

*Accelerated Access
Review: Proposition 2:
Getting ahead of the
curve*

&

**Recommendations
for accelerated
access pathways and
a flexible pricing
and reimbursement
framework**

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Executive summary



All the proposed pathways seek first and foremost to deliver faster patient access to safe and effective innovative medical technologies

This report summarises Strategy&'s independent recommendations which have been developed in support of the Accelerated Access Review (AAR). *The Strategy& work focused on two areas in Proposition 2: Getting Ahead of the Curve – area 1, developing accelerated access pathways and area 2, a flexible pricing framework for medicines, companion diagnostics, medical devices, and digital products. The AAR team will consider our recommendations before publication of the final report, due in April 2016. The Strategy& recommendations reflect feedback from over 150 stakeholders and consider how accelerated access can deliver innovative medical technologies with the patient at the centre.*

We have developed separate pathways for each of the medical technologies to reflect differences in regulatory and reimbursement pathways. We estimate that for medicines, implementation of the recommendations could result in one to six years earlier access post-MA, with potential for additional access pre-MA via the Early Access to Medicines Scheme. In revenue terms, this implementation could deliver additional sales from £11 million for an orphan indication, to £525 million for a product targeted at a larger population.

In addition, once the RWD (real world data) infrastructure and standards of care improve in the UK, we estimate that companies could save about £80 million in the costs of conducting these studies across the EU. Although the focus of our report is on improving these pathways for the most transformative products, we expect that streamlining the current processes will benefit all products launching in the UK market.

We have grouped the medical technologies into (1) medicines, (2) companion diagnostics, (3) medical devices including non-companion diagnostics, and (4) digital products including apps.

All the proposed pathways seek first and foremost to deliver faster patient access to safe and effective innovative medical technologies; patient safety will not be compromised. *The feedback from stakeholders reflects*

that the UK has set up some positive initiatives to improve clinical trial infrastructure and better support for medical device innovators with business case creation. However, the feedback also reflects the need to further strengthen infrastructure for data collection across the pathway, whether economic or clinical, for all medical technologies. In addition, stakeholders commented that a seamless pathway to patient access was required across the different stages of the pathway, and particularly to incentivise uptake of innovation by the NHS. Bureaucratic tendering and pricing mechanisms also were highlighted. Although the Strategy& work did not focus on how to incentivise uptake of innovation post-Health Technology Assessment (HTA), the proposed flexible pricing framework should help facilitate this.

First, for the proposed medicines pathway, post-early dialogue with key stakeholders, we recommend improving the value of the Early Access to Medicines Scheme (EAMS) by strengthening the signal of the Promising Innovative Medicine (PIM) designation with input from all relevant stakeholders, suggesting some level of funding pre-Marketing Authorisation (MA), and building on the existing clinical trials and Real World Data (RWD) infrastructure. In addition, we propose near-parallel regulatory review and HTA, followed by funding within the NHS on publication of the draft HTA recommendation. The HTA recommendation could either be a permanent or temporary funding decision, depending on the extent of evidence available.

Second, the proposed medical devices pathway establishes a mechanism by which innovators, providers, and patient groups come together to form partnerships to characterise the likely impact of a potential medical device on the healthcare system. On the basis of this potential impact summary, a product would be awarded a Promising Device designation. This would enable the collaborators to apply for funding from public and private sources, and access different initiatives across the NHS to collect clinical and economic evidence to develop a business case. The clinical evidence will contribute to the information required by Notified Bodies and the MHRA for CE marking. We then propose that there exist a national-level HTA of the business case associated with a funding decision.

Third, for companion diagnostics, we propose a forum in which pre-competitive collaborations flourish so that biomarkers are identified and validated in collaboration with academia, and with diagnostic/medicine innovators before commercial development commences. This forum should strengthen diagnostic and medicine innovator collaborations so that during medicines clinical trials, the companion diagnostic also is validated in advance of obtaining its CE (Conformité Européene, European Conformity) mark. This parallel development would result in

the companion diagnostic having its CE mark by the time the medicines innovator is due to submit its regulatory submission package to the regulator. This would allow the HTA process to consider the companion diagnostic whilst reviewing the medicine so that any diagnostic with the required functionality receives funding direction.

Lastly, for digital products we propose that the National Information Board (NIB) 1.2 process is used to identify the digital apps on the horizon that meet the needs of the NHS. Digital innovations may be validated via innovation exchanges. Following self-certification, based on a robust business case, we propose a similar process as for medical devices with a national-level HTA associated with a permanent or temporary funding decision. It is likely that the remaining digital products that impact patient diagnosis or treatment will come under the definition of a medical device and therefore will follow our proposed medical devices pathway.

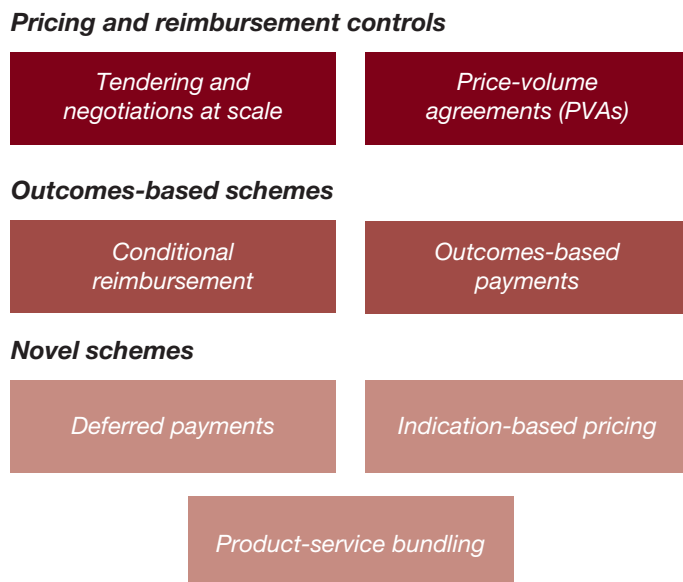
The proposed pathways will be supported by a flexible pricing and reimbursement framework available to all innovators with medical technologies under consideration for accelerated access. It is likely that other innovators, such as the broader non-accelerated access group, may benefit from this framework; but, the Strategy& work has focused on the former. The pricing schemes within the framework seek to balance affordability and budget predictability with risk-sharing around outcomes and recognition of innovation whilst increasing and accelerating patient access. It is recognised that within a fixed budget envelope, there may need to be prioritisation of resources if uptake of innovation is to be supported. Innovators proceeding on the accelerated access pathway will need to consider scenarios as early as is feasible to determine which of the pricing and reimbursement framework schemes will achieve the required cost-effectiveness during the HTA process. Additional pricing schemes may be product-specific e.g., for products targeting dementia, ultra-orphan products, and products to treat anti-microbial resistance, and those which will need to be discussed on a case-by-case basis. Our analysis across the different groups of medical technologies indicates the wide applicability of the different schemes within the flexible pricing and reimbursement framework. (See Exhibit 1 below for the flexible pricing and recommendation framework, next page.)

Should the AAR team adopt some of the Strategy& recommendations, we believe that a whole-system approach will be required with all stakeholders collaborating to deliver change in the coming months and years. There is a need for a cultural shift accompanied by the right incentives so that everyone across the system benefits from the proposed changes – from patients, to NHS procurement, to providers, to innovators. Innovators are committed to investments in the UK RWD infrastructure with the expectation of accessible, high quality, robust data that can be used in

A whole-system approach will be required with all stakeholders collaborating to deliver change in the coming months and years.

Exhibit 1

The recommended flexible pricing and reimbursement framework



Source: Strategy& analysis

other European HTA submissions. Furthermore, the intention of the accelerated access pathways is to bring products that can transform the care of UK patients earlier to the market, which means that these products will need to be managed carefully to protect patients whilst improving their care. We envisage that patients will need clarity about the process, including about the advantages of early access, whilst prescribers and other healthcare professionals will need clear guidance on the use of these products. The pathways will offer full acceleration of those products identified via early dialogue, and, we believe that streamlining the processes, will benefit other products.

The AAR could not have come at a more opportune time, given that many other countries across the globe are focusing on improving uptake of innovation whilst balancing budgets and encouraging innovators to perform clinical research within their healthcare systems. Many companies are likely to benefit by improvements made to the pathway even if they will not benefit from the full acceleration. Should the UK be successful, as a whole system, the benefits will more than outweigh the effort. In fact, the success would level the playing field between the UK and other EU countries such as France and Germany, which are leading the way with early access and strong uptake.

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Purpose of report and scope of recommendations

The Accelerated Access Review (AAR) focuses on how NHS patients can benefit from accelerated access to innovative products

The UK government announced the launch of the AAR in November 2014. The review was initiated in 2015. Specifically, the purpose of the review is to:

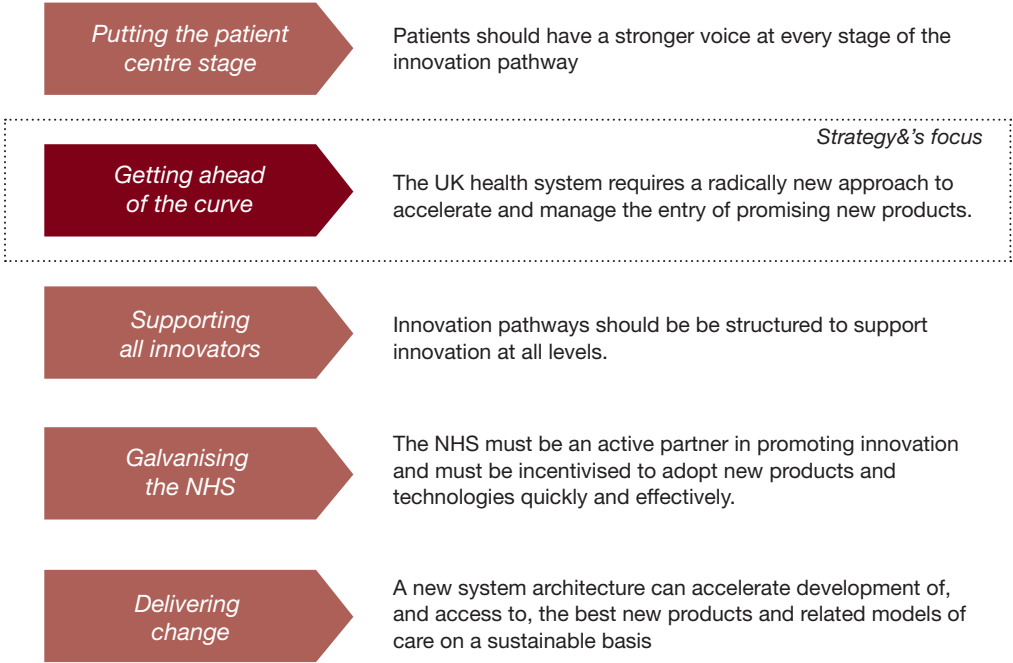
‘Ensure that NHS patients benefit from earlier access to innovative drugs, diagnostics and devices, and help Government lead the global race for life sciences investment by making the UK the best place for 21st century medical innovation and product development’. – Department of Health

The AAR’s interim review report, published on 27th October 2015, described the vision for a ‘lit runway for innovation’. The report highlighted five propositions that set out the AAR’s vision in more detail and described the areas of focus for the next stage of the review.

Strategy& is supporting proposition 2: getting ahead of the curve (*see Exhibit 2, next page*). The work on devising a flexible pricing and reimbursement scheme was funded by the Wellcome Trust.

Exhibit 2

Strategy&'s focus on proposition 2 of the AAR, Getting Ahead of the Curve



Source: Strategy& analysis

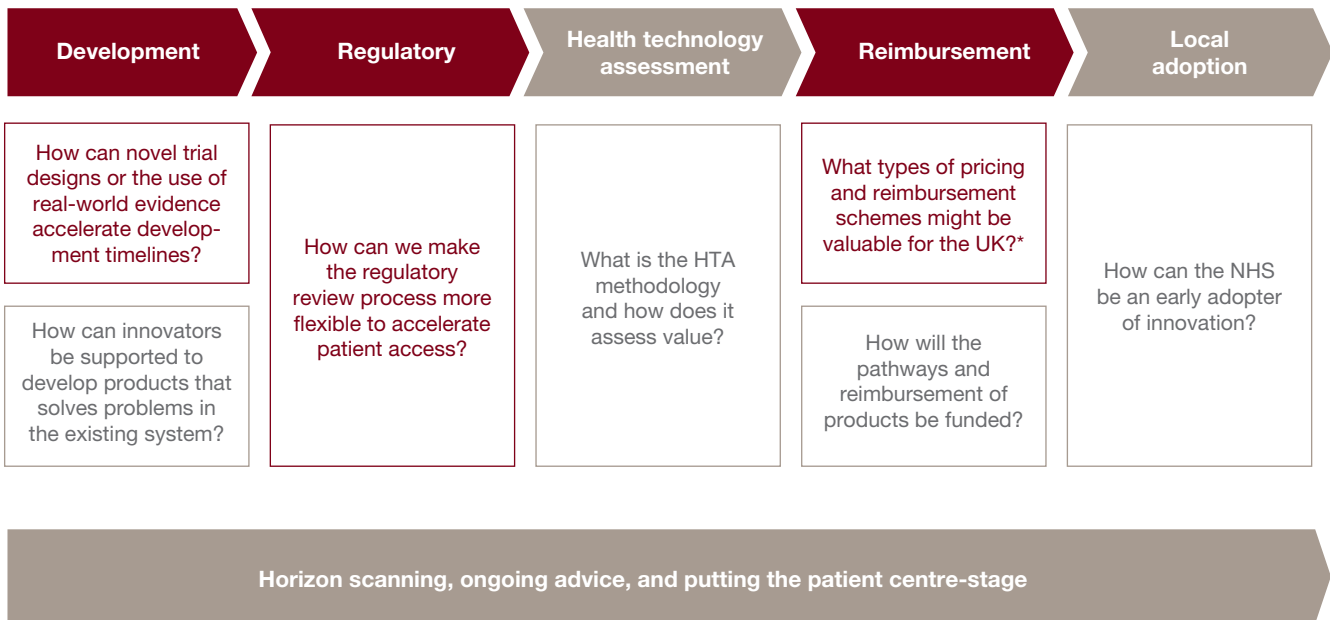
The Strategy& work proposes accelerated access pathways and a flexible pricing and reimbursement framework

The Strategy& independent recommendations seek to answer specific questions posed by the AAR team. (See Exhibit 3). The recommendations propose accelerated access pathways for each group of the medical technologies and summarise which of the pricing and reimbursement practices across the globe could be applied to the UK context to create a flexible pricing and reimbursement framework. These recommendations act as input to the AAR team’s work.

