

# The regulatory, evaluation, pricing and reimbursement pathway for medicines in the UK: combining innovation and access

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## Abstract

The United Kingdom has universal healthcare systems, the National Health System (NHS), in its four nations, with healthcare services provided free of charge at the point of delivery. Approximately 10.5% of the UK population has voluntary supplementary private health insurance. While the provision of inpatient medicines is free of charge, medicines provided in the outpatient setting have a dispensing fee in some of the nations, such as the case of England (co-payment). The UK marketing authorisation process is called product licensing and is overseen by the Medicines and Healthcare Products Regulatory Agency (MHRA). There are different licensing routes based on the intended market for launch. MHRA also offers early access schemes and pathways for products targeting unmet medical needs and promising technologies, that aim to accelerate and facilitate market and patient access to products in the UK. These schemes include the option for companies to engage early with regulators and other system partners such as health technology assessment (HTA) agencies. As soon as the technology is authorised, it is available at a list price. Prices for medicines are regulated in legislation and in schemes agreed between the industry association and the Department of Health and Social Care (DHSC). The prices for the NHS are negotiated between the government and the companies. Routine funding decisions in the NHS are guided by HTA evaluations informed by agencies such as the National Institute for Health and Care Excellence (NICE) in England, the Scottish Medicines Consortium (SMC) in Scotland, and the All Wales Medicines Strategy Group (AWMSG) in Wales. Many medicines and other technologies are subject to price negotiations in the NHS, sometimes with confidential price agreements. The NHS in England is legally mandated to routinely fund technologies recommended by NICE that have been evaluated by some of its programmes. The other UK nations have similar arrangements or recognise decisions made in England. The role and contribution of NICE and other HTA agencies in ensuring value for money and evidence-based decision making is well recognised worldwide.

**Keywords:** pharmaceutical preparations; United Kingdom; pricing; reimbursement; drug evaluation; health technology assessment.

## O caminho da regulação, avaliação, precificação e incorporação de medicamentos no Reino Unido: combinando inovação e acesso

## Resumo

O Reino Unido possui sistemas de saúde universais nas suas quatro nações, o Sistema Nacional de Saúde [*National Health System* (NHS)], com serviços de saúde fornecidos gratuitamente. Entretanto, aproximadamente 10,5% da população do Reino Unido possui seguro de saúde privado voluntário e suplementar. Embora o fornecimento de medicamentos de uso hospitalar seja gratuito, em algumas destas nações, como a Inglaterra, os medicamentos de uso ambulatorial são fornecidos com o pagamento de uma taxa de dispensação (co-pagamento). O processo de registro de medicamentos no Reino Unido é chamado de licenciamento de produto e é de responsabilidade da *Medicines and Healthcare Products Regulatory Agency* (MHRA). Existem diferentes rotas de licenciamento de acordo com o mercado pretendido. A MHRA também oferece distintos esquemas e rotas para produtos voltados para necessidades não atendidas e tecnologias consideradas promissoras, que visam a acelerar e facilitar a comercialização e o acesso pelos pacientes aos produtos farmacêuticos no Reino Unido. Estes esquemas incluem a opção das empresas interagirem antecipadamente com agências reguladoras e de avaliação de tecnologia em saúde (ATS). A partir do registro, a tecnologia está disponível pelo preço máximo (*list price*). Os preços dos medicamentos no país são regulamentados por meio de legislação e em programas acordados entre a associação do setor e o *Department of Health and Social Care* (DHSC). O preço para o NHS é acordado entre o governo e as empresas. As decisões sobre incorporação e financiamento no NHS são guiadas por avaliações de ATS informadas por agências como o *National Institute for Health and Care Excellence* (NICE) na Inglaterra, o *Scottish Medicines Consortium* (SMC) na Escócia, e o *All Wales Medicines Strategy Group* (AWMSG) no País de Gales. Muitos medicamentos e outras tecnologias estão sujeitos a negociações de preços no NHS, podendo incluir acordos confidenciais de preços. O NHS na Inglaterra é legalmente obrigado a financiar as tecnologias recomendadas pelo NICE, enquanto as outras nações do Reino Unido têm arranjos institucionais semelhantes ou reconhecem as decisões tomadas na Inglaterra. O papel e a contribuição do NICE e das demais agências de ATS em garantir a otimização dos recursos (*value for money*) e a tomada de decisão baseada em evidências são reconhecidos mundialmente.

**Palavras-chave:** preparações farmacêuticas; Reino Unido; precificação; incorporação; avaliação de medicamentos; avaliação de tecnologias em saúde.



