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Pharmaceutical Policy:

Balancing Innovation, Access and Affordability

Pharmaceutical Policy in the UK

Huseyin Naci, MHS, PhD and Robin Forrest, MSc
Department of Health Policy
The London School of Economics and Political Science

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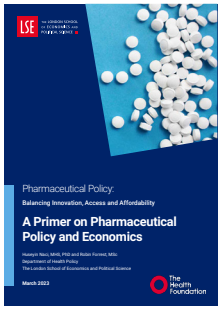
More from this series

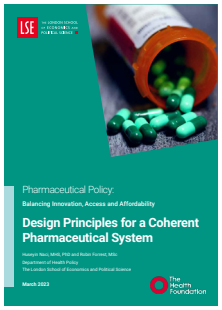
This is the third of three reports as part of a series commissioned by The Health Foundation on pharmaceutical policy and economics. This report focuses on pharmaceutical policy in the United Kingdom (UK).

Other reports in this series:



A Primer on Pharmaceutical Policy and Economics

This report describes the process and policy environment surrounding the discovery, development, approval, pricing and adoption of pharmaceuticals.



Design Principles for a Coherent Pharmaceutical System

The overarching purpose of this report is to present design principles for building a coherent pharmaceutical system.

Authors

Huseyin Naci, MHS, PhD, is an Associate Professor of Health Policy at The London School of Economics and Political Science (LSE). Huseyin conducts research and teaches on health care policy and practice in Europe and the United States (US). His research to date has evaluated the quantity and quality of the evidence base underpinning the approval, adoption, reimbursement and use of prescription drugs in Europe and the US. His research has appeared in leading medical and health policy journals, including the *Journal of the American Medical Association (JAMA)*, *The Lancet*, *The BMJ*, *Health Affairs* and *The Milbank Quarterly*. Huseyin has a PhD from the Department of Social Policy at LSE and a master's in Health Sciences from the Johns Hopkins Bloomberg School of Public Health, US. In 2018 to 2019, he was the recipient of the UK Harkness Fellowship in Health Care Policy and Practice, based at the Harvard Kennedy School of Government, US. Huseyin does not receive any funding from the pharmaceutical industry and does not have any conflicts of interest to declare.

Robin Forrest, MSc, is an MPhil/PhD student (Health Policy and Health Economics) and Research Analyst in the Department of Health Policy at LSE. His research focuses on pharmaceutical policy and economics. Prior to joining LSE, Robin worked in the health economics and regulatory affairs divisions of various global pharmaceutical and biotechnology companies. Robin has an MSc in International Health Policy from LSE, for which he was awarded the Brian Abel-Smith Prize for Best Overall Performance on the programme. Robin also holds a BSc (Hons) in Biochemistry from the University of Bath, UK. Robin does not receive any funding from the pharmaceutical industry and does not have any conflicts of interest to declare.

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A note to readers

Objectives of this report

The overarching purpose of this report is to describe the pharmaceutical policy landscape in the UK, in the context of global pharmaceutical policy and economics, and design principles for building a coherent pharmaceutical system, presented in the previous two reports in this series.

The aims of this report are to:

1. Provide an overview of the current regulatory and policy landscape in the UK.
2. Describe how the UK pharmaceutical sector fits within the global context, outlining its contribution to drug discovery and clinical research.
3. Highlight the roles and responsibilities of key stakeholders in the system – for example, the Medicines and Healthcare products Regulatory Agency (MHRA) at regulatory approval, and the National Institute for Health and Care Excellence (NICE) and NHS England at reimbursement, adoption and use.
4. Outline the role the UK pharmaceutical sector plays in the UK economy and how this role may shape the health and industrial policy decisions of the UK government.

Target audience

This report will be relevant to UK policymakers and their advisers, civil servants and others involved in pharmaceutical policy. Researchers and students in the field of health policy should also find this report useful for understanding the unique features of the pharmaceutical sector in the UK.

No prior knowledge of the pharmaceutical industry is required to understand the key concepts of this report. However, readers might find the first report in this series (*A Primer on Pharmaceutical Policy and Economics*) useful to introduce key policy issues and to provide additional context.

Table of contents

Section 1 Overview of pharmaceutical policy in the UK

Introduction

Prescription drugs play an important role in improving health outcomes. Over the past few decades, they have offered new opportunities to treat people with substantial unmet need, such as those with the human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), hepatitis C and many cancers.[1–3]

As the prevalence of chronic conditions in the United Kingdom (UK) is increasing, the use of prescription drugs is continuing to increase.[4] Around half of adults in England now take at least one prescribed medicine every week, with almost a quarter being prescribed three or more.[5]

In 2020/21, the total cost of hospital and community prescribing to the English National Health Service (NHS) after rebates was £16.7 billion.[6] As this cost continues to grow year on year, the affordability of medicines has become a primary concern for UK policymakers (**Box 1**).

As we outline in the first two reports in this series, ensuring affordability, incentivising innovation and achieving timely access to new medicines together constitute the primary objectives of pharmaceutical policy. The UK government attempts to balance these objectives alongside broader health and industrial policy objectives. Health policy aims to achieve an efficient allocation of available resources to maximise population health. Industrial policy seeks to improve the UK business environment for domestic and international pharmaceutical companies, to grow the UK economy.[7]

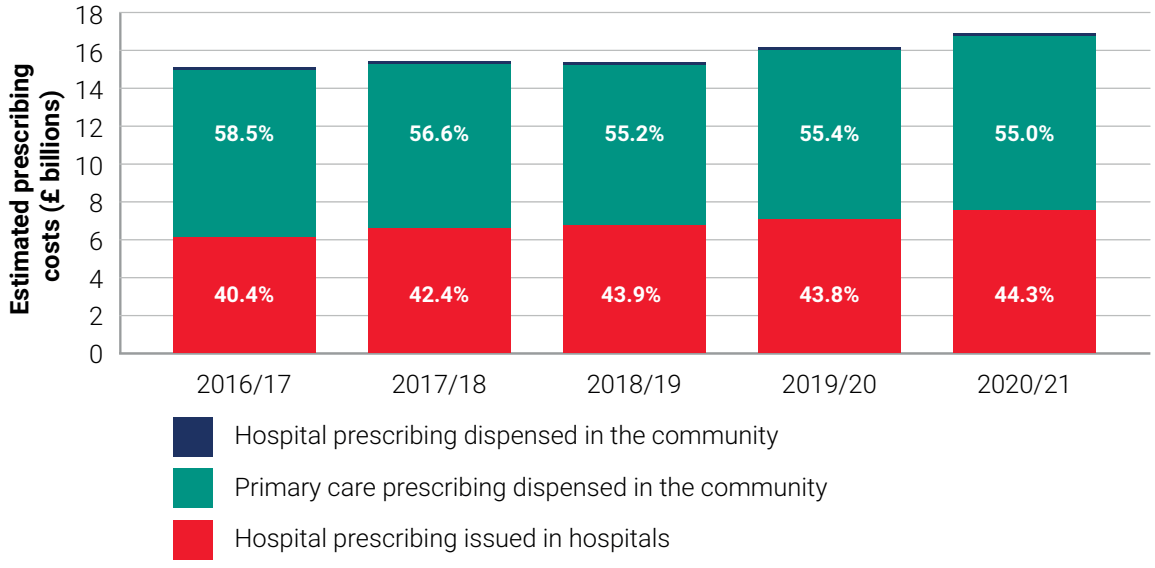
Box 1 – Pharmaceutical expenditure in the UK

- Pharmaceutical expenditure in the UK is growing at a rate faster than the growth of the annual NHS budget.[8]
- In 2020/21, the total cost of medicines (including hospital and community prescribing) to the NHS after discounts was £16.7 billion.[6]
- In 2019/20, the cost of medicines at list price accounted for around 14 per cent of the total core Department of Health and Social Care funding (£148.7 billion) and was the third-largest cost component behind inpatient and outpatient care.[9]

Trends in pharmaceutical spending

- Over the past 10 years, there was an average annual growth of around 5.5 per cent in spending on pharmaceuticals in the UK.[10] In comparison, the total NHS budget grew by roughly 1.4 per cent annually during the same period.[11]
- The rate of increase in prescribing costs has differed slightly between hospitals and primary care (**Figure 1**).
- Hospital prescribing accounts for the cost of drugs administered or dispensed during an episode of hospital care.
- Hospital prescribing costs have increased the most in recent years (**Figure 1**).

Figure 1. Prescribing costs (actual) in hospitals and the community in England, 2016 to 2021



Notes: 'Hospital prescribing dispensed in the community' represents prescriptions that health professionals in hospital wrote but which were dispensed in the community. 'Primary care prescribing dispensed in the community' refers to products prescribed and dispensed in primary care. 'Hospital prescribing issued in hospitals' represents prescriptions that health professionals in hospital wrote and which a hospital pharmacist dispensed.

Source: Adapted from NHS Digital[6]

Box 1 – Pharmaceutical expenditure in the UK (continued)

International comparison

The UK spends less on drugs prescribed in the community in real terms (US dollars per capita) and relative terms (as a percentage of health spending and Gross Domestic Product [GDP]) than the average for countries of the Organisation for Economic Co-operation and Development (OECD) and less than other countries of the EU5, Japan or the United States (US).[12] This is achieved mainly through Health Technology Assessment (HTA), price negotiation and regulation on spending, coupled with relatively high rates of generic prescribing (discussed in Section 5).

Broad objectives of national pharmaceutical policy

Health objectives

Innovation

Research and development (R&D) that leads to the development of new medicines that have meaningful clinical benefits is key to ensuring society captures the potential health benefits of new drugs now, and into the future. To maximise these health benefits, innovation must occur in areas of unmet medical need, which are not always the most profitable disease areas for companies developing new products. Across R&D, public sector research institutions fund research in an effort to stimulate later-stage industry funding, and strive to focus private investment in areas most likely to improve population health.

Access

Patients in the UK appropriately expect the NHS to provide timely access to new effective treatments, and for health outcomes to keep pace with those of other countries.[13] Whether through increasing public investment in R&D,[14,15] expedited regulatory approval pathways,[16,17] increasing the commercial flexibilities of NHS England[18] or through other means,[19] promoting faster access to new medicines has become an increasingly dominant feature of pharmaceutical policy in the UK. Many of these initiatives have been effective in achieving faster access to new drugs.[20]

But when decisions are taken to adopt a new drug into a health system, an inherent trade-off is made between evidence and access.[21] Faster access can come at the expense of greater uncertainty about the effectiveness of the new drug in the 'real world' (ie, outside of clinical trials).[22] Meanwhile, managing patients' expectations while ensuring new drugs are both clinically effective and cost-effective is politically challenging. Approval and reimbursement decisions in the UK often stimulate heated public debate and increase pressure on decision-makers to increase access.[23] Despite this, expedited development and approval of and access to new drugs does not always translate into tangible health benefits for patients or society,[24] as new drugs may have high opportunity costs and displace more health than they offer in the health system.[25–27]

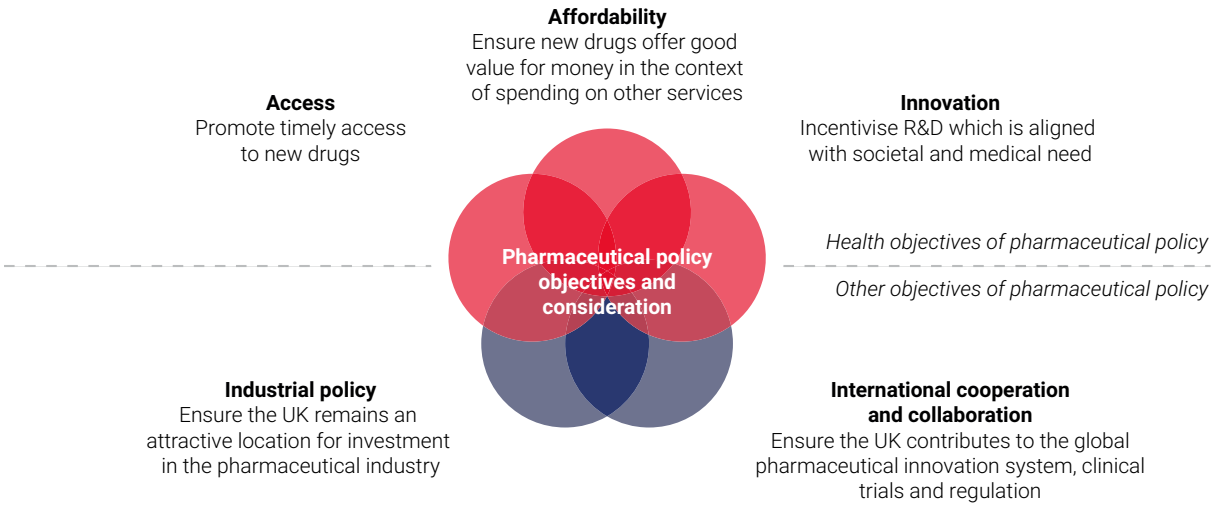
Affordability

Under increasing budgetary constraints, policymakers face pressure to ensure resources allocated to new drugs represent good value for money in the context of broader health spending across the NHS. Approval of new drugs with high prices has made achieving affordability increasingly difficult in recent years.[28] Between 1995 and 2013, list price per life-year gained for new cancer drugs increased from about £40,000 to approximately £150,000.[29] In other cases, new drugs may be cost-effective but are still unaffordable within the NHS.[30,31] Increasing the availability of highly priced medicines could have a large knock-on effect on the availability of other treatments across the NHS. Affordability mechanisms should promote good use of available resources across the NHS.