Exhibit 3

Strategy& recommendations focus on use of novel trial design and RWD, use of regulatory flexibilities and flexible pricing and reimbursement schemes

Accelerated access pathway



*How do we support innovators and help them navigate the regulatory, HTA, and local payer environment?
How can we improve the use of patient-led outcomes and ensure that patients understand the decision-making process?*

■ Strategy& focus ■ AAR team focus

*Any recommendations made are not intended to implicate the current Pharmacy Price Regulation Scheme (PPRS), nor do they intend to preempt any future PPRS negotiations, both of which are outside the scope of the AAR.

Source: Strategy& analysis

Methodology

Strategy& input into the Accelerated Access Review has been provided on an independent basis and takes into consideration stakeholder views captured via interviews, workshops, and presentation events.

In developing the accelerated access pathways, our approach has been to:

- *Review the current development, regulatory, reimbursement, and NHS adoption route for medical technologies in the UK, highlighting existing initiatives demonstrating leading practice and areas for further acceleration.*
- *Consider the proposed recommendations made in independent review of the UK's Early Access to Medicines Scheme, identifying opportunities for alignment.*
- *Incorporate and build on EU-wide legislative and regulatory changes, e.g., the proposed EU PRIME designation and upcoming revision of the Medical Device Directives.*
- *Share, test, and refine the proposed accelerated access pathways for the different medical technologies (medicines, companion diagnostics, medical devices, and digital products) to gain broad consensus across industry, government, and patient organisations.*

Supporting the proposed accelerated access pathways is a flexible pricing and reimbursement framework. To develop this, our key steps have been to:

- *Review international pricing and reimbursement schemes and understand their applicability to the UK, with findings published in this Case Study Report.*
- *Prioritise possible pricing and reimbursement schemes with stakeholders via workshops and an open-access survey launched on the Department of Health's Engage platform.*

Strategy& input into the Accelerated Access Review has been provided on an independent basis and takes into consideration stakeholder views captured via interviews, workshops, and presentation events.

- *Identify the component schemes which contribute to the flexible pricing and reimbursement framework and develop a set of principles for how the framework could operate in practice.*

In total, Strategy& has taken into consideration the views of industry, industry associations, patient groups, government, and arms-length bodies as part of this review. Our engagement with these stakeholder groups has been as follows:

- *Over 200 one-to-one interviews with input from approximately 150 individuals across 68 organisations.*
- *Ten workshops capturing insights from the perspective of patients, industry and government and arm's length bodies.*
- *Five presentations sharing and validating recommendations with industry, government and arm's length bodies, the devolved administrations, and the Accelerated Access Review Expert Advisory Group.*

A list of the organisations we have engaged with can be found in Appendix C.

Our primary research is supplemented by a review of over 30 peer-reviewed publications, government position papers. and industry policy positions. The desktop research focused primarily on:

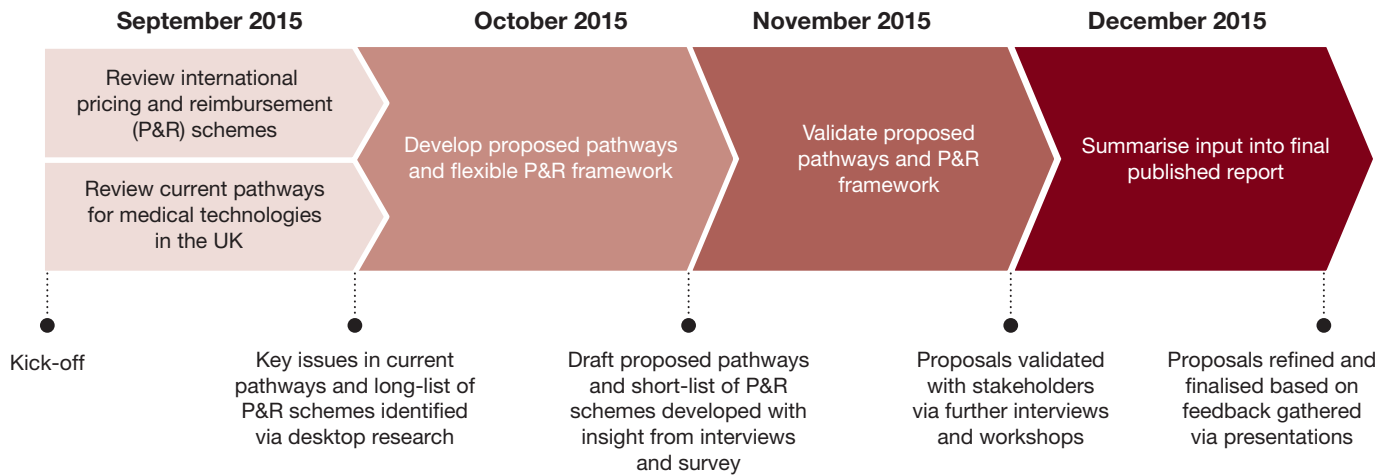
- Types, applicability, and limitations of novel clinical trial designs
- Examples of novel clinical trial designs and usage
- EU regulations
- EU payer systems and mechanisms
- Case studies and examples of innovative pricing and reimbursement schemes in different countries
- Use, needs, and limitations of real-world evidence
- Innovator pipeline products

An overview of the timeline of our approach is detailed in *Exhibit 4, next page.*

Strategy& has taken into consideration the views of industry, industry associations, patient groups, government, and arms-length bodies as part of this review.

Exhibit 4

Timeline for development of pathways and reimbursement framework



Source: Strategy& analysis

In addition, to the material above, three case studies provided a basis for estimating potential quantitative benefits for acceleration. The confidential and proprietary information shared by pharmaceutical and biotech companies included case studies -- an orphan indication, a niche oncology product, and a mainstream medicine. Because the estimates from the case studies were based on sensitive, confidential material, details of case study content published here is limited, as per agreement with the companies providing data, and in keeping with standard ethical guidelines.

Finally, via a series of presentations and workshops, these proposed recommendations have been shared with government, arm's length bodies, the devolved administrations, trade associations, and industry. Feedback from these stakeholders have been taken into consideration in this report.

Medical technologies overview

Medical technologies include medicines, companion diagnostics, medical devices (including non-companion diagnostics), and digital products

The Strategy& recommendations span all medical technologies encompassing medicines, companion diagnostics, medical devices and digital products. *(See Exhibit 5, next page.)*

Whilst developing our recommendations, we have considered how archetypal products may progress through the pathway, covering a wide range of potential therapeutic categories. For example, we have considered innovations including: ketolides for macrolide-resistant respiratory tract infections, an anti-CD38 molecular diagnostic test and an associated anti-CD38 monoclonal antibody for multiple myeloma, an artificial pancreas device for diabetic patients, and a digital support service for people suffering with mental health conditions.

We have considered how archetypal products may progress through the pathway, covering a wide range of potential therapeutic categories.

Exhibit 5

Archetypal products under each of the medical technology groups to indicate the types of products that could be considered for accelerated access and the flexible pricing and reimbursement framework

Medicines

Archetypal products:

Products for chronic conditions

- 5-HT6 antagonists for Alzheimer's disease
- PCSK9 inhibitors for familial hypercholesterolemia
- Anti-Interleukin-5 (IL-5) monoclonal antibody for asthma and chronic obstructive pulmonary disease (COPD)
- Sodium-glucose cotransporter-1/2 (SGLT1/2) inhibitor (gliflozin) for diabetes mellitus

Anti-infective products

- Ketolides for macrolide-resistant, community-acquired respiratory tract infections
- Protease and nucleoside polymerase inhibitors for hepatitis C

Products to treat less common conditions in a secondary-care setting

- Anti-CD20/25 monoclonal antibody for relapsing-remitting multiple sclerosis
- Autologous, Chimeric Antigen Receptor T-cells (CAR-T) for acute lymphoblastic leukaemia
- B-cell lymphoma 2 (Bcl-2) inhibitor for chronic lymphocytic leukaemia (CLL)
- Neuroprotective medicine for spinal muscular atrophy (rare disease, also in children)

Companion diagnostics

Archetypal products:

- Anti-CD38 diagnostic and anti-CD38 monoclonal antibody for multiple myeloma
- Beta amyloid diagnostic and anti-beta amyloid monoclonal antibody for Alzheimer's disease

Medical devices

Archetypal products:

- Artificial pancreas device for Type I diabetes mellitus
- Molecular diagnostic test for melanoma
- Balloon catheters for treatment of peripheral artery disease (PAD)
- 3D-printed heart for pre-surgical preparation

Digital products

- Assistive device with digital interface that improves quality of life of patients with spinal cord injuries
- Digital-support service for people suffering with mental health conditions
- Chip that alerts emergency services when an individual does not get up from a fall within 30 seconds

Source: Strategy& analysis

Proposed accelerated access pathways

All the accelerated access pathways have been developed with a common set of principles in mind

Based on Strategy& discussions with all the key stakeholders across industry, government, NHS and patient groups, we have developed some common principles that we have applied in the proposed accelerated pathways.

The accelerated access pathways should:

- *Deliver faster patient access to safe and effective innovative medical technologies*
- *Reduce the cost of drug development and/or time to revenue realisation for industry whilst improving or maintaining the quality of medicines*
- *Facilitate the identification of promising products while allowing unsuccessful products to fail fast, further reducing potential time and cost*
- *Receive buy-in from wider stakeholders including DH, NHS, and patient advocacy groups*
- *Enable the UK to take a leading position for accelerated access in Europe, supporting schemes such as EMA's PRIME designation*
- *Foster an attractive environment for SMEs and large companies to make the UK an early and key market for developing and launching their products*
- *Enable flexibility for innovators, payers, and NHS through pricing and reimbursement mechanisms that balance innovation and affordability*

We have developed some common principles that we have applied in the proposed accelerated pathways.

The pathways span product development, HTA, and uptake within the NHS

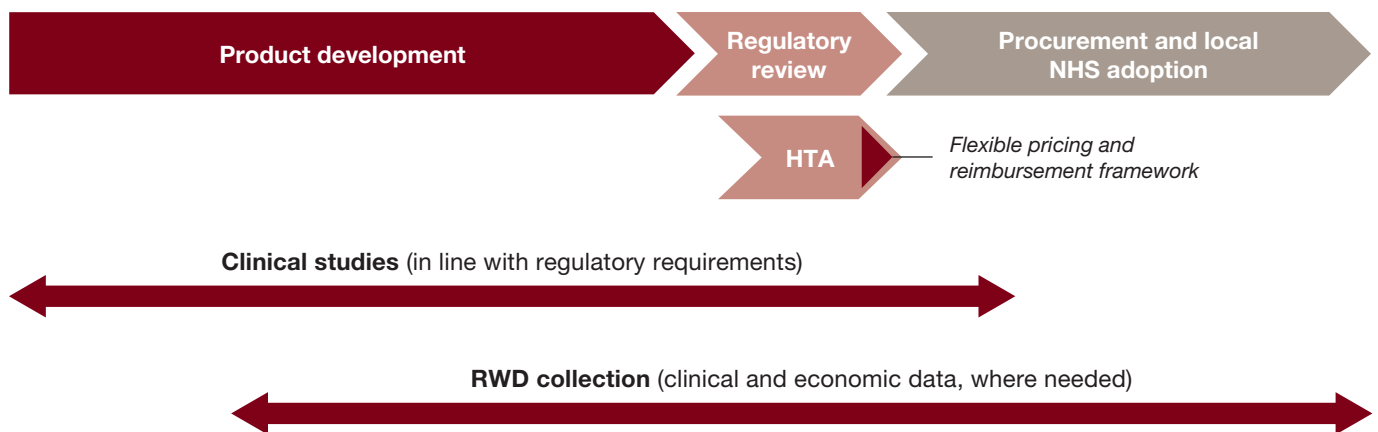
Across the medical technologies pathways, we describe how the UK potential accelerated access pathway could look from product development to regulatory review (Marketing Authorisation or CE mark, as appropriate), to HTA, to NHS uptake. (See Exhibit 6.)

We pick up the pathway after early dialogue with key UK stakeholders including the patient view represented by patient groups. This will help identify priority areas for the UK stakeholders. Thereafter, Strategy& analysis focuses on the development, regulatory, and reimbursement aspects of the accelerated access pathways (outlined in Exhibit 3, see page 9) as well as on a consideration of clinical and RWD studies which may be needed to support the pathways.