## The United Kingdom and the health systems

The United Kingdom of Great Britain and Northern Ireland (UK) consist of four nations: England, Wales, Scotland and Northern Ireland. In 2020, it had an estimated population of 67.1 million people, a gross domestic product of US\$2.8 trillion (US\$46,744 per capita), and an area of 241,930 km<sup>2</sup>.<sup>1-4</sup> In the same year the UK had a Human Development Index (HDI) of 0.932 (13th in the world), and in 2019, its index of Gini was 0.366 (where 0 represents complete equality and 1 complete inequality).<sup>5,6</sup> In 2019, the life expectancy at birth was 81.2 years and the rate of infant mortality was 3.7 (per 1,000 live births) in England and Wales.<sup>7,8</sup> A maternal mortality rate of 9.19 deaths per 1,000 maternities was reported for the UK for the period between 2015 and 2017.<sup>9</sup>

The UK left the European Union (EU) in 2020, after 47 years of membership, following a referendum held in the country in 2016. After negotiations with the European Council, four treaties establishing the terms of the United Kingdom's orderly withdrawal from the EU entered into force in 2020 and 2021 (some still provisionally).<sup>10</sup>

The four nations that form the UK have universal healthcare systems, namely National Health Service (NHS), which was established in 1948 and provides healthcare services free of charge at the point of delivery. Whilst the health systems in the four

nations work together, there are slight differences among them in some respects, for example concerning the provision of medicines (Figure 1. Health systems overview in the UK). Approximately 10.5% of the UK population have voluntary supplementary private health insurance.<sup>11</sup>

Building on the pandemic response, UK government launched a new life science vision in 2021, setting the path for shortening the gap between life-saving innovations and patient access, and to create opportunities for the life sciences sector growth and work collaboratively with government, academia, regulators and other stakeholders to focus on the major causes of morbidity and tackle future challenges.<sup>12</sup>

## Health and medicines expenditure

In 2020, the total current healthcare expenditure in the UK was estimated at \$391 billion PPP (Purchasing Power Parity) (£269 billion) [12.8% of the Gross Domestic Product (GDP)].<sup>13</sup> The government healthcare expenditure is estimated at \$320 billion PPP (£220 billion), corresponding to 82% of total healthcare expenditure.<sup>13</sup> In 2019, the pharmaceutical expenditure (prescription and over the counter, excluding hospital medicines) amounted to \$515 USD per capita, corresponding to 11.5% of the healthcare expenditure and 1.16% of the UK's GDP.<sup>14</sup> The government schemes were

**Figure 1.** Health systems overview in the UK

**NHS England** and NHS Improvement leads the National Health Service (NHS) in England.<sup>71</sup> It has centralised funding, primarily through general taxation and offers services through the NHS trusts, foundation trusts, charity institutions and social organisations. All English residents are entitled to free public health care, including hospitals, physicians, and mental health care.<sup>11</sup>

The system had a significant reform in 2012 with the "Health and Social Care Act".<sup>72</sup> The principles and values of the NHS are established in its Constitution.<sup>73</sup> Seven integrated regional teams manage and support local health systems, by playing a role of major leadership. All General Practitioners (GPs) are part of a Clinical Commissioning Group (CCG). There are 191 CCGs, responsible for planning, service commissioning (general practitioners - GP, dentists, pharmacy and opticians) at the local level and supervised by the NHS England, which is also responsible for "screening" services and immunisation programme.<sup>11</sup> Services are commissioned on a local, regional and national basis by CCGs and NHS England, 'specialised' services (such as treatments for rare conditions and secure mental health care), military and veteran health services and health services for people in prisons (including youth offender institutions) and some public health services are also commissioned directly by NHS England.<sup>74-76</sup>

The NHS Long Term Plan, published in January 2019, established that from April 2021, an "integrated care system" (ICS) will serve all parts of England. As a new partnerships among the organisations that meet health and care needs across an area, ICS coordinates services and plan for improving population health and reducing inequalities among different groups.<sup>75</sup>

Outpatient medicines in the NHS in England are accessed via private community pharmacies, with the payment of a prescription fee of £9.35 for each prescribed item, or through a pre-paid prescription certificate. Inpatient and a few other medicines are provided free of charge.<sup>77</sup> Prescriptions are free of charge for certain age groups (under 16, 18-18 in full-time education, or over 65), patients with some benefit schemes, tax credits, pregnant women and mothers who gave birth in the last 12 months, certain medical conditions, low income, people who receive War Pension Scheme or Armed Forces Compensation Scheme payments.<sup>78</sup>

**NHS Wales** was reorganised after a reform in 2009.<sup>79</sup> It has a deconcentrated administration with centralised funding, distributed among the different departments. Its governance comprises of the Department for Health and Social Services (DHSS), assisted by the National Delivery Group, chaired by the Chief Executive of the NHS Wales. This group oversees the development and delivery of NHS services across Wales.<sup>80</sup> Public Health Wales, 3 NHS Trusts, the Shared Services Partnership, and 7 Health Boards (LHBs), are responsible for service delivery. Each LHB has a Community Health Council, which are statutory lay bodies, underpinned by 23 area associations with strong local links.<sup>79</sup> Services are delivered by various providers, including community pharmacies and opticians. Prescription medicines are provided free of charge.<sup>81</sup>