Industrial policy and other considerations

Innovation, access and affordability are not the only concerns of policymakers at the national level. National policy objectives surrounding pharmaceuticals are complex, encompassing these three objectives, in addition to industrial policy objectives and global considerations (**Figure 2**).

Figure 2. Objectives and considerations for national-level pharmaceutical policy



Industrial policy may be considered as "any type of intervention or government policy that attempts to improve the business environment or alters the structure of economic activity toward sectors, technologies or tasks that are expected to offer better prospects for economic growth or societal welfare than would occur in the absence of such intervention".[32]

Over the past decade, the UK government has set a clear industrial strategy for UK pharmaceutical policy. Broadly, this consists of ensuring the UK is a favourable location for businesses to research, develop and market new products. The ultimate aim is to encourage investment in the UK life sciences sector to grow the economy.

The UK's industrial policy for the pharmaceutical sector is important as the sector has traditionally been one of the strongest-performing industrial sectors in the UK.[33] According to the Office for National Statistics, around 770 pharmaceutical businesses, with a turnover in excess of £40.7 billion, supported approximately 66,000 jobs in the UK in 2020.[34] Increasing skills through these high-paid jobs is a key driver of productivity and economic growth. However, as we discuss in this report, at times these industrial policy objectives do not always align with the aforementioned health objectives of pharmaceutical policy.

The pharmaceutical sector as a political actor in the UK

An additional consideration for policymakers is that the pharmaceutical sector is a powerful political actor in the UK.[35–38] Given the pharmaceutical industry's role in the economy, it has strong political influence and leverage in negotiations and national policy agenda setting.[39] In addition, the pharmaceutical sector also spends heavily on lobbying key decision-makers and influential groups in the UK, including patient organisations[40] and those responsible for resource allocation decisions such as clinical commissioners[41] and parliamentary groups.[42]

Influence of the UK pharmaceutical market in a global context

Industry R&D investment is primarily determined by expected (product) lifetime global revenues generated by sales (also taking into account the expected cost of drug development).[43] The UK market represents approximately 2 to 3 per cent of global pharmaceutical sales, significantly less than the European Union (EU) (20 per cent) and the US (50 per cent).[44] It is therefore no surprise that market incentives in the US drive global pharmaceutical R&D as they are most influential on expected global revenues.[45,46] Features of the US health system (eg, a fragmented payer landscape that allows companies to charge higher prices) also increase the influence of the US market on global innovation. New products tend to be launched first in the US market to maximise profits.[47] This results in health systems in other parts of the world – including the UK – approving and paying for products that were primarily developed for the US market.

Governance of pharmaceutical policy in the UK

Throughout this report, where possible, we refer to the entire UK policy landscape for pharmaceuticals. Where substantial differences exist between the four UK nations, we focus mainly on pharmaceutical policy in England, outlining key differences in Scotland, Wales and Northern Ireland where appropriate (**Box 2**).

Box 2 – Overview of health system governance in the UK

In the UK, the NHS ties together the English health system with the devolved administrations' health systems. General taxation largely funds the NHS, with the devolved administrations receiving a block grant from the UK government each year.[48,49] This structure results in England, Scotland, Wales and Northern Ireland each having their own framework for planning, providing and monitoring health services.[49]

Pharmaceutical policy in the UK

In line with the provision of health services in the UK's four nations, different bodies govern some aspects of regulation, and the Health Technology Assessment (HTA) of pharmaceutical products, in the UK (**Table 1**).

Table 1. Overview of regulatory agencies in the UK

UK nation	Drug regulatory agency responsible for issuing marketing authorisations concerning the benefits and risks of medicines	HTA agency responsible for issuing guidance on the adoption and use of pharmaceutical products concerning their cost-effectiveness
England	MHRA	NICE
Scotland		SMC
Wales		AWMSG
Northern Ireland		NICE

Notes: AWMSG = All Wales Medicines Strategy Group; HTA = Health Technology Assessment; MHRA = Medicines and Healthcare products Regulatory Agency; NICE = National Institute for Health and Care Excellence; and SMC = Scottish Medicines Consortium. NICE also issues guidance and recommendations on non-pharmaceutical interventions. NICE guidance is used to varying extents in Scotland, Wales and Northern Ireland.

UK pharmaceutical policy reflects the inputs, trade-offs and considerations of multiple departments, public bodies and agencies across government.

To illustrate the similarities and differences in the objectives of policymakers in the UK, and to provide context for the policy issues encountered throughout this report, below we consider the roles, responsibilities and interests of the main governmental departments, public bodies and agencies responsible for pharmaceutical policy in the UK (England).

Two main government departments direct pharmaceutical policy in the UK: the Department of Health and Social Care (DHSC) and the Department for Business, Energy and Industrial Strategy (BEIS)* (**Figure 3**). The Office for Life Sciences (OLS) sits between the DHSC and BEIS (**Figure 3**) and has played a pivotal role in shaping the UK pharmaceutical policy landscape in recent years. Each of these departments, their subparts and the context in which they appear throughout this report are briefly discussed on the next page.

*In February 2023, the Government announced that BEIS would be split into three new governmental departments: the Department for Science, Innovation and Technology, the Department for Energy Security and Net Zero, and the Department for Business and Trade.

Figure 3. Overview of the main governmental departments, public bodies and agencies responsible for pharmaceutical policy in the UK (England)

The Department for Business, Energy and Industrial Strategy (BEIS)

BEIS is responsible for business, energy, industrial strategy, science, research and innovation in the UK (among other non-pharmaceutical-related domains). According to its delivery plan (2021 to 2022), two priorities that sum up these roles are to "unleash innovation and accelerate science and technology [to] increase productivity and UK global influence" and "back long-term growth and boost enterprise".[50]

In practice, and in application to the pharmaceutical industry, the role of BEIS is to ensure the UK is a favourable place for domestic and international businesses to operate, to encourage pharmaceutical R&D and to ultimately grow and strengthen the economy. BEIS achieves this in two main ways: first, by mitigating the impact of external factors on the UK pharmaceutical sector, such as Brexit (the UK's departure from the EU); and second, by leveraging and enhancing internal factors that make the UK a favourable environment for the pharmaceutical industry. These efforts include:

- issuing incentives that lower the costs of drug development (ie, tax breaks or regulatory fee waivers)
- removing regulatory, logistical or political barriers to research (ie, through industry partnerships with academia and the NHS)
- providing a streamlined regulatory procedure for new drug approvals.

As we discuss later in this report, some of these industrial strategies are – both in theory and in practice – better aligned to health policy objectives than others.

Under BEIS sits UK Research and Innovation (UKRI). UKRI funds most publicly funded, early-stage research in the UK through the Medical Research Council (MRC). The critical role of the MRC in directing research into priority areas to encourage follow-on private investment is discussed in Section 2 of this report.

UKRI also funds Innovate UK, which supports business-led innovation in all industrial sectors including health and the life sciences. In Section 2, we provide some examples of UKRI-funded projects.

The Department of Health and Social Care (DHSC)

The DHSC is responsible for leading England's (along with some aspects of the devolved nations') health and social care provision. Under the DHSC, several agencies and public bodies influence the development, regulation, adoption and use of medicines in the NHS.

Although not an official agency of the DHSC, the National Institute for Health and Care Research (NIHR) utilises public funding to stimulate the clinical research of new medicines. In Section 3, we outline the complementary role of the NIHR to the MRC in incentivising innovation in areas of unmet medical need. We also outline how NIHR-led initiatives present a strong opportunity to jointly meet the health and industrial objectives of pharmaceutical policy through the promotion of clinical research, employment and investment in the UK.

The Health Research Authority (HRA) is an executive non-departmental public body, sponsored by the DHSC, which oversees several committees involved in the ethical review and approval of clinical research. We briefly refer again to the HRA in Section 3.

The Medicines and Healthcare products Regulatory Agency (MHRA) is an executive agency, sponsored by the DHSC. The main roles of the MHRA are to:

- ensure that medicines meet applicable standards of safety, quality and efficacy
- convey the risks and benefits of medicines to the public and health care professionals
- support innovation that promotes public health.

The MHRA must assess and approve all new prescription medicines in the UK before they are prescribed to patients. In Section 4, we look at the role of the MHRA in more detail, focusing particularly on the trade-offs in using expedited approval pathways as a means of aligning health and industrial objectives.

The National Institute for Health and Care Excellence (NICE) is an executive non-departmental public body, sponsored by DHSC to improve outcomes for people using the NHS, other public health services and social care services in England.[51] NICE has a number of workstreams, several of which relate to the evaluation and use of medicines. Of particular importance are the HTA and guidance development programmes discussed in Section 5. The devolved administrations have other agencies that perform similar roles to that of NICE (**Box 2**).

NHS England is an executive non-departmental public body, sponsored by the DHSC. Principally responsible for the commissioning of services across England, groups within NHS England are responsible for procuring medicines in England.[18] In Section 5, we outline the role of these groups in securing commercial arrangements and discounts with pharmaceutical companies to manage expenditure on medicines.

The Office for Life Sciences (OLS)

The OLS sits between BEIS and the DHSC to champion research, innovation and the use of technology in health and care services in the UK. In practice, the OLS is a specialist organisation, which is designed to jointly improve patient outcomes and support economic growth. Since 2011, working with other agencies and organisations across government, the OLS has shaped pharmaceutical (life science) policy in the UK. Throughout this report, we refer repeatedly to pharmaceutical policy issues and opportunities, which are at the intersection between health and industrial policy, and which are embodied in several strategy documents that the OLS has published over the past decade.[7,52–55]

There are important differences between the health system and industrial sector objectives of pharmaceutical policy. Governments often find it difficult to balance these sometimes-divergent objectives to ensure access to new medicines at affordable prices, while promoting innovation and growing domestic R&D activity and industry. This balancing act is not unique to the UK.

However, an integrated, coherent national pharmaceutical policy has the potential to mitigate the impacts of divergent interests and maximise the areas in which interests align to the benefit of patients, the health system, industry and the economy.

Overview of this report

The remainder of this report sets out the pharmaceutical policy landscape in the UK, describing, in turn, the key stakeholders and processes involved in the following phases of the pharmaceutical lifecycle:

1 Research and development

2 Clinical research

3 Regulatory approval

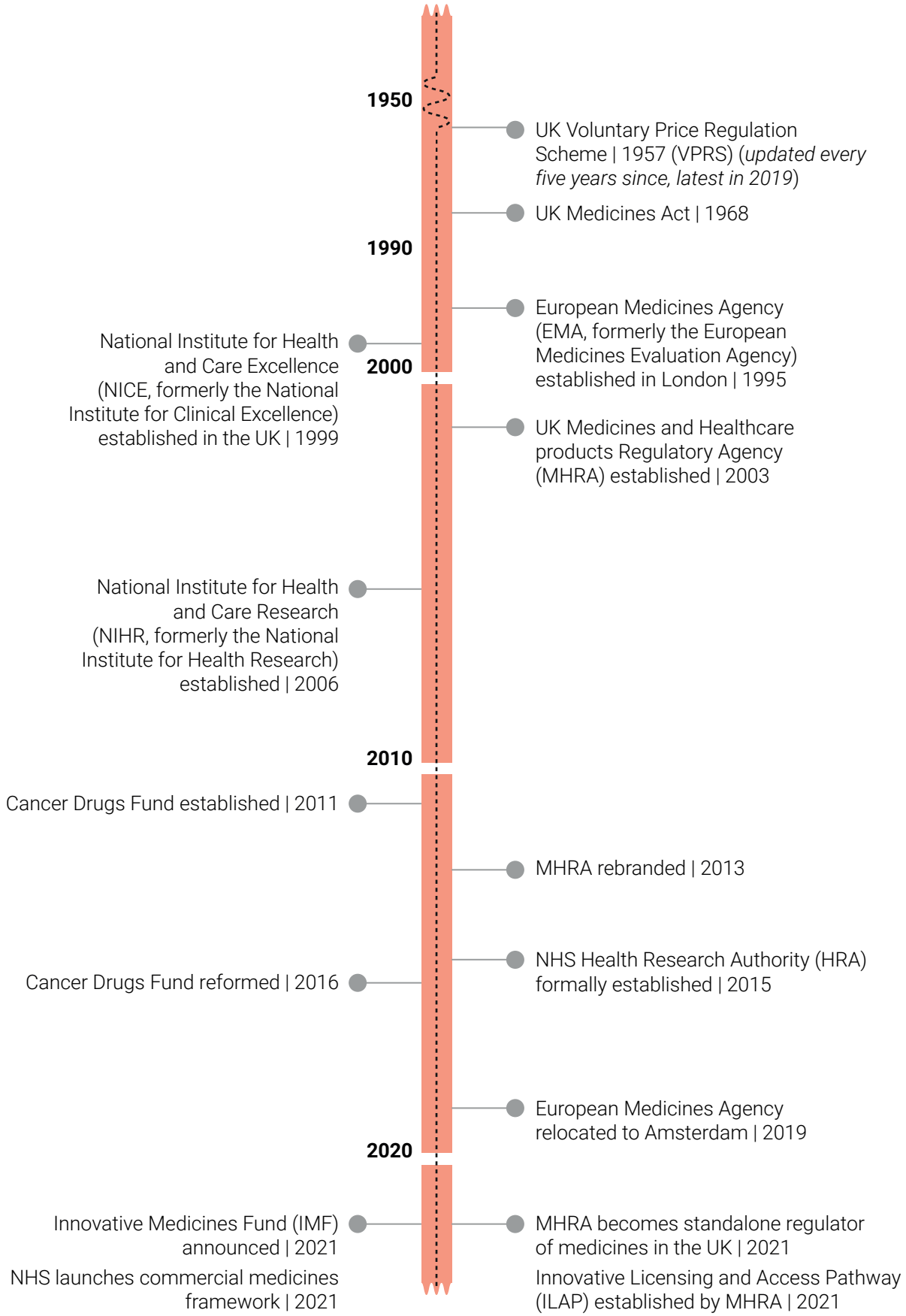
4 Pricing and reimbursement

5 Adoption and use of pharmaceuticals.

For each phase, we outline the inherent trade-offs that policymakers face relating to access, innovation and affordability, and, where appropriate, industrial policy objectives.