Strategy& recommendations will complement and feed into the broader work of the AAR team who also are considering recommendations relating to upfront horizon scanning, early and ongoing dialogue with key stakeholders. and local NHS adoption.

Exhibit 6

The proposed core components of the UK accelerated access pathways across medical technologies



Notes: The exhibit illustrates the common elements of the proposed UK accelerated access pathways for medicines, companion diagnostics, medical devices and digital products; detailed pathways for each of the medical technologies are exhibited in subsequent sections of the report. It is not possible to provide indicative durations of the different steps at this aggregate level given the variability of the speed of development across medical technologies.

Source: Strategy& analysis

Medicines pathway

Summary of Strategy & input into the AAR:

The intention of the UK is to position itself as a leading destination for industry to conduct clinical trials and collect real-world data to support EU-wide regulatory and reimbursement approvals for medicines. In order to achieve this we recommend:

1. The use of the Promising Innovative Medicine (PIM) designation to signal that the innovative medicine will be supported by the key stakeholder organisations in the UK e.g., MHRA, HTA body and NHS throughout the development, review, and uptake process.
2. Better signposting of the existing infrastructure for clinical trials, continuing to build capabilities within the NHS, and encouraging industry to uptake novel clinical trial designs.
3. Improving the Early Access to Medicines Scheme (EAMS) by improving the overall benefits package on offer to industry including funding pre-MA.
4. Use of a flexible pricing framework as part of the HTA assessment and provision of stronger guidance to industry on the expectations of HTA bodies around which of these should be used and the likely price that would be affordable for the NHS.
5. Testing the concept with established databases that collect real-world data to demonstrate how this data can be used to support regulatory and reimbursement decisions.

The intention of the UK is to position itself as a leading destination for industry to conduct clinical trials and collect real-world data.

Stakeholder interviews suggest that there is limited opportunity to accelerate clinical development but reveal an opportunity to reduce the gap to patient access post-MA

Most medicines innovators would not adjust clinical trial designs to reflect UK only requirements but would be prepared to conduct some add-on trials

Large global companies have shared their view that the global nature of clinical development and relative small market size of the UK means that there is limited opportunity for UK stakeholders to influence the global drug development process. However, these companies were prepared to invest to generate data in the UK if their investment would help market access in the UK and potentially in other EU markets. This was in part because of their confidence in the quality of clinical research in the UK and in the importance of the NICE opinion in some countries.

The opportunity was stated to be greater for SMEs and for products with new therapeutic modalities:

- SMEs, focused on gaining market access in a small number of key EU markets (typically the UK, Germany, and France), have shared that UK support and guidance with trial design and evidence generation could influence the direction of the development programme and could potentially shorten the time to revenue recognition. Innovators also see wider value in UK-generated data being used to influence market access decisions in other EU countries and in the US.
- In novel therapeutic modalities, such as advanced cell therapies, we have heard that the clinical development process is maturing and that there is currently no clear process for the HTA. For such therapies, there is an opportunity for the UK to support companies with new modes of evidence generation via novel clinical trial designs.

“We believe there is potential to reduce the drug development timeline via the use of adaptive trial designs. This could be achieved with UK support and build on EU efforts such as the adaptive licensing pilot.” – UK

Catapult Network

“As a small biotech, our priority is to gain access to the UK, German and French markets before considering the US. As such, I see a lot of value in MHRA and NICE guidance to support entry into what is one of our key markets.” – SME

Companies were prepared to invest to generate data in the UK if their investment would help market access in the UK and potentially in other EU markets.

We also heard from industry that there is further scope to improve ethics approvals and study start-up times within the NHS as part of the delivery of clinical data in the UK. In addition, all stakeholders shared that innovators and the UK healthcare system players needed to work together to consider and implement novel clinical trial designs more extensively, to explore whether they could indeed shorten product development timelines. The UK, after all, was home to the pragmatic clinical trial, the Salford Lung Study.

The potential criteria for entry into any UK accelerated access pathway should align closely to EMA's PRIME

The recently announced PRIME designation by the EMA provides innovators with a forum to discuss product development with the EMA and HTA bodies. This could lead to an accelerated regulatory review and potentially lead to an earlier, conditional marketing authorisation. The designation is due to be launched in Q1 2016 and has been welcomed by industry.

Whilst the Accelerated Access Review and UK EAMS is independent of the EMA's PRIME designation, innovators believe that any potential criteria for assessing entry into the UK accelerated access pathway need to closely align to the criteria for PRIME so that global innovators could leverage similar submission packages. The patient view should be taken into account when devising criteria.

“The MHRA has played a central role in the development of the EMA's upcoming PRIME designation and our belief is that the EU-level scheme will complement, rather than conflict, with the UK EAMS.” – MHRA

“Many of our membership companies are global Pharma who may be confused by the offerings of EU PRIME and UK EAMS. Unless the UK EAMS criteria aligns to those for PRIME, these companies will simply not use the EAMS.” – Trade Association

There is an opportunity to shorten the gap post-HTA via early dialogue

Innovators have stated that there is a significant opportunity to accelerate patient access by shortening the gap between the European Commission's MA decision and the HTA recommendation. To achieve this, industry and NICE have both expressed that they would like to engage in earlier dialogue such that draft HTA guidance can be issued immediately after the MA is approved. In addition, the HTA body should be able to recommend at what price medicines will be cost-effective. It would then be up to the NHS to have the discussions on affordability armed with this knowledge.

The recently announced PRIME designation by the EMA provides innovators with a forum to discuss product development with the EMA and HTA bodies.

“I am strongly in favour of early HTA by NICE and closer alignment to the EMA’s regulatory review. This move could reduce one of the major gaps in patient access which currently exists in the UK.” – SME

“We are happy to issue draft guidance as early as on the day of the MA decision. To achieve this, we welcome companies to come to us earlier so that we can conduct the assessment in parallel to the MA review.” - NICE

There are delays in the HTA process as a result of needing to adjust the commercial offer once the draft guidance is issued

Via interviews, we heard that innovators and the NHS need to further their understanding of how to effectively and efficiently use commercial arrangements to generate systems savings and improve patient outcomes, as often the default approach is to avoid outcomes-based schemes or conditional reimbursement because of the administrative burden on both sides

In addition, there was appetite to collect Real World Data (RWD) over the long-term to support UK market access. However, innovators faced several challenges when trying to use the existing infrastructure, which was considered to be patchy and difficult to access in some cases. See RWD section for further details of innovator concerns and opportunities for improvement.

In France the early access scheme, the ATU, is funded. Innovators have stated that they are now considering launching there earlier and collecting RWD – suggesting that the early access scheme has attracted investment into the country.

The lack of funding pre-MA is a barrier to entry for some companies although others were much more focused on the overall package the UK could offer to innovators

Separately, within the UK EAMS, the lack of funding remains a major barrier to entry for some companies. This is particularly the case for some SME and biotech innovators who have raised this as the reason they have not entered the scheme. For them, the cost of the supplying the product pre-MA is a barrier.

There is industry support for a funded early access scheme which recognises the innovator’s commitment to making the product available during the EAMS period. Via interviews and workshops, innovators told us they would like a funding mechanism with the following features:

Innovators faced several challenges when trying to use the existing infrastructure, which was considered to be patchy and difficult to access in some cases.

- Quick and simple to implement
- Confidential and therefore not subject to international reference pricing
- Not linked to the future “price” of the product which should be determined post-MA

“Small and medium sized companies will simply struggle to cover the cost of supplying some of their drugs during the EAMS period [without funding].” – Trade Association

“We are supportive of providing early access, but there should be recognition for the additional risks we take.” – Large Pharma

Uptake in the NHS was the greatest concern as it was not comparable to other leading EU markets such as Germany and France

There is consensus across industry that the greatest opportunity for accelerated access lies at the stage of NHS uptake. Multiple factors contribute to delays in uptake, including prescriber conservatism with regards to use of innovative medicines and cost-containment initiatives. Global innovators compared the UK to other EU markets. Uptake of UK products in the first five years lags behind Germany and France, amongst other EU markets. Data from the Office for Life Sciences¹ suggests that median rate uptake in the UK is 11.4%, 31.9% and 51.7% of international comparators in years one, three, and five, respectively.

“Adoption of our product is comparable to that of Estonia within the EU and far behind the other EU5 markets.” – Biotech

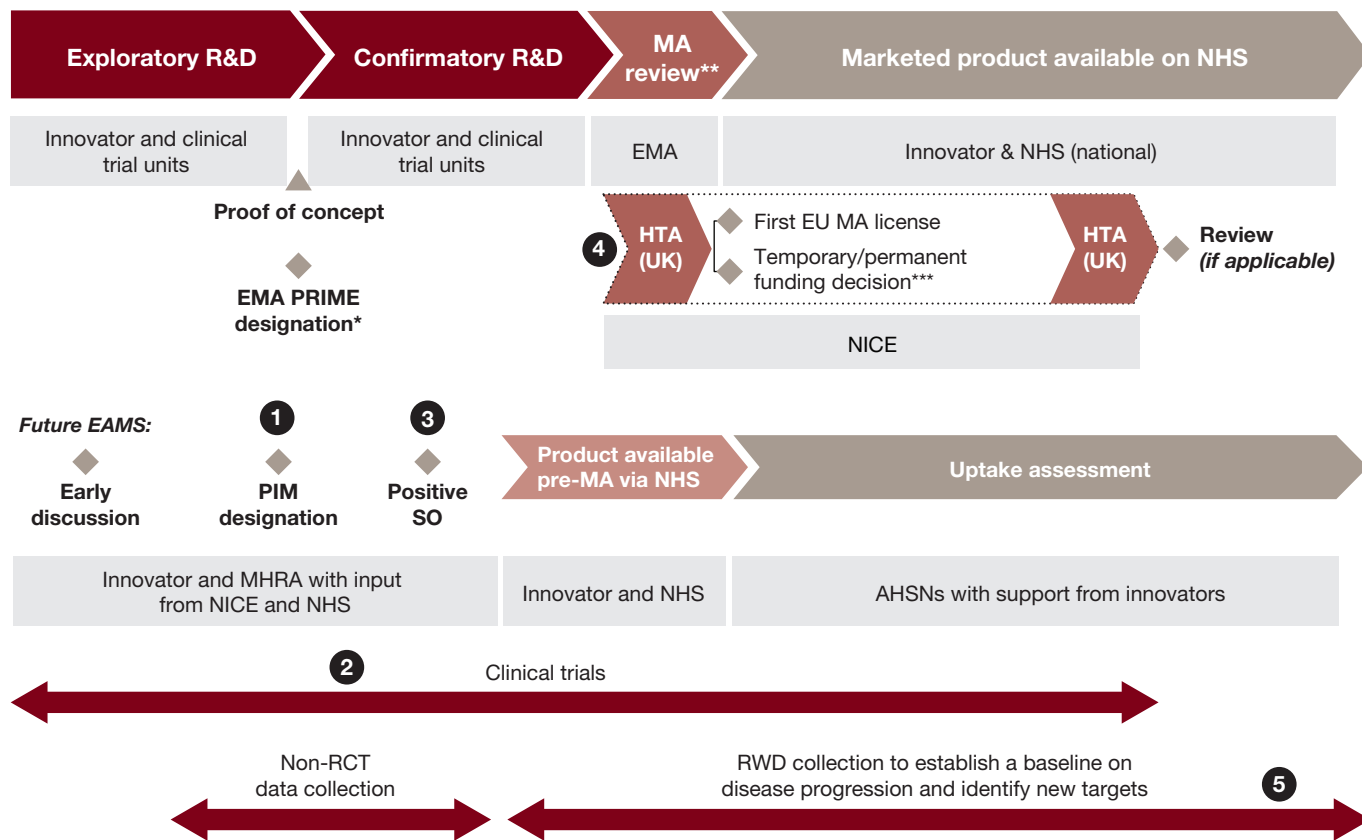
“We see that the uptake of innovative medicines within the NHS in the first five years from launch lags behind that of many international peers.” - Trade association

There is consensus across industry that the greatest opportunity for accelerated access lies at the stage of NHS uptake.

Our recommendations focus on improving the EAMS and using the PIM to signal a product's potential whilst facilitating clinical trials and RWD collection

Exhibit 7

A schematic of the proposed accelerated access pathway for medicines



Ongoing advice will also be available to innovators to provide support at checkpoints throughout the accelerated access pathway

■ key stakeholders – indicative only

Note: This pathway is indicative and shows a potentially accelerated route to patient access for transformative products. Not all products will go through each step or proceed at the same pace. Products that may not be classed as transformative will also benefit from a streamlined route.

Sources: Interviews held October – December 2015; Strategy& analysis

*The EMA is still consulting on the timing of PRIME designation for pharmaceutical firms versus biotech/not-for-profit organisations; this reflects the current position for pharma companies only.

**Market authorisation granted via different EMA pathways: conditional, exceptional circumstances, approval with conditions, full MA

***Funding decision may include the selection of a suitable pricing and reimbursement scheme (e.g. conditional reimbursement, outcomes-based payments etc.)

