



Insights on earlier adoption of medical innovations

An international review of emerging and effective practice in improving access to medicines and medical technologies

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EUROPE



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Preface

This documented briefing, prepared for the Office for Life Sciences, presents the findings from a short study to examine international examples of accelerating the use of drugs, devices and diagnostics.

The findings from this briefing were presented to the Office for Life Sciences on the 13th April 2015.

This is an independent report commissioned and funded by the Policy Research Programme in the Department of Health for the Accelerated Access review. The views expressed are not necessarily those of the Department or the review.

Policy Research In Science and Medicine (PRISM) unit provides research-based evidence to the UK's National Institute for Health Research (NIHR) to support the NIHR's research strategy, Best Research for Best Health. Alongside that PRISM aims to provide impetus to the science of science policy field in the UK, Europe and internationally.

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Accelerated Access Review: Context

In November 2014, the UK government launched the Accelerated Access Review to assess pathways for the development, assessment, and adoption of innovative medicines and medical technology. The review will consider how to speed up access for NHS patients to cost-effective new diagnostics, medicines and devices. The purpose of the review is to:

‘ensure that NHS patients benefit from earlier access to innovative drugs, diagnostics and devices, and help Government lead the global race for life sciences investment by making the UK the best place for 21st century medical innovation and product development’

As part of the review, a number of studies have been commissioned to further understand systems for regulation, assessment, adoption and reimbursement to accelerate the adoption of medical innovation in the UK.

RAND Europe, in collaboration with the Policy Institute at King’s College London, was asked to support the Accelerated Access Review by conducting a short study to examine international examples of accelerating the use of drugs, devices and diagnostics.



Accelerated Access Review: Context

The aims of this piece of work are:

- To identify the key features of systems in which drugs, devices and diagnostics are assessed from trials to patients quickly, by considering a number of global ‘front-runners’;
- To understand how these systems work in practice;
- To reflect on the challenges and opportunities to effectively translate into the UK’s health system, bearing in mind differing characteristics and economic/social/ideological backgrounds as well as identifying where legislative changes might be required.

A second piece of work is being led by Deloitte, in partnership with the King’s Fund and the Centre for the Advancement of Sustainable Medical Innovation (CASMI). It aims to map the current processes and pathways through which innovative medicines, devices and diagnostics are assessed in the UK, from proof of concept through regulation, cost-effectiveness assessment and adoption, and to identify issues, barriers and opportunities within the UK’s current approach.



Key conclusions

Comparable empirical data are not strong enough to identify across-the-board international ‘front-runners’

Studies have found that adoption rates vary among therapeutic areas and between countries. This suggests that studies in specific therapeutic areas cannot be generalised to other areas. Further, studies often compare level of use rather than rate of appropriate adoption, and they frequently focus on different sections of the pathway. Where these studies attempt to explain differences in use or adoption they often identify cultural or structural features of the health system as being important.

The UK system performs well in some comparisons and most of the international examples of interventions have UK parallels

Many interviewees felt that the NHS can be an exemplar of adoption for cost-effective innovation, but this is not a solved problem in any health system. It was striking that most international examples of interventions have UK equivalents. This commonality of approach is likely to be a consequence of international interactions and the significant role played by the National Institute for Clinical Excellence (NICE) and the Medicines and Healthcare Products Regulatory Agency (MHRA) in EU-wide programmes, such as the Adaptive Pathways pilot of the European Medicines Agency (EMA).

The approaches identified can be split into four conceptual groups each with different repercussions on the stakeholders in the health system

We identified 11 key interventions that speed up the adoption of medical innovation. We categorised them into four conceptual approaches: process improvement, risk sharing, process linkage, and addressing market failure/pricing. We discuss each intervention in turn, highlighting the countries which have adopted it, how the intervention works in theory and in practice, its strengths and weaknesses and the evidence for its effectiveness. We also discuss observations on these interventions’ applicability to the UK.



Key conclusions

The terminology used to describe interventions to speed up adoption is inconsistent

For example, mechanisms where the level of evidence required for regulatory approval is lowered are variously referred to as 'early access', 'expanded access', 'compassionate use', 'named-patient schemes' and/or 'pre-approval access'. In addition, mechanisms that are conceptually different are often pursued in tandem, which makes considering the repercussions of interventions or comparing them across different systems more challenging.

Three underlying capabilities of the health system can support interventions to speed up adoption

The key capabilities identified by our interviewees and literature review are effective clinical trial infrastructure, an efficient data infrastructure and systems to help generate evidence and a clinical culture which champions new medical innovations.

A systems approach to speeding up the adoption of medical innovation will be necessary

Given the particular features of the NHS, as well as the UK parallels for many of the international examples, there are unlikely to be 'silver bullets', that will transform adoption in the NHS. Rather our examples will provide insights into the important concepts and interventions that will help support a systems approach to improvement.

Two interventions stood out for their novelty in relation to the UK system and for their potentially transformative nature. First, the Prescription Drug Act of 1992 provided more resources to the U.S. Food and Drug Administration (FDA), and it set targets that significantly reduced review times. Second, the use of abbreviated review processes for medicines, devices or diagnostics that have been approved in other jurisdictions could allow the for focusing of resources on those medicines, devices and diagnostics that are of most value to the domestic health system.



Outline of the report

The first section of this briefing provides a brief overview of the key issues for innovation in the UK health system.

We then discuss each of the 11 interventions in detail, assessing the evidence base of the examples identified, examining the strengths and weaknesses of each approach and considering their applicability for the UK system.

We also identify three enabling factors that can underpin and strengthen these interventions: clinical trial infrastructure, data systems, and clinical culture.

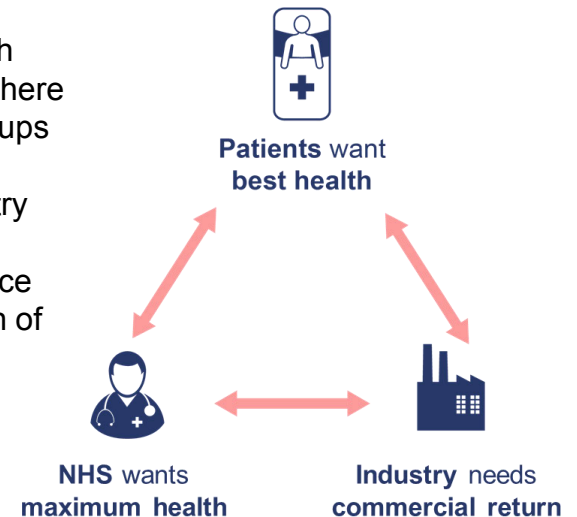
Finally, we present some interesting examples of instances where the interventions identified have been combined, either in the case of a particular disease (Ebola) or under a particular concept (Value-based Pricing & Adaptive Pathways pilot).



Overview of the UK health innovation system

Before we consider approaches in detail, we feel it is helpful to present some of the key characteristics of the UK health innovation system.

- **Innovation, adoption and diffusion are complex issues** – Medical innovation is an inherently multifaceted issue, and the factors that affect how innovations are diffused, disseminated and implemented are complex (Greenhalgh et al. 2005). Social structures and norms, individual and institutional contexts – as well as specific features of an innovation – have all been considered as key factors influencing the adoption and diffusion of medical innovations (Rogers 2003; Greenhalgh et al. 2005; Consoli & Mina 2009).
- **There are inevitable tensions in the UK health innovation system** – There are also inevitable tensions in the UK health innovation system which impact on the adoption of new medicines and medical technologies. First, there is tension among the interests, needs and concerns of key stakeholder groups in the health system. Patients and patient groups want the best health and demand earlier access to potentially life-saving medical innovations. Industry requires favourable regulatory and environmental conditions for stimulating innovation and ultimately needs a commercial return. The NHS must balance these tensions, within its own resource constraints, ensuring that the health of the population is maximised. Second, there is an inherent tension in the need to balance fast access to new medical innovations for patients and the need to ensure that comprehensive evidence is collected on the safety, efficacy and cost-effectiveness of these technologies.
- **Medical devices and diagnostics have a separate set of issues to medicines** – It is also important to note that categories of medical innovation, such as drugs, diagnostics and medical devices, each have a separate set of issues and that they therefore should be treated differently when we discuss adoption and diffusion. It was apparent from both the interviews and the literature review that evidence on the adoption of medical devices and diagnostics is limited compared with that available in relation to medicines. Where possible we have highlighted in our international examples how each intervention relates to each category of medical innovation.



Lack of comparable data on appropriate adoption

An important issue in the assessment of mechanisms that speed up the adoption of medical innovations is the lack of comparative empirical data on international adoption rates of medical innovations. Studies comparing various aspects of adoption are limited for a variety of reasons, including:

- They focus only on particular sections of the pathway (e.g. time for regulatory approval);
- They measure the level of adoption rather than the rate of adoption;
- They lack measures for the appropriateness of adoption (e.g. are higher levels of usage desirable?);
- They focus specifically on a particular disease or innovation type (e.g. drugs, devices).

For example, PricewaterhouseCoopers (PWC) (2011) surveyed 50 life sciences companies developing drugs, diagnostics and devices on the ease of regulatory approval processes versus the regulatory approval time for several OECD countries as part of their Medical Technology Innovation Scorecard. The UK was considered to have a shorter and easier approval process than the U.S., but it was considered slower than France and Germany.

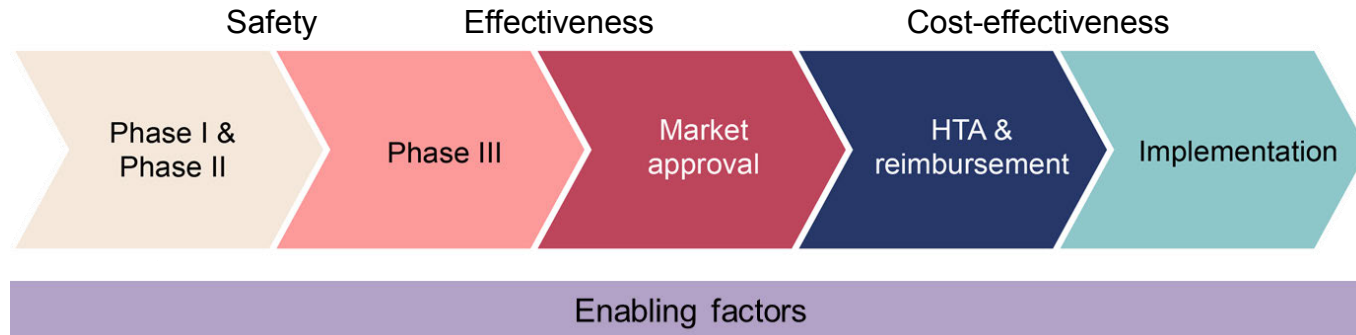


Source: PWC Innovation scorecard (2011)

There is no consistent message on which countries are the 'front-runners' and where the UK is relative to others. For example, while some studies note that contrary to the PWC report the UK is slow to approve new drugs (GlaxoSmithKline 2011), others suggest that the UK (and/or EU) performs better than the U.S. (Boston Consulting Group 2012).