Figure 4 summarises some of the key milestones in recent UK pharmaceutical policy.

Figure 4. Key milestones in recent UK pharmaceutical policy



Note: This figure is non-exhaustive.

Section 2 Research and development in the UK

Background: pharmaceutical research and development

R&D in the pharmaceutical sector has several unique features.

Pharmaceutical R&D is typically high-cost, with a high risk of development failure.[56,57] The cost of pharmaceutical R&D is often referred to as a global 'sunk' cost. This is because R&D for novel drugs takes place once globally, with firms incurring costs before a product reaches the market. After this point, the marginal costs of production are relatively low.[58]

Early-stage investment in R&D is typically undertaken in academic settings and by public sector research institutions.[59–61] This type of research stimulates and complements subsequent private sector investment.[62,63] The private sector mostly sponsors late-stage R&D leading up to drug approvals, based on expectations of future profits.[58] However, the public sector also plays a key role in late-stage development in some disease areas.[64,65]

Patent-based monopoly protection provides a financial incentive for pharmaceutical companies to invest in R&D. During the period of patent protection, higher-than-competitive prices can be charged, enabling companies to maximise profits.

Pharmaceutical R&D expenditures include spending on basic and applied research (including clinical trials – the costliest component of R&D). Part of industry R&D investment also funds 'incremental' innovation, product differentiation and other business activities. Therefore, not all R&D investment leads to the development of important drugs that offer meaningful benefits to patients.[66]

Government intervention in R&D

As we have previously outlined, expected global revenues determine industry R&D practices. Although government interventions that influence demand for prescription drugs can also have a knock-on effect on pharmaceutical R&D, such policies are unlikely to be equally effective in all markets. In theory, government policies will only be proportionately effective at incentivising R&D – according to the market size of the country in which they are implemented. Predictably, government policies influencing demand in the US (50 per cent of the global market) have had measurable impacts on R&D investment, clinical trial activity and product launches.[67,68]

Outside of the largest global markets, such as the UK, government policies affecting supply-side factors have greater potential to incentivise R&D investment. Supply-side policies aim to leverage public funds, knowledge, infrastructure and regulation to reduce the (cost, scientific and logistical) burden of R&D, and to stimulate industry investment. For example, public funding during early-stage drug development is key to focusing and incentivising later-stage private investment in R&D. For decades, the MRC has played an important role in directing public funding towards early-stage research in the UK. This role is reflected in its priorities, which include disease areas such as antimicrobial resistance, neuroscience, infectious diseases and other areas that have traditionally seen less investment from industry.

Public funding of early-stage R&D has a disproportionately large effect on the development of drugs that offer meaningful therapeutic benefits.[59–61,64,69] Public funders of scientific and clinical research act as important catalysts to stimulate R&D in areas that are of greatest importance to population health. Increased public investment in R&D is therefore most likely to translate into tangible benefits for patients.

The benefits of increased levels of R&D also extend beyond health to the economy. In the UK, the pharmaceutical sector employs around 66,000 individuals, of whom around half are directly involved in pharmaceutical R&D.[34] Many of the jobs involved are highly skilled and paid, and contribute to the upskilling of the UK workforce and productivity growth. The UK government recognises these benefits of industry R&D and often places them at the centre of its industrial strategy.

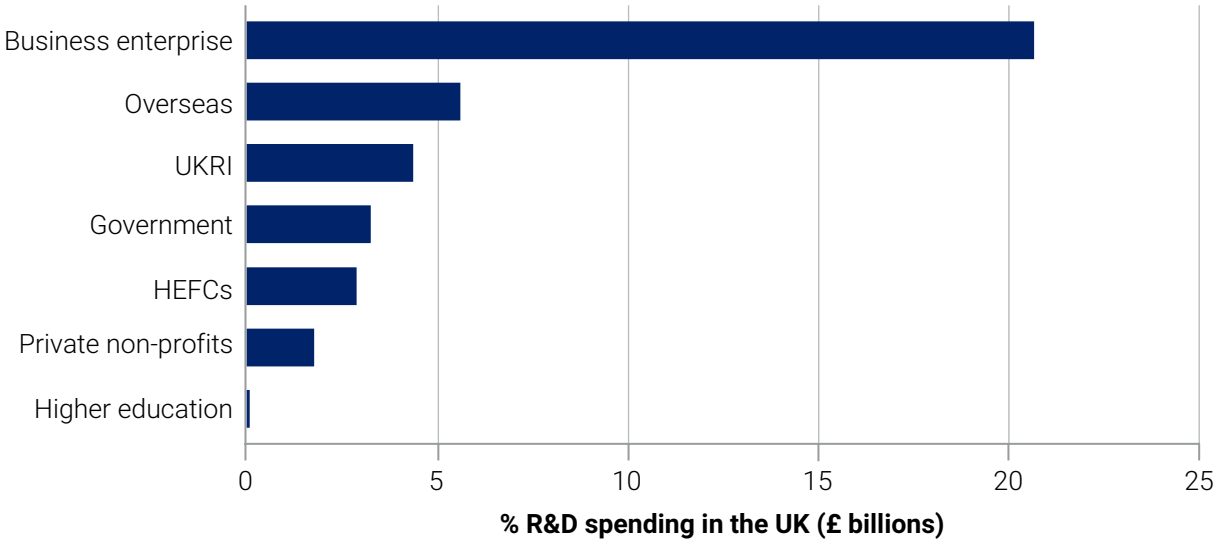
UK investment in R&D compared with the OECD

In relative terms, in the UK across all industrial sectors, gross domestic expenditure on R&D as a percentage of GDP lies significantly below the OECD average. In 2018, the UK spent 1.7 per cent of GDP on R&D, compared with an OECD average of 2.4 per cent.[70,71] For further comparison, in 2018, Germany invested 3.1 per cent of GDP into R&D, the US 2.9 per cent and France 2.2 per cent.[70] It is important to note, however, that the differences in R&D spending may in part reflect the relative balance of industries across different countries, as more 'capital-intensive' sectors tend to require more R&D investment.

Private investment in the pharmaceutical industry outweighs public investment, with this gap growing in recent years. Over the past decade, OECD countries (including the UK) have seen a general decline in the amount of public investment in R&D relative to private investment.[72] In real terms, the OECD estimates that governments collectively budgeted about $53 billion (equivalent to £37 billion in 2016) for health-related R&D (a broader category than pharmaceuticals) in 2016 globally.[73] In comparison, according to the OECD, the pharmaceutical industry invested around $100 billion (equivalent to £70 billion in 2016) directly to pharmaceutical R&D globally in 2016. Of this private funding, almost two-thirds occurred in the US ($65 billion), with a significant share also in Europe ($20 billion), Japan ($13 billion) and China, where spending on pharmaceutical R&D has more than doubled in the past decade.[73,74]

In 2019, the UK showed the lowest percentage growth in expenditure on R&D since 2013, at a total of £38.5 billion.[75] Similarly to trends seen globally, businesses accounted for the majority (67 per cent) of R&D expenditure in the UK, with businesses (all sectors) spending £20.6 billion in 2019, of which the pharmaceutical industry accounted for around 25 per cent (£4.8 billion).[75] In comparison, public sector institutions (ie, government departments, UKRI and Higher Education Funding Councils) collectively spent around £10.5 billion in 2019 (**Figure 5**).[75] In 2019, overseas investment made up 15 per cent of total R&D funding in the UK (£5.5 billion), a decrease from 18 per cent in 2014.[76]

Figure 5. R&D spending in the UK by sector, 2019



Note: Government spending is comprised of government departments (government), UK Research and Innovation (UKRI) and Higher Education Funding Councils (HEFCs).

Source: Office for National Statistics[75]

The UK's contribution to global pharmaceutical R&D

The UK has a strong history of pharmaceutical R&D.[77] From sequencing the first genome, to developing and approving the first globally adopted vaccine for COVID-19, a network of highly skilled scientists underpins medical research in the UK.

Using patent filing data, evidence suggests that between 1992 and 2004, more than 10 per cent of new drugs were developed in the UK, which contributed proportionally more to drug development than most other countries, relative to GDP, during this period.[78] Similar data also show that between 2000 and 2009, the UK was the leading innovator behind the US of new drugs.[79]

Drug discovery in the UK benefits from dedicated facilities in academic centres, charitable organisations and industry.[69,80] According to a survey that the Office for National Statistics conducted, the number of pharmaceutical companies operating in the UK increased steadily from 376 in 2008, to 770 in 2020.[34] However, it should be noted that the survey did not detail the levels of R&D that these businesses conducted.[81] Among the companies are two of the top-20 global pharmaceutical companies by sales revenue (AstraZeneca and GlaxoSmithKline).[82,83]

Although several global pharmaceutical companies still operate major R&D centres in the UK, most have recently decreased their employment for in-house drug discovery in the UK, closing several large R&D sites.[84] This shift coincides with a broader trend of pharmaceutical companies moving away from in-house R&D.[69] In recent years, pharmaceutical companies have outsourced both early-stage and late-stage R&D. For example, so-called 'contract research organisations' are increasingly responsible for running clinical trials on behalf of pharmaceutical companies.

There has been increasing investment in the UK aimed towards high-tech and small and medium-sized enterprises as well as towards an 'open innovation model'.[85] This model integrates internal and external expertise by connecting large companies with smaller, more agile, small and medium-sized enterprises, government initiatives and academic research centres. Adopting this approach presents a strong opportunity for the UK government to further increase the attractiveness of the UK to early-stage R&D.

Innovate UK plays a distinct role in identifying and driving the scale-up of science and technology innovations that are likely to grow the UK economy. The Cell and Gene Therapy Catapult provides a notable example of these efforts. Set up by Innovate UK, the Catapult Network specialises in a number of different areas, offering facilities and expertise to enable businesses and researchers to collaborate on key problems and develop new products on a commercial scale.[86] The Cell and Gene Therapy Catapult provides clinical trial, technical, manufacturing, regulatory and market access expertise to developers, working with industry, academics and the NHS. In 2019, the UK accounted for more than 12 per cent of global cell and gene therapy clinical trials, the majority of which industry sponsored.[87] Innovate UK has also set up a number of additional 'Catapult' initiatives – in manufacturing, precision medicines and medicines discovery, among other areas – to bring industry together with academia and scale up small businesses in the UK.

Research and development in the UK – summary

- Public funding plays an important role in developing new treatments that are most likely to impact population health. Public investment helps to overcome market failures by acting as a catalyst for later-stage private investment.
- Early-stage R&D presents an opportunity for the UK government to jointly incentivise innovation in areas of unmet medical need and to grow the UK economy. Broadly speaking, current industrial strategy well recognises this opportunity, with several initiatives set up under UKRI to achieve both health and industrial strategy objectives.
- To continue to increase the attractiveness of the UK as a destination for private investment in R&D, efforts should focus on increasing public investment in R&D research and upskilling and training the current and future workforce, thereby strengthening the UK offer for early-stage R&D.

Section 3 Clinical research in the UK

Background: clinical research

Clinical trials are prospective studies that compare the effects of a treatment against a control on study participants.[88] Evidence generated through clinical trials is used to provide information on the safety and efficacy of new drugs from which their benefit–risk profile is determined during regulatory approval. Information from clinical trials is also used downstream of regulatory approval to inform pricing, reimbursement and coverage decisions. Lack of sufficient evidence generated in clinical trials can lead to high levels of uncertainty about a drug's benefits, risks and comparative effectiveness (how well it works compared with existing treatments).

Clinical trials are the most risky and time-consuming stage of drug development. Estimates suggest that around 10 to 15 per cent of investigational products that enter early-stage clinical trials obtain regulatory approval. On average, this process of clinical development takes eight years.[56] Despite the risk of development failure, companies investing in clinical trials do so based on expected profits.

Clinical trials are also the costliest stage of drug development, with late-stage clinical trials (so-called 'pivotal trials') accounting for the largest share of total R&D costs.[89,90] The pharmaceutical industry sponsors most late-stage trials that lead to new drug approvals.

Internationally, strict codes of conduct govern scientific, ethical and regulatory aspects of clinical trials.[91–93] In addition to these standards, the MHRA and the HRA oversee the conduct of clinical trials in the UK.[94]

In recent years, inefficiencies in clinical trial conduct have become a concern.[95] Ensuring the feasibility of well-designed and informative clinical trials is a key opportunity for policymakers.[96]

The UK's contribution to global clinical research

The UK is internationally recognised for its contribution to clinical research. Historically, it has played a leading role in many important clinical research advances globally. In 1946, researchers in the UK conducted the first randomised controlled trial (RCT).[97] Since then, the RCT design has become the 'gold standard' of clinical trials to elicit the benefits and harms of new drugs.[98,99] To this day, scientists and research groups from the UK continue to promote high-quality clinical research and pioneer novel trial methodologies. For example, clinical research in the UK has transformed the treatment landscape for COVID-19 (**Box 3**).[100]

Box 3 – Targeted public funding and a favourable clinical research environment – the UK's research response to the COVID-19 pandemic

The UK's research response to the COVID-19 pandemic showcased the ability of public funders to effectively target areas that are of most importance to public health. In 2020, the RECOVERY trial, supported by UKRI (funder of the MRC and Innovate UK) and the University of Oxford, became the world's largest and most successful clinical trial to evaluate COVID-19 therapeutics.