1. Using the Promising Innovative Medicines (PIM) designation to signal to stakeholders the potential of an innovative medicine to transform patient care

Following early dialogue with the relevant stakeholders (MHRA, HTA bodies and the NHS) about the applicability of the accelerated access pathway for their product, the innovator will generate exploratory clinical data and receive a PIM designation from the MHRA. Early dialogue also will identify UK priorities and the potential evidence generation plan. The PIM will signal to the innovator and other stakeholders the UK stakeholders' support in the development and entry of the product into the UK market. It is intended that the PIM designation is announced before the EMA's PRIME designation at Proof of Concept (PoC) for large pharmaceutical companies so that the UK can best support companies with shaping the clinical development of the product.

2. Advising innovators and facilitating access to the extensive clinical trial infrastructure to collect robust clinical and real world data in the UK that contribute to the overall global submissions

Via early dialogue, the innovator will discuss the evidence package required for patient access in the UK and how to meet the needs of the regulator, HTA bodies, and the NHS. Using the existing infrastructure (including the Clinical Research Network, NIHR Biomedical Research Centres and Units, NIHR Office for Clinical Research Infrastructure, and the Experimental Cancer Medicine Centres amongst others) available within the NHS, the UK will support innovators in selecting the most efficient and effective clinical trial mechanism. This will enable innovators to generate the evidence package locally that is required for smooth UK market access and, more importantly, access across other EU markets. *See "Enablers – Novel clinical trial designs" for further information.*

3. Improving the Early Access to Medicines Scheme (EAMS) by improving the overall benefits package on offer to industry including pre-MA funding

Building on what the EAMS has achieved to date, we recommend an evaluation of the overall benefits package to continue to attract applications from industry. Via interviews, survey and workshops, we identified four key opportunities which could increase the overall appeal of the EAMS. These are:

Via early dialogue, the innovator will discuss the evidence package required for patient access in the UK and how to meet the needs of the regulator, HTA bodies, and the NHS.

- Clearer guidance on the benefits of participation and entry requirements of the EAMS
- Consideration of a simple and confidential funding mechanism to cover the cost of supply for companies where the lack of funding pre-MA represents a significant deterrent to entry
- Support with real world data generation, beginning during the EAMS patient access period and continuing post-MA
- A smooth transition from EAMS patient access pre-MA to rapid product uptake in the NHS post-MA

For more information about the current EAMS process and the potential opportunities for improvement including on our recommendations on pre-MA funding, please refer to Strategy&'s independent review of the scheme (conducted September – December 2015).

4. Using a flexible pricing framework as part of the HTA and provision of guidance to innovators on the scheme(s) which may be most suitable for their product

As part of the HTA and following early dialogue, innovators will be able to discuss a range of pricing and reimbursement schemes tailored to the particular product taking into account input from the NHS on affordability. During early dialogue the patient view will be taken into account as it currently is during the HTA process. Innovators will need to have selected and included any proposed pricing schemes in their submission so that NICE can issue its guidance in a timely manner.

As part of this framework, we recommend that suitable schemes are proposed by innovators and negotiated centrally. A combination of schemes could be applied and may provide either a temporary or permanent funding decision. Further details can be found in the “flexible pricing and reimbursement framework” section of the report.

5. Testing the concept with established databases that collect real-world data to demonstrate how this data can be used to support regulatory and reimbursement decisions

RWD can be collected throughout the product development lifecycle, including early in the development process to support target identification before Proof of Concept (PoC) and to better understand natural disease progression and key events for specific conditions. This use of RWD is already extensive, but we believe that RWD holds more potential. *See RWD section for further details.* Specifically for medicines

RWD can be collected throughout the product development lifecycle, including early in the development process.

our recommendations focus on:

- Testing how RWD could be used to support ongoing clinical trials to demonstrate the full value proposition of the product and support its rapid uptake in the NHS
- How RWD can be collected in collaboration with patients and the NHS

Our view, and that of the different stakeholders we spoke to, is that RWD should complement the clinical trials defined as part of an innovator's global development plan, and that the nature of data collected should be highly tailored to the product and the UK market. However, as the standard of care improves in the UK, innovators should consider how RWD could support HTA submissions in other EU markets such as Germany and France, which are seen to be leading in terms of uptake of innovation. Conducting RWD studies in the UK was attractive to innovators given the current size of the UK medicines market.

"I think there is an opportunity for us to use the real world data collected in the UK to support reimbursement decisions elsewhere in Europe. Germany is one market where this could work." – Biotech

"It is important to recognise that RWD should complement, rather than supersede, RCTs and that the UK should support companies to collecting the former if it is to be used as a key component of HTA or funding decisions." – Trade Association

Most stakeholders we spoke to agreed that collection of RWD would not curtail the duration of any pivotal clinical trials. They agreed that collection would run alongside these trials starting from the time of a positive Scientific Opinion (SO) as part of the EAMS. Both the MHRA and innovators also agreed that it would not be possible to provide a positive SO too far in advance of an innovator submitting their regulatory submission package to the EMA, given the trend to submit as soon as is feasible. This is because of the regulatory flexibilities allowed by the EMA, where innovators can use adaptive pathways, accelerate approval processes, and achieve conditional regulatory approval. Therefore, we expect that RWD collection would be feasible pre-MA for up to 12 months, and we would expect it to continue post-MA, particularly if the HTA review resulted in a temporary funding decision predicated on collection of further data over two to three years.

"As part of a global Pharma, I think the earliest point at which we could start collecting RWD in the UK is approximately at the stage of MA application submission. This is because we wouldn't want the data to conflict with the evidence package coming from our global clinical trial programme." – Large Pharma

Most stakeholders we spoke to agreed that collection of RWD would not curtail the duration of any pivotal clinical trials.

Companion diagnostics pathway

Summary of Strategy & input into the AAR:

Accelerating the development of CDx is complex as products can be developed either on their own or in partnership with the medicines innovator. Where the diagnostic product is not co-developed with a medicine, but can be used to stratify patients for one or more medicines, we have included these products in the medical device pathway. CDx development isn't a long process; the level of acceleration will be minimal; but the proposed pathway seeks to be optimal. We recommend:

1. *Better signposting to platforms* such as AHSNs, MRC/EPSRC pathology nodes, the NIHR Office for Clinical Research Infrastructure, the Precision Medicine Catapult and the Genomics England database through which CDx innovators can engage in pre-competitive collaborations with academia and NHS clinicians to identify new biomarkers.
2. *Using existing forums to bring together diagnostics and medicines innovators* in order to facilitate biomarker validation and avoid duplication of research efforts.
3. *Incentivising pathology and diagnostic lab service providers to perform robust quality and cost-effectiveness assessments* as part of their procurement processes for CDx irrespective of whether the tests are in-house manufactured or commercially available.

Accelerating the development of CDx is complex as products can be developed either on their own or in partnership with the medicines innovator.

We define CDx as diagnostic products that are developed either in parallel or in tandem with a medicine, which are used to select which patients receive the medicine. They are a type of medical device. Diagnostic products that are not co-developed with a medicine, but can be used to stratify patients for one or more medicines, are included in the medical device pathway.

CDx innovators commented that closer collaboration with medicines innovators and the NHS could accelerate biomarker validation

Incentives are lacking for CDx innovators to accelerate development as often there is a disadvantage to getting to market first or before the medicine

Global diagnostics innovators have told us that the UK environment for developing and commercialising CDx is currently challenging. There is no incentive to conduct clinical validation studies in the UK as other EU markets achieve better access post-CE marking.

“The development of our products happen primarily in the US. The UK market is seen as a relatively naive for uptake of CDx and lags behind many of its European peers.” - CDx innovator

In particular, CDx innovators have highlighted the following issues with the development process for CDx:

- Developing CDx without a Pharma / Biotech partnership can be financially unviable as NHS uptake is often short-lived or limited.
- CDx CE marking needs to align with regulatory approval for the medicine; acceleration of the pathway for CDx is only possible if the acceleration is also possible for medicine development.
- IP protection for CDx is weak and there is often no benefit to be “first to market”. In fact, it can be a disadvantage to be first, as the first innovator validates the biomarker while the other innovators can focus on R&D on improving the test characteristics and interface rather than biomarker validation.
- NHS providers develop in-house tests therefore reducing the incentive for NHS organisations to collaborate with commercial innovators.

It can be a disadvantage to be first, as the first innovator validates the biomarker while the other innovators can focus on R&D.

The revised EU regulations increase the regulatory requirements for commercial CDx innovators whilst exempting in-house tests developed by the NHS which does not create a level playing field

The European Commission is currently revising the EU Medical Device Directives to strengthen regulatory standards and improve patient safety. Two revised regulations, covering medical devices and in vitro diagnostics, are due to be published by June 2016 and will be rolled out over a three-year and five-year implementation period, respectively.

Whilst details of the new legislations are yet to be finalised, draft proposals indicate that a significantly greater proportion of CDx will be expected to obtain a CE mark from a Notified Body and that this mark must be obtained before use in the pivotal clinical trials where the CDx would be used to stratify patients and assign treatments. Diagnostics which are not used to stratify patients can still be used in clinical trials to undergo validation; medicines innovators will need to then retrospectively assess diagnostic status to link it to patient outcomes.

Another proposal is that CDx innovators may be required to submit an application to the Notified Body before using their product in an interventional performance study. The EMA and MHRA are also likely to play a role in the delivery of these future regulatory changes, details of which will be finalised in the coming months.

CDx innovators we have interviewed welcome the regulatory review, but have raised a significant concern with respect to an EU-wide exception afforded by Directive 98/79/EC for in-house tests to undergo regulatory review before they are used by the NHS, but not for commercially developed tests. The intention of the changes we propose was not to reduce competition from in-house tests, but to establish equal quality standards for commercially and non-commercially developed products.

“The upcoming revised regulations will place a greater required on companion diagnostics manufacturer to seek a CE mark certification from Notified Bodies. However, there is still some uncertainty around the exact details of the legislation as the European Commission finalises the draft proposals for launch in 2016.” - MHRA

“I recognise that the revised, more stringent regulations will ultimately benefit patients. However, in-house tests are exempt from these requirements, saving NHS laboratories the associated costs and time involved in this process.” - Diagnostics innovator

CDx innovators we have interviewed welcome the regulatory review, but have raised a significant concern with respect to an EU-wide exception.

There is lack of clarity amongst CDx innovators as to the types of HTA for CDx and furthermore, post-HTA, CDx products are often funded by medicines innovators rather than in their own right

CDx innovators have shared, as medical devices innovators, that in their view there is no advantage to having a HTA performed whether as a stand-alone diagnostic product or as part of the medicine HTA. In addition, there isn't clarity amongst innovators as to which assessment to apply for. In England, CDx are reviewed by NICE using two pathways:

- *For CDx developed in combination with a new medicine, the HTA process follows the route of the medicine and is assessed via the Single Technology Appraisal (STA) or Multiple Technology Appraisal (MTA). A positive outcome provides a funding mandate for the medicine-device combination but does not recommend a specific brand of the CDx for uptake. The price at which the CDx is cost-effective is known. Nonetheless, typically it will be the medicine innovator that will fund the CDx test rather than the NHS, at least in the first year post-launch of the medicine.*
- *For complex CDx developed independently of the drug, e.g., for repurposed medicines, the product is evaluated via the Diagnostics Assessment Programme. There is currently no funding mandate for products recommended following the Diagnostics Assessment, which creates a two tiered system for CDx.*

“There is a lot of confusion about the HTA process for CDx. In my eyes, it is a simple process - we see that CDx developed with new medicines jointly entering the Single Technology Appraisal. For high cost and complex diagnostics developed independently of the medicine, these are eligible for the evaluation via the Diagnostics Assessment Programme.” - NICE

Post-HTA uptake within the NHS is limited, as in-house tests are often seen as more cost-effective, and of equivalent quality, and other CDx innovators are likely to launch similar products

Post-HTA, NHS pathology providers are able to choose freely between in-house tests and commercially developed tests. The decision is typically made by the local pathology service. CDx innovators have told us that in-house tests often receive faster uptake due to the perception that they are of comparable quality and come at a lower cost relative to commercially developed tests. However, we also heard from CDx innovators and some NHS stakeholders that in-house tests are not always the most cost-effective as many costs aren't taken into account when calculating their cost-effectiveness during procurement processes.

We also heard from CDx innovators and some NHS stakeholders that in-house tests are not always the most cost-effective.

In addition, even if a CDx is first to market, within several months, many other CDx innovators will have launched similar products that may improve on specificity, speed, or other diagnostic characteristics thereby removing any first mover advantage. Whilst not wanting to reduce competition, which is favourable for the NHS, it is important that consistent quality standards and methodology are used to assess true cost.

“The biggest problem with CDx is uptake. There is simply no clear way for products to receive funding from the NHS. In-house tests often outcompete commercially developed tests due to cost even though it is the commercial company that has invested in the upfront R&D.” - Diagnostics innovator

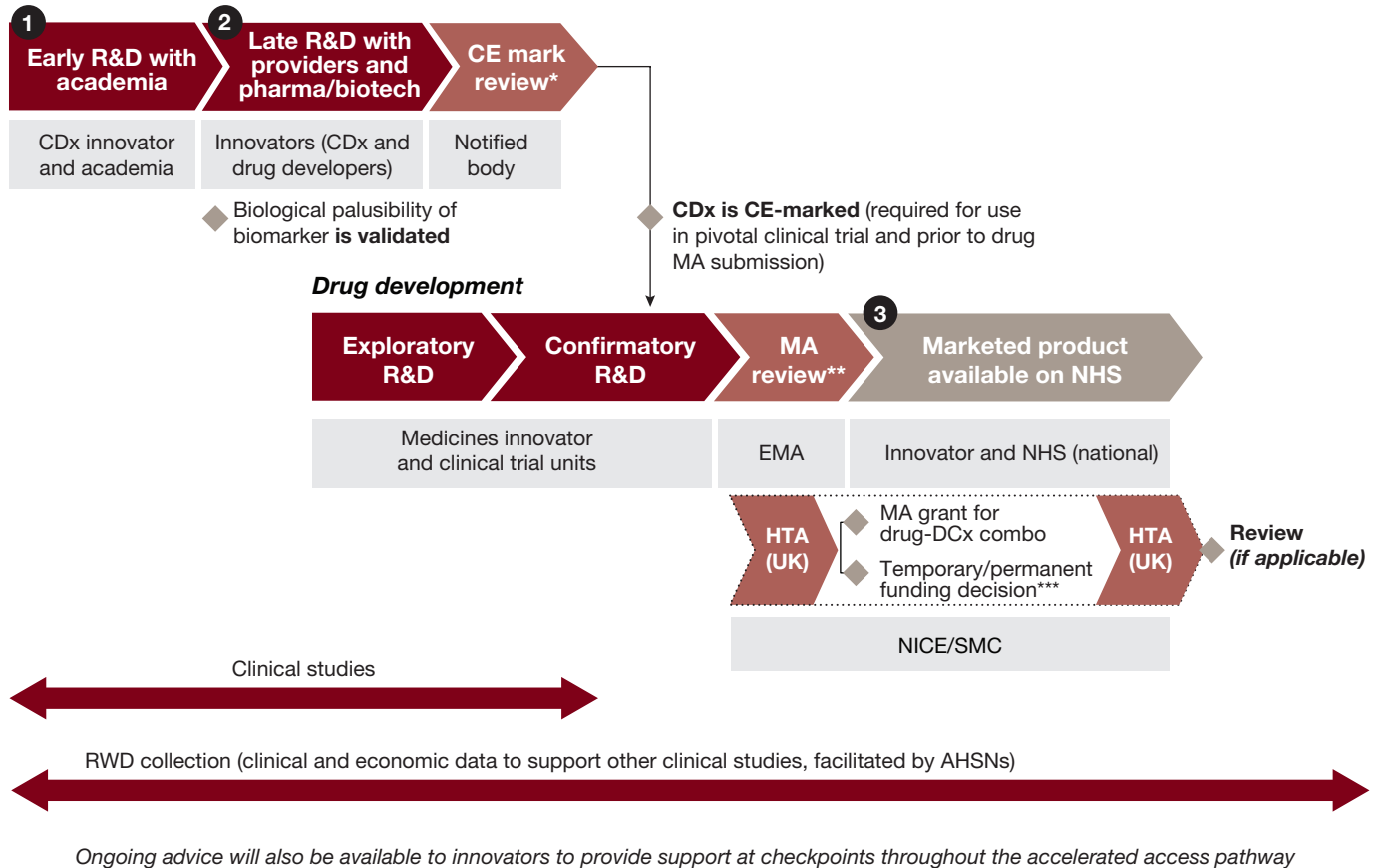
“There needs to be more rigorous testing of the quality and cost-effectiveness of in-house tests vs. commercially developed tests prior to local NHS uptake.” - Trade association

Our proposed CDx pathway seeks to facilitate collaborations to validate biomarkers and create a mechanism by which CDx can be funded in their own right

Exhibit 8

A schematic of the proposed accelerated access pathway for companion diagnostics

CDx development with academia and providers



■ key stakeholders – indicative only

Notes: 1. This pathway is indicative and shows a potentially accelerated route to patient access for transformative products. Not all products will go through each step or proceed at the same pace. Products that may not be classed as transformative will also benefit from a streamlined route.
2. The CDx innovator could be a for-profit organisation or the NHS.

Sources: Interviews held October – December 2015, Strategy& analysis

*Regulations for in vitro diagnostics including companion diagnostics are currently under revision by the European Commission (with an anticipated publication date of June 2016) and will be subject to change.

**Market authorisation granted via different EMA pathways: conditional, exceptional circumstances, approval with conditions, full MA

***Funding decision may include the selection of a suitable pricing and reimbursement scheme (e.g. conditional reimbursement, outcomes-based payments etc.)

1. Facilitating pre-competitive collaborations can streamline the identification of new biomarkers and ultimately contribute to lower costs in CDx development

There are several existing forums, for example the MRC / EPSRC pathology nodes and NIHR Office for Clinical Research Infrastructure, where CDx innovators can contribute to discussions on which biomarkers are relevant for UK clinicians and for medicines innovators' upcoming pipeline products. Signposting to these forums more clearly would encourage CDx innovators and the NHS to participate and form pre-competitive collaborations to advance the next generation of biomarkers. It is hoped that by reducing duplicative efforts where multiple CDx innovators search for the next generation of biomarkers, costs of early research will be reduced. These pre-competitive collaborations between medicines and CDx innovators could also then lead into commercial partnerships in which CDx are brought to market together with an innovative medicine.

2. CDx and medicines innovators can also come together in different forums, e.g., via the Precision Medicine Catapult, to develop the CDx and medicine in parallel

The proposed pathway brings CDx and medicines innovators closer together earlier in the development pathway so that there is every chance for the two products to be developed in parallel. Innovators could be for-profit organisations or NHS diagnostics providers. There also are forums that support collaborative efforts later in development, including cost-effectiveness assessment e.g., Diagnostics Evidence Co-operatives (DEC)s sponsored by NIHR. The two innovators would need to collaborate to conduct clinical trials where there CDx is used, and retrospectively, patient outcomes are linked to biomarker status. An agreement would need to be reached as to data ownership, but at the end of the clinical studies, and potentially before the pivotal clinical study, the biomarker and CDx would be validated. The CDx innovator at this stage could either proceed for CE marking on the basis of this data or collaborate further with the medicines innovator to collect further data during pivotal studies in the same way as before. Anecdotally we have heard that medicines innovators do use pre-CE marked CDx for stratifying patients; it remains to be seen whether this practice will continue post the publication of the new EU regulations. Current regulatory thinking is that under the new regulations, the CDx should be CE-marked for any product clinical trials intended to be the anchor of the regulatory submission. The UK could be the centre of the collaboration globally given its multiple forums that facilitate development and data collection, particularly if this is coupled with improved procurement processes that result in uptake of the most cost-effective products within the NHS.

It is hoped that by reducing duplicative efforts where multiple CDx innovators search for the next generation of biomarkers, costs of early research will be reduced.

The proposed pathway brings CDx and medicines innovators closer together earlier in the development pathway so that there is every chance for the two products to be developed in parallel.

3. Reinforcing a robust procurement process which includes quality assessment and may also result in recognition of the value of clinically validated CDx

Post-HTA there will be a clear view on the cost-effective price of the CDx and this could be set as the ceiling price for any subsequent procurement process. To incentivise CDx to get first to market, the procurement process should start as soon as a CDx product is launched rather than wait until further tests are launched. If other tests were in development and the procurement team was aware of this, they may choose to issue the tender to cover one year only to allow further competition the next year. This approach meets two objectives: (1) to accelerate funded access to the CDx for patients and (2) to recognise the investment in validating the biomarker and getting to market first. In addition, in light of the upcoming regulations, it is anticipated that NHS providers and the UK National External Quality Assessment Service will implement processes requiring that in-house tests undergo more stringent quality testing. This would level the playing field further making the UK comparable to other EU markets in terms of the prominence of in-house tests. This will maintain quality standards and allow the NHS to benefit from clearly understanding the cost of the product. We discuss other levers that are relevant to improve uptake later on in the report as these levers straddle all the medical technologies.

To incentivise CDx to get first to market, the procurement process should start as soon as a CDx product is launched rather than wait until further tests are launched.

Medical devices and digital pathways

Summary of Strategy & input into the AAR:

The medical devices pathway applies to medical devices, diagnostics (not CDx) and non-app digital products. For app-based digital products we propose to build on the National Information Board (NIB) 1.2 process which confirms that a particular App has a robust enough evidence base to be recommended for use within the NHS. To achieve this, we recommend:

1. *Use of innovation exchanges to promote dialogue between medical device innovators, the NHS, and other stakeholders* such as patient groups on areas of unmet need and new product ideas. The AHSNs amongst other forums can facilitate this dialogue at a local level including publication of desired product specifications by the NHS so that innovators are able to develop products with a clear view of provider needs and have a platform for more national uptake thereafter.
2. *Introducing a Promising Device Designation as a clear signal* that a medical device has potential to positively transform the workflow within the NHS for specific procedures and conditions by reducing costs of care and/or improving patient outcomes. *For app-based digital products this will be achieved via the NIB 1.2 process* which includes a community evaluation and further assessment of the potential impact of the App.
3. *Signposting and using existing forums* e.g. Collaboration for Leadership in Applied Health Research and Care (CLAHRC), Diagnostic Evidence Co-operatives (DEC)s and NHSE Test Beds amongst others to collect clinical utility and economic data, respectively to support both the regulatory and HTA processes. This may include RWD pre- and post-HTA to generate and then validate the business case respectively.
4. *Introducing funding mandates post-HTA* for both medical devices and app-based digital products. The cost-effectiveness assessment would define the price that would act as the maximum price in procurement exercises. During the HTA process like for medicines, it may be that schemes from the flexible pricing framework are used to achieve cost-effectiveness.

For app-based digital products we propose to build on the National Information Board (NIB) 1.2 process which confirms that a particular App has a robust enough evidence base to be recommended for use within the NHS.

Medical devices encompass a range of products from wheelchairs, to stents, to molecular diagnostics, to digital products. We consider any digital product that is not an app, but which makes a claim to treat or diagnose either directly or indirectly as a medical device in terms of how it would proceed through our proposed pathways. Digital products which are apps fall under the scope of the NIB 1.2 process and have a slightly different pathway.

Both medical device and digital products innovators struggle with articulating the value their products can bring to the NHS

The new EU medical device regulations will require medical device innovators to generate robust clinical evidence before CE marking

The development route of medical devices varies significantly depending on the type of medical device but it is recognised by innovators that the current EU regulatory regime offers a rapid route to market.

“The required for CE marking is not cumbersome and does not represent a barrier from my perspective. There are far greater problems at the stage of funding and NHS uptake.” - Large medical devices innovator

However, once the new EU medical devices regulations come into force over the coming years, many more medical devices will need to generate clinical evidence, which will be assessed before CE marking. This will be particularly challenging for digital product innovators who have not had to do this in the past.

“The development process for our products are relatively short, certainly faster than for medicines due to the comparatively lower regulatory standards required for a CE mark. However, much of the evidence generation occurs after the CE mark and it is at this stage that we are delayed as we look to demonstrate the value of our product to payers.” - Large medical devices innovator

“The revision of the current EU directives has been ongoing for several years and will see stricter standards imposed across a wider spectrum of devices when they are introduced in 2016. These revisions will help us ensure that the safety of patients using such devices continue to be protected.” - MHRA

Although medical device innovators aren't overly concerned about the regulations change due to its five-year long implementation period, it is clear that they would value support on how to generate this data most

Although medical device innovators aren't overly concerned about the regulations change due to its five-year long implementation period, it is clear that they would value support on how to generate this data most effectively and efficiently within the NHS.

effectively and efficiently within the NHS. In contrast, digital product innovators are concerned about the implications of the regulation changes, given that they will need to conduct clinical studies for future CE marking.

“We did not need to obtain a CE mark for our digital product and I am a little concerned about what the upcoming regulations will mean for us. In particular, I would like to know how the CE marking is compatible with the rapidly evolving and iterative nature of digital products whereby new versions are developed every few months.” - SME digital innovator

Finally, we have heard from SMEs (both medical devices and digital products) that they are often unclear on what evidence package is required and how to articulate the full value proposition of their product to the NHS. In addition, they are concerned about the data package that will be required to support product enhancements which will also need to be assessed by Notified Bodies. This is of particular concern to digital product innovators because of the fast cycling of new versions.

“We don’t have a clear view of what it takes for our product to receive NHS support and uptake. Whilst there are opportunities to work with academia and clinicians, we do not have the perspective of NHS individuals who actually make the commissioning decision. As such, it is difficult to know if we are generating the right evidence for uptake.” - SME digital innovator

The lack of a funding mandate following HTA means that medical device innovators try to avoid a national level assessment of cost-effectiveness and focus on local assessments

The HTA process for medical devices is complex and products could be assessed via one of six different appraisal procedures from NICE². Of these, only the Technology Appraisal Processes provide a funding direction. The most common process, the Medical Technologies Evaluation Programme, simply provides advice and has limited impact on NHS uptake. As a result, several medical device innovators have shared that they see little value in the process because the risk of a negative outcome and the high application cost is perceived to outweigh the value of a positive recommendation.

“The mass majority of medtech products are not assessed by NICE and even when they are, products are routed via processes which have no funding direction.” - Large medical devices innovator

“The NICE HTA process accommodates drugs well but is too complex and confusing for medical devices.” - SME medical devices innovator

“The HTA process by NICE does little to impact subsequent uptake.” - Trade association

The HTA process for medical devices is complex and products could be assessed via one of six different appraisal procedures from NICE.

“Ironically, a positive recommendation from NICE does more for market access in other countries than it does for the UK market. Global markets respect the advice of NICE and this helps us with gaining local uptake across the EU. However, domestically, the outcome has limited direct impact on NHS adoption.” - SME digital innovator

We have also heard from NICE that often the information provided by medical device innovators is insufficient to perform a cost-effectiveness assessment. In addition, currently there isn't a HTA process for digital products; assessment of value to the NHS is often part of a procurement process by those who aren't qualified to do this type of assessment. Finally, unlike for medicines where there is room to introduce a Patient Access Scheme (PAS), this flexibility is not extended to medical devices and digital products.

Furthermore, even if innovators successfully achieve access via a local pilot, it is difficult to replicate across many localities, particularly for SMEs who have minimal marketing muscle

Not dissimilar to what we heard for medicines, uptake of new medical devices and digital products is poor and comes at a high cost to the innovators of local procurement processes and local promotion efforts. There is no national-level procurement process, and therefore these innovators often have to respond to a large number of tenders across the different CCG/NHS Trusts. This is challenging, not least because the procurement teams are not equipped to assess the level of system change that is required or the likely total system benefit of any innovative medical device or digital product.

We also have heard that the need to promote the product locally is prohibitive for SMEs, particularly for digital product innovators who may not have the necessary marketing and sales muscle. Finally, even if local promotion is successful in one area, it often becomes difficult to scale the pilot activity to other localities.

“NHS commissioners tell me that they require a full business case to consider whether to commission our product. It takes the company a significant amount of time and financial resource to get to this stage of evidence generation with little visibility of uptake. I think we should be working more collaboratively with the NHS and piloting the product at an earlier stage via risk-rewards schemes whilst collecting real world data.” - SME digital

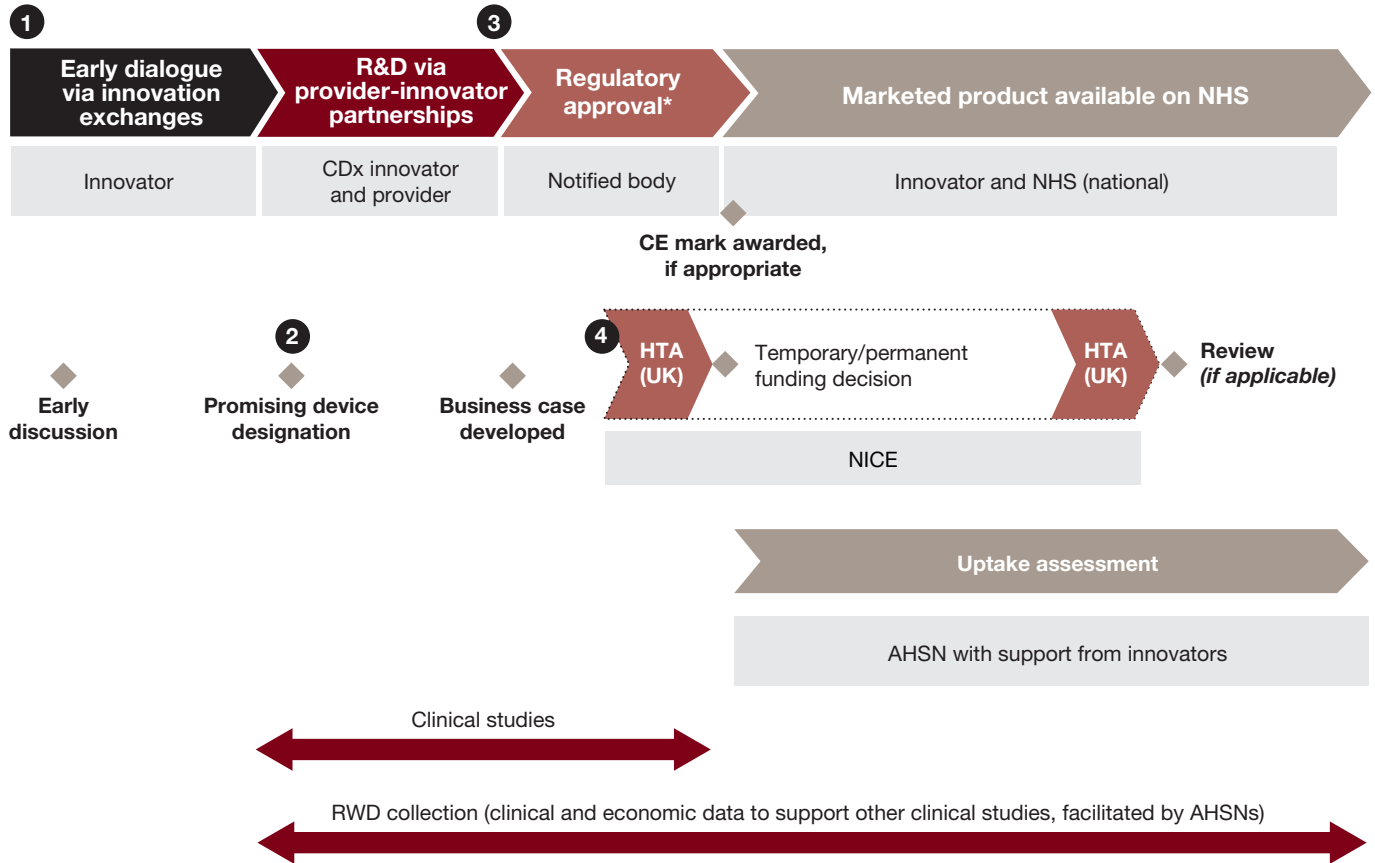
“I would like to see fewer barriers to the uptake of medical devices across local health economies.” - SME medical devices

We also have heard that the need to promote the product locally is prohibitive for SMEs, particularly for digital product innovators who may not have the necessary marketing and sales muscle.

Supporting innovators to develop a robust business case and implementing a national level HTA with a funding mandate will increase the attractiveness of the UK for medical devices and digital product launches

Exhibit 9

A schematic of the proposed accelerated access pathway for medical devices



Ongoing advice will also be available to innovators to provide support at checkpoints throughout the accelerated access pathway

■ key stakeholders – indicative only

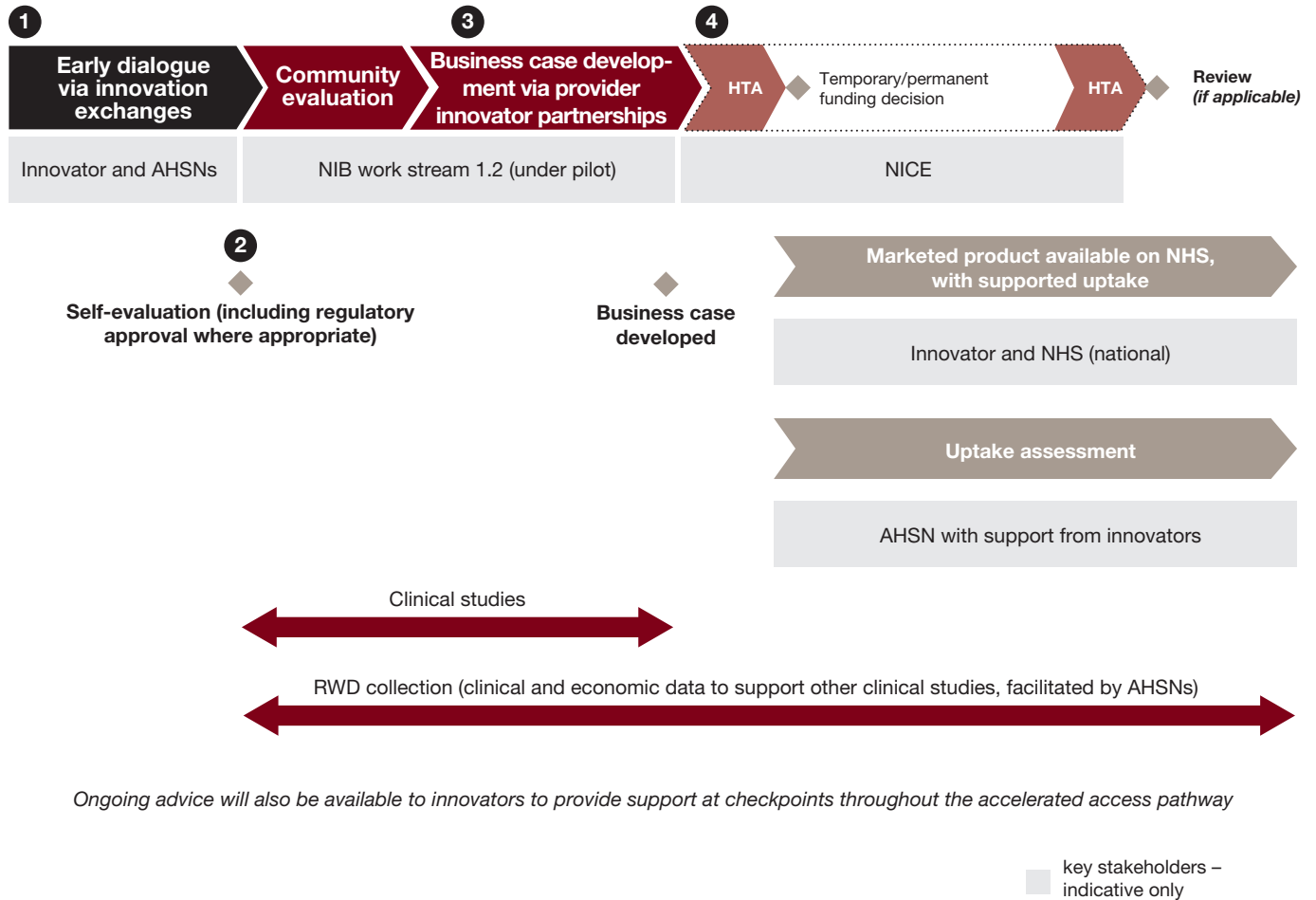
Note: This pathway is indicative and shows a potentially accelerated route to patient access for transformative products. Not all products will go through each step or proceed at the same pace. Products that may not be classed as transformative will also benefit from a streamlined route.

Source: Interviews held October – December 2015, Strategy& analysis

*Regulations for medical devices are currently under revision by the European Commission (with an anticipated publication date of June 2016) and will be subject to change.

Exhibit 10

A schematic of the proposed accelerated access pathway for digital products



Ongoing advice will also be available to innovators to provide support at checkpoints throughout the accelerated access pathway

Notes: This diagram outlines the pathway for apps as defined by the National Information Board. Non-app digital products will go through the medical devices pathway. This pathway is indicative and shows a potentially accelerated route to patient access for transformative products. Not all products will go through each step or proceed at the same pace. Products that may not be classed as transformative will also benefit from a streamlined route.

Sources: Interviews held October – December 2015, Strategy& analysis

1. Innovation exchanges hosted by AHSNs can create an environment for early dialogue around unmet need and collaborative working for medical device innovators

Medical device and digital product innovators themselves have shared with us that they often are product- or technology-led rather than led by where there may be unmet need.

For medical devices, it is hoped that with an evolved offer, AHSNs could host local discussions to collate ideas from providers and patient groups on the areas of unmet need. At the same time, AHSNs could collate input from innovators on the types of products they are thinking of developing. The AHSNs would then broker an introduction where the unmet need and technological capabilities align so that provider-innovator partnerships are formed. They also could advise digital product innovators as to whether their particular product would be classed as a medical device or an app-based digital product. Finally, these partnerships would jointly assess what impact the proposed innovation could have on the NHS before proceeding to collect the relevant clinical and economic data that would be needed for CE marking and HTA.

2. For medical devices including non-app-based digital products, after an initial assessment at the local AHSN level of the likely impact on the NHS, national-level stakeholders (e.g. NICE, MHRA, Notified Bodies, patient groups, NHS and procurement) consider the evidence in order to designate a Promising Device

These stakeholders review the analysis of the potential impact prepared by the provider- innovator partnership in order to grant the designation. Once the designation is made, this allows the innovator to draw on expertise from the different stakeholders in order to design the clinical studies, the RWD mechanism and the economic data collection. The designation also may be used to attract additional funding for R&D, either through application through existing grants (e.g., SBRI contracts) or through private investment.

The NIB 1.2 four-step process which is being tested takes the place of the open forum for discussion around unmet need and how well the proposed digital product can meet the local NHS needs. Following a self-certification step, the app-based digital product proceeds through a community evaluation of its potential, and then an independent assessment of its economic impact on the particular NHS locality. The outcome of the process is a pre-screened digital product which could have a positive impact on the NHS nationally. Although the NIB 1.2 process is performed locally, it results in recommendations for uptake

Medical device and digital product innovators themselves have shared with us that they often are product- or technology-led rather than led by where there may be unmet need.

nationally. However, we know that digital product innovators struggle to get other localities to adopt the product, in part because each local economy has slightly different patient flows and process workflows. Therefore, we propose that once the NIB1.2 process has certified the App for use in the NHS, the business case created undergoes a streamlined HTA.

3. Having gained the designation, innovators will be offered additional support along the accelerated access pathway

There will also be signposting and use of existing forums e.g., Collaboration for Leadership in Applied Health Research and Care (CLAHRC), Diagnostic Evidence Co-operatives (DECs), Biomedical Research Centres and Units, Health Technology Co-Operatives, the NIHR Office for Clinical Research Infrastructure, and NHSE's Test Bed programme. All these forums facilitate collection of clinical utility and economic data. This may include RWD pre- and post-HTA to generate and then validate the business case respectively, bringing clinical and RWD data together from across primary, secondary and social care, if possible.

Data collected during the course of this programme can be used to demonstrate the clinical, social, and economic value of the product in a real world setting as well as its impact on current care pathways. In conjunction with NHS delivery partners, the innovator will use the evidence generated to develop a business case that will be presented to the HTA body.

4. The HTA body will assess the business cases using the data collected in the concept testing phase in the specific localities and assess (1) the cost-effectiveness of the product based on the business case and (2) whether the local evidence will translate across other localities

Post-HTA we propose to *introduce funding mandates* for both medical devices and app-based digital products, defining cost-effective prices for these products that act as the maximum price in procurement exercises. During the HTA process, like for medicines, it may be that schemes from the flexible pricing framework are used to achieve cost-effectiveness. It is noted that given the faster development cycle of non-medicinal medical technologies and, therefore, that less data is available, it will be even more important to be clear about what data is required post-conditional reimbursement. Uptake of the products will be collated by the AHSNs to feed into national level tracking in order to highlight pockets of leading practice in terms of uptake of innovation.

Post-HTA we propose to introduce funding mandates for both medical devices and app-based digital products, defining cost-effective prices for these products that act as the maximum price in procurement exercises.

Flexible pricing and reimbursement framework

Summary of Strategy & input into the AAR:

- The AAR should consider the implementation of a flexible pricing and reimbursement framework that provides innovators access to a range of commercial arrangements.
 - Further consideration will need to be given to the criteria that will be used to select pricing and reimbursement schemes for products.
- The framework should be applied to products receiving support through the accelerated access pathway but could be extended to a wider set of products in the UK.
- The potential framework could be composed of seven prioritised schemes, selected after receiving input from a wide number of stakeholders.
- The pricing and reimbursement schemes applied to products under the framework could be applied singly or in combination, and the selection of schemes will need to be guided by the product characteristics.
- Via early dialogue throughout the development process, industry would agree an approach with the NHS and HTAs including any potential commercial arrangements before submitting the HTA package.

The AAR should consider the implementation of a flexible pricing and reimbursement framework that provides innovators access to a range of commercial arrangements.

The flexible pricing and reimbursement framework provides a range of schemes...

We propose that a key component of the accelerated access pathways for all of the medical technologies is the availability of a flexible pricing and reimbursement framework. This is particularly important where products may not have the full evidence required at the point of regulatory approval which also impacts the HTA review. The objective of this framework will be to provide innovators with access to a range of commercial arrangements that are flexible enough to cater for a wide variety of transformative products, while maintaining affordability for the NHS. It is recognised that working within a fixed budget, the NHS would need to re-prioritise resources/funds to support innovation uptake or otherwise funding would need to come from elsewhere.

We propose that this framework could be applied to all products that receive accelerated access. However, the principles of this framework could be applied to a broader set of products.

...that can be used in combination and be applied on a permanent or temporary basis post-HTA

To meet the objective described above, we believe the flexible framework should align with the following core principles:

The proposed flexible pricing and reimbursement framework should...

- 1. Present sufficient options for innovators to pursue a commercial arrangement that prioritises patient access, while not being so large as to increase complexity in the system.*
- 2. Allow the selection of schemes on a product-by-product basis so that commercial agreements are tailored to the properties of a product (e.g., product type, availability of data, impact of healthcare system, target patient population, etc.).*
- 3. Allow for schemes to be applied in combination, where appropriate, to gain a fair recognition of product value and provided that the complexity of implementation would outweigh the benefits of the arrangement.*
- 4. Provide for schemes to be applied on a conditional or permanent basis so access to patients is prioritised where products are promising, and to allow for review when more product data becomes available. Alternatively, products which have sufficient data at the point of HTA*

We propose that this framework could be applied to all products that receive accelerated access. However, the principles of this framework could be applied to a broader set of products.

should be eligible for permanent reimbursement decisions that are not necessarily subject to review after further data becomes available.

The components of the flexible pricing and reimbursement framework are based on international examples

The flexible pricing and reimbursement framework is comprised of a range of pricing and reimbursement schemes that can be applied to products. To establish which schemes could be included as part of the framework, we scanned international markets for schemes that could be applied to the UK. In surveying these schemes, we have not considered schemes that require a fundamental shift to how healthcare is delivered in the UK. For example, we have not considered schemes that propose changes to the use of cost-effectiveness, the QALY threshold, the level of co-pay, or the principles of free-pricing within the UK.

We compiled a long list of 13 different pricing and reimbursement schemes, publishing this in our Case Study Report. We also published a survey alongside this report to gather feedback from a wide variety of stakeholders on the applicability of the long-listed schemes for the UK. The long-listed schemes are shown. (*See Exhibit 11.*)

Exhibit 11

The long-listed Pricing and Reimbursement Schemes based on feedback from interviews and workshops with DH and NHS stakeholders

Pricing and reimbursement controls

<i>Scheme</i>	<i>Description</i>
<i>Price-volume agreements</i>	The price for a single unit (for example, of a drug) drops as the quantity of units purchased increases. This could include a cap above which the payer and developing company share risk.
<i>Tendering and negotiation at scale</i>	Group purchasing of medical technologies at a hospital, regional, or national level to realise cost-savings; necessary by EU procurement law for medical devices in particular.
<i>Therapeutic reference pricing</i>	Medical technologies priced in line with similar technologies (e.g., the same pharmacological class for a drug) or against the existing standard of care.
<i>Disease-specific pricing and reimbursement pathways</i>	An alternative pricing and reimbursement pathway for high-profile or -cost diseases, which features different selection criteria. These could include a cost-plus approach for ultra-orphan products.
<i>Wider value in cost-effectiveness</i>	Pricing and reimbursement decisions factor in a wider considerations of value, such as societal impact.
<i>Budget-capping</i>	The developing company and payer agree on either the total expenditure or the cost per product and/or indication. If the cap is exceeded, companies must rebate some of the revenue.
<i>Dose-capping</i>	The payer will reimburse a maximum number of doses over a specified time. Further doses are supplied at the cost of the company or with a rebate. (This only applies to medicines.)

Outcomes-based schemes

<i>Scheme</i>	<i>Description</i>
<i>Conditional reimbursement</i>	Companies receive reimbursement for the technology pending additional data on the treatment or device. For non-medicine medical technologies, this includes data on the effectiveness of changes to workflow processes.
<i>Outcomes-based payments</i>	The product price varies according to patient clinical outcomes and, for non-medicines, changes in process flows. If the product does not demonstrate the agreed-upon outcomes, the developing company rebates some of its revenue to the payer.

Novel schemes

<i>Scheme</i>	<i>Description</i>
<i>Deferred payments</i>	Payment for a medical technology is spread over a pre-agreed period of time to manage the upfront cost.
<i>Guaranteed revenue model</i>	Revenue is guaranteed to innovators in indications where it is necessary to stagger or restrict access (eg. antibiotics).
<i>Indication-based pricing</i>	Prices for the same medical technology is different when used for different indications, particularly for cancer products.
<i>Product-service bundling</i>	Products and services are bundled along a particular disease pathway or for a patient at a particular point in time, at a price discount.

Source: Strategy& analysis

The schemes were prioritised taking into account UK stakeholder objectives such as being able to increase access whilst maintaining affordability

To establish which of the long-listed schemes could be included within the framework, we considered how each of them aligned with a set of prioritisation criteria. These criteria were developed together with the AAR, DH, and NHS teams with input from industry via telephone and face-to-face interviews. The intention of the objectives is that they represent a suitable balance between the recognition of value for innovators and an appreciation of the priorities of the NHS.

- *Increases speed of access* – does the scheme provide a mechanism through which products could be made available to patients faster?
- *Shares risk around outcomes* – does the scheme involve the collection of outcomes data, prioritising outcomes for patients, and aligning with an outcomes-oriented direction of travel?
- *Aligns with integrated care* – does the schemes align with the integrated care ideas set out by in the NHS ‘Five Year Forward View’?
- *Increases affordability* – does the scheme recognise product value while remaining affordable for the NHS to sustain?
- *Enables budget predictability* – does the scheme enable commissioners and NHS budget holders to more accurately predict spend for products?
- *Incentivises innovation* – does the scheme appropriately recognise the value of innovative products and make it attractive for innovators?

We sought feedback on the pricing and reimbursement schemes in the following ways:

- In response to the pricing and reimbursement case study report, published on the AAR website, we received 42 completed responses to our survey and comments from a further eight organisations.
- We spoke to representatives from 29 innovative companies and trade associations, as well engaged through a workshop and presentation session.
- We held three workshops with members of the DH, NHS, and arms-length bodies.

To establish which of the long-listed schemes could be included within the framework, we considered how each of them aligned with a set of prioritisation criteria.

We launched a survey on the AAR Engage website to gather input from a wider array of stakeholders on the long-listed pricing and reimbursement schemes. Respondents were asked to identify which schemes they considered the most and least attractive opportunities for the UK, and provide reasoning for their selections. Results from the survey responses can be found in *Exhibit 12, next page*.

Across the stakeholders who responded to the survey outcomes-based payments, wider-value in cost-effectiveness, and conditional reimbursement received the greatest number of votes for ‘most attractive’. Deferred payments, therapeutic reference pricing, disease-specific P&R pathways and indication-based pricing received the most votes for ‘least attractive’.

When considering the responses from NHS and Industry stakeholders, who make up the majority of respondents, viewpoints were aligned around outcomes-based payments and deferred payments as the most and least attractive schemes respectively. The view of industry more closely aligned with the overall scheme rankings which indicates a greater degree of consensus around the most attractive schemes among industry stakeholders compared to NHS/DH.

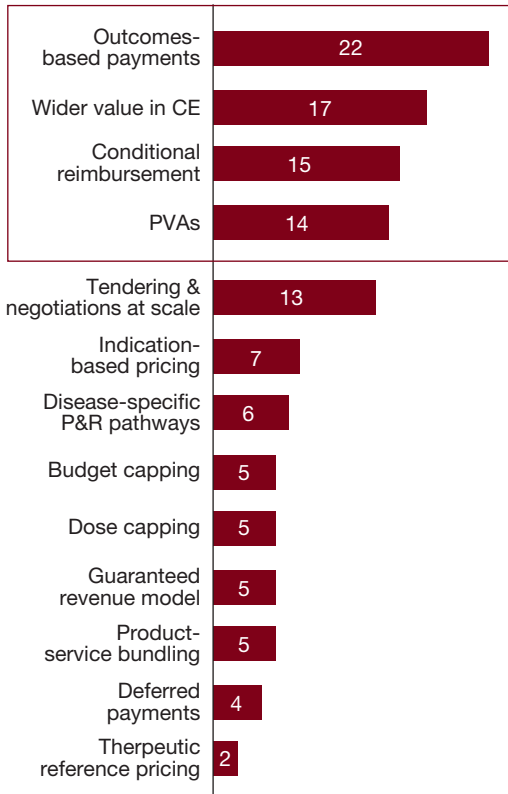
Exhibit 12

Pricing and Reimbursement (P&R) Scheme Survey Results

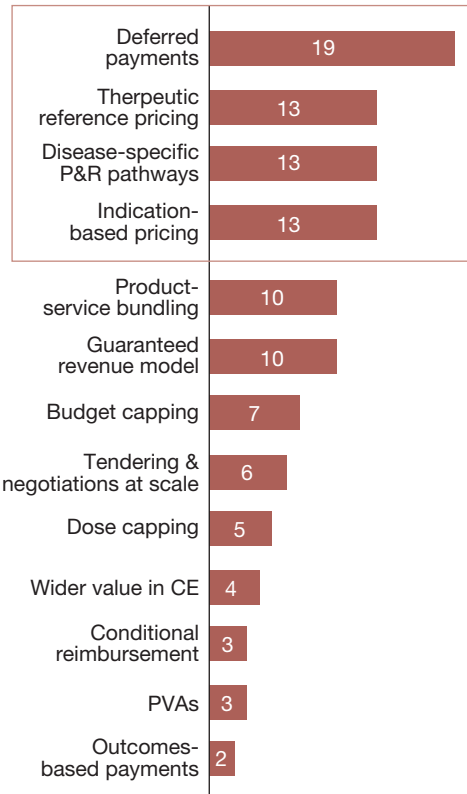
respondents (n=42)



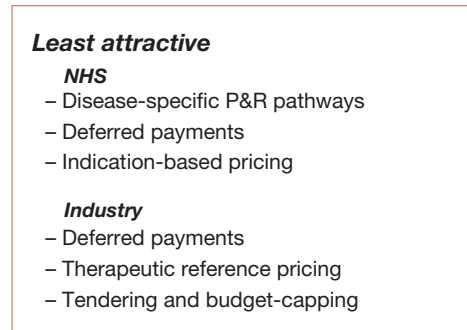
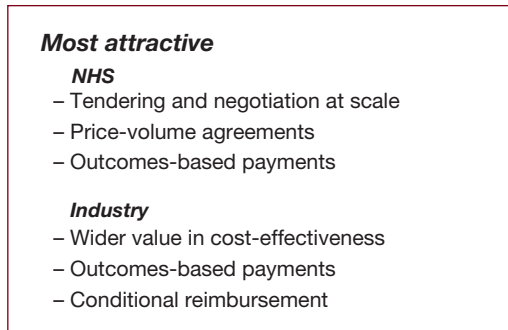
Most attractive schemes



Least attractive schemes



Schemes ranked by respondents



Source: Strategy& analysis

Based on the input from a variety of stakeholders to assess the suitability of each of the long-listed pricing and reimbursement schemes for implementation in the UK, we recommend the inclusion of the following pricing and reimbursement schemes, as part of the framework. (See Exhibit 13.)

Exhibit 13
Recommended Pricing and Reimbursement Framework

Pricing and reimbursement controls



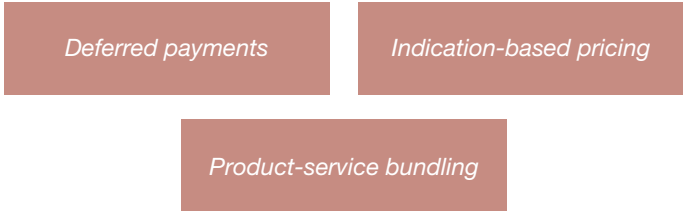
These schemes are already implemented within the UK and used extensively for medical devices and digital products. They enable the NHS to leverage scale as a single payor.

Outcomes-based schemes



Outcomes-based schemes are broadly viewed favourably as a way to reward innovators for effective products, while prioritising patient outcomes.

Novel schemes



The novel schemes challenge the way products are currently funded in the UK but could yield considerable value for companies, the NHS, and patients. There was less consensus on their value, as they apply to a narrow range of products, but we have included them here because they can improve affordability and value recognition.

Source: Strategy& analysis

It is critical to note that these schemes represent a series of options that will need to be applied to products on a product-by-product basis, either singly or in combination. For example, for products for anti-microbial resistance, dementia, and ultra-orphan, additional schemes could be applied. We put forward some recommendations as follows:

Anti-microbial resistance – The guaranteed revenue model could be applied for high-priority products designed to tackle AMR. This mechanism may incentivise innovators to invest in research into new antibiotics by guaranteeing revenue streams, even when the product is subject to stewardship in the market. The ongoing O’Neill review³ is

looking into how to tackle drug-resistant infections with recommendations for solutions expected in Spring 2016.

Dementia products – To align with the Prime Minister’s challenge on dementia 2020, schemes based on R&D royalty investments could be considered, where private funders invest on the future returns of R&D products. This investment structure could be extended as part of a Health Impact Bond, under which private investors securitise government bonds with manufacturers, who are contracted to provide services to a specific patient group and are measured on health outcomes.

Orphan disease products – A variety of schemes could be applied to orphan disease products, which challenge both innovators and payers. To contain cost, payers could move to a cost-plus methodology for setting prices, akin to how orphan disease products are priced in Japan. This is unlikely to be welcomed by innovators and will raise similar issues regarding how total costs are calculated, as is seen abroad. Alternatively, dose and budget caps could be applied to orphan populations that are readily identifiable and predictable.

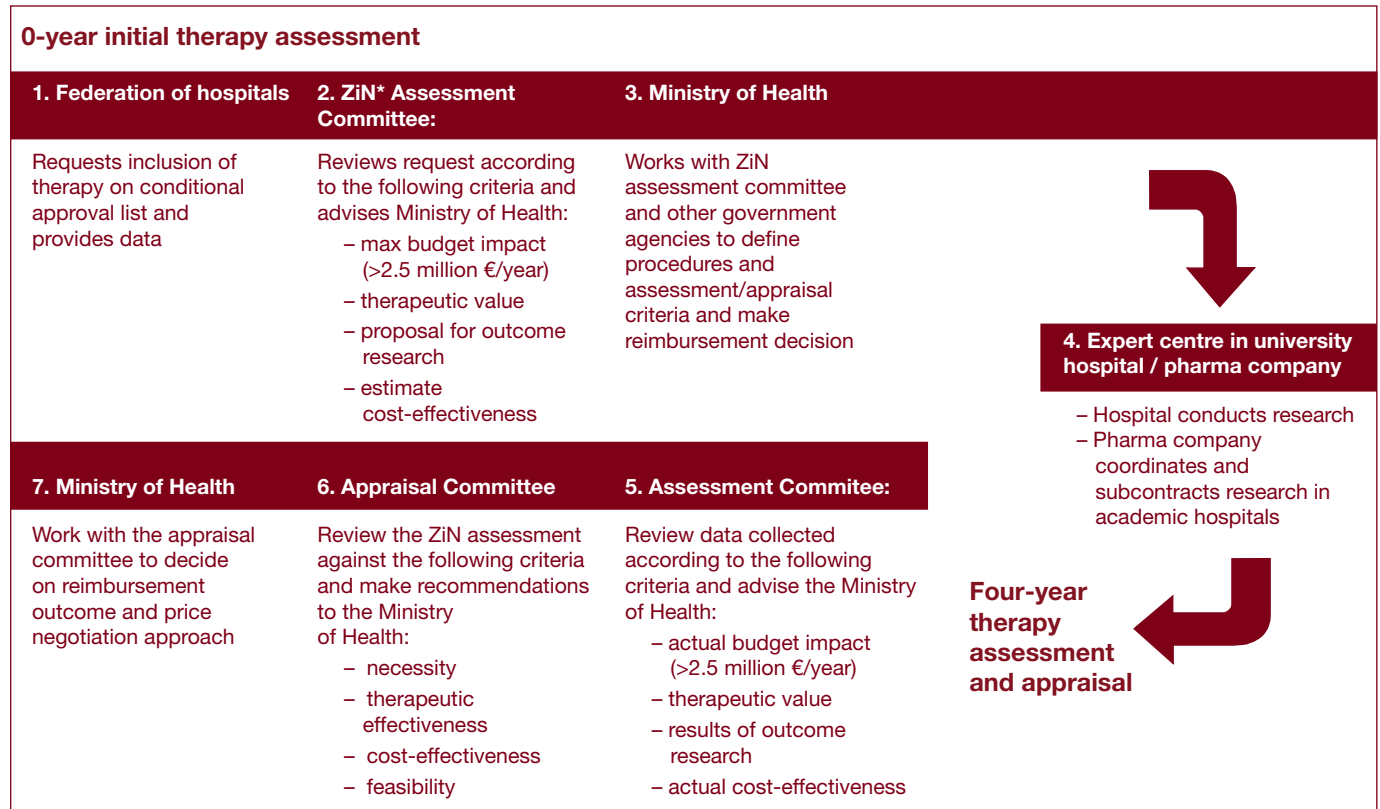
Case study: Conditional reimbursement (The Netherlands)

Description

In 2006, the Dutch Ministry of Health introduced a conditional reimbursement scheme that would allow certain types of therapies

with clinically and economically poor data sets—specifically those with high costs and those for orphan conditions—to be temporarily approved for reimbursement and then reevaluated after four years.

During that period, manufacturers work to establish the therapy’s therapeutic value and cost-effectiveness in daily practice.



* “ZiN” is the Zorginstituut Nederland (The Care Institute), which oversees the Dutch healthcare system

Source: ‘Governance of conditional reimbursement practices in the Netherlands’ Boon, Mertins and Koopmanschap, ‘Conditional Reimbursement in The Netherlands’ Caroline van de Meijden, ISPOR 2013.

Successes

- The scheme has allowed The Netherlands to respond to pressure from patient organisations and the public concerning the lack of support and access to therapies that treat unmet medical need and rare disease.
- Patients can now access expensive and orphan therapies in an accelerated and equal manner.
- Manufacturers are allowed the time to further detail their data sets whilst realising income and the onus is on them to demonstrate the performance of their product.
- Payers have the ability to review the product dataset at a point in time and re-assess their reimbursement and pricing decision.

(continued, next page)

Challenges

- Aligning across different parties and establishing a single driving force seems to be an issue as the model for conducting the research varies—ownership sometimes lies with expert centres in university hospitals, sometimes with the pharma company and sometimes with neither taking the lead.
 - The collection of rich data remains challenging as there are often small sample sizes and a lack of consistency in data collection / missing data. Four years remains a challenging time frame to provide comprehensive data sets in some patient populations.
 - Until now, no therapies that have been conditionally reimbursed and subsequently had their reimbursement re-assessed have been delisted mainly due to public pressure and ethical considerations reducing the relevance of evaluating the cost-effectiveness data. This is a challenge for the country to curb pharmaceutical spend.
-

Case study: Outcomes-based payments (Italy)

Description

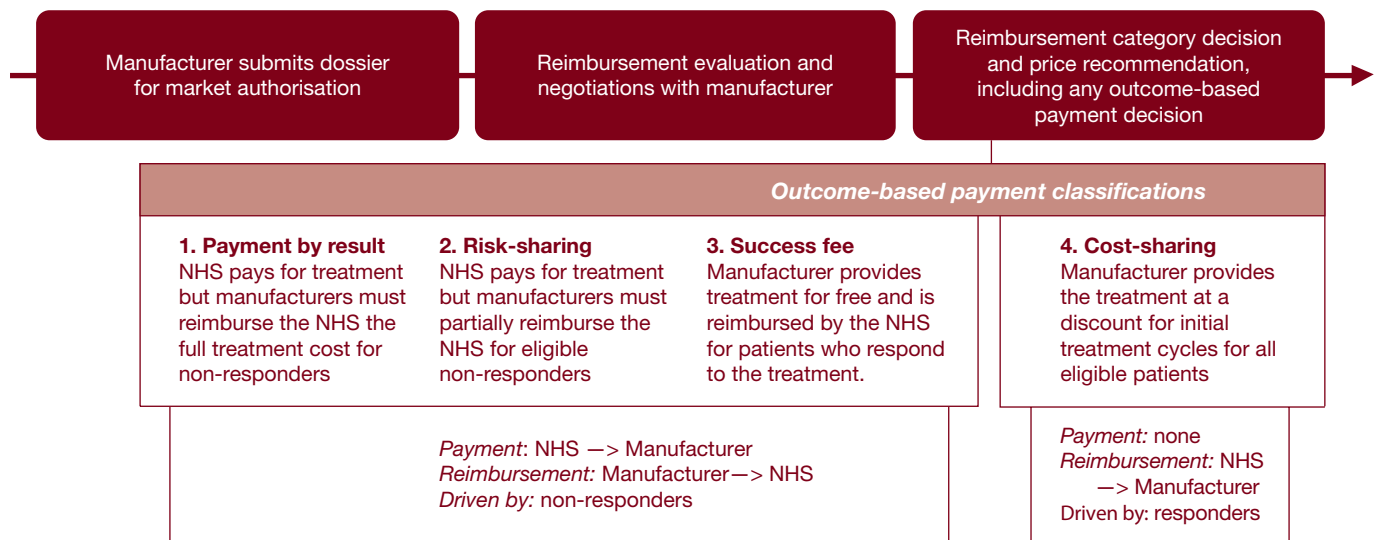
Italy has been a pioneer in implementing innovative pricing models. In 2006, it implemented an outcomes-based payment scheme for high-cost therapies.

The country has a plethora of performance-based pricing options, which the National Health System uses to make price recommendations and reimbursement decisions for a given therapy. Between 2006 and

2012, 22 drugs were reimbursed through this scheme, providing patients with earlier access and mitigating uncertainty about new therapies, the schemes are complex and present significant challenges.

The Italian Medicines Agency (L'Agenzia Italiana del Farmaco, AIFA):

centralised institution for all pharmaceutical pricing and reimbursement decisions



Negotiations between AIFA and the manufacturer determine the specific outcomes that will distinguish between responders and non-responders

Prescribing centres



¹ In relation to the success fee scheme, any failure of the prescribing centre to submit outcomes to the manufacturer is considered a successful treatment

² Refunds from the manufacturer are made to the hospital general budget and not directly to the prescribing centre.

Source: 'Do the Current Performance-Based Schemes in Italy Really Work? "Success Fee": A Noel Measure for Cost-Containment of Drug Expenditure' Navarra et al, 2015.

Successes

- Patients have accelerated access to expensive and innovative therapies that may be clinically effective, especially in oncology.
- The reimbursement directly links to its success in real-world clinical settings, providing the NHS with value for money and manufacturers with fair reimbursement for effective therapies.

(continued, next page)

Challenges

- There is a responsibility gap between the stakeholder that receive the reimbursement (hospital) and the actual body in charge of the reimbursement procedure (prescribing centre). This stakeholder misalignment is likely to affect the quality of data collection and the commitment to submitting refund requests.
- These reimbursement schemes have complex processes and interfaces that are difficult to navigate, creating administrative inefficiencies.
- Manufacturers and the NHS sometimes struggle to define precise data-collection periods and endpoints, which can often result in reimbursement and/or payment disputes.

Each of the schemes demand system changes so that they can achieve their intended objectives

Many of the schemes included as part of the pricing and reimbursement framework are implementable as part of the existing system, for example through complex Patient Access Schemes (PAS). However, the schemes suggested, although largely possible now, have been historically difficult to arrange and implement, which is reflected in the relatively low number of complex schemes that have been agreed upon (70% of the schemes currently in place are simple PAS). From a NHS perspective, simple discounts are by far the easiest way to guarantee affordability. The intention is to have a range of schemes from which industry can choose while achieving some level of standardisation on time horizons and outcomes to monitor so as to reduce the complexity to manage.

For each of the schemes included in the pricing and reimbursement framework we have outlined some of the considerations that are critical for implementation. (*See Exhibit 14, page 57.*) There are several additional factors that will need to be true for implementation of the framework to be successful, outlined here:

Implementing the flexible pricing and reimbursement framework will require clarity as to how products enter and exit the framework

Before the framework is included as part of an accelerated access pathway, further consideration will need to be given to the types of products that the AAR would like to support through the pathway. Our view is that the pricing and reimbursement framework could be applied to a wide set of products, broader than those that would receive support along the current pathway.

There are several sets of criteria that will need to be clearly articulated and applied as products access the accelerated access pathway and/or the pricing and reimbursement framework. Significantly, criteria will need to be established for how products exit the pathway, particularly if products are given only temporary funding. