed, 87 (60%) are for non-oncology diseases. However, in England a higher proportion of oncology OMPs receive a HTA appraisal and are reimbursed when compared to non-oncology OMPs. There may be various explanations for this discrepancy, including the existence of a dedicated conditional approval process for oncology products through the Cancer Drugs Fund.
PART 2: IMPROVING ACCESS IN EUROPE

Case studies of Germany, France and Scotland

GERMANY

Context
The German health system has a policy of allowing automatic reimbursement of medicines following a marketing authorisation by the EMA. This has allowed Germany to provide the widest availability of OMPs throughout Europe. Alongside a policy of automatic reimbursement, the German system has adopted a policy of using health technology assessment to inform rather than limit patient access to medicines.

Policy Developments
Following concerns about rising healthcare costs, the German Government introduced the ‘Act on the Reform of the Market for Medical Products’ (AMNOG) in 2011, to introduce a health technology assessment process into the adoption of new technologies. Pharmaceutical manufacturers were required to demonstrate whether a new drug offered additional clinical benefits over existing drugs. This introduced more scrutiny and oversight over investment decisions in new medicines, which did not affect patient access but enabled the health system to work with manufacturers to reach an optimal pricing solution.

Under AMNOG, evaluation of medicines is undertaken by the Institute for Quality and Efficiency in Health Care (IQWiG) which provides the Federal Joint Committee (G-BA) with evidence-based evaluations. An evaluation typically takes 6 months and begins with the submission of an evaluation dossier by the manufacturers, which is assessed by IQWiG to determine the probability of additional process. The final decision related to extent of additional benefit is made by the G-BA, which rates the level of benefit on different grades such as “minor”, “considerable”, “major” and “no additional benefit”.

For orphan medicines, given the limited data availability on efficacy and additional benefit, a separate process was established. Rather than the IQWiG advising on the additional benefit of an orphan medicine, a special protocol was established that accepted the EMA’s marketing authorisation as proof of additional benefit, as long as the annual budget impact did not exceed €50 million. When the G-BA makes a final declaration of the additional benefit of orphan medicines they are prevented from using the categories of “no additional benefit” or “less benefit” that can be applied to non-OMPs.

The additional safeguards and limitations on the use of HTA in evaluating orphan medicines is in part a consequence of the political prioritisation of rare diseases. The National Action Alliance for People with Rare Diseases (NAMSE) was initiated under the leadership of the German Minister of Health. The alliance, in which the G-BA is represented, generated an action plan for the improvement of health care for those suffering from rare diseases and helped to assist patient access to OMPs.
FRANCE

Context

Since 2000 France has been one of the leading European countries in developing specific policies to improve the quality of care for rare disease patients. In 2005 its first National Plan for Rare Diseases outlined ten strategic priorities to ensure “equity in the access to diagnosis, to treatment and to provision of care” for those suffering from a rare disease. This plan was updated again in 2010, with the updated plan consolidating the objectives of the first plan into three key areas: improve the quality of care for rare disease patients; develop research on rare diseases and amplifying European and international cooperation in the field of rare diseases.

Policy Developments

The Haute Autorité de santé or French National Authority for Health (HAS) is responsible for undertaking HTAs on new medicines, including OMPs. As part of its evaluation, the HAS provides an ASMR scale which included five different levels – major therapeutic benefit, significant therapeutic benefit, modest therapeutic benefit, minor improvement and no improvement. They are used to determine the rate of reimbursement that the statutory health system will provide - with those in the first three categories entitled to a price premium - though patients with rare diseases typically have their full medical expenses covered under the French system. Moreover, the assessment of “added therapeutic value” is based on the same clinical evidence submitted for the EMA marketing authorisation. Medical benefit is also considered to be proven if the total budget impact for the medicine is less than €30 million.