Set up in just six weeks, the trial took off on a scale and at a speed that were unprecedented, with as many as 3,500 doctors, nurses and research staff involved throughout the NHS. By November 2021, more than 45,000 patients had participated in the ground-breaking trial. It is estimated that results from the trial saved the lives of around 22,000 patients in the UK and more than a million lives globally by March 2021.[134,135]

The RECOVERY trial was designed as a platform trial in which patients with COVID-19 were randomly assigned to a group of different therapies on the basis of a decision algorithm to determine whether any therapy has benefit.[136] Such trial designs are efficient in terms of time and resource requirements and collect minimal data, which can be used to answer more than one research question.

The data infrastructure, which enabled the quick identification, enrolment and monitoring of patients in the RECOVERY trial, was key to its success. Data on diagnoses, procedures and discharges were drawn from NHS hospitals; data on cause-specific mortality were obtained from community records; patient demographics and medical history were drawn from primary and critical care records; and COVID-19-specific data were obtained from the UK's so-called 'Lighthouse Labs'.[137] The NHS Health Data Research Hub for Clinical Trials (NHS DigiTrials) was also useful in these data-sourcing activities.

In 2019, the UK accounted for 2.8 per cent of patients recruited to clinical studies globally.[101] Latest data from the NIHR suggest that patient participation in clinical trials in England is increasing, with the NIHR Clinical Research Network recruiting more than 700,000 participants into research studies in England during the year 2019/20.[102] However, data from the MHRA show that the number of new clinical trial applications has remained stable for all-phase clinical trials in England over the past decade.[103]

The importance of public and private funding for UK clinical trials

As we outlined above, the MRC plays a pivotal role in funding early-stage biomedical research and drug discovery in the UK. Similarly, public funding plays an important role in late-stage research.

In 2006, a landmark review of UK health research funding demonstrated the risk of the UK "failing to reap the full economic, health and social benefits that the UK's public investment in health research should generate".[104] Later that year, the Department of Health (which was renamed the Department of Health and Social Care in 2018) established the National Institute for Health Research (NIHR, which in 2022 became the National Institute for Health and Care Research) in England. The NIHR has become the second major funder of health research in England, after the MRC. While the role of the MRC is to fund early-stage R&D, the NIHR takes a complementary role of funding later-stage translational and applied clinical research.[105]

The NIHR was established as a virtual national research facility, ensuring that research that the NHS and universities carried out focused on the needs of patients and the public.[106] The largest of the NIHR programmes, the HTA programme, also supports independent research about the effectiveness, costs and broader impact of health care treatments in the NHS. Since its inception, the broad aims of the NIHR have remained largely the same and the NIHR has become the largest national clinical research funder in Europe, gaining international recognition for pioneering innovative trial designs, reducing avoidable waste in research, improving transparency and leading patient and public involvement in research.[107–110]

Although trials that NIHR runs are often clinically important and can make major contributions to public health, as we outlined previously, businesses account for the majority of investment (almost 70 per cent) in R&D (including clinical trials) in the UK.[111] Industry sponsors the majority of late-phase clinical trials, which lead to new drug approvals in the UK (and also globally).[112]

According to the NIHR, clinical trials conducted in the UK "contribute to the health and wealth of the population".[113] In England, clinical research was worth £2.7 billion in 2019 alone, reportedly supporting more than 47,000 jobs.[113] Therefore, increasing the attractiveness of the UK as a destination for clinical research is important from an industrial policy perspective.

The NHS is a favourable destination for conducting clinical research

Several features of the UK health system create a favourable destination for conducting clinical research. Unlike many other health systems where payers and providers are fragmented, the UK has an integrated health care delivery system, which employs most physicians and other health professionals, as well as paying for pharmaceutical products.

The UK also has an established clinical research ecosystem, with many of the world's top universities and teaching hospitals. For many years, the UK has invested in designated Clinical Trial Units, which were set up to design, conduct, analyse and publish clinical trials, and have been successful in simplifying and promoting clinical research across the UK.[114]

Inefficiencies in clinical trial conduct (eg, in terms of patient identification, recruitment and retention) can increase costs and delay research outcomes, resulting in research waste, and discourage investment in clinical research.[95,115,116] The NIHR Clinical Research Network aims to mitigate many of these barriers by supporting study start-up and making clinical trial conduct in the UK more streamlined for industry, while also aligning both health and industrial policy objectives. To further increase efficiency and reduce waste, the NIHR has also supported the development of novel trial designs.[108] These trials may be novel in relation to their methodology, set-up, recruitment or delivery. To truly maximise the health benefits of clinical research in the UK, attention should duly be paid to ensuring that industry-sponsored trials address clinical questions that are most relevant to patients in the NHS and are designed to be most informative for adoption and use in UK clinical practice. Research suggests that currently this is not always the case.[117,118]

The UK has made significant strides in clinical trial transparency in recent years.[119] The transparency of clinical trials is essential to ensure that health care decisions are based on all the available evidence. Until recently, a substantial share of UK clinical research remained unpublished.[120,121] As part of the HRA's 'Make It Public' research strategy, clinical trials conducted in the UK are now (since 2022) automatically registered to a clinical trials registry recognised by the World Health Organization, to "guarantee a full picture of research taking place in the UK", improve transparency and reduce duplicative and wasteful research.[122–124]

The UK benefits from a data environment that allows researchers to access routinely collected information from across different health and care settings in the NHS. This environment has, over time, created several useful databases such as the Clinical Practice Research Datalink (CPRD)[125] (primary care) and Hospital Episode Statistics[126] (hospital care). According to government sources, 19 of the top-20 global pharmaceutical companies have used the CPRD's data services.[55] Nationwide cohorts such as UK BioBank[127] and disease registries such as the Myocardial Ischemia National Audit Project (MINAP)[128] offer rich clinical data that complement routinely collected administrative data. Linking these datasets can help piece together a patient's journey in the health care system.[129]

The UK's data environment and data science capabilities can also be leveraged to conduct clinical trials at greater scale, including those that pharmaceutical companies sponsor.[130] For example, ORION-4 is a co-industry-sponsored research study designed to find out if a new cholesterol-lowering injection (inclisiran) safely reduces the risk of heart attacks and strokes in people with a history of heart disease.[131,132] The study has enrolled 15,000 participants (12,000 in the UK and 3,000 in the US), with a planned follow-up duration of five years. By using NHS Digital data from the Hospital Episode Statistics discharge dataset, eligible individuals in the UK could be quickly identified at a limited number of study sites, reducing the cost to an estimated one-tenth of the usual cost of a similarly sized randomised trial.[126,133]

Clinical research in the UK – summary

- Patients and the pharmaceutical industry can jointly benefit from clinical research conducted in the UK.
- As major funders of medical research in the UK, the MRC and NIHR have complementary roles in incentivising early-stage and translational health research. They play a particularly important role in promoting transformative research.
- The pharmaceutical industry invests heavily in late-stage clinical trials, which support new drug approvals.
- The UK health system provides a favourable data and research environment to conduct clinical trials. The NIHR's efforts to streamline study start-up, patient identification, recruitment and retention are innovative ways to increase levels of clinical research in the UK and attract industry investment. Despite these efforts, further endeavours are needed to improve clinical trial efficiency.[138]

Section 4 Regulatory approval in the UK

Background: regulatory approval

The primary role of regulatory agencies is to protect public health by ensuring that new drugs' benefits outweigh their risks. During regulatory assessment, agencies evaluate the safety and efficacy data generated through clinical trials, and provide information to doctors and patients on the relative benefits of a new drug versus its risks (the benefit–risk profile).

Following approval, regulatory agencies continue to periodically assess the benefit–risk profile of medicines as new data become available from post-marketing studies and regulatory surveillance efforts.

In recent decades, policymakers have targeted the regulatory assessment of new drugs as an additional lever to incentivise drug development in certain areas. For example, regulators now routinely facilitate expedited clinical development and regulatory assessment.

Regulatory agencies must balance a trade-off between requiring companies to generate good-quality evidence on clinical effectiveness and safety, and granting early approvals.

Image by usertrmk on Freepik

UK drug regulation overview

The MHRA's regulation of medicines in the UK is based on the Medicines Act 1968, which established the legal basis for the independent testing of new drugs in the UK.[139] In 2012, the government consolidated and replaced existing UK medicines legislation (including those set out in the Medicines Act 1968 and its subsequent amendments) with a new set of regulations – the Human Medicines Regulations 2012.[140] The new regulations underpin the manufacture, import, distribution, authorisation, sale, supply, labelling, advertising and pharmacovigilance (ongoing safety surveillance) of medicinal products for human use in the UK.

Before Brexit, most prescription drugs intended for use in the UK were required to be assessed via the European Medicines Agency's (EMA) 'centralised procedure'. Under this procedure, pharmaceutical companies submit a single marketing authorisation application to the EMA, before the European Commission grants a marketing authorisation, which is binding in all member states.[141] The EMA draws on the expertise available from each of the individual member states' drug regulatory agencies that carry out the scientific assessments of new medicines.

From 1995, London had been host to the EMA, with the UK MHRA playing an integral role in its collaborative procedure to regulate medicines.[142,143] Estimates suggest that the MHRA previously assessed up to 30 per cent of all EU medicines.[144,145]

On 31 January 2020, the UK left the EU. Following an initial 11-month 'transition period' (1 February to 31 December 2020), during which EU pharmaceutical law continued to apply to the UK, on 1 January 2021 the MHRA became the UK's standalone medicines and medical devices regulator (with the exception of Northern Ireland).[146] In 2019, the EMA headquarters relocated to Amsterdam.

Post Brexit, the move to a single, independent drug regulatory agency in the UK presents both opportunities and potential challenges.

On the one hand, the move has facilitated the introduction of a new route to market authorisation in the UK,[16] which provides an opportunity for the MHRA to work more closely with manufacturers.[147] The MHRA has also established several regulatory programmes that closely resemble those available at the EMA, such as an Accelerated Assessment Procedure[17] and a Conditional Marketing Authorisation pathway.[148] On 2 December 2020, the MHRA became the first regulatory authority to approve a COVID-19 vaccine outside of China and Russia, following a rolling review procedure. It should be noted, however, that the authorisation was in fact permitted under EU legislation during the Brexit transition period. Since then, the MHRA has become the first drug regulatory agency globally to approve an oral antiviral for COVID-19.[149]

On the other hand, the MHRA's departure from the EU's centralised procedure led to concerns about the possibility of pharmaceutical companies 'deprioritising' the UK due to its relatively small market share outside of the EU.[150] Pharmaceutical companies conventionally launch their products in different settings in order of market size and the potential to maximise revenues (the US first, followed by the EU).[47,151,152] The location of the EMA in London also attracted private investment to the UK, with pharmaceutical companies looking to benefit from access to the European regulator, a pull factor that no longer exists.[150] Early estimates suggest that fewer new drugs were being approved in the UK compared with the EU following Brexit.[153,154]

The MHRA and the speed of approvals

Rigorous evidence requirements for new drug approvals protect patients and public health by ensuring new drugs are safe and efficacious. In the 1960s, regulatory agencies implemented new evidence requirements in the aftermath of the 'thalidomide disaster' – when a commonly used drug was found to cause severe birth defects.[155] These new requirements meant that pharmaceutical companies had to demonstrate the safety and efficacy of investigational drugs in pre-clinical and clinical studies before applying for a marketing authorisation. Although evidence requirements were implemented to protect public health, they inevitably led to longer development programmes for companies and longer review periods for regulatory agencies.[156] In the decades since, the duration of clinical development – the time it takes from early clinical trials to regulatory approval – has led to criticism from pharmaceutical companies and some patient groups.[157]

Accordingly, a key feature of modern drug regulation has been the flexibility to grant early patient access by speeding up the development, review and approval of new drugs. In Europe, in the US and in other regions, regulatory agencies have increasingly turned to so-called 'expedited approval pathways' to speed up patient access.[24] Most of the MHRA's newly formed expedited approval pathways take learnings from, or are adaptations of, existing pathways at other regulatory agencies (**Table 2**).

Table 2. Overview of the MHRA's expedited approval pathways

Pathway	Eligibility	Key features	Similar pathways (EU/US)
Accelerated Assessment[16]	• All 'high-quality' new applications for new and existing drugs (including drugs for rare diseases) • Manufacturers are required to pay a fee	• Shortens the duration of regulatory review	• Accelerated Assessment (EMA) • Priority Review (FDA)
Rolling Review[147]	• New drugs • Manufacturers are required to pay a fee	• Regulator commits to review data as they become available (compared with the standard procedure of reviewing once all data are available)	• Rolling Review (EMA) • Rolling Review (FDA)
Innovative Licensing and Access Pathway[17]	• New and existing drugs (if they treat a clinically significant new indication), including drugs for rare diseases • Treatment aligns with UK public health priorities • Manufacturers are required to pay a fee	• Manufacturer benefits from early and frequent interactions with and advice from the regulator (and other stakeholders, such as NICE and NHS England) • Manufacturer benefits from an 'Innovation Passport' designation and a 'Target Development Profile'	• PRIority MEdicines (PRIME) Designation (EMA) • Breakthrough Therapy Designation (FDA)
Conditional Marketing Authorisation[148]	• For medicines that fulfil an unmet medical need (eg, for serious and life-threatening diseases where no satisfactory treatments are available) but existing data are incomplete for full approval	• Manufacturer is required to conduct a post-approval study (or studies) to demonstrate the drug's benefits • Valid for one year (renewable annually)	• Conditional Marketing Authorisation (EMA) • Accelerated Approval (FDA)

Note: FDA = Food and Drugs Administration, EMA = European Medicines Agency, NICE = National Institute for Health and Care Excellence.

Launched in January 2021, the Innovative Licensing and Access Pathway (ILAP) is the UK's latest expedited regulatory programme, which aims to speed up the process by which new medicines are developed, approved and reimbursed in the UK, expediting their progression from clinical trials through to adoption in the NHS. By involving multiple stakeholders (eg, the MHRA, the NHS, NICE and the SMC), the pathway provides eligible manufacturers opportunities for enhanced regulatory and other stakeholder input. In February 2021, the first 'Innovation Passport' under the scheme was granted to a treatment for adults with von Hippel-Lindau disease, a rare genetic disorder that causes cancer.[158]

Eligibility criteria for different expedited programmes are often overlapping; therefore, manufacturers can benefit from multiple programmes simultaneously. In the US, approximately four-fifths of all new drugs now benefit from at least one expedited programme. By contrast, only a third of drug approvals in 2000 were expedited.[159] In Europe between 2007 and 2017, 15 per cent of newly approved drugs qualified for accelerated assessment or conditional marketing authorisation.[24] Since 2016, 29 medicines have also been approved with a PRIority MEdicines (PRIME) Designation, with many more currently in development under the scheme.[160,161] Data on the use of expedited pathways in the UK are not yet available.

The link between expedited drug development and approval and uncertainty

From an industrial policy perspective, expedited regulatory pathways benefit pharmaceutical companies by:

- reducing the cost of development
- facilitating frequent interactions with regulators
- securing early market access for new drugs, leading to quicker returns on investment.

Providing a flexible regulatory landscape conducive to quick and simple drug approvals is therefore viewed as one potential strategy to increase the attractiveness of the UK market to launch drugs post Brexit.

However, expedited development and approval pathways create different types and levels of evidence at approval than conventional approval pathways.[162] Such differences often lead to greater uncertainty about a drug's benefits and risks at approval.[24] For example, shorter trials, with smaller sample sizes often associated with expedited drug development, can be 'underpowered', making it difficult for researchers to determine whether any benefit is statistically or clinically significant.[163] Use of surrogate endpoints that have a weak association with clinical outcomes is also common in trials of drugs in expedited pathways.[164] Uncertainty at the time of regulatory approval can be further amplified during HTA and complicate pricing and reimbursement decisions.[163,165] Speeding up drug development and approval, therefore, is associated with an inherent trade-off between evidence and access.[22]

Earlier research from the US suggests that expedited programmes are associated with greater safety concerns in the post-marketing period.[166–170] Analyses of post-marketing safety data of drugs evaluated through the new MHRA expedited approval pathways will likely not be available for several years.

There has been growing interest in compensating for uncertainty at approval by moving, extending or carrying out new studies in the post-approval phase.[171] Studies conducted in the post-approval phase, or 'real-world' settings, are important as they are much more likely to find new safety signals.[172]

However, many post-marketing studies are delayed or remain incomplete several years after approval.[173,174] Even when completed, they often have observational designs (rather than randomised designs), lack meaningful active comparators and do not collect patient-relevant outcomes, meaning they are unable to make up for uncertainty around approval and reimbursement.[175]

Policymakers in the UK increasingly face difficult decisions surrounding drug approvals. In Section 5 we outline how, in England, NICE further evaluates all new medicines that the MHRA approves. NICE bases its decisions on whether, and at what price, the NHS should pay for new drugs, largely on the same clinical evidence that is submitted to the MHRA for approval. Evidence standards of the MHRA are therefore critical to downstream pricing and reimbursement decisions.

Box 4 – MHRA incentives for innovation

In addition to ensuring that the benefits of new drugs outweigh their risks and providing information to patients and prescribers, the MHRA (in line with regulators in other countries) issues incentives to encourage innovation in areas of unmet need, rare (orphan) diseases, paediatric medicines and 'innovative' or 'advanced' therapies.[176] These incentives include discounts on assessment fees, scientific support, accelerated approvals and extended periods of market exclusivity, which offer greater potential for revenue generation from the sales of products in the UK.

As an example, new drugs intended for the treatment or prevention of a disease that affects no more than five in 10,000 people in the UK may be eligible for orphan drug status.[177]

Orphan drugs in the UK benefit from up to 10 years of market exclusivity (from the date of marketing authorisation).[177] This prevents any competitors (similar products) from being approved in the same orphan indication. Small and medium-sized manufacturers of orphan products receive 100 per cent discounts on assessment fees, with other applicants receiving between 10 per cent and 50 per cent discounts.[178] Applicants also receive discounts on MHRA scientific advice.[179] Incentives for orphan drugs are comparable to those that the EMA and the FDA issue.

Patient-centred drug regulation is a top priority for the MHRA

In 2020, an Independent Medicines and Medical Devices Safety Review detailed the failure of the MHRA, clinicians and other health care professionals to address significant patient-reported harms from medical treatments.[180] Recently, in response, the MHRA published its commitment to patients in a new delivery plan for 2021 to 2023: *Putting Patients First: A new era for our agency*.[181] To become a patient-focused regulator, the MHRA plans to include patients on all decision-making committees and support the development of patient-reported outcome measures in clinical trials.[182,183] The MHRA's focus on patient-centredness is aligned with the goals of other medicines regulators globally.[184]

Regulatory approval in the UK – summary

- Drug regulatory agencies are responsible for ensuring that the harms of investigational drugs are outweighed by their benefits prior to marketing authorisation. The MHRA performs this role in the UK.
- Since the MHRA became the standalone regulator for medicines in the UK in 2021, it has prioritised efforts to expedite the development, review and approval of new drugs. These efforts are aligned with industrial policy objectives to reduce barriers to market entry.
- Shortening the duration of a drug's R&D inevitably reduces the amount of clinical trial data available for regulatory assessment. Therefore, there is a potential for conflict between the MHRA's role as a public health agency and broader industrial policy objectives.[185]
- The 'evidence versus access' conundrum that the MHRA faces is not unique. All regulatory agencies must be mindful of the uncertainty that can be created from limited availability of evidence at approval and recognise that the potential to generate this evidence post approval is often not realised.
- In the UK, any uncertainty about drug benefits can be carried into reimbursement decisions, with adverse consequences for population health. If drugs with only uncertain benefits are recommended for adoption in the NHS, resources may be diverted away from established and cost-effective treatments that offer meaningful health benefits.

Section 5 Pricing and reimbursement in the UK

Background: pricing and reimbursement

Rationale for pricing regulation in the pharmaceutical industry

Under fixed health care budgets, health lost as a result of the displacement of existing interventions to fund new interventions (eg, new drugs) is known as the 'health opportunity cost'. If the price of a new drug is not aligned with the value it provides (relative to the value of other interventions), then resources allocated to the new drug have high health opportunity costs.

Pricing regulation aims to ensure the efficient allocation of resources to existing drugs as well as other health care services and interventions.

Background: pricing and reimbursement (continued)

Pricing regulation is required in the pharmaceutical industry for reasons outlined below.

The market for pharmaceuticals is imperfect in a number of ways

- In a perfectly competitive market, there are many buyers and sellers, perfect data about products' benefits relative to their prices, many substitutable products and no barriers to market entry or exit. Under these conditions, competition effectively reduces prices (towards that of marginal costs).
- However, the market for pharmaceuticals is imperfect. Patents and market exclusivity granted by regulatory agencies reduce competition between on-patent drugs. The cost of drug development also reduces the number of substitutable products and sellers in the market, further limiting competition, and in turn thwarting its price-reducing effects.
- Imperfect information on the effectiveness of new drugs at the time of approval (uncertainty) can further limit the price-decreasing effects of competition. It limits the ability of payers to differentiate between competing products because the additional costs, benefits and risks of new drugs are uncertain.
- Third-party payers (social health insurance, private health insurance or tax-based health system coverage) largely shield patients and physicians from high prices, indirectly incentivising companies to charge higher prices. Without price regulation or government intervention, these factors can result in high prices, which may not necessarily reflect a new drug's clinical value.

Pricing regulation can effectively lower drug prices

- Third-party payers' collective purchasing of prescription drugs increases their buyer power, which can be leveraged in negotiations with pharmaceutical companies.
- Pricing regulation may be considered broadly as actions that governments take to lower the price paid for prescription drugs. Examples of price regulation include referencing to the price that other countries pay (external price referencing), referencing to similar drugs or therapy areas (internal price referencing), profit controls and prescribing budgets.
- Health Technology Assessment (HTA) is the multidisciplinary evaluation of the clinical effectiveness and/or cost-effectiveness of a new intervention. In the context of drug pricing, HTA can be used (at least in theory) to align price with the clinical benefit of new drugs.

An introduction to drug pricing in the UK

The price and volume of drugs procured and prescribed within the NHS drive pharmaceutical expenditure in the UK.

Several supply- and demand-side factors influence the volume of drugs prescribed in the NHS, including changes in the demographics of the UK population (changes in health needs), advances in technology, the availability of new drugs, changes in prescribing practice and patient behaviour.[186] We outline the main policy initiatives that aim to influence demand for prescription drugs (eg, physician prescribing practice and patient behaviour) in Section 6. Below, we focus on supply-side initiatives to directly control drug spending.

The pricing of on-patent drugs is largely responsible for increases in prescription drug spending.[186] Latest figures from the OECD demonstrate that in primary care, on-patent drugs account for around 15 per cent of volume in the UK but almost two-thirds of spending.[12] In the past decade, there have been several highly publicised cases of the NHS paying for new medicines at unprecedented costs. Among these medicines are new expensive technologies such as cell and gene therapies.[187] Financial pressure on the NHS, and political pressure to provide access to these expensive drugs, are only likely to increase in the future with the development of new highly specialised technologies.[188]

Globally, the manufacturer-set (list) prices of new drugs are high and increasing.[29] In some cases, highly priced drugs can provide novel options to treat previously untreatable diseases or rare (orphan) diseases, or provide marked improvements over existing treatment options.[189] In the UK, even when drugs are deemed cost-effective, they may have a large impact on the NHS budget, making them unaffordable or warranting new payment mechanisms.[190] Under fixed budgetary constraints, effective regulation of drug pricing strives to ensure the affordability of new and existing medicines within the NHS.

To achieve the efficient allocation of resources across the UK health system, new cost-incurring drugs must provide good value for money relative to the benefits that other treatments across the NHS provide. In funding decisions, the NHS must consider the health lost as a result of the displacement of these existing interventions to fund new drugs – the 'health opportunity cost'.

Pricing policy in the UK attempts to balance health policy objectives and industrial policy objectives. Striking this balance is challenging. To an extent, profits expected during the on-patent period serve as a 'pull' factor to incentivise future investment in R&D in the pharmaceutical sector.[191]

Ultimately, however, paying prices for new drugs that exceed the marginal cost-effectiveness of NHS treatments, and therefore do not represent value for money, results in a net reduction in population health.[192] Evidence suggests that this may be the case for many new medicines approved at or close to the NICE cost-effectiveness threshold.[25,26,193]

Regulation of on-patent drug prices in the UK

Several main factors drive on-patent drug prices in the UK. On the one hand, the market for pharmaceuticals is imperfect. Patents and regulatory exclusivity afford new drugs protection from competition, during which higher-than-competitive prices can be charged. In addition, asymmetric information exists between pharmaceutical companies and patients, with the latter lacking information about the benefits and harms of new drugs.

On the other hand, the NHS (as a third-party payer) is the single gateway to the market in the UK, with significant negotiating power to secure lower prices. The government also has the legal power to mandate the economic evaluation of new medicines and implement spending caps on prescription drugs.

These downward pressures, paired with evidence-based prescribing policies (discussed in Section 6), help to promote efficiency in the NHS around medicines spending.

Pricing and reimbursement landscape in England

Below, we describe some of the existing mechanisms for managing prices and overall expenditure on pharmaceuticals:

- HTA
- budget impact tests for high-cost drugs
- flexible commercial arrangements to manage uncertainty
- a spending cap on branded medicines
- special funds.

Health Technology Assessment

In recent decades, the number of new, costly medical technologies has increased dramatically. In the 1980s and 1990s, policymakers, clinicians and economists expressed the need for a more evidence-based approach to health care, including the development of clinical practice guidelines and a strategy to take into account the cost of new technologies within the NHS.[194] In 1999, following the development of explicit methods for technology assessment in health care, originating in the US,[194] NICE (the National Institute for Clinical Excellence, later to become the National Institute for Health and Care Excellence) was established. Then, the aim of NICE was to produce clear guidance for clinicians and assess new drugs for their clinical effectiveness and cost-effectiveness.[195]

From this point, new medicines had to overcome a 'fourth hurdle' in England, demonstrating not only that new drugs were high quality, safe and efficacious, but also that they provided good value for money in the NHS.[196]

Health Technology Assessment (HTA), which NICE undertakes, encompassing cost-effectiveness analysis, is now the primary method used to ensure that the NHS in England pays prices for pharmaceuticals that are commensurate with their benefits. Scotland and Wales adopt a similar approach to the HTA of new medicines, with Northern Ireland recognising the decisions that the other devolved nations of the UK make (**Box 2**).