**NHSScotland** responsibility is to protect and improve their population's health and for deliver frontline healthcare services. It is formed by 14 territorial health boards, 8 special health boards, including ambulance service, NHS Health Scotland and NHS Education for Scotland and one public health body. Launched in May 2010, the Healthcare Quality Strategy for Scotland, has a shared vision of world-leading safe, effective and person-centred healthcare, setting out the 2020 Vision for NHSScotland, for achieving sustainable quality in the delivery of health and social care in an integrated manner across Scotland. In Scotland, prescription medicines have been provided free of charge since 2011.<sup>82,83</sup>

**Health and Social Care (HSC) in Northern Ireland:** is part of the National Health Service in the UK. The HSC was restructured by The Health and Social Care (Reform) Act (NI).<sup>84</sup> Health services and social care are integrated, with prescription medicines provided free of charge for all. Health and social care services are overseen by The Northern Ireland Department of Health. The Health and Social Care Board (HSCB) and its 5 local commissioning groups commission and provide health services, covering the same geographical areas of the 5 health and social care trusts.<sup>85</sup>

responsible for 59% of the pharmaceutical expenditure, while 41% corresponded to out-of-pocket.<sup>15</sup> In 2018, the average household expenditure on medicines and healthcare products was \$3.2 PPP (£2.2), from which \$0.44 PPP (£0.3) with NHS prescription charges and payments, \$2.33 PPP (£1.6) on medicines not covered by the NHS and \$0.29 PPP (£0.2) on other medical products.<sup>16</sup> The high uptake of generics in the NHS (85%), the use of HTA for supporting decision-making, price negotiations, among other strategies, contribute towards cost-containment.<sup>17-19</sup>

## Pharmaceutical market

The life sciences-industry has an important role in the UK. In 2020, there were 2,270 businesses in the biopharmaceutical sector in the UK, employing 129,900 people across 2,630 sites, with a combined turnover of \$89.15 billion PPP (£61.3bn), which accounts for 36% of businesses, 46% of the employment and 69% of the turnover of the life science industry.<sup>20,21</sup> The core biopharmaceutical sector, which includes companies from small Research and Development (R&D)-focused biotech to large multinational pharmaceutical companies, generates the largest turnover of the life science industry [\$59.2bn PPP (£40.7bn); 46% of total]; 57% of which is generated within the top 25 global pharmaceutical companies.<sup>20,21</sup> In the UK, generics correspond to 85% of the market share in terms of volume and 36% in terms of revenue.<sup>15</sup>

## Overview of medicines regulation

The Medicines and Healthcare Products Regulatory Agency (MHRA) is the national regulatory authority in the UK. Its remit covers all types of health technologies, including medicines, medical devices and blood components for transfusion. The MHRA is an executive agency of the Department of Health and Social Care (DHSC). The UK marketing authorisation process is called product licensing and can be issued for the whole of the UK, Great Britain (England, Scotland and Wales) or Northern Ireland.<sup>22</sup> The licensing route is classified according to the intended market of launch as national or international. The latter provides the opportunity for companies to benefit from reliance mechanisms from regulatory agencies in different countries (Figure 2. Routes for product licensing in the UK).<sup>23</sup> MHRA also conducts other regulatory activities, including post-market surveillance, pharmacovigilance, adverse drug reaction reporting through the yellow card scheme, and safety monitoring (table 1).<sup>24</sup>

There are regulatory mechanisms to stimulate innovation and facilitate access to innovative medicines in the UK, such as the Early Access to Medicines Scheme (EAMS) and the Innovative Licensing Access Pathway (ILAP) provided by the MHRA (Figure 3).<sup>25-27</sup> These mechanisms are aligned with the MHRA's Delivery Plan 2021-2023, which aims to put patients at the heart of regulation and stimulate innovation.<sup>28</sup> These early access regulatory schemes have been criticised by some authors as not being necessarily focused on patient's interest but rather on attracting the pharmaceutical industry.<sup>29</sup>