Nearly all OMPs will enter the French Market as part of a price-volume agreement (PVA), with the goal to restrict treatment to the target population by defining a tiered repayment for different levels of sales – with a price cut taking place at the end of the agreed period. The French system includes an additional process to accelerate patient access to new OMPs. The Authorisation for Temporary USE (Autorisation Temporaire d’Utilisation, ATU) allows OMPs which have not yet received Marketing Authorisation a temporary authorisation for use (ATU) which will ensure early access to medicines. An ATU can come in two forms:

A ‘named patient ATU’ concerns a single patient, designated by name, that cannot participate in biomedical research. The patient receives the drug at the request and under the responsibility of the prescribing physician.

A ‘cohort ATU’ affects a group of patients. They are treated and monitored following the criteria defined in a protocol for therapeutic use.

Alongside these safeguards on the use of HTA and the availability of patient access schemes the French system includes a range of incentives to promote OMP access. These include OMP developers being exempt from a range of taxes, including the turnover of medicinal products (under €20 million) and the promotion of medicinal products on the basis of promotion costs (under €30 million), amongst others.

Another feature of France’s access process is a specific managed access agreement for OMPs, where the French pricing committee may agree to an OMP costing over €50,000 per patient per year if the prices is similarly high abroad. In return, the company must agree to restrict its annual sales to a certain limit and to provide the drug to all patients who are eligible for the treatment.
SCOTLAND

Context

The Scottish Medicines Consortium (SMC) has the responsibility for appraising all new medicines, the usual submission of which is 18 weeks although a 22-week assessment is required for OMPs. The decisions made by the SMC are not mandatory on reimbursement. However, SMC advice is followed in most of the cases by NHS Boards and local Area Drugs Therapeutic Committees. In recent years, there has been concern that many of the medicines for rare conditions received a ‘not recommended’ status from the SMC. Patient groups and clinicians developed a growing concern that the SMC may be denying access to medicines for rare conditions purely based on cost, despite the medications being proven to be clinically effective.30

Policy developments

A review of the SMC’s procedures took place in 2013 and recommended a number of changes to improve the assessment of OMPs:

New definition for “ultra-orphan” medicines with the retention of the EMA’s definition for orphan medicines

Orphan and ultra-orphan status are included as a ‘modifier’ criterion. The use of modifiers in submissions became common in 2013/14, especially for cancer medicines, allowing the acceptance of a higher incremental cost-effectiveness ratio (ICER). This allowed the SMC to accept greater uncertainty in the calculation of cost effectiveness and a higher calculated cost per QALY (when supported by a robust clinical and economic case) i.e. more than £30,000.

A new decision making framework for the assessment of ultra-orphan medicines that was not based on the Quality Adjusted Life Year (QALY).

Patient and Clinical Engagement Groups (PACE) provide patient groups and clinicians a stronger voice in the SMC decision making process, and allows a more flexible approach in considering medicines for end of life treatment and rare diseases

Patient group submissions, including patient and carers views and experience, became part of the information to be evaluated.31

The Scottish Government also created the New Medicines Fund in 2014, which now contains £90 million to support the costs of prescribing OMPs, to drive improved access to OMPs in Scotland.32

The Montgomery Review, published in December 2016, acknowledged that Scotland had made considerable progress in improving access to orphan medicines but also highlighted the need for further reform to improve provision of ultra-rare orphan medicines.33 All the recommendations of the review were accepted by Scottish Government’s Health Secretary Shona Robison. Notably, the Scottish Government pledged to implement a revised approval process for ultra-orphan medicines that will see the final decisions on low-volume high-cost medicines being made without the SMC. The SMC will also be afforded the option to consider accepting a medicine on an interim basis, so that its clinical effectiveness can be further assessed.
PART 3: BARRIERS TO ACCESS

Policymakers in the English health system and all health systems have faced a number of barriers that have limited access to orphan medicines. While some countries have been able to overcome some of these challenges, in England there has been more limited success in developing processes and structures to approve these medicines.

MACRO-BARRIERS:

In all health systems policymakers face a number of recurring challenges that hinder faster and more equitable access to orphan medicines:

Small patient populations mean there are limitations in data for rare diseases:
Standard pharmaceutical value assessment processes place a great deal of emphasis on the quantity and quality of clinical data. However, the nature of rare disease research makes it extremely hard to generate sufficient data to meet the evidence levels expected. The largest problem being that given the small patient population, it is difficult to enrol sufficient numbers of patients in clinical studies. The epidemiology of rare diseases is also less well understood making the projections of long-term benefit beyond the end of the trial more speculative. The absence of alternatives and an existing standard of care makes it harder to benchmark cost effectiveness. While patient registries are improving, and have the potential to provide new insights on OMP efficacy, collection is hindered by incomplete patient records in many systems. This lack of data increases the uncertainty facing decision-makers when considering the value of orphan medicines.

Increasing pressures on health care budgets mean rare disease funding is threatened:
Health systems around the world continue to face significant pressure on finances. Slow growth in spend on health and continued pressures on funding come at a time of increasing demand driven by demographic change and rising costs of healthcare delivery. In this context, policymakers are increasingly focusing on common conditions and delivering basic access standards to maintain public confidence in national health systems. Consequently, health systems have started to restrict access to high cost innovations, particularly where the patient population might be small and not high profile.
CHALLENGES TO OMP ACCESS IN THE ENGLISH HEALTH SYSTEM

Since 2001, OMP access in the English health system has fallen behind other major European nations in terms of the breadth or speed of availability. Some of the specific structures and features of the English health system have meant that English policymakers have faced difficulty in prioritising rare diseases. National systems to regulate and reimburse medicines in the English NHS have not always been aligned with the specific challenges of OMPs. While some initiatives, such as the introduction of AGNSS and NICE HST, have had the potential to allow appropriate assessment of ultra-orphan medicines, many changes to the NHS’s specialised commissioning structure have had the impact of creating more barriers to access.

Lack of national leadership and prioritisation for rare diseases:
While some national governments have prioritised rare diseases following the EU Regulation, the UK has not consistently seen national leadership. The UK’s Rare Disease Strategy was published 13 years after the EC Regulation and was shared between the four Governments of the UK, however there was no implementation plan in the English NHS. The Department of Health or NHS England have not introduced their own strategy or plan for the English health system. While in Scotland Ministers have recognised the need to reform the approach used by the SMC to assess OMPs, there has not been similar leadership in England.

Absence of a dedicated assessment pathway for OMPs and use of cost per QALY thresholds:
Since it was established in 1999 there have been few changes to the HTA process used by NICE. While there has been greater flexibility when assessing end-of-life treatments and a separate process for ultra-orphan medicines, most OMPs are assessed under the standard single or multiple technology appraisal process with rigid thresholds per QALY. Typically, OMPs with high incremental cost effectiveness ratios are unlikely to receive a positive appraisal under a standard technology assessment. While other European systems have allowed OMPs to have a more conditional HTA assessment if their budget impact is below a set level, as is the case in Germany or France, there are no exceptions in the English system.

Prioritisation of cost effectiveness and affordability over other system objectives:
Since 2000, many health systems have adopted various processes to assess the cost effectiveness and economic impact of new health services and innovations leading to greater scrutiny over the price and cost of new treatments. While value for money is an important priority for any health system that is mainly funded by public revenue, national health systems have other objectives that are harder to quantify. National systems will have normative priorities such as equity, prioritisation of severity and unmet need and patient and carer experience that can be neglected in a strictly economic evaluation.