With regards to the 2012 European Commission Transparency Directive that targets a 'time to access' of 120 days for reimbursement decisions, only Germany and the UK are currently compliant (Flostrand 2014). Interviewees noted that many of the international differences in adoption rates are driven by country-specific factors, which are often difficult to change. This finding was also reflected in the literature; for example, Brekke et al.'s (2013) study of the diffusion of anti-TNF drugs across Europe found that 'large parts of the cross-country variation are explained by time-invariant country-specific factors (e.g. disease prevalence, demographics, health care system)'.

New healthcare innovations follow a pathway



Innovation is not a linear process. Development and adoption processes can occur in parallel and inform each other. Nevertheless, while the development of a medical innovation is not linear, **the pathway of adoption in healthcare often follows a common set of stages.** Although the pathway depicted in the figure above, is a simplified version of the route to adoption for drugs, devices and diagnostics, it provides an overview of the gateways for evidence assessment on safety, effectiveness and cost-effectiveness that are needed for medical innovations.

The pathway from development to adoption, implementation and diffusion into clinical practice also involves a number of key stakeholders including researchers, industry, regulators, payers, health service providers, clinicians and patients. Interventions to accelerate adoption can occur at any stage of this pathway and often involve a number of stakeholder groups. Underpinning these interventions are a series of **enabling factors** which provide a conducive environment for them to work.

For the purpose of this review we consider the adoption of innovative medicines and medical technologies from proof-of-concept to practice. Although interventions aimed at stimulating basic research are equally crucial to effective medical innovation, they are outside the scope of this study.

We also observed a **lack of international examples on interventions at the implementation stage** of the pathway, although we recognise that these may be crucial in accelerating adoption.

Interventions for accelerated pathways

Our findings suggest there are a number of different examples of interventions, which can occur at each stage of the pathway. We have grouped these interventions into four overarching categories:

- **Process improvement**
Interventions that aim to shorten one stage of the process through providing additional resources, focusing resources, pooling resources across countries or conducting the processes in parallel.
- **Risk sharing**
Interventions that blur the decision points among stages by spreading risk across different stakeholders; for example, allowing early access to drugs still under review.
- **Process linkage**
Interventions that aimed to align the expectations and priorities of stakeholders along the pathway to reduce duplication of effort.
- **Addressing market failure/pricing**
Interventions that aim to address market failures or pricing barriers, such as widening cost-effectiveness measures or using non–outcome-based reimbursement mechanisms.





Process improvement	Accelerated review	Parallel review	Verification review	
Risk sharing	Pre-approval access	Non-standard authorisation	Coverage with Evidence Development	Performance based reimbursement
Process linkage	Stakeholder engagement	Human factors approach		
Addressing market failure/ Pricing	Wider cost-effectiveness measures	Special pricing agreements		

Process improvement: Accelerated review



What is it? How does it speed up adoption?

The term accelerated review refers to mechanisms intended to lead to faster market authorisation, where regulators offer more resources, greater engagement, or faster/rolling reviews of medical innovations

International examples



In the U.S., the FDA currently offers three mechanisms to accelerate and facilitate the regulatory approval of new drugs through provision of greater resources and/or prioritisation of review applications (**Fast Track** designation, **Breakthrough Therapy** designation and **Priority Review** pathway). Each mechanism is distinct from the other ones and is intended for use in slightly different contexts. Fast Track, and to an even greater extent Breakthrough Therapy, offers earlier and more intense engagement with regulators. By contrast, Priority Review reduces the processing time of a new drug application from the standard 10 months to 6 months.

With respect to resourcing regulators, one option is to charge applicants for the provision of regulatory services. For instance, Darrow et al. (2014) credit the **1992 Prescription Drug User Fee Act**, which allowed the FDA to collect fees from drug producers, with helping expedite the US review process.



Under the EMA's Accelerated Assessment (equivalent to the FDA's Priority Review), the standard limit of **210** days for approval is reduced to **150** days. The authorization application needs to pertain to a product that is [of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation].



Japan's **Sakigake** designation, provided by the Ministry of Health Labour and Welfare (PMDA) aims at accelerating adoption of Japanese-made innovative pharmaceutical products, medical devices, and regenerative medicines. Its benefits are similar to those offered under the FDA's mechanisms in that Sakigake offers increased and early consultation with regulatory authorities and prioritisation of the approval application review.

Process improvement: Accelerated review



Comparison of accelerated review programmes

Mechanism	Eligibility	Benefits	Evidence requirements
Fast Track (FDA)	<ul style="list-style-type: none"> • Serious condition • Unmet medical need 	<ul style="list-style-type: none"> • More frequent engagement with FDA • Eligibility for Accelerated Approval and Priority Review pathways • Rolling review of applications 	<ul style="list-style-type: none"> • Standard unless participating in Accelerated Approval (see below on non-standard authorisation)
Breakthrough Therapy (FDA)	<ul style="list-style-type: none"> • Serious condition • Preliminary evidence of improvement over existing therapy 	<ul style="list-style-type: none"> • All Fast Track benefits • Early FDA guidance • Senior FDA involvement 	<ul style="list-style-type: none"> • Eligibility: Effect on clinically significant endpoint • Market authorization: Standard unless participating in Accelerated Approval
Priority Review (FDA)	<ul style="list-style-type: none"> • Potential for significant improvement over existing therapy 	<ul style="list-style-type: none"> • Faster review of new drug application 	<ul style="list-style-type: none"> • Standard unless participating in Accelerated Approval (see below on non-standard authorisation)
Accelerated Assessment (EMA)	<ul style="list-style-type: none"> • Of major interest to public health 	<ul style="list-style-type: none"> • Faster review of new drug application 	<ul style="list-style-type: none"> • Standard
Sakigake (PMDA)	<ul style="list-style-type: none"> • 'Dire need of therapy' • Improvement over existing therapy (based on Phase I, II data) • Developed in Japan 	<ul style="list-style-type: none"> • Early consultation and designated senior support • Pre-application consultation • Priority Review • Extension of post-market verification period 	<ul style="list-style-type: none"> • Standard

Process improvement: Accelerated review



Strengths and weaknesses

Fast track designation and other similar mechanisms that involve early and intensive collaboration among drug developers and regulatory agencies are very resource-demanding. Any potential benefits stemming from fast track mechanisms can be reaped only if the regulatory body in question has the resources necessary to carry out expedited reviews. Therefore, any trends and differences in review times need to be seen at least partially as a function of available resources.

Mechanisms are not necessarily mutually exclusive. For instance, by earning the Fast Track or Breakthrough Therapy designation, a drug is eligible for the Priority Review pathway. In addition, these mechanisms can be used in conjunction with programmes that may authorise the marketing of a medicinal product based on a lower evidentiary standard.

Similarly, early engagement among regulators and industry is dependent on the drug developers' willingness to enter into such a relationship. One interviewee observed that this is far from automatic because product developers may fear that early collaboration with regulators may lead to an increased workload and thus additional costs. As a recent PWC report observed (2015), this may be particularly applicable to smaller companies with limited resources.

There is evidence that setting tight deadlines for regulatory review may be associated with increases in clinical safety issues post market authorisation (Carpenter et al. 2008, 2012). However, it should be noted that this evidence pertains to drug review in general, rather than review under one of the accelerated mechanisms. Where there is literature on the effect of faster reviews, it also points tentatively in the direction of increased post-marketing adverse effects (Olson, 2013). However, such findings remain controversial (Darrow et al. 2014).

What is the evidence?

Schulman and Brown (1995) compared the length of the regulatory phase of Subpart-E (an early form of the Fast Track pathway) drugs approved between 1998 and 1993 with a comparison group of similarly rated non-fast-tracked drugs approved during the same period and found that the fast-tracked regulatory phase (i.e. IND submission to NDA approval) was on average 3.3 years shorter.

The effects of individual accelerating mechanisms can be further magnified by their combined use.

The impact of accelerated review pathways can also be indirectly inferred from drug manufacturers' willingness to purchase FDA's Priority Review Vouchers (PRV) in order to ensure a speedier processing of their new drug applications. For instance, in November 2014, Gilead Sciences paid \$125 million to buy a PRV from Knight Therapeutics (MarketWired 2014).

Applicability to the UK

In the UK, the MHRA Innovation office can provide early advice to drug and device manufacturers, though it falls short of a clear fast track designation. It also entails a 'Promising Innovative Medicine' designation, which may be somewhat akin to the FDA's breakthrough therapy one.

Process improvement: Parallel review



What is it? How does it speed up adoption?

Parallel review involves a medical product going through processes of market authorisation (i.e. regulatory review) at the same time as aspects of cost-effectiveness and coverage for reimbursement are decided (i.e. pharmacoeconomic review).

It focuses on aligning timeframes and logistical aspects of the review processes to improve efficiency.

International examples



In 2008, Canada ran a pilot programme of parallel review as a collaboration among its regulatory and HTA bodies: Health Canada and the Canadian Agency for Drugs and Technologies in Health (CADTH), respectively. Parallel review was initiated for breakthrough drugs: i.e. immediately life-threatening diseases or drugs that could save at least \$2.5m to reimbursement recommendations under Canada's Common Drug Review (CDR) programme. The pilot was further extended to oncology drugs. As of November 2012 CADTH announced that all new drugs would go through parallel review as part of a revised CDR process.



Regulatory review is carried out in Australia by the Therapeutic Goods Administration (TGA), with recommendations on pricing being made via the Pharmaceutical Benefits Advisory Committee (PBAC). Both agencies are involved in providing non-binding advice to industry in the design of Phase III trials, as well as the preparation of manufacturers' dossiers for review. Parallel review has been available in Australia since January 2011. Applications for reimbursement can be submitted at any time following registration, but as the timelines for PBAC (~4 months) are shorter than TGA (~9 months), decisions on reimbursement are not released publically until after the TGA has reached its decision.



The US is currently undertaking an extended pilot programme (initiated in 2011) for parallel review of medical devices, due to complete end 2015. This programme offers concurrent marketing approval (via the FDA) and coverage determination (via the Centers for Medicare & Medicaid Services (CMS)) of up to five devices p/a that meet one of a number of criteria, including class III (i.e. high-risk) medical devices that require pre-market approval (PMA) submissions to the FDA.

Process improvement: Parallel review



Strengths and weaknesses

The Canadian approach involved a trial of new methods to share information among regulatory and HTA authorities. Since parallel review was initiated for all new drugs as part of Canada's Common Drug Review (CDR) process in 2012, there is no longer a need for a standalone priority (i.e. accelerated) review process – as the backlog of all CDR applications had been cleared. This would suggest that parallel review can be successfully implemented given sufficient resources and appropriate sharing of information.

Nevertheless, caution must be exercised when basing reimbursement decisions on pharmacoeconomic analyses submitted by manufacturers. Yong et al. (2013) found up to one third of such submissions had significant problems that could distort the results and hinder recommendation committees in their assessment of cost-effectiveness. They recommended improving simple sensitivity analyses around key variables and following best practice guidelines for reporting economic evaluations.

While no studies could be found to highlight the effectiveness of the US parallel review programme, Rome et al. (2014) highlight a number of issues arising from the pre-marketing approval process as it relates to cardiac devices (discussed as part of *Coverage with Evidence Development* section, below).

What is the evidence?