**Figure 2.** Routes for product licensing in the UK.



**Figure 3.** Mechanisms to stimulate innovation and facilitate access to innovative medicines in the UK

There are regulatory mechanisms to stimulate innovation and facilitate access to innovative medicines in the UK offered by the MHRA. These include the Early Access to Medicines Scheme (EAMS) and the Innovative Licensing Access Pathway (ILAP). The Early Access to Medicines Scheme (EAMS) is a voluntary scheme aiming to provide patient access to promising medicines before marketing authorisation to address unmet medical needs. It does not replace the normal licensing procedure. To be issued with an EAMS, the medicine must previously obtain a “Promising innovative medicine (PIM) designation” and an EAMS positive scientific opinion from MHRA, which is valid for one year. The PIM designation is granted based on early clinical data. The scientific opinion is based on the benefit/risk balance of the medicine based on the available data at the time of EAMS submission. Once a medicine receives an EAMS designation, it can be used in the NHS but it must be provided free-of-charge by the company during the EAMS period, that is, the period between receiving a positive EAMS designation and the time of receiving marketing authorisation.<sup>26</sup> The MHRA, NICE and NHS England provide opportunities for early engagement with companies which have obtained a PIM designation, supporting them to navigate the process for obtaining an EAMS scientific opinion and preparing for subsequent evaluation and patient access.<sup>25</sup>

The Innovative Licensing Access Pathway (ILAP) covers new chemical entities, biological medicines, new indications and repurposed medicines. This scheme aims to accelerate and facilitate market and patient access to medicines. It comprises of an Innovation Passport designation, a Target Development Profile (TDP), providing a roadmap and a toolkit to support all stages of the product life cycle from design to approval. Early dialogues between companies and health system partners are part of the offer for companies that want to engage to discuss their technologies value proposition or evidence development plans. These support services are provided by a collaboration between regulators and other stakeholders including the MHRA, the All Wales Therapeutics and Toxicology Centre, NICE and the Scottish Medicines Consortium (SMC). Other partners might include NHS England and NHS Improvement, the Health Research Authority (HRA) and the NIHR. The TDP is updated as new evidence is generated. It is a living document, based on the product’s characteristics.<sup>27</sup>

## Overview of the economic regulation

The DHSC is the pricing authority in the UK. The drug tariff is the official list, containing the prices known as “list price” (without value added tax, VAT), applicable for medicines to be used in the NHS.<sup>30</sup> New active substances launched within 36 months of the launch of the first indication in the UK, and their license extensions have freedom to establish their list price at launch. Nevertheless, the company needs to confirm their intention to price the medicine at a level considered cost-effective by the National Institute for Health and Care Excellence (NICE), either through the agreed list price, or through a confidential discount or commercial arrangement with the NHS. For license extensions launched after these 36 months, DHSC decides if the proposed new price for the same medicine is acceptable based on specific criteria that may include clinical need, price of therapeutically equivalent or comparable products, external reference pricing, operational costs, patent status, among other information. The companies can request amendments to the list prices.<sup>31</sup>

Prices for prescription drugs in the NHS are set through discussion between companies and the Government.<sup>32</sup> Pricing is currently guided by the voluntary scheme for branded medicines pricing and access (2019) and the statutory scheme established under the Branded Health Service Medicines (Costs) Regulations 2018. They are intended for branded medicines to be used in the NHS.<sup>31,33,34</sup> The DHSC does not regulate over-the-counter drugs.<sup>31</sup> Generics prices were not regulated, nevertheless prices rising unexpectedly were investigated by the National Audit Office in 2017 and new regulations came into force in 2018.<sup>17,19</sup>

Similar regulations to the 2019 voluntary scheme for branded medicines pricing and access have been in place since 1957 and are negotiated between the DHSC on behalf of all UK nations and the Association of the British Pharmaceutical Industry (ABPI) on behalf of the pharmaceutical companies every 5 years. The current agreement is voluntary and non-contractual, and is in place since 2019 until 2023.<sup>31</sup>

The products covered by the voluntary scheme for branded medicines pricing and access include new medicines, branded generics, biosimilars and parallel imports. It excludes centrally procured vaccines and over-the-counter medicines but does apply to NHS sales of branded pharmacy.<sup>31</sup> Details on pricing for all other products, as well as details on requests for price increase or decrease are also described in the scheme.

The voluntary scheme also includes a cap on NHS spending on branded medicines at an agreed growth rate to ensure that the pharmaceutical expenditure in the NHS remains within the pre-specified limits. As a result of the cap, companies within the scheme need to proportionally pay back for the amount that exceeds the agreed growth rate.<sup>31</sup> It is mandatory for the companies to report their revenues and aggregate reported sales and payments.<sup>31,34</sup>

The Statutory scheme was amended in December 2018 by the Brand Health Service Medicines (Cost) Regulations 2018, and applies mostly to small companies that benefit from light administrative requirements.<sup>35</sup>

Many products are subject to price negotiations with the NHS, with discounts not always reflected in the list price. Once the medicines are available in the NHS, there are mechanisms in place to conduct negotiations, tenders and contracts, integrating all or some of the nations.<sup>36</sup>

## Overview of the medicine’s reimbursement

Reimbursement of health technologies in the UK is guided by health technology assessment (HTA) with agencies such as the National Institute for Health and Care Excellence (NICE) in England, Scottish Medicines Consortium (SMC) in Scotland, or All Wales Medicines Strategy Group (AWMSG) in Wales having such remit.<sup>37–39</sup> The methods and the steps in the process for evaluation followed by HTA agencies in the UK are similar to those at NICE. NICE’s methods and processes are described below.<sup>37,40,41</sup> Further information on each of the HTA agencies can be found in their respective websites (table 1).

### National Institute for Health and Care Excellence (NICE)

NICE became a legal entity in April 1999. Its remit was to develop evidence-based guidelines and guidance for the NHS. Over the years, its role and responsibilities have expanded alongside its legislative status and name. In 2005, NICE changed its name to the National Institute for Health and Clinical Excellence to account for the merge of the Health Development Agency responsibilities. In 2013, following the publication of the Health and Social Care Act 2012, it turned into a non-departmental public body and became the National Institute for Health and Care Excellence, taking on responsibilities in developing evidence-based guidance and standards in social care.<sup>42</sup>

**Table 1.** Regulation, pricing, and reimbursement in the UK: relevant websites

Description	Content	Web address
Medicines and Healthcare products Regulatory Agency (MHRA) – Licencing	Information about medicines Licencing in the UK	<a href="https://www.gov.uk/government/collections/licencing-how-to-apply">https://www.gov.uk/government/collections/licencing-how-to-apply</a>
Medicines and Healthcare products Regulatory Agency (MHRA) – Products	Search page to access information on licensed products, Summaries of Product Characteristics (SPCs), and Patient Information Leaflet (PILs) and Public Assessment Reports (PARs).	<a href="https://products.mhra.gov.uk/">https://products.mhra.gov.uk/</a>
Voluntary scheme for branded medicines pricing and access	This site provides information on the 2019 Voluntary Scheme	<a href="https://www.gov.uk/government/publications/voluntary-scheme-for-branded-medicines-pricing-and-access">https://www.gov.uk/government/publications/voluntary-scheme-for-branded-medicines-pricing-and-access</a>
Transparency data	Voluntary scheme aggregate net sales and payment information: August 2021	<a href="https://www.gov.uk/government/publications/voluntary-scheme-aggregate-net-sales-and-payment-information-august-2021">https://www.gov.uk/government/publications/voluntary-scheme-aggregate-net-sales-and-payment-information-august-2021</a>
Drug Tariff	The NHS Business Service Authority publishes the Drug Tariff monthly on behalf of the DHSC. The Drug Tariff outlines: <ul style="list-style-type: none"> <li>amount to be paid to pharmacy contractors for NHS services provided either for reimbursement or for remuneration</li> <li>dispensing rules to be followed</li> <li>value of the fees and allowances to be covered by patients</li> <li>drug and appliance prices to be paid by patients</li> </ul>	<a href="https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff">https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff</a>
All Wales Medicines Strategy Group (AWMSG)	Access to the AWMSG resources and advice	<a href="https://awttc.nhs.wales/">https://awttc.nhs.wales/</a>
Scottish Medicines Consortium (SMC)	Information about the SMC, how the SMC assesses the medicines and outcomes of the assessment.	<a href="https://www.scottishmedicines.org.uk/">https://www.scottishmedicines.org.uk/</a>
NICE health technology evaluations: the manual	Information on NICE’s Health Technology Evaluation programme	<a href="https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-technology-appraisal-guidance">https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-technology-appraisal-guidance</a>
NICE health technology evaluations: the manual	NICE’s methods and processes guides	<a href="http://www.nice.org.uk/process/pmg36">www.nice.org.uk/process/pmg36</a>
NHS England Commercial Framework	Information on commercial flexibilities offered by NHS England	<a href="https://www.england.nhs.uk/publication/nhs-commercial-framework-for-new-medicines/">https://www.england.nhs.uk/publication/nhs-commercial-framework-for-new-medicines/</a>
Information Regulations	The Health Service Products (Provision and Disclosure of Information) Regulations 2018	<a href="http://www.legislation.gov.uk/uksi/2018/677/contents/made_">http://www.legislation.gov.uk/uksi/2018/677/contents/made_</a>
National Audit Office report	NHS spending on generic medicines in primary care (generics vs branding medicines spending)	<a href="https://www.nao.org.uk/wp-content/uploads/2018/06/Investigation-into-NHS-spending-on-generic-medicines-in-primary-care.pdf">https://www.nao.org.uk/wp-content/uploads/2018/06/Investigation-into-NHS-spending-on-generic-medicines-in-primary-care.pdf</a>
Life Science sector	Statistics related to the UK bioscience industry	<a href="https://www.gov.uk/government/statistics/bioscience-and-health-technology-sector-statistics-2020/bioscience-and-health-technology-sector-statistics-2020#fn:7">https://www.gov.uk/government/statistics/bioscience-and-health-technology-sector-statistics-2020/bioscience-and-health-technology-sector-statistics-2020#fn:7</a>