NICE undertakes HTA to establish whether a new drug provides good value for money. It does this in four main ways:

1. It carries out a systematic review of the evidence of the drug's clinical benefits and its economic costs.
2. It conducts a scientific assessment of the new drug. This process compares the clinical and economic consequences of the new drug against existing treatments in the NHS. Economic evaluation (cost-effectiveness analysis) is undertaken at this stage to quantify and compare the incremental costs and benefits of the new drug against those of existing treatments. As part of the economic evaluation, NICE uses quality-adjusted life years (QALYs) as a generic summary measure of health outcomes, which are used to compare the effectiveness of interventions across the NHS (discussed below).
3. An independent appraisal committee – composed of patients, members of the public, academics and NHS and industry representatives – carries out an appraisal of the evidence.[197] The committee can make five types of recommendations (**Table 3**). Since 2000, around 83 per cent of appraisal recommendations have been 'positive' (recommended, optimised or recommended for use in the Cancer Drugs Fund) (**Figure 6**).[198]
4. During their appraisal, NICE committees also make social value judgements, which encompass the consideration of equity in health care and ultimately affect the allocation of NHS resources.[199]

Table 3. NICE technology appraisal committee recommendations

Recommendation	Meaning	Circumstances under which recommendation is made	Example NICE recommendations
1 Recommended	• The drug or treatment is recommended for use in line with the marketing authorisation from the regulator	The drug is: • more clinically effective and less costly than existing alternatives (extremely unlikely) • equally effective and less costly than existing alternatives (unlikely) • more effective and equally costly (very unlikely) or • more effective and more costly than existing alternatives (if under the cost-effectiveness threshold) (most likely)	"Ustekinumab is recommended within its marketing authorisation for treating moderately to severely active Crohn's disease."
2 Optimised	• The drug or treatment is recommended for a smaller group of patients than originally approved by the regulator	• When the drug or treatment is cost-effective as a treatment option only for a specific group of people at the manufacturer-set list price	"The use of cladribine is only recommended in specific circumstances. It is only considered to be a cost-effective use of NHS resources for people with: • rapidly evolving severe relapsing–remitting multiple sclerosis … or • relapsing–remitting multiple sclerosis that has responded inadequately to treatment with disease-modifying therapy."

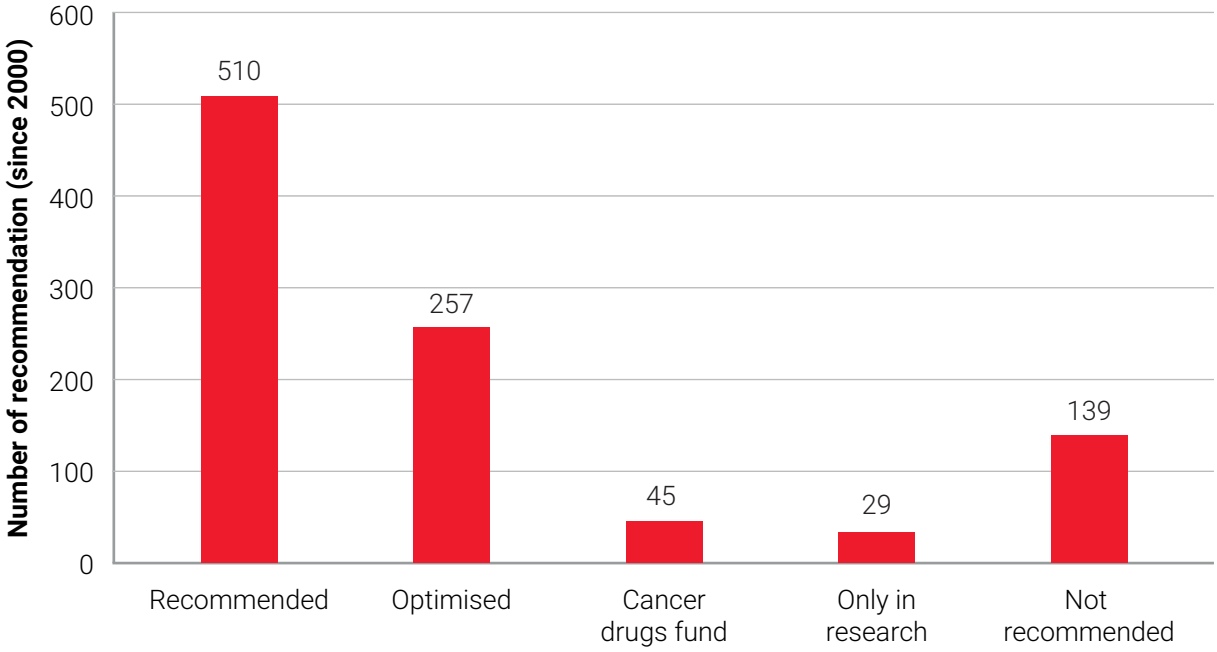
Source: Adapted from NICE (undated)[200]

Table 3. NICE technology appraisal committee recommendations (continued)

Recommendation	Meaning	Circumstances under which recommendation is made	Example NICE recommendations
3 Recommended for use in the Cancer Drugs Fund	• NICE can recommend it for use within the Cancer Drugs Fund (discussed below)	• If early evidence suggests that the drug has some benefits for cancer patients, but still needs more evidence to demonstrate its cost-effectiveness at the manufacturer-set list price	"Crizotinib is recommended for use within the Cancer Drugs Fund for treating ROS1-positive advanced non-small-cell lung cancer in adults."
4 Only in research	• The drug or treatment is recommended for use only in the context of a research study, for example in a clinical trial	• There is not yet enough clinical evidence to make a recommendation for use in the NHS – this sometimes happens for new technologies	"In 2000, the appraisal committee recommended that laparoscopic surgery for colorectal cancer can only be used as part of a randomised controlled clinical trial. The Medical Research Council carried out a clinical trial of the technology. When the technology appraisal guidance was reviewed in 2006, the committee recommended the use of the intervention based on the additional evidence collected."
5 Not recommended	• The treatment is not recommended for use in the NHS	• There is a lack of evidence for the clinical effectiveness of the technology • It is not considered to be a cost-effective use of NHS resources compared with current NHS practice	"Lesinurad was not recommended for treating chronic hyperuricaemia in people with gout."

Source: Adapted from NICE (undated)[200]

Figure 6. Recommendations that NICE technology appraisal committees have made since 2000



Source: Adapted from NICE technology appraisal data[198]

If NICE's technology appraisal process finds a new intervention to be more clinically effective and less costly than the existing alternative, then NICE will recommend it and it will be made available for use in the NHS (**Table 3**). However, this rarely happens, as most new drugs cost more than existing alternatives. If a drug is more effective but more costly, NICE implements a cost-effectiveness 'threshold' – the maximum amount the NHS should pay per additional QALY gained from the treatment compared with existing alternatives. In England, NICE uses a threshold range of £20,000 to £30,000 per QALY. It is likely to recommend treatments for routine funding in the NHS below the upper bound of this range.

In 2009, NICE implemented an additional threshold of £50,000 per QALY for end-of-life situations, and in 2016, a scale of between £100,000 and £300,000 per QALY for certain new drugs targeting very rare conditions and used in highly specialised services.[201,202] Use of these additional thresholds, above £20,000 to £30,000 per QALY, illustrates that NICE takes into account in its technology appraisals other factors such as disease rarity and severity.[203]

One main criticism of QALYs (among others discussed below) is that they do not adequately capture the quality of life gains that new treatments offer for different diseases or patient populations.[204] NICE's earlier implementation of the end-of-life criteria was partly based on an assumption that society may value health gains in some disease areas/patient populations over others. Yet, in 2018, evidence suggested that there was only mixed public support for the use of an end-of-life premium, which has since been modified.[205]

NICE methods review (2022)

In 2022, NICE updated its process and methods manual for HTA, replacing existing end-of-life criteria with disease 'severity modifiers'. Broadly, such modifiers can be thought of as characteristics of the intervention, disease or patient population that decision-makers give priority to.[206] The modifiers act as weights for QALYs, account for disease severity and the improvement in quality of life that new treatments offer and adjust the incremental cost-effectiveness ratio (ICER) threshold accordingly. Whether these modifiers are better aligned with societal preferences for resource allocation is unknown.[207]

Main issues

At some point, paying increasing amounts for additional health gain becomes detrimental to population health. When this occurs, the opportunity cost of paying for incremental benefits is outweighed by the benefits of other cost-effective treatments, which are displaced elsewhere in the NHS. The main criticisms of NICE's technology appraisal process are concerned with how NICE determines this point using cost-effectiveness thresholds and QALYs.

Derivation of the cost-effectiveness threshold is a contentious issue in the UK. Setting the threshold at the health system's true opportunity cost would ensure that resources are allocated efficiently to new drugs relative to other treatments across the NHS. However, there is no empirical evidence to support NICE's current threshold (£20,000 to £30,000 per QALY). In 2015, empirical research estimated the cost-effectiveness threshold to be around £13,000 per QALY.[208] This estimate would suggest that a new intervention would be cost-effective if 'within' the threshold and below £13,000 per QALY. However, paying anywhere between £13,000 per QALY and up to the current threshold would represent poor value for money and do more harm than good to population health. Any upward adjustments to the ICER threshold further exacerbate this harm.[26]

The use of QALYs may be misinterpreted as a method to put a value on a person's life, which is ethically and morally challenging.[209] Further critiques of the QALY are discussed in detail in the literature. [210]

NICE assessment takes place shortly after regulatory approval. Therefore, technology appraisal relies on almost identical clinical data as a basis for evaluating the comparative clinical effectiveness and cost-effectiveness of a new drug versus existing alternatives. As uncertainty in the evidence base supporting regulatory approvals of new drugs has increased in recent years, this has had spillover effects on NICE assessments.[211,212] Uncertainty of clinical effectiveness at the time of regulatory approval is often exacerbated in cost-effectiveness analyses.[213]

Budget impact tests for high-cost drugs

In 2014, sofosbuvir, a highly effective new drug for hepatitis C, was approved in Europe, and launched in the UK with a list price of around £35,000 for a 12-week, one-off treatment.[30] The following year, NICE evaluated sofosbuvir along with other novel hepatitis C treatments and deemed the new treatments more effective but more costly than existing treatment options. NICE still concluded that these treatments offered good for value for money, recommending their use in the NHS.[214–217]

Although NICE found the treatments to be cost-effective, NHS England considered them to be unaffordable. At that time, NHS England was unprepared to budget an estimated £700 million to £1 billion for broad coverage of the new treatments.[218] For the first time, NHS England did not fulfil its statutory obligation to make funding available for treatments that NICE recommended within 90 days.[218] Instead, it prioritised access to only a relatively small number of patients with acute disease.

To avoid similar situations, in 2017, NICE introduced a budget impact test to manage access to high-cost drugs. If the budget impact of a new drug exceeds £20 million in any of the first three years, NHS England may engage in commercial discussions with the drug's manufacturer to secure price discounts and mitigate the impact that funding the technology would have on the rest of the NHS.[219] If commercial negotiations are successful, funding will be made available within 90 days of NICE recommendation.

During the first two years of implementation of the budget impact test, around 100 treatments were subjected to the test, with 31 found to have a budget impact of £20 million or more.[220] Of these cases, all except one were successfully addressed via commercial agreements, one case was resolved by a change of NICE guidance and none of the tests resulted in NHS England having to formally request variations to the funding requirements or delays to access.[220] As an increasing number of new, cost-effective drugs with high budget impact will continue to become available in the UK in the future, the budget impact test sets an interesting precedent for drug reimbursement in the UK. However, focusing on the budget impact of cost-effective new drugs may neglect the importance of their value to the health system.[190]

Flexible commercial arrangements to manage uncertainty

Often, the 'list price' of a new drug is not what the payer reimburses. In the UK, companies often provide confidential discounts through 'Patient Access Schemes'[221] or commercial arrangements to the NHS in order to improve the cost-effectiveness of their medicines and meet NICE's threshold, rather than completely forgo reimbursement by the NHS. Although these types of negotiations occur between manufacturers and payers globally, NHS England as the single payer is well placed to undertake such negotiations.

In recent years, as the list prices of medicines have increased, NHS England has found it increasingly difficult to stay within budget.[222] The government has taken a number of steps to enhance the ability of NHS England to negotiate prices and manage budget impact. Although the fastest (and preferred) route to market is via simple discounts, the NHS recently published a commercial framework for medicines. This framework formalises how the NHS, NICE and industry can work together to support access to clinically effective and cost-effective treatments in the NHS while maximising value for money for taxpayers (**Figure 7**).[18]

The 2021 NHS Commercial Framework for New Medicines

Figure 7 lists the options for companies in the UK to improve the cost-effectiveness of their products so that they fall under the NICE cost-effectiveness threshold. In England, these commercial options can (in theory) be used to manage risk and uncertainty, limit budget impact, improve cost-effectiveness and facilitate patient access. Many of these commercial options have been available to companies for several years both internationally and in the UK, with varying levels of success (**Box 5**).[223,224]

Figure 7. Commercial options for new medicines in the UK

Patient Access Schemes (PASs)	PASs are the **default option** which provide a mechanism for companies to improve **the cost-effectiveness** of a treatment under NICE appraisal by reducing their list price. There are two types of PAS: • **simple PAS (confidential)** - these are the preferred option and provide a fixed price percentage discount on list price • **complex PAS (transparent)** - these are more complex and administratively burdensome (eg, outcomes-based dose caps, rebates and upfront free stock to set up).
Commercial Access Agreements (CAAs)	CAAs are used in unusual or unique circumstances where launching a product would be particularly challenging or commercially unviable. Examples include: • **budget caps** - the maximum spend for a product beyond which a central rebate is payable • **price/volume agreements** - the price agreed for a set volume of patients and then reductions are staged based on additional patient numbers, or the company pays back the full amount (similar to a budget cap) • **cost-sharing** - the company funds the initial cost of therapies such as offering the first month free • **stop/start criteria** - rules on eligibility for when patients should stop/start therapy • **outcomes-based agreement/ payment by results** - a discount or rebate applied if a product does not perform as expected or for non-responders.

Source: Adapted from NHS England (2021)[18]

Figure 7. Commercial options for new medicines in the UK (continued)

Managed Access Agreements (MAAs)	Two main sources of uncertainty exist at the time of NICE technology appraisal: • **clinical uncertainty** - how well will the new treatment work outside of clinical trials within the NHS? • **financial uncertainty** - given clinical uncertainty, what will the benefits of the new treatment be, relative to its cost? These factors may result in uncertain cost-effectiveness estimates. To mitigate uncertainty, MAAs consist of: • a data collection agreement, and • a CAA, simple PAS or complex PAS. While more data are collected, the company must offer the treatment at a price which is cost-effective. Following data collection, the cost-effectiveness can be revaluated, with prices altered accordingly. MAAs are often used in conjuncton with the Cancer Drugs Fund or the Innovative Medicines Fund.
Budget Impact Schemes	If the potential net budget impact of a new treatment is expected to exceed £20 million per year in any of the first three years of a technology's use in the NHS, NHS England will engage in commercial discussions. The purpose is to mitigate the affordability challenge of immediately funding the technology. If an agreement between the NHS and the company is not reached, NHS England may then request a variation to the statutory funding requirement.

Source: Adapted from NHS England (2021)[18]

Box 5. Emergence and evolution of flexible commercial arrangements in the NHS

When NICE was first established in 1999, pharmaceutical companies had a single opportunity to supply evidence demonstrating the health gain associated with their products relative to price. If a product's ICER was below NICE's threshold, NICE would typically recommend it for use.[203]

In 2009, the 'Patient Access Scheme' was introduced as part of a five-year voluntary agreement between the UK government and the pharmaceutical industry (discussed below).[225] The 2009 agreement established a liaison unit with whom companies could negotiate commercial arrangements to improve the cost-effectiveness of new drugs that were not found to offer good value for money for the NHS at the time of initial assessment. In effect, this flexibility grants pharmaceutical companies multiple opportunities at setting a price that will be considered cost-effective in the NHS. Evidence suggests that these companies now maximise their price up to the threshold level.[226]

Some of the commercial options presented in Figure 7 are more preferable for NHS England than others. For example, a simple discount improves cost-effectiveness with little administrative burden. The main shortfalls of more complex arrangements are that they can be administratively burdensome, hard to implement, time-consuming and often do not adequately generate meaningful evidence to address clinical or financial uncertainties.[227,228] An illustrative example is the Multiple Sclerosis Risk-sharing Scheme, which was set up in 2002. It later emerged that the drugs in the scheme had performed worse than predicted and some experts deemed the scheme a "costly failure".[229]

There is a trade-off between potentially using price transparency to promote the accountability of industry on the one hand and promoting access on the other. If confidential price agreements that the NHS secured were made public, it is likely that other countries would use them as 'reference' prices or the basis for price negotiations. If this was the case, pricing transparency in the UK could act as a disincentive for price discounts in the NHS.

A spending cap on branded medicines

A voluntary scheme and a statutory scheme control spending on branded medicines in the UK. The 2019 UK Voluntary Pricing and Access Scheme (VPAS)[230] is the latest iteration of a series of voluntary agreements made between the Association of the British Pharmaceutical Industry (ABPI) and the DHSC. For more than 60 years, these voluntary agreements have been renegotiated between industry and government every five years. The latest agreement aims to ensure the predictability and affordability of drug spending for the NHS. For the industry, the agreement includes several provisions aimed at improving the uptake of new medicines in the NHS. The agreement also strives to tackle broader industrial policy objectives by encouraging investment in the UK life sciences sector.

To ensure the predictability and affordability of expenditure on branded medicines (which are mostly patent-protected medicines), the latest agreement includes a cap of 2 per cent growth in the total cost of branded medicines from 2019 to 2024.[230] Beyond 2 per cent of growth in spending, depending on how much above the agreed level of spending growth, repayments are shared across members of the VPAS agreement. It is important to note that new drugs do not contribute to the individual contributions for the initial 36 months on the market. While this 2 per cent figure is an increase on the previous agreement (0 to 1.9 per cent, 2014 to 2019),[231] it does ensure that the growth in spending on branded drugs will not exceed the growth rate in overall NHS spending.

The 2019 voluntary agreement includes more than just a spending cap on branded pharmaceuticals. In many ways, the agreement reaffirms the pricing landscape which we set out above. For the first time, it lists NHS England as a party to the scheme, signalling greater involvement in securing new commercial options and 'flexibility' for medicines procurement via the new commercial framework. The agreement also states that all new drugs, and new uses of existing drugs (as opposed to a selection of drugs), will undergo NICE appraisal, accompanied by a funding mandate, if recommended. The agreement states that NICE's threshold of £20,000 to £30,000 per QALY will be retained for the duration of the agreement. It also formalises the use of NICE's budget impact test.

Companies that choose not to join the voluntary scheme are subject to a statutory scheme, which sets spending growth at 1.1 per cent at its latest iteration (with higher corresponding payment percentages).[232] The terms of the statutory scheme are therefore less financially attractive for companies, serving as an incentive to participate in the voluntary scheme.[233]

Special funds

The Cancer Drugs Fund (2011)

In 2011, against a backdrop of heated public debate about timely access to new drugs in the NHS, the UK government set up the Cancer Drugs Fund (CDF) to provide access to cancer drugs not available through the NHS, because they were yet to be appraised, they were under appraisal or NICE did not recommend them. Before the CDF, there was no precedent for a 'hypothecated' or 'ringfenced' fund to pay for drugs in the UK, although the strategy has been used in other areas of (health) policy.[234]

Despite an initial budget of £50 million per year, costs escalated quickly and reached £416 million per year in 2015, with around 80,000 people receiving drugs through the fund.[235] By 2015, several issues with the CDF had been identified, and despite significant expenditure, there was "no evidence that the NHS cancer drugs fund has delivered meaningful value to cancer patients and the wider NHS".[235,236] Approximately half of the patients that the fund supported received drugs that NICE had not recommended because they did not meet its clinical effectiveness and/or cost-effectiveness threshold, meaning that the fund "cut across, rather than complemented" the work of NICE.[235]

The fund was heavily criticised as representing poor value for money, doing more harm than good in the context of other cost-effective treatments that could have been funded across the health system.[25] At that time, empirical evidence suggested that greater improvements in overall health would have occurred across a variety of diseases, including cancer, if the fund's money had been shared across other services in the NHS.[25] Evidence also suggested that the fund may have been more aligned with perceived – rather than actual – societal values.[237]

Reformation into a 'managed access' Cancer Drugs Fund (2016)

In 2016, the government modified the CDF and appraisal process for cancer drugs, adding a new option for NICE to recommend drugs for use within the CDF.[238] The new 'managed access' CDF now provides: (1) an early or interim funding source while technologies are under NICE appraisal; and (2) a source of funding, via Managed Access Agreements, for treatments while uncertainty remains about their clinical effectiveness and/or cost-effectiveness. According to NHS England, the reformed fund also has clearer entry and exit criteria, greater integration with NICE and an expenditure control mechanism to ensure there is no overspend. The budget for the managed access CDF was fixed at £340 million per year, with proportional rebates from all pharmaceutical companies receiving any funding from the CDF in the event of overspend.

Between July 2016 and July 2020, approximately 49,800 patients were registered to receive treatment via the reformed CDF, with 82 drugs treating 170 different cancer indications.[239]

Special funds going forward (2021)

In 2021, the government announced an additional £340 million of ringfenced funds for an Innovative Medicines Fund.[240] This fund will function similarly to the reformed CDF, but support patients with any condition, including those with rare and genetic diseases, while there is significant uncertainty around the medicines' cost-effectiveness, and further evidence is generated for NICE appraisal.

In total, there will now be £680 million of ringfenced NHS England funds annually to speed up access to new drugs for which their effectiveness is uncertain (£340 million from the CDF and £340 million from the Innovative Medicines Fund).

Pricing and reimbursement in the UK – summary

- Manufacturer-set prices of new drugs are increasing globally. In the UK, high drug prices are placing additional pressure on the NHS budget.
- In the UK, pricing regulation is primarily achieved through a complex set of indirect mechanisms such as the rigorous HTA process that NICE conducts. As the single purchaser of medicines in the UK, the NHS is also able to negotiate directly with pharmaceutical companies.
- Nevertheless, there is growing concern that UK prices still do not fully account for the health opportunity costs of adopting new drugs in the NHS. NICE's cost-effectiveness threshold is considerably higher than the current best estimate of the marginal productivity of the NHS.
- The uncertainty of evidence supporting new drug approvals compounds the complexity of determining the cost-effectiveness of new drugs.
- NHS England has recently adopted a comprehensive negotiating strategy to secure discounts for new drugs that NICE has judged not to be cost-effective. However, the basis on which decisions are made and the final price agreed remain confidential.

Section 6 Adoption and use of pharmaceuticals in the UK

Background: adoption and use of pharmaceuticals in the NHS

Following regulatory, pricing and reimbursement decisions, prescribers' and patients' adoption and use of new and existing medicines provide an important opportunity for policymakers to influence demand for prescription drugs. At this stage, policy interventions can be used to determine how, and to what extent, new and existing drugs are adopted and used within the health system.

Physicians, patients, payers, pharmacists and industry can also influence the demand for pharmaceuticals.

By influencing the nature and extent to which new drugs are adopted and used within the health system, the demand side of the pharmaceutical system provides an opportunity for governments and payers to improve the efficiency of medicines spending and enhance population health.

Pharmaceutical companies invest heavily in efforts aimed at increasing the adoption and use of their products because they benefit financially from this.

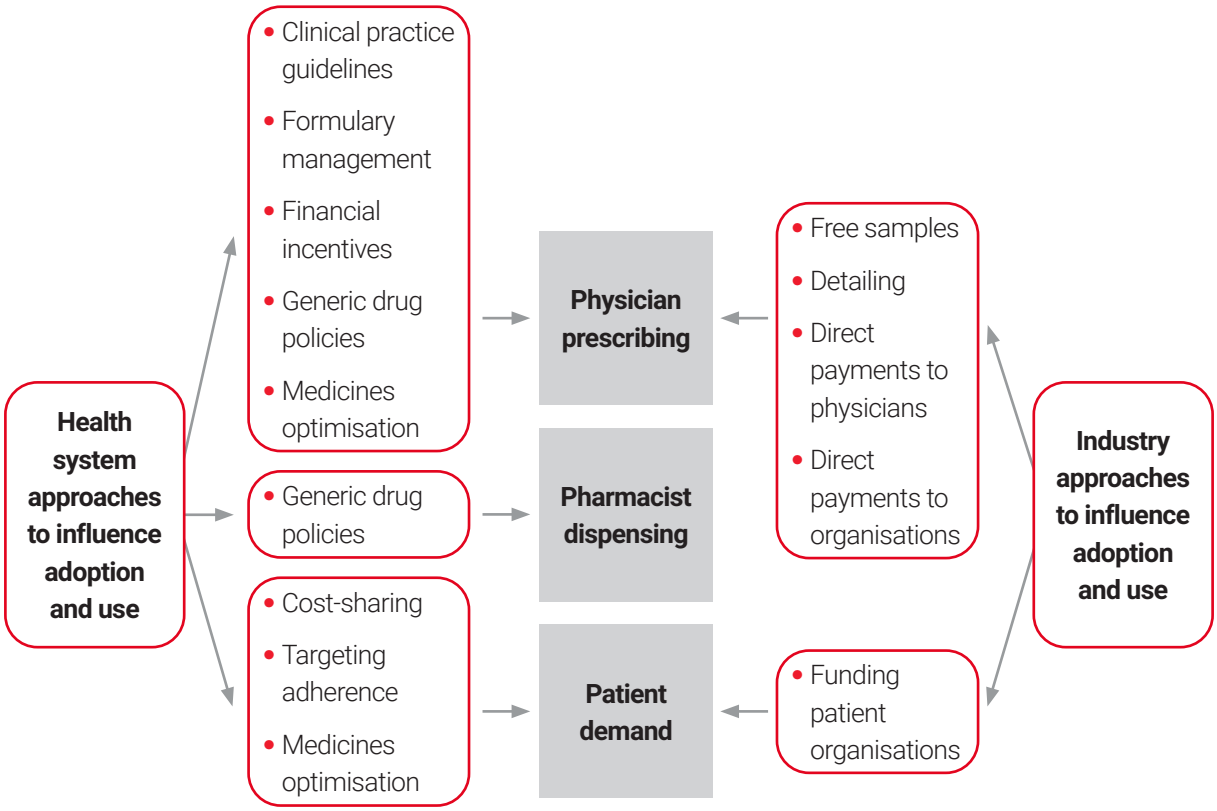
Influencing demand for pharmaceuticals in the NHS

The NHS is both the single payer for and provider of public health care services in the UK. It is also the single largest purchaser of prescription drugs. This financing structure facilitates policy attempts to effectively influence the adoption and use of new and existing drugs in the health system. From the health system perspective, policy aims are two-fold: (1) to improve the efficiency of medicines spending; and (2) to enhance population health. These aims have grown in importance in recent years.