Different agencies' strategies in dealing with clinical uncertainty and unfavourable cost-effectiveness can lead to different recommendation decisions for the same drugs. Chabot and Rocchi (2014) describes a relationship among the pressures of negotiating solutions to improve incremental cost-effectiveness ratios, and the outcome of HTA recommendations, when looking at cancer drugs approved in Canada vs. the UK.

While evidence is limited on the impact of parallel review mechanisms, studies highlight as a particular challenge the influence that manufacturers exert over the submission of cost-effectiveness data, and the limitations of state regulators to mandate post-marketing surveillance and comparative effectiveness research.

Applicability to the UK

Chabot and Rocchi (2014) found that there was a tendency for the UK to favour risk-sharing agreements and price negotiations with manufacturers during HTA review to meet a defined incremental cost-effectiveness ratio, resulting in approval of fewer cancer drugs when compared to Canada, who favoured pressure by provincial payers to negotiate prices with manufacturers post-approval, and as a result approved more drugs.

Process improvement: Verification review



What is it? How does it speed up adoption?

‘Verification review’ involves guaranteeing a faster regulatory review based on approvals by at least two international benchmark reference agencies.

Harmonisation and international benchmarking of regulatory processes may allow cost/resource savings.

International examples



The process was introduced in Singapore in 2003. The review guarantees regulatory review within 60 days (as opposed to 270 days) and requires a verification dossier to be submitted within three years from the date of approval by the chosen primary reference agency. Currently, Singapore uses the following reference agencies for review:

- Australia Therapeutic Goods Administration (TGA)
- Health Canada
- FDA
- European Medicines Agency (Centralised Procedure)
- UK Medicines and Healthcare products Regulatory Agency (MHRA)

In Singapore, an ‘Abridged review’ is also offered which only requires one reference agency’s approval and guarantees the review in 180 days.



New Zealand pursues an abbreviated evaluation process for certain drugs that have already been approved by a trusted overseas regulatory authority. Drugs also have to have been approved within the last five years.



For medical devices, the Medical Device Single Audit Program (MDSAP) have recently launched a pilot among the US, Canada, Australia, Japan and Brazil to harmonise regulatory requirements for medical products. The pilot allows authorised organisations to ‘conduct a single audit of a medical device manufacturer that will satisfy the relevant requirements of the medical device regulatory authorities participating in the pilot program’.

Process improvement: Verification review



Strengths and weaknesses

This process has the potential to save costs & duplication of resources across countries.

While this may not be an option for all applications, it may be a more feasible option for less complex dossiers.

However, the process may raise issues of liability if the decision to register medicines was based on an assessment by an overseas regulator and strict criteria would need to be developed to ensure that assessments are being conducted with consistent quality standards.

There may also be occasions where there is disagreement among trusted regulatory organisations on whether a medicine is appropriate for certain indications while another trusted regulator rejects the medicine for the same indications.

This scheme would limit a country's ability to be a 'front-runner' in adopting new medical innovations as it would depend on medicines having already been through at least one other regulatory process.

What is the evidence?

To our knowledge there has not been any evaluation of the 'verification review' system in Singapore or New Zealand.

Nevertheless, a number of countries have begun considering abridged and verification reviews for medicines. For example, in a recent review of their regulatory systems for pharmaceuticals, Australia is considering developing a set of transparent criteria to assess whether 'trusted' overseas regulators can be used.

Applicability to the UK

If the UK were to adopt a verification review based on an assessment by an overseas regulator a strict criteria for 'trusted' regulators would need to be established.

In addition, the UK may be limited to products outside the scope of the EMA.

For devices there has been a 'mutual recognition agreement' between the U.S. and Europe since 1998, although the agreement does not harmonize the legislative requirements and neither the CE mark nor an FDA-approved device has official status in either respective region.

Risk sharing: Pre-approval access



What is it? How does it speed up adoption?

These mechanisms and programmes allow patients to access drugs and other medicinal products that have otherwise not been authorised for wider marketing, irrespective of whether such authorisation is planned or not). They are typically applied in instances of seriously ill patients or where all other treatment efforts have failed. They are therefore sometimes referred to as ‘compassionate use’ policies and programmes. They speed up the adoption of new products by a very narrow group of people since these patients can access medicinal products without the need to wait for regulatory review and approval.

International examples



Expanded Access. Under certain circumstances, the FDA allows individual patients to access drugs that have not yet been authorized for marketing, i.e. are still being investigated. Eligibility is restricted to serious or life-threatening conditions with no existing comparable therapy and, in addition, the potential benefits need to be deemed to outweigh the costs and an individual’s participation in the scheme must not undermine any ongoing or any future clinical trials (FDA 2014). Once eligible, however, applicants are rarely rejected by the FDA (Gaffney 2014).

Similarly, concerning medical devices, a **Humanitarian Device Exemption (HDE)** may be granted for items treating or diagnosing a condition that affects a small number of people and, as such, its development costs would exceed its market returns. Under an HDE, an application is not required to provide evidence of the device’s effectiveness but a positive balance among its probable benefits and possible risks of injury or illness from its use needs to be demonstrated (FDA 2014b).



The TGA in Australia also maintains three schemes that are intended to allow patients access to unauthorized therapeutic goods under exceptional circumstances. These are **Authorised Prescribers** (intended for medical practitioners who would prescribe a product unapproved by the TGA), **Special Access Scheme** (for patients to access unapproved products on a case-by-case basis), and **Personal Import Scheme** (for individuals to import unapproved products for their personal use) (Department of Health Therapeutic Goods Administration (TGA) 2014).

Risk sharing: Pre-approval access



International examples (contd.)



In France, the **Temporary Authorisation for Use (ATU)** system, which was set up in 1992, allows patients to access medicines that do not have any marketing authorization, provided that they are intended for the treatment of serious or orphan diseases and there is an absence of alternative appropriate treatment. Treatments can be administered on either a 'named patient ATU' or 'cohort ATU' basis, which makes it unique in that the ATU is one of the few European early access programmes to allow cohorts of patients (Degrassat-Théas et al. 2013).

Hospital pharmacies are responsible for administering ATUs to patients, and negotiate directly with pharmaceutical companies to determine the price. The cost of the ATU is then fully reimbursed by the National Health Insurance (NHI).

In addition to the ATU system, off-label use prescription is also authorised, known as a Recommendation of Temporary Use (RTU) in the absence of an ATU or market authorisation. The scheme allows the monitoring of off-label prescribed medicines, provided that there are no alternative therapies and that the evidence base on effectiveness and safety is presumed to be favourable. Products are authorised by the French National Agency for Medicines and Health Products Safety (ANSM) and should not exceed use for over 3 years.

Degrassat-Théas et al. (2013) note that while patients receive treatments earlier under this scheme, the impact of the programme on the market access of these drugs for the wider population, is often an increase in approval times.



Japan's **Sakigake Designation** includes a 'scheme for rapid authorization of unapproved drugs'. It is intended to accelerate the use of unapproved drugs for serious and life-threatening diseases. Under this scheme, patients are allowed earlier access to drugs that have not been yet approved in Japan, although products' eligibility for inclusion in this scheme is comparatively limited. Also, in contrast with the schemes discussed above, one of the explicit aims of this programme is to facilitate the eventual approval of the product in question and data collected through this scheme are intended to be used as part of the final approval application (Ministry of Health, Labour and Welfare 2014).

Risk sharing: Pre-approval access



Strengths and weaknesses

Expanded/pre-approval access schemes are frequently surrounded by controversy. The pharmaceutical industry is not always favourably disposed towards them for several supply-side reasons. First, there may be a limited supply of experimental drugs and drug manufacturers might wish to preserve available supplies for ongoing or planned trials (Kesselheim et al. 2014). Similarly, the Expanded Access Programme places administrative burden and other costs on drug manufacturers, who may prefer to divert those resources the conduct of clinical trials (Darrow et al. 2015).

In this context, it is very difficult for drug manufacturers to recover the costs stemming from their participation in the scheme. FDA sets a ceiling on the prices of experimental drugs, which is invariably lower than the eventual post-market price, and, perhaps more importantly, it is problematic for drug manufacturers to charge for their products. This is due to risks of bad publicity and because the experimental drugs are unlikely to be covered by insurers, including public programmes such as Medicare (Kesselheim et al. 2014).

In addition, there are legal issues with FDA's Expanded Access. As currently designed, an application must be filed by the drug manufacturer, patients (and less frequently their physicians) can only informally petition the industry for access to experimental drugs. Courts have been asked to weigh in on the issue whether seriously ill individuals are entitled to access to experimental drugs and, along similar lines, several U.S. states have passed 'right-to-try' laws to achieve a similar effect. However, courts have found no such right of terminally ill patients and 'right-to-try' state laws can have only very limited impact since they cannot alter existing federal regulations (PWC 2015; Darrow et al. 2015).

Finally, there are also ethical issues to consider with respect to pre-approval access schemes. On one hand, an argument can be made that it would be unethical to deny terminally ill people access to potentially effective drugs. On the other hand, it is questionable to what extent fully informed consent is achievable, given poor levels of risk and health information comprehension among general public (Institute of Medicine of the National Academies 2004).

What is the evidence?

There are several ways to consider the effectiveness of pre-approval schemes. From a strictly procedural point of view, the FDA's Expanded Access Program is effective in that virtually all applications, regardless of their category, are accepted by the FDA and therefore patients seen in need are provided with the product in question (Silverman 2014).

However, the effectiveness of the medicinal product itself is far less likely. In fact, some authors point out that the probability of an effective therapy in this experimental setting can be as low as 10% or less (Darrow et al. 2015; Horstmann et al. 2005).

From the perspective of speeding adoption, pre-approval schemes shorten the time needed for new products to be available for eligible participants. While the extent of this acceleration varies substantially across individual products and depends on the stage at which early access is requested, it is worth recalling that the estimated average length of the drug development process from discovery to marketing approval exceeds 10 years (DiMasi and Grabowski 2012).

However, this faster adoption serves only a very narrow group of people and it is unclear what the scheme's impact on the wider approval process is. One of the reasons why industry is often reluctant to engage in the Expanded Access programme are concerns that the regulatory review may be negatively impacted. Beneficiaries of the programme tend to be more seriously ill than other trial participants, which may jeopardise the final approval or lead to additional labelling requirements (Darrow et al. 2015).

Applicability to the UK

The UK has an equivalent in the early access to medicines scheme (EAMS). Under this scheme, patients with 'life threatening or debilitating' conditions may be given access to an unapproved drug, pending MHRA's opinion on the balance of its benefits and risks. A condition of eligibility for the EMAS scheme is that the product in question receives a 'Promising Innovative Medicine' designation by the MHRA (MHRA 2014). However, there is some uncertainty about how the EAM S scheme fits in with existing EMA frameworks, particularly its adaptive licensing programme (ABPI 2014).

Risk sharing: Non-standard authorisation



What is it? How does it speed up adoption?

The mechanisms described below can speed up adoptions by relaxing or modifying evidentiary standard required for marketing authorisation of a new product. This applies in situations where meeting standard level of evidence would either protract the regulatory review or would not be feasible either for ethical or practical reasons. Often, the use of these mechanisms is conditional on continuing with evidence collection once a product has been marketed. In contrast with accelerated review, these mechanisms do not alter the processing time of an authorisation application, they alter the degree of evidence required for this authorisation.