NICE produces guidance across all health technologies (medicines, medical devices, diagnostics, digital health technologies, interventional procedures, etc.), clinical areas, public health and social care. All the guidance applies to Wales too.<sup>39</sup>

NICE also offers opportunities for the life science industry to engage early to discuss aspects that might impact the future evaluation of a technology or market access, such as the clinical and economic development plans or the value proposition, through its office for Market Access and the Scientific Advice programmes. These services are associated with a fee.<sup>43,44</sup>

#### The NICE HTA programmes

The NICE Technology Appraisals (TA) programme is one of the most well-known HTA programmes. Through it, NICE develops guidance that assesses the clinical and cost-effectiveness of health technologies, mostly new medicines and biologics. Technologies for very rare conditions are evaluated by the NICE Highly Specialised Technologies (HST) programme.<sup>45</sup> Since 2019 NICE charges the life sciences industry a fee for the evaluation of technologies conducted

by the TA and HST programmes. The Medical Technologies Evaluation and the Diagnostic Assessment programmes assess non-pharmaceutical technologies.<sup>46</sup>

The 2019 voluntary scheme for branded medicines pricing and access requires NICE to issue a TA or HST guidance on all medicines that receive a new marketing authorisation in the UK or significant license extensions.<sup>31</sup> For other topics, NICE identifies the priorities of the health and care system by engaging with stakeholders.<sup>47</sup>

Horizon scanning is provided through collaboration with the National Institute for Health Research Innovation (NIHR) Observatory, from companies through different horizon scanning databases or from direct notifications to NICE from stakeholders or members of the public.<sup>47</sup>

Selection of topics is undertaken by a Topic Selection Oversight Panel comprised of NICE staff, the DHSC, NHS England, clinical experts and lay members. Routing to the particular HTA programme under which the technology will be evaluated is NICE’s responsibility. For TA and HST evaluations, NICE seeks a ministerial referral once a topic has been selected for evaluation.<sup>47</sup>



There are slightly different processes depending on the type of evaluation. Generally, once a topic has been selected, the population, intervention, comparators and outcomes for the evaluation are defined through the scoping phase. At this point, stakeholders are invited to participate. Once the scope has been finalised, the evaluation starts, and the company and other stakeholders such as patient organisations and clinical professional groups are invited to submit evidence to NICE.<sup>48</sup>

During the assessment process, External Assessment Groups, independent academic groups commissioned by the NIHR, critically assess the clinical and cost-effectiveness evidence submitted, alongside with NICE reviews. The resulting report is presented to the independent multi-disciplinary committee, who appraises the evidence, taking also into account expert testimony from patients, clinicians and NHS England provided during the committee meeting.<sup>45</sup>

The committee makes a preliminary recommendation to NICE regarding the clinical and cost-effectiveness of the technology for use within the NHS, which is publicly consulted on. NICE collates comments received during the consultation for the committee's consideration, who will then form its final recommendations. Recommendations from NICE may fall in one of the five categories: recommended, optimised, only in research, not recommended or recommended for use within managed access.<sup>45</sup>

Each evaluation may contain more than one recommendation, which are then subject to appeal by stakeholders if they fall within one or more of the two allowed grounds of appeal, procedural unfairness or if the recommendations appear not to be justified by the evidence available. If there are no appeals, or an appeal is not upheld, the final recommendations are published.<sup>49</sup>

NHS England is legally obliged by the 2012 NHS Constitution to fund technologies recommended by NICE's Technology Appraisals and Highly Specialised Technologies programmes within 3 months (unless otherwise specified) of their date of guidance publication.<sup>41</sup> Mandatory funding for some technologies recommended by the NICE Medical Technologies Evaluation or the Diagnostic Assessment programmes is also provided by NHS England under the MedTech funding mandate (an initiative for accelerating patient's access through the uptake of selected innovative medical devices, diagnostics and digital products).

The NICE TA programme considers the clinical and cost-effectiveness of the technology alongside other elements of value for decision-making. The health benefits should be expressed in quality-adjusted life years (QALYs) and the economic analysis should be based on a cost-utility analysis. The concept of opportunity cost underpins the decisions.<sup>45</sup>

NICE considers that a new technology is likely to be a good use of NHS resources if its incremental cost-effectiveness ratio is below £20,000 to £30,000 per QALY gained, which corresponds to approximately \$29.1k to \$43.6k PPP at 2020 exchange rate. This threshold is reflected in the 2019 Voluntary scheme for branded medicines pricing and access, which states that such threshold cannot be varied for the duration of the voluntary scheme.<sup>31</sup> When analysing the opportunity cost for incorporating new medicines in the NHS, some authors have claimed that the existing threshold adopted in England should be lower.<sup>50-52</sup>