Inappropriate use of HTA and fixed QALY thresholds:
Many health systems have introduced HTA agencies to approve use of new healthcare technologies. The increasing use of national HTA processes, and in particular the use of cost per QALY thresholds, have presented considerable challenges for the approval of OMPs that will often have higher incremental cost effective ratios. In addition, proportional improvements in health outcomes generate smaller QALY gains in severe patient populations than in healthier ones, affecting OMPs in particular as, by definition, they target life-threatening or chronically debilitating diseases. While some systems have introduced separate processes for OMPs to put less emphasis on fixed QALY thresholds, other systems continue to use standard HTA approaches.
Multiple and fragmented routes to commission OMPs:
There has long been inconsistency in which organisations in the English health system are reviewing and commissioning OMPs. Before 2010, certain medicines were appraised and commissioned by the National Specialist Commissioning Advisory Group and others were commissioned by local Primary Care Trusts. While the creation of the Advisory Group for National Specialised Services was meant to introduce more consistency for ultra-orphan medicines, since 2013 and the creation of NHS England there have emerged multiple routes to assess and commission orphan medicines. Alongside the role of NICE, NHS England has been responsible for commissioning many treatments, with advice from multiple Clinical Reference Groups. As well as lack of resource within NICE to undertake HST evaluations, there is continued uncertainty on the criteria by which some medicines and not others are assessed via HST. This absence of clarity has created confusion and uncertainty for patients and manufacturers. Consequently, NHS England is now undertaking assessments through the Rare Diseases Advisory Group for many ultra-orphan treatments. This has led to calls for NHS England to make significant changes in order for the process to become “fit for purpose”.

Inappropriate cost effective assessment by NHS England:
With NICE only able to undertake a small number of HST evaluations, many treatments for rare diseases have been assessed by NHS England. The prioritisation process has undergone a series of changes since 2013 but patient groups have expressed concerns that the process places considerable emphasis on affordability and cost, at the expense of other factors such as severity, unmet need or wider societal benefit. Particular concern has been expressed that as the process seeks to prioritise funding for all conditions, treatments for rare diseases are unfairly disadvantaged because of the limited availability of data to support orphan and ultra-orphan medicines. While the prioritisation process is meant to make allowances for rare disease and the Clinical Priorities Advisory Group is supported by the Rare Disease Advisory Group, how these safeguards work in practice is not clear. In contrast to NICE technology appraisals, there are fewer opportunities for patient groups and manufactures to engage with the process. The proposal to introduce a threshold of £100,000 per QALY for HST means that in the future many ultra-orphan medicines will be reviewed by NHS England despite the widespread concerns that this process is not fit for purpose.

Strict commissioning policies and lack of pricing flexibility:
Even when OMPs are approved for routine commissioning, reimbursement is often bound by strict start and stop measures based on the severity of patient need, meaning that access is not always automatic. Health systems, including the English health system, have begun to introduce managed access agreements and discount schemes to allow for reimbursement of OMPs. More complex risk sharing schemes have been considered as part of the recent Accelerated Access Review and it is possible that in the future NHS England will be able to undertake novel pricing and commercial agreements with manufactures to allow for faster reimbursement. Finally, while the MHRA has introduced the Early Access to Medicines Scheme to provide patients with life threatening or seriously debilitating conditions access to medicines that do not yet have marketing authorisation, as this scheme is voluntary and does not allow for immediate reimbursement it has not had the success of similar schemes introduced in other European nations.

Limitations in the use of Individual Funding Requests:
Like other health systems the English health system does include routes for patients to get access to treatments that are not routinely commissioned. However, the Individual Funding Request (IFR) process, as administered by NHS England, places extremely strict criteria on applications that limits its use to “exceptional” cases. Moreover, the IFR route is capped at 20 per indication, meaning that the scheme can become a “bottle neck” for access if more than 20 patients attempt to use it to access a treatment.
PART 5: DELIVERING REAL CHANGE FOR RARE DISEASE PATIENTS

The UK Strategy for Rare Diseases set out an ambition to achieve equity of access and to ‘ensure no one gets left behind just because they have a rare disease’. However, despite the increased availability of orphan medicines since 2001, the English health system has not been able to provide the same breadth or speed of access to treatment that other major European health systems have achieved. As improved treatments for rare diseases become available across Europe, it is increasingly vital for the English health system to introduce the necessary changes to those systems charged with regulating and reimbursing medicines, to ensure that English patients are no longer left behind.

As part of a wide-ranging agenda to make the English health system a world leader for rare diseases, the Rare Disease Medicines Steering Group, identified a series of recommendations for policymakers across four key areas:

- Prioritisation and leadership
- Dedicated funding
- Harnessing data
- Reform to medicines evaluation

PRIORITISATION AND LEADERSHIP

Strong cross-party and cross-governmental commitment is needed to help drive access to OMPs across the UK. There is well documented public and political support for greater prioritisation for rare diseases. As well as the verdict of NICE’s Citizen Council, more recent polling found that a majority of people agree or strongly agree that access to treatments on the English NHS for very rare diseases should be based on clinical need and not the NHS’s ability to pay. Polling of MPs also indicates a breadth of political support for this goal. The principle of equity of access for all patients and the responsibility of the Health Secretary to promote universal access are both set out in the NHS Constitution and the 2012 Health and Social Care Act.

To overcome the lack of leadership across the UK and drive change across all the UK’s health systems, an annual inter-governmental summit or steering group is required to drive forward the aspirations of the UK Rare Disease Strategy and commit individual health systems to effective implementation. This annual summit should include the Health Ministers from individual UK governments as well as senior officials and key patient groups.

The summit should prioritise an implementation plan for the existing Rare Disease Strategy, but in light of recent changes within each health system, such as the Five Year Forward View in England and the Montgomery Review in Scotland, the summit should commit to introducing a refreshed Rare Disease Strategy no later than 2018. There is a precedent, with France updating its National Plan for Rare Diseases in 2010 following its first publication in 2005, and the UK should look to follow suit, ensuring the vision for
the future of the rare disease community remains fit for purpose in an evolving landscape. As part of a refreshed strategy, all administrations should consider those areas of policy that were not included in the first iteration, such as improving access to orphan medicines.

As well as stronger and refreshed leadership at a UK level, there is a need for more committed leadership and direction in the English NHS. Since the 2012 reforms, leadership and accountability has been split between NHS England and the Department of Health. While the Department of Health led the development of the Rare Disease Strategy, NHS England is responsible for commissioning the majority of orphan medicines. Despite the centrality of access, equity and universal coverage in the 2016-17 Mandate, NHS England has not consistently supported the rare disease community in delivering on those objectives. To ensure that NHS England is taking steps to prioritise treatment for rare diseases the next version of the Mandate should include a specific commitment to provide equity and access to rare disease patients.

With better access to rare disease treatment set as an objective for NHS England, a member of the NHS England board, such as the Medical or Nursing Director, should be made accountable for rare diseases. In addition, a new National Director for Rare Diseases should be appointed to drive forward improvements and provide leadership to the rare disease community. Working in partnership with patient groups, clinicians and experts, the National Director should develop a Rare Disease Plan for England, along the lines of the Five Year Forward View for Primary Care or Mental Health.

DEDICATED FUNDING

At present, rigid financial rules for commissioners and providers, based on a fixed annual budget, limit the introduction of innovative new treatments that can create value for patients over a longer time line. As such, greater flexibility is needed in accounting for investment in innovation, potentially introducing multi-year budgets, which would help the English health system deliver the smoother introduction of innovation that will benefit patients and deliver value across the system.

As of 2017, the Department of Health has received £1.5 billion from industry through the PPRS rebate scheme. However, there is uncertainty and a lack of clarity around how and where the rebate money is being reinvested. The Scottish New Medicines Fund is financed from the rebate paid to the Scottish government through the agreement, and consideration should be given to using the PPRS rebate to support innovation directly, as is the case in Scotland to fund rare disease medicines.
At present, the approach taken across the English health system to evaluate and commission specialised treatments for patients with rare diseases is not fit for purpose. There are multiple levels of assessment and inconsistent decision making, which lead to inequalities of access. The situation is complex, resulting in delayed patient access to rare and innovative medicines.