International examples



Under the **Accelerated Approval pathway** a drug can be approved if it has an effect on a surrogate (e.g. marker considered 'reasonably likely to predict final clinical benefit') or an intermediate clinical endpoint. If an accelerated approval is granted, the drug developer has a subsequent requirement to verify the drug's clinical benefit in Phase IV confirmatory trials.

FDA is currently proposing to establish a similar mechanism for medical devices – **Expedited Access for Premarket Approval** – which would combine elements of Fast Track programmes and the Accelerated Approval pathway described above. The proposed EAP is a voluntary programme designed for medical devices that 'demonstrate the potential to address unmet medical needs for life threatening or irreversibly debilitating diseases or conditions'. Participation in EAP would be voluntary and offer earlier and more intensive engagement with the FDA. In addition, evidence requirements under EAP may include intermediate and surrogate endpoints, two-phase studies or in-vitro studies.

FDA also uses the '**Animal Efficacy Rule**' to give approval to products for 'serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances'. Under this rule, new products can be approved based on safety studies in humans and effectiveness studies in animals. The reason for waiving the requirement for efficacy testing in humans is that this would be either unethical or infeasible as the rule is intended to cover very rare situations.

Risk sharing: Non-standard authorisation



International examples (contd.)



EMA's **Conditional Marketing Authorisation** is similar to the FDA's Accelerated Approval Pathway in that it accepts lower level of evidence in return for further post-market requirements. However, the conditional authorization is valid for one year and is renewable annually, providing the specific obligations for the approved product are met and benefit/risk balance remains positive. It is also not based on any surrogate endpoint likely to predict final benefit but on the likelihood of data completion post-authorisation.

In situations in which the product developer is unable to provide comprehensive clinical evidence due to practical or ethical reasons, such as rarity of the disease or insufficient existing scientific knowledge to collect robust data, EMA may grant **Marketing Authorisation under Exceptional Circumstances**. It is not expected that such data collection will be possible in the future and therefore an Marketing Authorisation under Exceptional Circumstances will typically not be converted into a 'traditional' authorization. This authorisation is valid for 5 years and is renewable.

Risk sharing: Non-standard authorisation



Strengths and weaknesses

All the mechanisms described in this section accept a lower level of evidence for market authorisation, often under the condition of further confirmatory post-market studies. However, issues may arise when these are not conducted in a timely manner and available evidence suggests that this is the case with a considerable share of products approved conditionally. For instance, a review of cancer drugs approved via FDA's Accelerated Approval among 1992 and 2010 (Johnson et al. 2011) found that out of 47 included items, 14 had not been subject to trials by the time the review was conducted.

FDA's Animal Rule and EMA's Authorisation under Exceptional circumstances are intended to cover very unusual situations (the Animal Rule was enacted by the Congress in the wake of the 9/11 attacks and with bioterrorism concerns high on the policy agenda) (Snoy 2010). As such, the number of products marketed under these mechanisms remains very limited – for instance, the first product licensed under the Animal Rule, a drug against plague, was not approved until 2012 (Gaffney 2014a).

The two mechanisms described above may also be suitable as response mechanisms to sudden outbreaks of serious diseases. For instance, the FDA Animal Rule is widely regarded as an instrument that will be applied in an eventual approval of a drug against Ebola (Gaffney 2014b). In the context of Ebola, it is worth noting pre-approval schemes, such as 'compassionate use' mechanisms, have also been used to accelerate patients' access to drugs (FDA 2015).

What is the evidence?

Johnson et al. (2011) assessed the effect of accelerated approval on the availability of oncology drugs in the US. The authors found that the average time between accelerated approval and its conversion to regular approval based on confirmatory post-market trials was 4.7 years (median 3.9 years). This represents a substantial improvement in the availability of medicinal products to patients, though it is unclear whether drug producers sustain their work tempo after a marketing approval is granted. In other words, data are not available on how fast a regular approval would have been achieved in the absence of the accelerated approval pathway.

Shulman and Brown (1995) found that applying the accelerated pathway to fast-tracked drugs shaved approximately 1.5 years off the duration of their regulatory approval phase.

With respect to the FDA's 'Animal Rule', it is important to keep in mind that acceleration of adoption is not its primary objective, even though it can be combined with the Accelerated Approval pathway. On its own, the length of the approval process under the 'Animal Rule' may even exceed that of a regular review (Estep 2009).

Applicability to the UK

There is no UK equivalent of market authorisation mechanisms that would incorporate the element of relaxed or modified evidentiary requirements, although the UK is included in the EMA schemes on Conditional Market Authorisation.

Risk sharing: Coverage with evidence development



What is it? How does it speed up adoption?

Coverage with evidence development (CED) refers to schemes that enable temporary funding of innovative medical products, so long as additional evidence of their effectiveness in wider populations is generated to address the uncertainties surrounding reimbursement and secure ongoing coverage (Hutton et al. 2007).

It allows healthcare decisionmakers to make available a medical product in a controlled manner while also defining what evidence is required to support further diffusion of the technology.

International examples



CMS's Coverage with Study Participation (CSP) programme focuses on providing reliable evidence of benefits and risks in a wider population so long as items or services are furnished in the context of approved clinical studies or with the collection of additional clinical data.



The Australian scheme for managed/shared risk in pricing (the 'Managed Entry Scheme') was launched in 2011. This was based on listing of medicines by PBAC at a price justified by the levels of existing evidence, and pending availability of more conclusive evidence of cost-effectiveness (Wonder et al. 2012). By February 2013, 17 special pricing arrangements were in place (Vitry & Roughead 2014) under this scheme.



The French Ministry of Health (not manufacturers) initiates CED processes, having first defined the numbers of patients to be involved, conditions of use, funding period, and which hospitals lead the study (Martelli & van den Brink 2014). Additional payment for in-hospital devices is only applicable to implantable devices and to those included on the list of products and services qualifying for reimbursement (LPPR). To apply for reimbursement, manufacturers must apply to the National Committee of Medical Devices and Health Technologies (CNEDIMTS) for assessment.



Recognising the need for a mechanism allowing innovation within the German diagnosis-related group (G-DRG) system, the Institute for the Hospital Remuneration System (InEK) created an 'top-up' funding process for innovative products. Approved applications are subsequently monitored by InEK to ensure the technology is being used adequately and is cost-effective. While the system may accelerate innovation, it requires significant effort from users.

Risk sharing: Coverage with Evidence Development



Strengths and weaknesses

CED can enable more patients to receive treatment – but with the challenge that this requires careful patient selection (i.e. limiting use to those most likely to benefit and avoiding ‘treatment creep’ in cases where inappropriate patients may be offered therapy).

Garber et al. (2014) flag issues that can be inherent in carrying out the necessary post-marketing surveillance required for CED: studies were found to have design flaws, insufficient funding, and insufficiently sound scientific data collection to formulate sound coverage policy.

Rome et al. (2014) suggest that the US legal system unfairly pre-empts manufacturers of high-risk devices from damages claims from patients in the event of their failure, reemphasising the importance of clinician and patient engagement in well-designed post-marketing surveillance and comparative effectiveness research.

In 2014, out of a list of 618 qualifying products/procedures, 114 received ‘Nu-B’ clearance status for negotiation of reimbursement with Germany’s providers of statutory health insurance, however the outcomes of these being adopted into the G-DRG system are not clear.

What is the evidence?

Implantable cardiopace defibrillators (ICDs) are cited by Garber et al. (2014) as an effective example of CED expanding patient access to treatments for secondary prevention of sudden cardiac death.

However, Rome et al. (2014) raise a number of concerns around the US pre-marketing authorisation processes, to warn clinicians of the issues relevant to adopting high-risk cardiovascular devices as part of post-marketing evaluation studies.

Methods of CED vary considerably among countries, though the International Society For Pharmacoeconomics and Outcomes Research (IPSOR) task force has attempted to begin a process of harmonisation by introducing best practices in ‘performance-based risk-sharing arrangements’, and by providing examples of different countries’ approaches and their relative successes (Garrison et al. 2013).

Applicability to the UK

In the UK, NICE has two designations for extending coverage based on further evidence generation

- ‘*Only in Research (OIR)*’ – recommending treatments only to be used in the context of randomised trials or studies
- ‘*Only with Research (OWR)*’ – recommending further research alongside use

Longworth et al. (2013) found that the majority of OIR/OWR recommendations were for technologies considered to be cost ineffective and noted that the use of OIR/OWR recommendations has been decreasing over time.

Risk sharing: Performance-based reimbursement



What is it? How does it speed up adoption?

Performance-based reimbursement (PBR) is a payer–manufacturer arrangement by which the performance of the medical technology is tracked in a defined patient population over a defined period of time and the reimbursement is based on the health outcomes achieved in the defined patient population (Garrison et al. 2013).

Because reimbursement is contingent on real-world performance, the approval of innovative medical technologies is not held back until satisfactory trial-based evidence is available, thereby accelerating adoption (Garrison et al. 2013; Carlson et al. 2011).

International examples



One recent example is the relatively new class of oral antidiabetic medications dipeptidyl peptidase-4(DPP4) inhibitors. In the first round of negotiation the French pricing committee (PC) was willing to offer only a small premium over alternative drugs for dual therapy: same efficacy for glycemic control as prior drugs and longer efficacy to lower haemoglobin A1C, which was supported only by experimental data. In a second round of negotiation the PC agreed to let the manufacturers conduct a large real-world study to demonstrate their claim of longer efficacy to lower haemoglobin A1C in exchange for a higher price. The condition agreed was that the payer would receive a retrospective pay back on all sales corresponding to the difference between the agreed-upon price and the initial price, if the study did not support the manufacturers' claim. The final results of the study are not yet available in the literature.

A similar agreement was made for glitazones, another antidiabetic drug. Manufacturers also claimed that this drug would delay escalation of insulin therapy. In this case, the real-world study did not support the claim and the prices were adjusted downwards.

A third example refers to a controlled-release form of risperidone for treatment of patients with schizophrenia. The PC concluded that the clinical efficacy of the new drug was similar to that of conventional treatments and granted a rating which led to a price similar to existing medications. The manufacturer argued for a higher rating (and higher price), claiming that the controlled release form would lead to fewer hospital admissions. The PC agreed on a higher price under the condition that the post-launch study would have to demonstrate fewer hospital admissions. The study supported the manufacturer's claim.

Risk sharing: Performance-based reimbursement



International examples (contd.)



In Italy, innovative and expensive medicines are usually assessed by PBR schemes, termed conditional reimbursement schemes, linking the use of the medicine to the clinical outcomes obtained. These include:

- ‘Cost sharing’: price reduction for initial cycles of treatment until it is clear that patients are responding followed by full price afterwards.
- ‘Payment by results’: payer receives a payback for non-responders.
- ‘Risk sharing’: only 50 % of the costs of the non-responders is paid back by the manufacturer.
- Pivotal to the Italian PBRs are the drug-monitoring online registries, which are developed by the Italian Medicines Agency (AIFA). These registries collect patient-level data on drug safety and effectiveness in real world conditions. For example, the Cancer Drugs Register covers all the prescription centres, with a total of more than 100,000 oncology patients.
- One example of a registry created for a new drug is the case of aliskiren (Rasilez) used in the treatment of hypertension. Two years of observational data showed that aliskiren reduced both systolic blood pressure and diastolic blood pressure in patients enrolled and that it had a good safety profile. Several decisions were taken based on the data collected in the registry, including a price reduction of aliskiren to align the price to that of other hypertensive medicines.