Historically, other elements of value to be considered in decision-making have included the level of innovation of a technology, equality issues, other health benefits or end of life, whether a technology shows evidence of extending survival in patients with a short life expectancy.<sup>53</sup> After a recent revision of its methods for health technology evaluation, NICE included new elements of value, such as the degree of severity, health inequalities and the level of uncertainty, to be considered in decision-making. Severity is meant to act as a quantitative modifier for decision-making, replacing the previously applied 'end-of-life criteria', and where the QALYs gained through technologies for severe or very severe conditions would be valued more than those for less severe conditions.<sup>45</sup>

If a technology is not deemed to be cost effective by NICE, companies may offer commercial deals to NHS England in order to improve the cost effectiveness of the technology under evaluation. The types of negotiations are outlined in the NHS England commercial framework (Figure 4).<sup>54</sup>

A cost-comparison analysis against relevant comparator(s) is used for technologies that are likely to provide a similar or greater health benefits at similar or lower cost. The Medical Technologies Evaluation programme utilises the same kind of comparison.<sup>45</sup>

The NICE Highly Specialised Technologies programme considers some other elements of value. A highly specialised technology is likely to be regarded as a good use of NHS resources if its incremental cost-effectiveness ratio is below \$145,432.76 PPP (£100,000) per QALY gained, with the option of assigning a higher weight to the QALYs gained the bigger the magnitude of benefit. The committee can apply a weight between 1 and 3 to this threshold, using equal increments, for a range between 10 and 30 QALYs gained over the lifetime of patients.<sup>45</sup>

The budget impact is presented to inform the committee's views on the level of decision-making uncertainty, although, is not part of the deciding factors for the committee. Furthermore, NHS England may engage in commercial discussions with the company if the budget impact exceeds £20million, in any of the first 3 years.

**Figure 4.** NHS England Commercial Framework for new medicines

The NHS England commercial framework for new medicines was developed in the context of the 2019 Voluntary Scheme for Branded Medicines Pricing and Access. It includes the allowed flexibilities and associated requirements for companies wishing to propose a pricing scheme to the NHS. The framework describes three different types of schemes available:<sup>54</sup>

**Patients access schemes:** these are the preferred type of commercial negotiation by NHS England. They can be simple (i.e., simple discount from the list price) and treated confidentially, or complex (such as rebates or upfront free stock) and be transparent. Patient access schemes apply to all indications that the branded medicine is licensed for, this is what is meant by the term 'uniform pricing'.<sup>25,31</sup>

**Commercial access agreements:** these are an additional confidential commercial mechanism to improve the likely cost-effectiveness of a technology. In these circumstances NHS England will seek to achieve a deal that delivers additional value than that required for a technology to be considered cost-effective by NICE. It requires negotiation between NHS England and the company. These agreements enable NHS England to offer greater commercial flexibility, in exchange for an enhanced value proposition.<sup>54</sup>

**Managed access agreements:** when a technology has a plausible potential to be clinically and cost-effective, but there is high uncertainty at the time of the evaluation, these schemes are used. They are time-limited and include a data collection agreement and a commercial access agreement. Once the data collection period expires, the technology is subject to re-evaluation by NICE.<sup>54</sup>

If there is no agreement during the commercial negotiation, NHS England may request a variation in the funding mandate period, and ask NICE for an extension in the implementation period.<sup>45</sup>

When a promising technology cannot be recommended by NICE for routine commissioning because of its associated clinical uncertainties, this can be recommended within a managed access fund in England,

for a pre-specified period of time while further evidence is being generated. There are two managed access, ring-fenced funds in England, the Cancer Drug Fund (CDF) and the Innovative Medicines Fund (IMF) (Figure 5).<sup>55-57</sup> NHS Scotland have a different arrangement to increase patient access to new drugs, introduced by a reform in 2014. It is applicable to new drugs for cancer, end-of-life or rare conditions.<sup>58</sup>

**Figure 5.** The Cancer Drug Fund and the Innovative Medicines Fund

The Cancer Drugs Fund (CDF) was set up by the Government in 2011 to offer access to some cancer drugs not routinely available on the NHS that either had not been evaluated or not recommended by NICE. It was heavily criticised because of the financial pressures it put in the system, as its budget overspent, and because the limited benefits in terms of clinical outcomes for patients receiving treatments funded through the CDF.<sup>50,55</sup> An assessment of the clinical benefit of 47 approved indications covered by the CDF, showed that only 38% (18 drugs) demonstrated a statistically significant overall survival benefit, with 3.1 months (1.4–15.7 months) of overall median survival.<sup>52</sup>