To address these inequalities, **NICE, NHS England and the Department of Health should work together with patient groups and industry to establish a fair process of appraisal for orphan medicines, which reflects the wider societal benefits of investing in orphan treatments and recognises the scale of unmet need in rare diseases.**

International evidence has shown there are a number of challenges associated with using health technology assessment and cost per QALY thresholds to assess ultra-orphan medicines.**Any future system of OMP appraisal should include safeguards or limitations on the use of cost effective ratios,** such as the processes used in Germany or France to create more flexibility in decision making or allow for more statistical uncertainty. **A fit for purpose process to assess OMPs should also consider the use of a multi-criteria decision making approach to incorporate all relevant elements of OMP value into a funding decision, in a structured, transparent and consistent manner.**

Alongside the development of a dedicated pathway or more flexibility within standard technology appraisals for orphan medicines, **it is essential that NICE’s HST route for ultra-orphan medicines is maintained and not made subject to a £100,000 per QALY threshold.** In the future, NICE need to set out clearer criteria for selection for the HST route and properly resource HST evaluation, to ensure more consistency and clarity in the system.

**HARNESSING DATA**

Adaptive and efficient processes need to be developed to optimise the use of real world data collected before and after an OMP value assessment. At present, pricing and reimbursement assessment of OMPs are complicated by uncertainty around the clinical profile and the evidence base of new treatments, with the nature of rare disease research making it challenging to generate sufficient data to meet the evidence levels required to meet the expected HTA processes.

This is where early access programmes have the potential to deliver significant benefit and should be further explored. Such programmes offer opportunities for policymakers and regulators to incorporate real-world, locally-derived data into the value assessment process “while facilitating patient access to new drugs for diseases with great unmet need”. Programmes have been particularly successful across France, Italy and the Netherlands, and opportunities should be explored for their further roll-out and uptake across the UK.

As orphan and ultra-orphan medicines are targeted at small patient populations, it can be difficult to enrol sufficient numbers in clinical studies to generate credible data on cost effectiveness. As such, **there should be greater flexibility around what data is used as part of an assessment, greater clarity from NHS England on the feasibility of these evidence requirements, and structures in place to support the sharing of data internationally, across borders including through patient registries.**
APPENDIX 1

Improving access in the NHS 2000 to 2016

Between 2001 and 2016, access to orphan medicines in the English NHS, as determined by the number of OMPs receiving reimbursement or the time taken before medicines became available, did not keep up to the levels of access in other European systems. During this time the English health system has undertaken a number of changes to the regulation and commissioning of specialised services, including orphan medicines. Alongside these changes there has been growing recognition that orphan medicines require specific and fit for purpose assessment processes. However, the impact of national changes to assessment and commissioning has been mixed, with recent policies and proposals in particular having a negative effect on patient access.63

2000 – 2010
A SYSTEM NOT SUITABLE FOR OMPS

Before 2000 there was little structure to the adoption of orphan medicines in the English health system. Individual health authorities were responsible for taking decisions on the use of orphan medicines and given the rarity of these conditions there was often little consistency or security of these funding decisions. However, since the creation of NICE, the National Institute for Clinical Excellence, in 1999 there has been greater scrutiny on the cost effectiveness of medicines.

NICE and health technology assessment

As part of its appraisal of new medicines for routine use in the English health system, NICE adopted an increasingly rigorous health technology assessment process that put considerable emphasis on fixed thresholds on the financial value of the volume and quality of increased life expectancy a treatment provides (Quality Adjusted Life Year – QALY). For its appraisals of new treatments, NICE applied a cost-per-QALY threshold of £30,000 and after recognition that treatments provided to patients who are at end-of-life are likely to have a much higher incremental cost effective ratio (ICER), a degree of flexibility was introduced for end-of-life treatments. However, while the creation of NICE lead to a new rigour in the assessment of medicines, and a formalised process by which access can be provided to treatments, policymakers were slow to recognise the specific needs of orphan medicines and the need to adapt national structures. Consequently, between 2000 and 2009 NICE only approved two OMPs for use.64

Citizens’ right to treatment

In the years following the EC Regulation and the increasing availability of orphan medicines there was some debate about whether the English health system should adopt new policies to facilitate better access. In 2004 NICE’s Citizen Council, a consultative body of 30 members of the public, was asked to consider whether the English health system should pay higher costs for treatments for rare conditions, balancing the high cost of treatment with the need to ensure rare disease patients’ right to fair treatment as recognised. A majority of NICE’s Citizen Council came to the conclusion that the English health system should accept the high up front price of treatments and provide access, particularly taking account of three conditions: the degree of severity of the disease; if the treatment will provide health gain, rather than just stabilisation of the condition; if the disease or condition is life-threatening.65 However following the Citizen Council recommendation no changes were made to adapt NICE’s HTA process to assess orphan medicines.
**Fragmented commissioning**

While NICE evaluated few OMPs in this period and did not adapt its HTA process to make more appropriate assessments for these medicines, commissioning structures became increasingly nationalised. Since 1996 a National Specialist Commissioning Advisory Group had taken the lead for commissioning a small number of highly specialised services and providing advice to Ministers on the designation of specialised services. However, with some conditions covered by national arrangements others were not and it was up to local Primary Care Trusts to make investment decisions. More national coordination of local commissioning was introduced following the 2006 Review of Commissioning Arrangements for Specialised Services, however the funding for orphan medicines still came from local Primary Care Trusts, often working in consortiums called Specialised Commissioning Groups.

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2010 – 2014

**RECOGNISING THE NEED FOR A FIT FOR PURPOSE APPROACH**

With more orphan medicines being introduced into the English health system, there came greater awareness that rare disease patients were not always receiving the care and treatment that was available and current policies were not fit for purpose. Following the publication of the NHS Constitution in 2009 there was also an additional emphasis on the notion that all patients, including those with rare diseases, should have equal access to treatment. The Coalition Government introduced or considered wider proposals to place less emphasis on QALYs and allow for more holistic assessments of value including the Cancer Drugs Fund and value-based pricing. Alongside these wider reforms, specific initiatives were introduced to develop appropriate assessment of ultra-orphan medicines.

**UK Strategy for Rare Diseases**

The EU regulation on access to Orphan Medicinal Products mandated individual member states to publish strategies to improve care for patients with rare diseases. The UK Strategy for Rare Diseases was published in 2013. The strategy was jointly published by the health departments of all four nations in the UK, the first time that they had come together in such a way. The aim of the Strategy was to "ensure no one gets left behind just because they have a rare disease". While the strategy did not include any specific proposals to improve access for OMPs, either through reforms to HTA or national commissioning structures, it did provide a further call to action to improve the quality of care and access to treatment for rare disease patients.

**Advisory Group for National Specialised Services & Ultra-orphan medicines**

In 2010, the National Specialist Commissioning Advisory Group was replaced by the Advisory Group for National Specialised Services (AGNSS). As well as taking on the responsibility on advising Ministers which services should be commissioned nationally, AGNSS was tasked to undertake responsibility for assessing high cost medicines. Working in partnership with academics, industry and patient groups, AGNSS developed a multi-criteria decision making framework approach to ultra-orphans with a prevalence of less than 1 in 100,000 patients. This systematically considered additional criteria beyond cost effectiveness, such as societal preferences, equity, benefits to caregivers, disease rarity and severity. However, with the passage of the Health and Social Care Act AGNSS was disbanded and its responsibility for assessing ultra-orphan medicines moved to NICE.
**NICE and Highly Specialised Technologies**

Assessment of ultra-orphan medicines was transferred to NICE in April 2013 and a new approach was developed that would place less emphasis on QALY thresholds and be “robust, independent and transparent.” Building on the AGNSS process NICE’s Highly Specialised Technologies (HST) programme sought to include a wider range of factors and considerations in assessing the value of medicines for ultra-rare conditions, including indirect benefits and severity of need. By moving beyond traditional evaluation methodologies, the HST process sought to account for the wider benefit of investing in OMPs and meet some of the obligations first recognised by the NICE Citizen’s Forum and the NHS Constitution. Yet while NICE estimated that it would be able to undertake three HST evaluations each year, in practice NICE has undertaken three assessments since 2013.

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**2013 – 2016**

**FOCUS ON AFFORDABILITY**

While the Coalition Government introduced reforms that had the potential to improve access to OMPs since 2013 and the creation of NHS England, the system has put a renewed emphasis on affordability and cost in its consideration of rare disease medicines. Changes to NHS England’s specialised commissioning policies have come at a time when more orphan medicines are being developed and launched in the English health system.

**NHS England and specialised commissioning**

The 2012 Health and Social Care Act made NHS England the national commissioner for all specialised services. With NICE undertaking a small number of assessments for ultra-orphan medicines and in the continued absence of a HTA route for orphan medicines, NHS England took responsibility for undertaking the majority of reimbursement decisions through its Clinical Reference Groups (CRGs). The Clinical Reference Groups are panels of clinicians, commissioners, public health experts and patients and are responsible for determining service specifications and contracting arrangements for different specialised services. CRGs are responsible for making recommendations to the Clinical Priorities Advisory Group (CPAG), which is advised by the Rare Disease Advisory Group. CPAG makes final recommendations on investment decisions. How this decision-making process works and the respective role of the different advisory groups has undergone a number of structural and procedural changes. Patient groups and industry leaders have expressed concern that policies were not always consistent, transparent and consultative, and in contrast to AGNSS and HST, placed greater emphasis on cost and affordability in their decision making.

**NHS Affordability consultation**

In October 2016 NHS England and NICE proposed a series of changes to the commissioning and evaluation of medicines that sought to mitigate the impact of some new technologies on the NHS budget. The proposals included the introduction of a QALY threshold of £100,000 for evaluating Highly Specialised Technologies. Medicines above this range are to be considered through NHS England’s process for prioritising other highly specialised technologies. NHS England and NICE suggested that this change would better align the HST and NHS England process and provide greater clarity to patients and companies. However, industry has highlighted that none of the medicines that have been approved by HST to date would fall under this threshold and NHS England’s process is poorly aligned to the specific needs of orphan and ultra-orphan medicines.
APPENDIX 2

Methodology

OHE Consulting Ltd, commissioned and funded by Shire, undertook a data extraction from the European Medicines Agency’s (EMA) and Directorate General for Health and Food Safety’s websites on medicinal products with an orphan designation and marketing authorisation. The extraction included OMPs from the implementation of the EU Regulation on Orphan Medicinal Products in 2001 to June 2016. OHE Consulting Ltd calculated all the medicinal products and indications which have received an orphan designation and which have been authorised by the European Commission as orphan drugs, regardless of the subsequent expiry of the market exclusivity. Those orphan indications with marketing authorisation were matched with a national health technology assessment, commissioning and/or a reimbursement decision using available national sources (in the UK, Spain, Italy, France and Germany). This has been used to demonstrate patient access in individual markets; access is defined from a patient affordability perspective as a full or partial reimbursement of the OMP by the public healthcare system and to cover systems that have variable rates of reimbursement through the public system (France) where your private insurer is responsible for paying the rest. Therefore, it is technically possible for medicines to be reimbursed but not affordable for patients.

For the UK, OHE Consulting Ltd did a further analysis of England, Scotland and Wales. For these countries OHE Consulting Ltd undertook an analysis of the health technology assessment decisions made by the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG). Northern Ireland was not included in the analysis as there is no HTA agency in the country. In practice, most NICE decisions are implemented locally which means that a positive NICE decision leads to reimbursement in Northern Ireland too.
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28. Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products - https://www.bioindustry.org/document-library/highly-specialised-technologies-programmes/