Risk sharing: Performance-based reimbursement



Strengths and weaknesses

PBR schemes may accelerate the adoption of new medicines because they give patients access to novel and potentially beneficial medical technologies despite uncertainty about their cost-effectiveness. The alternative would be to delay the reimbursement approval until satisfactory evidence on cost-effectiveness is available.

PBR schemes also have the societal benefit of changing the structure of incentives for manufacturers towards one that explicitly rewards health outcomes for patients.

Operationalisation requires a clear definition of many key parameters upfront, namely, health outcome measures of interest, target patient population, period of time for data collection, methods to collect evidence, how to monitor data collection, who is responsible for data collection, and penalties in case of noncompliance with agreement/contract (e.g. failure in collecting the data as agreed or delays in collecting the data).

Enforceability of the contract might be difficult, particularly when some of the key parameters above are not clearly defined upfront.

Retrospective claims on reimbursements may be challenging to ensure. In the case of the UK, Williamson (2010) finds that response-based payback schemes pose significant challenges about tracking patients and thereby ensuring claims for reimbursements for non-responders.

Additional evidence of good quality can be challenging to obtain: reliable data on clinical effectiveness in the real world are heavily dependent on the study and research design, patients groups selected, etc.

What is the evidence?

The evidence on effectiveness of PBR schemes is very limited. In a review to assess the effectiveness of PBR schemes, Puig-Peiró et al. (2011) found that more than 40% of the papers assessing effectiveness of PBR focus on the case of the UK multiple sclerosis drug risk-sharing scheme, which is considered by many as highly unsuccessful.

The Italian PBR schemes appear to have been successful in speeding adoption of innovative medicines. This may have been due in part to the use of a national electronic patient registration system, which is considered to reduce substantially the costs of collecting real-world data and ensure a good level of quality of the data collected (Garrison et al. 2013).

Applicability to the UK

The UK has what are known as 'Patient Access Schemes' (PASs), which are agreement-specific arrangements. These include a few PBR cases. The best documented ones are the bortezomib (Velcade) agreement and the UK multiple sclerosis drug risk-sharing scheme (Pickin et al. 2009; Raftery 2010).

The experience with PBR in the UK and elsewhere suggests that the success of PBR schemes is heavily dependent upon how appropriate, hands-on, and enforceable the design of the scheme is, in particular in the scheme's consideration of:

- Outcome measures by which the success of the scheme will be assessed
- Appropriate evidence collection
- How to implement, govern and report the results

Process linkage: Stakeholder engagement



What is it? How does it speed up adoption?

Stakeholder engagement involves stakeholders at different parts of the pathway communicating and collaborating. This helps to align the expectations and priorities of stakeholders along the pathway to reduce duplication of effort. Engagement can be introduced at all stages of the adoption pathway, and can be used either to accelerate the development of specific drugs, devices or diagnostics that appear to provide a clear clinical impact, or to determine new systems and processes aimed at accelerating and improving adoption.

International examples



The FDA has been involved with early engagement in a number of projects: e.g. developing a regulatory pathway for the development of drugs for cognitive impairment associated with schizophrenia (CIAS) in collaboration with academia and industry, and the Critical Path Institute, born out of the FDA's **Critical Path Initiative**, U.S., which provides neutral ground where FDA scientists, industry and academic partners can work together.



MaRS Excellence in Clinical Innovation Technology Evaluation (EXCITE) The results used to obtain licensing and regulatory approval for health technologies may not be sufficient to prove the value of technology to the health system, and to get the health system to buy in and adopt it. EXCITE connects health technology innovators with experienced researchers to enable them to get the evidence and data needed to show the value of their product. EXCITE facilitates discussions with health system stakeholders to determine what is required for successful adoption of their product.



Biosciences Accelerator at The Hamner Institutes for Health Sciences, U.S. The Biosciences Accelerator connects emerging companies with access to a state-of-the-art research facility as well as scientific and business development support to assist them in commercialisation. The Hamner Institutes have links with industry, academia and government, allowing for shared resources. One project involves accelerating drug development in China, under US regulatory standards, with the aim of bringing the product to the worldwide market.

Process linkage: Stakeholder engagement



International examples (contd.)



New Drug Development Paradigms (NEWDIGS), U.S. There is awareness that new development drug paradigms will be required for the regulation and adoption of innovative medicines. The Massachusetts Institute of Technology (MIT) has set up the New Drug Development ParadIGmS (NEWDIGS) program as a collaborative international ‘think and do’ tank focused on enhancing the capacity of the global biomedical innovation system to reliably and sustainably deliver new, better, affordable therapeutics to the right patients faster. NEWDIGS takes a systems engineering approach to designing, evaluating and catalysing important advancements that are so complex and cross-cutting that they cannot be addressed by a single organization or market sector. It brings together international pharmaceutical companies, regulators, academia, payers and other relevant stakeholders in a safe haven setting to work on innovative drug development systems. Its first project, started in 2010 and finished in 2014, focused on the concept of adaptive licensing and how it could be put into practice. The EMA has now launched an adaptive licensing pilot.



The Italian Horizon Scanning Project This is an early warning system for identifying and assessing the potential clinical and economic impact of emerging technologies can help decision-makers make decisions and plan appropriately. The Italian Horizon Scanning Project collects data on emerging technologies, prioritises them, and produces reports 36, 18 and 12 months before the EMA will pass judgement, giving data on development plans and clinical and economic impact. These data are used by the Italian national health service to identify useful research areas which may be interesting to them but not to pharmaceutical companies, to plan and optimise the most appropriate use of resources, and to help decide upon the appropriate level of reimbursement.

Process linkage: Stakeholder engagement



Strengths and weaknesses

Stakeholder engagement and collaboration can create an environment which is more efficient at converting discovery into therapeutics that benefit human health and are adopted by the health system.

Transparency and clarity of process for obtaining regulation helps companies ensure they have obtained the necessary evidence before applying for regulation; this can reduce delays and accelerate adoption.

Stakeholder engagement can encourage collaboration among small to medium enterprises (SMEs) and academia, giving SMEs access to expertise that will help them generate the evidence needed for regulation and adoption more efficiently.

The ability to carry out stakeholder engagement is a function of the resources of all parties involved.

Stakeholders on both sides need to be willing to engage.

Stakeholder engagement may require stakeholders to align their priorities and work together.

What is the evidence?

There is widespread agreement among our interviewees that improving transparency and clarity of process for obtaining regulation will accelerate adoption.

Because these schemes are new, there are no evaluations yet; therefore, we have not found evidence of their effectiveness.

However, stakeholder engagement schemes are increasing in number, and NEWDIGS is growing in size, indicating that people believe they will give results.

Applicability to the UK

Stakeholder engagement is being introduced to the UK via a variety of schemes. From September 2013 there has been a new National Institute for Health Research (NIHR) scheme, Diagnostics Evidence Co-operatives, aimed at connecting device companies with experts in health economics, human factors, clinical trials and other skills required to generate the evidence they need to get to market. These centres aim at being one-stop shops with the infrastructure to streamline innovations into clinical practice. There are currently no similar UK schemes for devices or drugs.

The EMA was already involved in NEWDIGS; as of November 2014, NICE also became involved.

Interviewees reported that whilst there is a system for drug horizon scanning in the UK (UK PharmaScan), there is a disconnect between this system and budget holders, so that it is not used effectively. They reported that the Scottish Medicines Consortium, which also uses UK PharmaScan and other sources, makes better use of this information; we have not found any wider evidence to support this.

Process linkage: Human factors approach



What is it? How does it speed up adoption?

Human factors refers to the idea that adoption of a medical product, in particular medical devices, will depend not just on its availability but also on its ease of use, the burden the product puts on patients or doctors, and perceived fears. A well-designed product that can be used easily and correctly is more likely to have good uptake.

International examples



The FDA has incorporated human factor testing into regulatory approval. The main motivation for doing this is to improve safety, by reducing the risk that a device will be misused.



Similarly, the EMA has also introduced requirements for device manufacturers to establish and follow a Usability Engineering Process within the EU's Medical Device Directive.



In Canada there is a Healthcare Human Factors team within Toronto General Hospital that researches human factors and helps companies prepare for FDA human factor testing.

Process linkage: Human factors approach



Strengths and weaknesses

Introducing human factor testing increases the burden, in terms of time and cost, on both the company and the regulator. This could increase the time it takes for a product to be designed and go through regulation. However, once on the market, a more appropriate and user-friendly product is more likely to be adopted.

Appropriately designed products are less likely to be used incorrectly or inappropriately; they therefore should be safer.

Human factor approaches can also be applied to guideline design and to wider aspects of the health system.

Human factor approaches require an extra set of skills that many companies may not currently contain. Stakeholder engagement could help SMEs obtain access to these skills.

Regulating bodies also need human factor skill sets to be able to carry out the appropriate testing.

The testing carried out needs to be chosen appropriately, so that the product is tailored to the individuals who would be using it.

While policy interventions may encourage a human factors approach to the development of medical innovations, it will ultimately be the responsibility of the manufacturer to ensure that products developed are suitably designed.

What is the evidence?

Innovation literature identifies cultural factors as being important for adoption.

From our interviews and literature search, we have not found evidence that they speed up adoption.

However, we have found examples of bad design causing a lack of adoption of technologies.

Applicability to the UK

The new NIHR Diagnostic Evidence Cooperatives set up in part to enable SMEs to access all of the expertise required to get their product licensed and on the market, include human factor specialists.

Pricing: Wider cost-effectiveness measures



What is it? How does it speed up adoption?

Wider cost-effectiveness measures (WCEM) broaden the notion of value by considering such factors as severity of disease and wider societal factors (e.g. productivity gains, costs savings to other services), along with health gains for individual patients derived from extension and/or improvement of quality of life.

It may speed up adoption to the extent in which it gives a premium to 'valuable' factors that would otherwise be ignored. Without the consideration of a wider set of 'valuable' factors, many medicines may have an incremental cost-effectiveness ratio above the maximum cost per QALY at which the medicine is deemed cost effective, and thereby fail to be recommended for adoption by appraisal bodies (Claxton et al. 2008).

International examples



Sweden was an early adopter of WCEM (starting in 2002) as part of their value-based pricing (VBP) scheme. Sweden is the international example that comes closer to the WCEM approach suggested for the UK (as part of the VBP consultation) in terms of breadth of potential 'value' factors (Sussex et al. 2013). Manufacturers propose a price which is compared against an adjusted threshold that takes into account a breath of 'value' factors such as:

- Cost savings in healthcare
- Cost savings in any other sectors/budgets, e.g. savings for other publicly funded services, cost savings to patients, relatives and carers
- Value of lost production
- Greater willingness to pay for benefits in case of diseases with more severe consequences and diseases for which few or no treatments are available



Australia provides an example of a country where reimbursement is primarily based on clinical and cost effectiveness for patients measured by QALYs, but it also takes into account a few additional elements of 'value', namely:

- Innovativeness of the medicine (premium of approximately a 30% margin on costs)
- Prescription volumes
- Level of activity undertaken by the company in Australia (including new investment, production and R&D)

Pricing: Wider cost-effectiveness measures



International examples (contd.)



Italy represents an example of a country that incorporates several elements of 'value' in determining the reimbursement price of medicines, by using a score system (as opposed to a monetary value) to value the several factors and negotiation to convert 'value' into a price (as opposed to comparing manufacturer price with a threshold). The 'value' of a medicine depends on:

- Clinical effectiveness, measured by surrogate clinical endpoints (as opposed to QALYs) and leading to three scored categories
- Availability of therapeutic alternatives, classified in three scored categories
- Severity of the disease, classified in three scored categories
- Degree of innovativeness of the product, classified in two scored categories

Pricing: Wider cost-effectiveness measures



Strengths and weaknesses

WCEM more closely align therapy priorities with the value the public gives to such therapies.

In the long run, prices based on value to patients and the wider society give signals about priority areas so that research efforts can be directed to areas where breakthrough medicines are in need.

An adjusted cost-effectiveness threshold that provides more health than is displaced is key. Setting the threshold too high will lead to medicines being reimbursed at prices that 'displace too much health elsewhere in the health-care system'. Setting the threshold too low may mean society will not benefit from medicines that would have improved net health (Claxton et al. 2008).

WCEM can be used in conjunction with ex-post-review mechanisms, e.g. coverage with evidence development. The only country where there is evidence of WCEM (Sweden) combines WCEM with CED, and this combination is seen as pivotal to speed up adoption.

Operationalisation requires a clear set of rules. WCEM requires the prior definition of what 'value' criteria to include, how to measure each criterion, how to aggregate the value of the several criteria and how to convert the aggregated value into the maximum reimbursement.

In a fixed budget, it reprioritises treatments delivered, because one would need to recalculate all previous therapies against WCEM. There will be winners and losers in terms of approved therapies.

What is the evidence?

Evidence from Sweden summarised by Persson (2012) suggests that WCEM schemes may be well placed to reward, encourage and speed up the adoption of innovative medicines.

This is particularly true for orphan drugs. Orphan drugs often fail to obtain reimbursement because their high cost-per-QALY ratios usually exceed the accepted threshold. In Sweden, from June 2003 to April 2010, TLV received 30 requests for orphan drugs reimbursements and awarded reimbursements to 29. However, as pointed by Persson (2012), the fact that Sweden used CED schemes in conjunction with WCEM played an important role in this high rate of approval of orphan drugs.

Applicability to the UK

Much of what is needed to operationalise WCEM for medicines in the UK is already being used by NICE in assessing health technologies. Currently NICE looks only at NHS costs, although it has been suggested that this should be extended beyond just NHS costs (e.g. carers' costs, changes in employment) (Raftery, 2013). The existing process would need to be strengthened to form a suitable vehicle for price negotiation. The UK has defined a broad set of 'value' criteria as part of the VBP public consultation conducted in 2010, which, by and large, have already been taken into account by NICE. However, the international examples of RCE approaches show that only a limited subset of these have been implemented in practice.

This would require the clear definition of:

- What 'value' factors to consider alongside with health gains for patients (as captured in QALY)
- How to measure and value the benefits and costs associated with each 'value' factor
- How to aggregate the value of the several factors
- How to convert the overall measure of value into the maximum price the NHS would reimburse
- The challenge of assessing all current treatments against the new standard

Pricing: Special pricing agreements



What is it? How does it speed up adoption?

In addition to outcome-based managed entry agreements, such as performance-based reimbursement and coverage with evidence schemes, financial agreements also exist to address the uncertainty and high prices commonly associated with new medical innovations.

These can include price–volume agreements (PVAs), which define a threshold of expenditure, or dose/time capping schemes, which applies a cap to expenditure, linked to either time or dosage, after which the manufacturer would pay any additional costs.

Some countries have also used their market power, price sharing and taxation to negotiate lower prices for medical innovations.

International examples



In 2003, Australia launched its first non-outcome-based agreement, and by 2013, 71 medicines were designated with special pricing agreements. For example Australia pursues expenditure caps for certain drugs, such as etanercept for rheumatoid arthritis, where authorities agreed to cover AUS\$100 million a year and the manufacturer picks up any additional costs (Walker et al. 2012)



In France, the cost of Sovaldi, a Hep C drug, was negotiated down by 27% (from \$71,100 to \$51,400 per 12-week regimen). This was achieved through sharing price information with 13 other European countries, and selectively taxing drug makers when the total cost of their medicines exceeded a certain amount each year. While France got the cheapest price, other European countries (including the UK) also benefited from the lower prices.



The Italian national health system has adopted several special pricing agreements including discounts, price-volume agreements and ‘AIFA notes’ – which limit reimbursement of the relevant drugs to population subgroups. Underpinning many of these interventions is a sophisticated drug monitoring registries system, which aim to generate data to ensure the appropriate use of drugs. It is also important to note that of the 78 therapeutic indications that have special pricing agreements, 28 also have performance-based reimbursement strategies linked to them.

Pricing: Special pricing agreements



Strengths and weaknesses

In combination with performance-based mechanisms, these interventions have the potential to address budget impact and use, access and cost-effectiveness assessments – ultimately helping to speed up adoption.

Special pricing agreements offer flexibility in assessing new medical innovations, allowing uncertainty and costs to be reduced.

Research shows that the majority of special pricing agreements are for cancer and auto-immunity drugs.

Pricing arrangements also allow the pricing to reflect the production costs because standard prices for every dose provide a small return in the short-term and then a higher return in the long term.

Pure financial agreements often fail to take into account health outcomes, and many of these mechanisms should be integrated into wider efforts to generate evidence on effectiveness.

A proliferation of special pricing agreements may result in manufacturers submitting higher unit costs for new medical innovations, through anticipating potential cost reductions.

A lack of transparency on many of these pricing agreements makes it difficult to generate cross-country findings.

What is the evidence?

Evidence sources for the effectiveness of these interventions in speeding up the adoption of new medical innovations remains limited.

According to Ferrario and Kanavos (2015) ‘there has been no published evidence comparing the different approaches used by countries to improve access and no comparison of governance structures around MEAs with the aim of explaining their implementation’.

In addition, the confidential nature of many of these pricing agreements means that the evidence base for evaluations across countries is low.

Applicability to the UK

The UK pursues a number of different pricing agreements. For example, capping schemes exist in the UK – such as Lenalidomibe, a drug for multiple myeloma, where the manufacturer pays for the cost of the drug if more than 26 cycles are needed. Discounts are also applied to certain drugs, such as Sunitinib for the treatment of renal cell carcinoma, which is provided for free for the first cycle.

Due to relatively free pricing policies, price negotiations may not be applicable to the UK. It is important to note, however, that price negotiations are often a lengthy process and that time limits for pricing and reimbursement decisions, as set by the EU Transparency Directive, are regularly exceeded by Member States.

Enabling factors

Many of these interventions are underpinned by a series of enabling factors in addition to the need for a conducive policy context and interventions which aim to stimulate initial innovation. While these factors are not interventions, they were identified by a number of interviewees as important elements in accelerating the adoption of medical innovations.

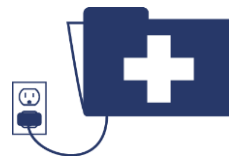
Policy interventions can be used to tackle different aspects of innovation, and they occur at various stages of the innovation pathway, from the interventions to stimulate R&D through to development, approval, implementation and diffusion of innovations in healthcare. Prior to obtaining proof-of-concept, an evaluation of which is outside the scope of this study, the right environment is needed to stimulate R&D and develop medical innovations. While supply-side incentives have traditionally formed the basis for the majority of policies to encourage innovation, innovative demand-side policies, such as innovation prizes and innovative procurement, may incentivise further medical innovation (Love & Hubbard 2009).

To support the interventions discussed above, we outline three enabling factors in the health system that are useful:



Clinical trial infrastructure

- Patient recruitment, retention
- Spillover effects



Data infrastructure

- Electronic health records
- TeleHealth
- Data linkage



Clinical culture

- Variations in prescribing practices

Clinical trial infrastructure



Having affordable and accessible clinical trial infrastructure, underpinned by a system that supports high recruitment into clinical trials and ensures transparent and efficient approval processes, is crucial to accelerated access to new medical innovations.

Patient recruitment can account for 50–60% of a clinical trial timeline and up to one-third of a trial's costs, so interventions that improve recruitment are crucial (Europe Economics, 2012).

A number of studies have also shown that the adoption of new medical innovations is increased in situations where clinicians are closer (whether geographically or socially) to where the clinical trials took place.

Europe Economics (2012) note that 'not only is there an information spillover effect, but the skills to administer new treatments are more likely to be in place if physicians have been involved in the development process'.



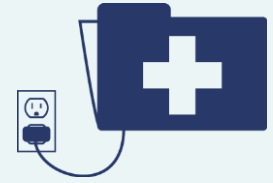
Policy interventions into clinical trials have a direct impact on the adoption times of new medical innovations. Lambers Heerspinck et al. (2008) suggest that 'the introduction of the European Union Clinical Trials Directive appears not to shorten the duration of regulatory procedures within Europe [and that] the duration of regulatory approval procedures is shorter in the U.S. compared with Europe'.

A recent Association of the British Pharmaceutical Industry (ABPI) paper also noted that 'around 80% of clinical trials do not meet patient recruitment timelines, and on average last 30-42% longer than companies initially plan for' (ABPI 2014).

Some have noted that the UK could consider moving towards a centralised trialling system which may improve recruitment rates and reduce the costs of clinical trials. However, more centralised systems may result in fewer and less varied trials (Europe Economics 2012).

Others suggest that advances in technologies, such as social media, e-health and data monitoring may help to improve recruitment, retention and engagement of patients in clinical trials (Shah 2013).

Data infrastructure



Many of the interventions outlined above rely on the ability to ensure that new medical innovations continue to be safe and effective post-launch, which requires robust, effective data systems.

A well-managed data system that can capitalise on the benefits of electronic health records (EHR), home-monitoring and/or telemedicine devices can allow for better monitoring and evidence assessments to take place throughout the adoption pathway, thus ensuring accelerated adoption of drugs, devices or diagnostics.

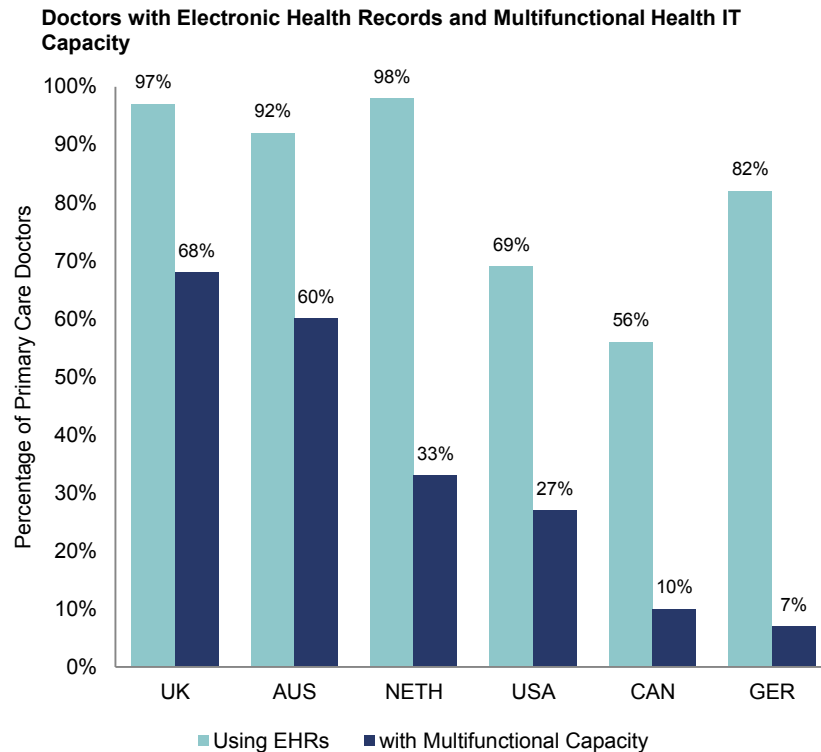
There are a number of challenges with implementing comprehensive data systems. According to our interviewees, the UK is considered to have good data systems but linkage among databases is limited.

A systematic review of barriers to the acceptance of EHR found eight major categories, namely: financial; technical; time; psychological; social; legal; organizational and change process (Boonstra & Broekhuis, 2010).

Nordic countries have particularly comprehensive health registers, which collect data on risk factors and health and health outcomes, and which can be linked to other registries and events in both the past and the future.

One interviewee noted that the 'UK struggles to connect data on drugs in the pipeline with healthcare priorities'. A recent ABPI (2014) study also noted that 'Other countries have more comprehensive and complete anonymised medical data available for healthcare research than the UK' (ABPI 2014).

In relation to EHRs, a recent US study showed the UK to be performing well compared with other countries: 97% of primary care doctors were using EHRs, of which 68% were multifunctional. The multifunctionality of EHRs is important because it can allow for the generation of patient information, such as lists of patients' medications; generation of patient registry and panel information, such as lists of patients due for preventive care; order entry management, such as electronic prescribing; and decision support, such as alerts about potential adverse drug interactions.



Source: Porter (2013) *Adoption of Electronic Health Records in the United States*

Clinical culture



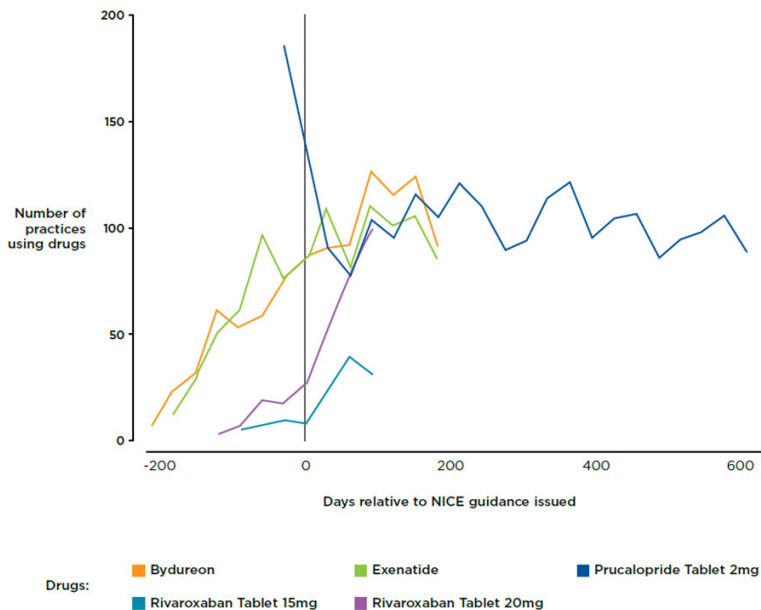
Finally, a conducive environment for approved drugs to be taken up and diffused throughout a country is an important enabler in the later stages of adoption.

In the UK, once drugs, devices & diagnostics obtain market authorisation and are issued under NICE guidance, there is still variation in adoption and diffusion.

A number of interviewees noted that the culture of prescribers in the UK can be quite conservative, thus slowing down the adoption of new innovations. Efforts to engage clinicians in research were seen as a key to improving adoption rates.

While drug usage can vary considerably both among countries and across different regions within a country, 'it is important to recognise that there is uncertainty about the optimum level of drug usage in different disease areas and the extent to which high or low usage point to inappropriate use' (Nolte & Corbett 2014).

Adoption rates of selected drugs relative to issuing of NICE guidance



Source: NESTA (2014) *Which doctors take up promising ideas?*

Lublóy's (2014) systematic review of factors affecting medicine uptake highlights both:

- **Prescriber-level factors:** doctors' scientific orientation, prescribing habits, exposure to pharmaceutical marketing, and interpersonal communication.
- **Patient-level factors:** doctors with younger patients, patients with higher socioeconomic statuses, and/or patients with poorer health statuses were more inclined to prescribe new drugs early.

A recent Nesta study (Stokes et al. 2014) on the early adoption of promising new ideas in primary care stressed the importance of local intermediaries such as Academic Health Science Networks and Clinical Commissioning Groups, in accelerating adoption.

The study found that GPs ranked **availability of evidence** and **platforms for engagement with other clinicians** to discuss new innovations highly as key factors in enabling the adoption of new innovations at their practice.

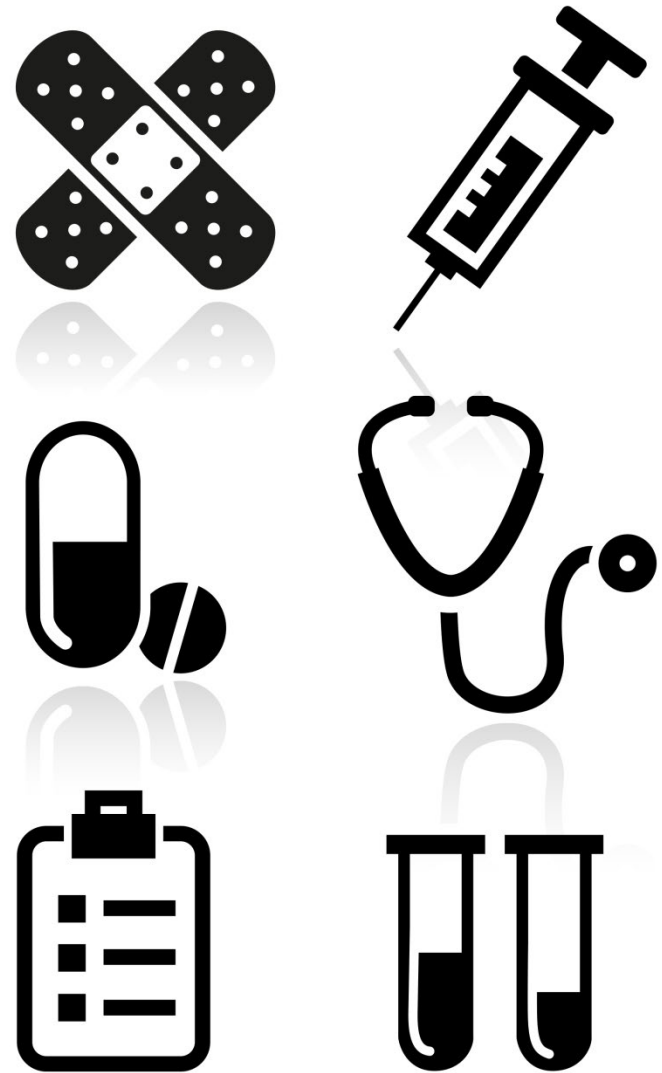
There are many more studies on the uptake of medicines than on medical technologies/diagnostics.

Interventions can be combined

As noted above, the interventions we identified were split into four conceptual groups, as each example has different repercussions on the stakeholders in the health system.

However, many of these interventions often occur in parallel and are not mutually exclusive. Here we briefly discuss:

- Interventions that are combined for a specific disease
 - Ebola
- Interventions that are combined under one concept
 - Value based pricing
 - Adaptive Pathways pilot



Interventions can be combined for specific diseases:

Lessons from Ebola

The recent Ebola outbreak in West Africa highlights how some of the interventions discussed above have been used to accelerate the adoption of medicines for a particular disease. The proposed interventions are discussed below:

Process improvement

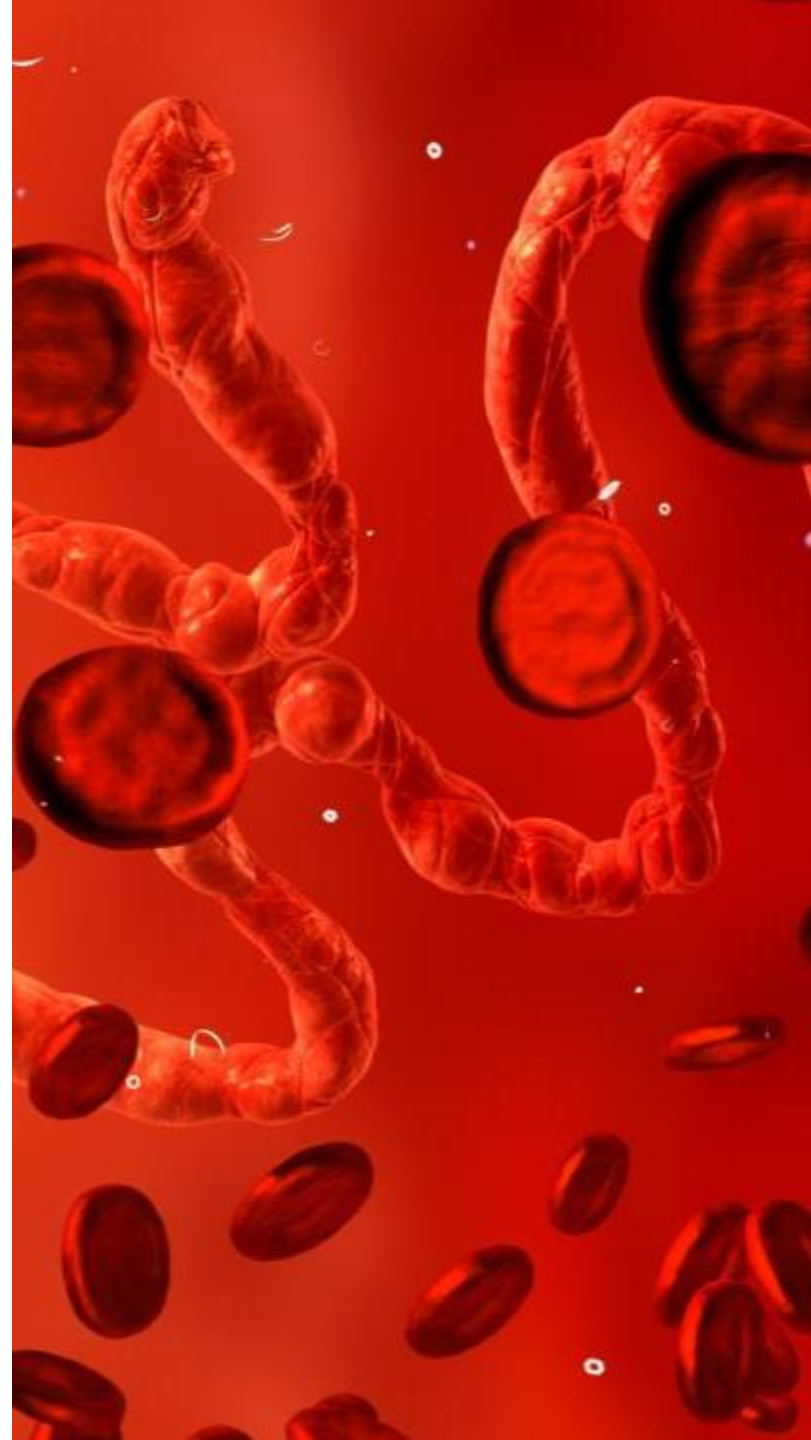
- In the US TKM-Ebola, an experimental drug treatment developed by Tekmira, was granted '**Fast-track**' status (FDA) to expedite its approval.
- In the EU, the EMA has encouraged developers of Ebola treatments/vaccines to apply for 'Orphan Drug' designation (EMA 2014). This designation ensures that further resources are provided by the EMA, including free scientific advice, fee waivers and 10 years of market exclusivity post-authorisation.

Risk sharing

- As previously noted, the '**Animal Rule**' will also be used by the FDA as an instrument that will be applied in an eventual approval of treatments against Ebola. TKM-Ebola is currently being developed under the 'Animal Rule'.
- The FDA's **Expanded Access** protocol to allow compassionate use of drugs pre-market approval has also been applied to TKM-Ebola.

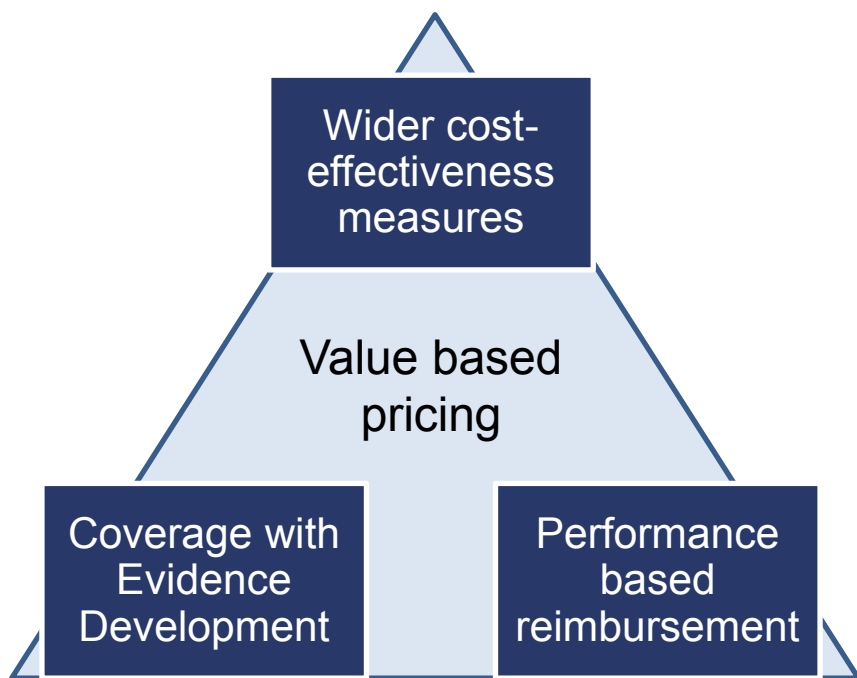
Process linkage

- The EMA has also encouraged developers to apply in parallel to both the FDA and the EMA. Both organisations are working closely on sharing information, helping to spread resources and avoid duplication across countries.
- Orphan designation also encourages early engagement among regulators and developers.



Interventions can be combined under one concept:

Value-based pricing



Value based pricing (VBP) at its essence is a method of setting up prices of medicines based on perceived benefits to the patients and the wider society (Persson et al. 2010).

Conceptually this combines both performance-based reimbursement strategies (risk-sharing) and a widening of cost-effectiveness measures (pricing).

Countries that use VBP also tend to employ review mechanisms, such as coverage with evidence development (CED), to ensure that decisions taken initially under great uncertainty remain valid.

VBP creates a set of incentives affecting the behaviour of both pharmaceuticals and the NHS (or its international counterparts), ultimately affecting the adoption pace of new medicines. By considering wider benefits along with clinical effectiveness, VBP affects the behaviour of pharmaceutical companies with respect to R&D, pricing and launching strategies.

As previously noted, evidence from Sweden suggests that a VBP scheme may be well placed to speed up the adoption of innovative medicines when used in conjunction with CED schemes (Persson 2012).

PBR schemes are used with WCEM as part of Italy's VBP approach. In particular, registers have been set up 'to monitor prescribing against licensed indications as well as monitor their therapeutic value in practice to guide future management and reimbursed prices' (Adamski et al. 2010).

Interventions can be combined under one concept:

The EMA's Adaptive Pathways pilot

The adaptive pathways approach (formerly known as 'adaptive licensing') is part of the European Medicines Agency's efforts to improve timely access for patients to new medicines.

The concept builds on the idea of adaptive licensing which is defined as follows:

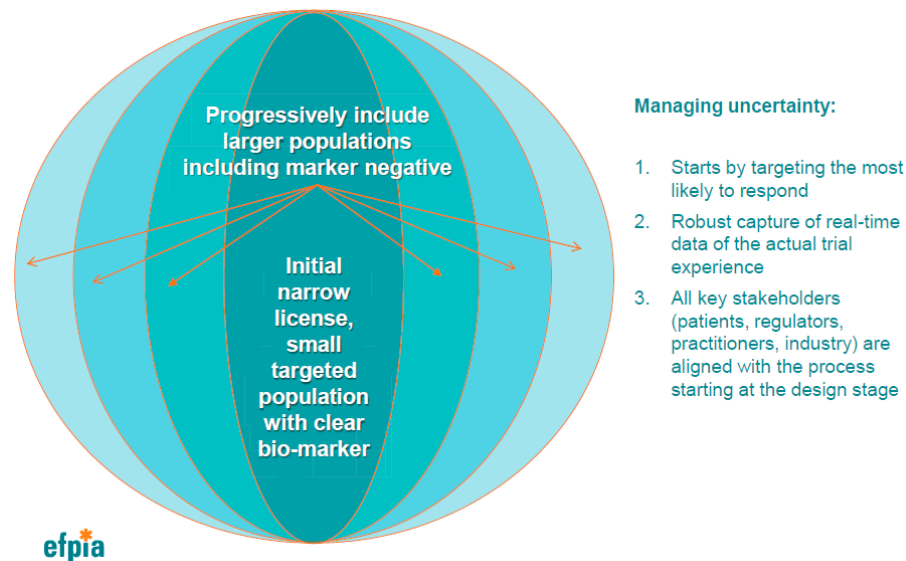
The Adaptive licensing is a prospectively planned, flexible approach to regulation of drugs and biologics. Through iterative phases of evidence gathering to reduce uncertainties followed by regulatory evaluation and license adaptation, AL seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with the need to assess and to provide adequate evolving information on benefits and harms so that better-informed patient care decisions can be made. (Eichler et al. 2014)

More recently, the concept has been expanded to the Medicines Adaptive Pathways to Patients (MAPPs) approach. In addition to regulatory aspects of access, this now also includes post-market authorisation decisionmaking and appropriate use in clinical practice.

The proposed pilots combine:

- **Risk-sharing** – through combining early access, non-standard authorisation and coverage with evidence schemes.
- **Process linkage** – through early engagement with key stakeholders such as regulators, payers and industry.

An example of how MAPPs could work in practice



NRDD vol. 10, July 2011

Source: Schulthess, et al. (2014). *Medicine adaptive pathways to patients (MAPPs): using regulatory innovation to defeat Eroom's law*

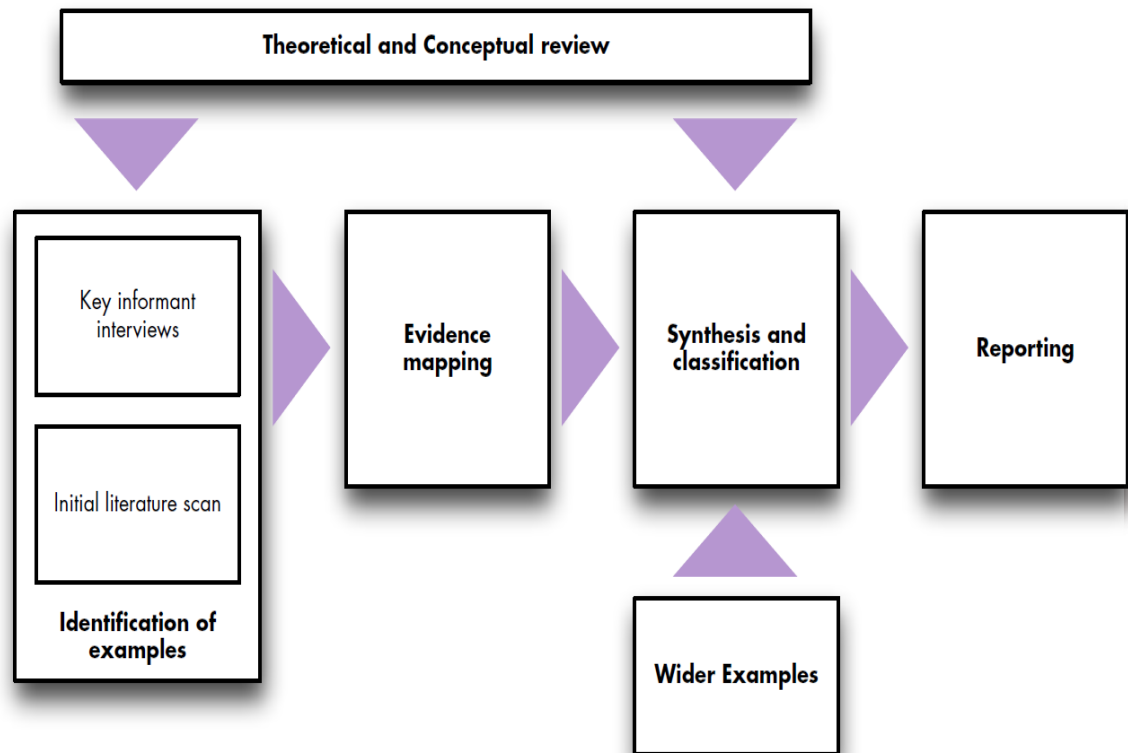
Methodology

Theoretical and conceptual review. The first phase of this study focused on understanding the theoretical foundations that underpin the adoption of innovative medicines and medical technologies. This initial stage was used to develop interview protocols and search terms for the subsequent phases of the research.

Identification of examples. We conducted 20 key informant interviews with a range of stakeholders, including industry, academia and practitioners, to collect their suggestions of different international examples of processes that have accelerated the adoption of innovative medicines and medical technologies and to examine the barriers to and opportunities of transferring these examples into the UK health system.

Evidence mapping. Focusing on suggestions from the previous stage, and covering the three areas of interest (drugs, devices and diagnostics), we reviewed various academic, grey literature and policy sources to assess the current evidence and international experience around a given topic. The evidence gathered in this stage was used to validate and triangulate findings from the key informant interviews.

Synthesis and classification. Based on the evidence collated we developed a set of case studies for the 11 interventions identified.



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