In 2016, NHS England reformed the CDF to provide faster access to promising cancer treatments via managed access arrangement, conditioned to the collection of further evidence for addressing clinical uncertainty. NICE can recommend technologies to be used in the NHS by a time-limited period through the new CDF, while further evidence is being collected.<sup>55</sup> After this period, based on the additional data, the medicine will be re-evaluated by NICE, for recommending or not its routine use in the NHS. Since 2016, 91 drugs funded via the new CDF were provided to more than 73,000 patients for the treatment of 205 cancers.<sup>57</sup>

In 2021, NHS England announced the creation of an Innovative Medicines Fund (IMF), following the experience from the CDF. It will consider technologies for any condition, including rare and genetic diseases indications. The total funds for the CDF and the IMF will amount to \$988.9 million PPP (£680 million) of ringfenced funding.<sup>55-57</sup>

For both, the CDF and IMF, companies must commit to a managed access agreement, which comprises a data collection agreement and a commercial access agreement. NICE will use the data collected during this period to issue a final recommendation regarding the NHS routine use.<sup>57</sup> The costs of data collection, validation and analysis will be shared. Companies will be responsible for paying a proportionate share of the production of a data/statistical analysis plan; for submitting new evidence to NICE at the end of the data collection period. If NICE is unable to recommend the drug's routine use in the NHS at the point of re-evaluation, companies are also mandated to cover costs for any patients who were prescribed the medicine when it was in the fund.<sup>57</sup>

The CDF and IMF include an expenditure control mechanism by which companies must paid back on a proportional basis if the budget overspends. The process for the IMF is currently under public consultation until February 2022 after which NHS England and NICE will consider all comments submitted before its final publication.<sup>57</sup>

## Pricing and reimbursement outcomes and effects to the health system

Reviews of NICE's functions have concluded that NICE plays an important role, particularly in financially constrained times.<sup>59</sup> There is evidence that the price the NHS pays for drugs is used as a benchmark by other countries.<sup>60-62</sup> There are concerns about the opacity of the listed prices, due to confidential discounts to the NHS. It warrants caution for other countries that use these publicly available list price in their external reference for pricing strategies, as they may be different from the actual prices paid by the NHS. Evidence suggests that estimated confidential discounts range from 20 to 29% of the list price but can also be much higher.<sup>60,63,64</sup>

The Innovation Scorecard reports, published twice a year, can be used for monitoring the uptake and use of technologies recommended by NICE Technology Appraisal programme in the NHS in England.<sup>65</sup> In terms of access to new treatments and timeliness, NICE made a positive recommendation in over 80% of Technology Appraisals between April 2013 and March 2021. In 2020/21, the average time for drafting a TA guidance was 1.5 months and 3.3 months to final NICE TA guidance, from marketing authorisation.<sup>66</sup> NICE also publishes a list of guidance that could generate cost savings for the NHS based on the NICE's resource impact reports and templates, so the NHS can estimate savings for their local setting more accurately.<sup>67</sup>

## Final considerations

The discrepancy between the benefits to be offered by new medicines, their often high prices and how much the NHS can afford to pay is one of the challenges for ensuring patients' access to these new medicines, whilst granting companies market access and return for their investments.<sup>50</sup> These issues seem to be addressed in the UK by a combination of factors: the highest uptake of generics among the OECD countries; a diverse health systems pathways with an interinstitutional life-science approach, integrating research incentives, aligned with regulatory evaluation, pricing and reimbursement policies and mechanisms for incentivising innovation and patient access supported by evidence-based decision-making. New medicines with high prices, and limited evidence and clinical benefits are in the global agenda as an area to be addressed, with increasing transparency and collaboration.<sup>68</sup>

HTA plays a key role in the UK in ensuring the sustainability of the health care system. The HTA agencies provide unbiased funding recommendations for different health technologies based on evidence, contributing to ensuring value for money in fixed-resource contexts like the NHS. Transparency is one of the principles that underpin how NICE develops its guidance. This is shown in the publication and availability of evaluation reports, the associated evidence underpinning the decisions, and the processes and methodologies being followed.

NICE's methods and process for health technology evaluation are respected around the world. NICE collaborates with other

countries that aim to improve their nation's health and wellbeing by sharing expertise in guideline development and health technology assessment.<sup>69</sup> Its collaboration with Brazil and other Latin American Countries with technical support and workshops in recent years have strengthened the efforts to support evidence-based decision-making in the Region of Americas.<sup>70</sup>

### Collaborators

AMIB and PPD contributed equally with conceptualisation, writing original draft, writing – review and editing. ANB contributed with conceptualisation, writing – review, and editing. All authors reviewed and approved the final version of the work and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

### Conflict interests statement

The authors have no interests to declare.

### Disclaimer

The views expressed in this article are from its authors, and do not necessarily reflect those of the Brazilian Health Regulatory Agency (Anvisa), the Executive Secretariat of the Drugs' Market Regulatory Chamber (SCMED), the National Institute for Health and Care Excellence (NICE) or The University of Sheffield.

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### Series' Guest Editors

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