For example, over the past few years there has been a sharp increase in the diffusion of cancer products onto the global market, reflective largely of US government reimbursement policies, and an increasing willingness to pay for cancer drugs and political pressure in the US.[241,242] Following approval in the US, manufacturers of these drugs may seek regulatory approval from the MHRA and a positive recommendation for NHS reimbursement from NICE. Availability of these medicines comes at a price, and can displace other high-value treatments across the health system. As we outlined in Section 5, identifying new products that offer value for money for the NHS and offer the greatest health benefits for UK patients has become increasingly important.

The NHS employs several strategies to promote the appropriate and efficient adoption and use of prescription drugs. Industry can also influence adoption and use to maximise revenue (**Figure 8**).

Figure 8. Health system and industry approaches to influence the adoption and use of prescription drugs



Policy interventions to influence the demand for pharmaceuticals in the UK is not a novel concept. In 1952, patient (user) charges were introduced to offset the rising cost of prescription drugs in the NHS.[243] In 1957, the government commissioned a report led by Sir Henry Hinchliffe on the cost of prescribing.[244] The landmark report outlined several recommendations to influence prescribing, including the training of general practitioners to understand clinical and economic evidence regarding the use of new drugs.

Below, we describe the primary strategies used to influence the adoption and use of prescription drugs in the NHS.

Clinical practice guidelines

Clinical practice guidelines are systematically developed statements or guidance which assist physicians and patients in medical decision-making.[245] In England, NICE is responsible for producing these guidelines. These documents make recommendations to physicians about which drugs are preferable for the treatment of certain conditions and patient populations, how to prescribe or administer the drugs, and for how long. Similarly to NICE's technology appraisal process, the current best evidence informs the development of clinical practice guidelines, and involves multiple stakeholders, including members of the public, subject area experts and representatives from the NHS.[246]

Evidence suggests that clinical practice guidelines effectively standardise care delivery and reduce unwarranted variation.[247] In England, uptake of guideline recommendations has been variable.[248–250]

Under the latest voluntary agreement between the UK government and the pharmaceutical industry (2019), NICE undertakes the assessment and appraisal of all new drugs and all new uses of existing drugs, which receive marketing authorisation in the UK. Those that receive a positive recommendation are incorporated into NICE clinical practice guidelines. Subsequently, the NHS is legally obliged to fund new treatments recommended through NICE's technology appraisal process.[198] Although NICE's clinical practice guidelines are non-mandatory, physicians are "actively encouraged" to follow their recommendations.[251]

Theoretically, NICE (as an agency that undertakes the appraisal of new technologies) is well placed to promote the efficient adoption and use of new and existing drugs in the NHS through clinical practice guidelines. Because of its dual role, there is an opportunity to place cost-effectiveness and 'value for money' at the centre of its guidelines, aimed at optimising the use of medicines within the NHS. However, as we highlighted in Section 5, this is dependent on NICE's ability to implement a willingness-to-pay threshold that is aligned with the marginal productivity of the NHS.[192,193]

Financial incentives: pay for performance

Financial incentives are designed to 'reward' prescribers for high-quality prescribing, or 'penalise' them for inefficient prescribing practices. In the NHS, they target either individual prescribers (eg, individual general practitioners) or organisations (eg, hospitals).

In the early 2000s, it was recognised in a landmark report that the NHS "lacks the incentives many private sector organisations have to improve performance".[252] In response, in 2004, the Quality and Outcomes Framework (QOF) was introduced, linking up to 25 per cent of UK general practitioners' income to performance according to several indicators, including measures of prescribing quality.

Evidence suggests that the success of these financial incentives is mixed,[253] with some improvements in aspects of prescribing for which financial rewards are available, but slower improvements or even decreased performance in other areas for which financial incentives are unavailable.[254] It is also unclear whether 'improved performance' in the QOF translates into improved patient care and health outcomes.[255] Broader evidence from other pay-for-performance programmes in high-income countries suggests that improvements in prescribing quality linked to financial incentives are mixed, may be marginal, short term or non-existent.[255]

In the NHS, doctors are paid a salary, which an independent review body determines.[256] An extensive review of physician payment methods internationally shows that salaried physicians prescribe fewer medicines than physicians compensated under different payment models such as fee-for-service.[257]

Medicines optimisation – getting the best value out of medicines and pharmacy

The appropriate use of medicines is important for population health. Some prescription medicines can potentially cause harm to patients. Between 5 and 10 per cent of all hospital admissions are medicines related, of which two-thirds are preventable.[258] The NHS also estimates that 30 to 50 per cent of medicines prescribed for long-term and chronic conditions are not taken as prescribed.[258]

Medicines optimisation in the NHS "looks at the value which medicines deliver, making sure they are clinically-effective and cost-effective" and "[ensures] people get the right choice of medicines, at the right time, and are engaged in the process by their clinical team".[259,260]

Before 2013, many commissioning groups employed their own medicines management teams or contracted with external providers to provide a medicines management service. In 2013, the Royal Pharmaceutical Society published a report entitled *Medicines Optimisation: Helping patients make the most from their medicines*.[261] Since then, many of these teams have been formally called 'medicines optimisation teams', staffed mostly by pharmacists (clinical experts) and pharmacy technicians.[262] In practice, these groups promote safe, legal, evidence-based, clinically effective and cost-effective prescribing, supply and use of medicines within the resources available within the NHS.[262]

Other strategies to increase efficiency and improve health outcomes include patient education,[263] reducing the overuse of antibiotics,[264] encouraging the uptake of generic medicines (discussed below) and decreasing the use of ineffective medicines.[265] In 2016, NICE also issued a quality standard for medicines optimisation.[266]

As the number of patients with a chronic health condition and the number of patients with multi-morbidities managed largely by prescription drugs increase,[267] medicines optimisation is likely to be key to ensuring the appropriate use of medicines within the NHS.

Generics and biosimilar policy

Generic drugs are essentially identical to on-patent drugs, containing the same active ingredients, with equivalent quality, safety and efficacy profiles. However, a competitive market structure for generic medicines post patent expiry means that they can be sold at a fraction of the price of their on-patent counterparts. The lower price of generics is accounted for by substantially lower costs associated with bringing them to market (ie, without the expense of clinical trials), and the fact that the market for their use already exists (reducing the expense of marketing and promotional activities).

Today, generic prescribing accounts for more than 80 per cent of prescribing in the NHS, one of the highest rates among high-income countries.[268] This has resulted in substantial savings for the NHS. Estimates suggest that between 1976 and 2015, the NHS saved around £7.5 billion through generic prescribing, freeing up resources to be used elsewhere in the health system.[269] If there was no growth in generic prescribing during this period and prescribing remained unchanged, spending would have had to increase eight-fold in real terms to account for increasing costs.[270]

With such high prescribing rates for generic drugs, some argue that the scope for further savings in the NHS through generic prescribing is limited.[269] In addition, higher prices of future generic drugs may mean that the NHS will not yield the same savings as in the past.[271,272] However, 29 per cent of medicines prescribed generically are dispensed as proprietary.[270] This is one area where the NHS could potentially achieve further improvements in efficiency, likely driven by improved data or benchmarking, and additional guidance for pharmacists and physicians.

Biological medicines (biologics) are currently the largest cost and cost growth areas in the NHS medicines budget. In 2018, one biologic (adalimumab) alone cost the NHS more than £400 million.[273,274] As increasing numbers of drugs' patents have expired in recent years, a greater proportion of equally clinically effective drugs (biosimilars) has become available. By educating patients of the value of biosimilars, and providing a commissioning framework[265] that enables physicians to prescribe these medicines,[275] the NHS is able to take advantage of £300 million in savings per year (2020/21).[276]

Cost-sharing in the NHS: prescription charges

In 1952, prescription charges were brought into the NHS at a rate of one shilling for each prescription form issued.[243] Adults in England now pay prescription charges at a rate of £9.35 (as of November 2022) per prescribed item.[277] (Prescriptions are now free in Scotland, Wales and Northern Ireland – see below.) In 2018/19, the NHS in England raised £576 million through the prescription charge, equal to 0.5 per cent of its resource budget.[278]

NHS prescription charges are a form of 'cost-sharing' where the cost of prescriptions is shared between patients and the NHS. Cost-sharing aims to make patients more aware of, and more accountable for, prescribing costs, to prevent them from consuming additional 'extra' or 'unnecessary' prescription drugs.[279] Cost-sharing can take several forms. The NHS prescription charge is a form of co-payment – a flat-rate charge per prescription item regardless of its cost. In other countries, co-insurance payments can be based on a fixed percentage of the total cost of a prescription or service, and in insurance markets, deductibles (or 'excess' in the UK) require patients to pay a fixed amount of the total cost of a prescription, or to spread the cost over a certain time period (eg, a year).

Several studies have been conducted on the impact of cost-sharing in relation to prescription drugs. For example, studies have shown that cost-sharing reduces demand for 'low-value' and 'high-value' drugs alike,[280–282] has the greatest impact on demand from the sickest and poorest patients,[280] worsens adherence and leads to more frequent discontinuation of therapy.[283] Studies suggest that reduced demand for prescription drugs can directly translate into worsened patient outcomes.[280]

In England, several exemptions to prescription charges are in place, depending on age and socioeconomic and health status. In addition, Prescription Prepayment Certificates (PPCs) allow a patient to pay a flat fee for a defined period and receive their medicines at no additional charge, further protecting them from large out-of-pocket payments.[284] Owing to these exemptions, it is estimated that around 90 per cent of prescriptions are dispensed free of charge in the community.[285]

In Wales, prescription charges were abolished on 1 April 2007. Evidence suggests that since then, the number of prescription items dispensed per head of population has increased by around 25 per cent, although this was deemed to be in line with the overall increase in prescribing before charges were abolished.[286] In Scotland, prescription charges were reduced gradually from 2007 and abolished on 1 April 2011.[287] In Northern Ireland, prescriptions were made free of charge in April 2010.[243]

Fast-tracking the adoption and use of drugs in the NHS

In 2014, the UK government commissioned a review to make recommendations on how to accelerate access for NHS patients to innovative medicines, medical technologies, diagnostics and digital products. In response to the review,[288] the government set up the Accelerated Access Pathway to streamline regulatory and market access decisions for 'breakthrough' products.[289] To facilitate faster uptake of technologies into the NHS, the government also set up the Accelerated Access Collaborative (AAC) – a partnership between patient groups, government bodies, industry and NHS bodies aimed at facilitating the faster adoption and use of technologies in the NHS.

Between 2020 and 2021, the AAC claims to have provided "more than 320,000 patients with access to '*proven*' health and care innovations", "supported over 3,700 innovations" and created more than £100 million in savings for the NHS.[290] Independent evidence on the success of the programme to date is limited. In practice, it is difficult to discern the benefits of the AAC for patients in a pharmaceutical policy landscape that is already crowded with several other attempts to accelerate access.[291]

Industry influence on adoption and use in the UK

In the UK, industry can attempt to influence the adoption and use of their products in several ways to maximise profits. For example, industry is able to legally make significant payments to health care organisations, physicians and patient organisations. In 2015, a total of 4,028 health care organisations received 19,933 direct industry payments worth approximately £50 million.[292,293] Recent studies show that the prevalence of industry funding of patient organisations ranged from 20 per cent to 83 per cent across different settings.[294] Research shows that patient groups with industry funding are likely to support the sponsoring company's position on controversial issues.[294]

Notably, transparency surrounding industry payments has improved in recent years. Disclosure UK is a searchable database, formed as part of an EU-wide initiative, published on the ABPI's website, detailing industry payments made to health care professionals and health care organisations.[295] However, some have argued that the voluntary nature of Disclosure UK is an important limitation and gives only an 'illusion of transparency', as doctors are not mandated to submit data to the database.[296–301]

Adoption and use of pharmaceuticals in the UK – summary

- Pharmaceutical policies aimed at influencing the adoption and use of medicines within the NHS create scope for improving the efficiency of medicines spending, and enhancing patient outcomes. Inefficient spending on pharmaceuticals risks harming population health by diverting limited resources away from other cost-effective services and treatments.
- Evidence-based clinical practice guidelines that NICE issues provide a strong foundation for high-quality prescribing decisions.
- To date, the NHS has achieved some of the highest generic drug prescribing rates internationally.
- Improving patient education, reducing the overuse of some medicines, continuing to encourage generic prescribing and decreasing the use of ineffective medicines under medicines optimisation efforts are likely to improve patient outcomes and maximise efficiency in the NHS.
- Cost-sharing, in the form of prescription charges, has been abolished in all nations of the UK except for England. Evidence suggests that such charges can have a negative impact on patient outcomes and the appropriateness of medicines use. However, around 90 per cent of adults in England are exempt from these fees, and many others are supported by annual caps on fees.
- The pharmaceutical industry in the UK makes substantial payments to health care professionals, health care organisations and patient groups. The transparency of industry payments has improved in recent years but remains voluntary.

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For more information, contact:

Dr. Huseyin Naci
Department of Health Policy
London School of Economics and Political Science
Email: **h.naci@lse.ac.uk**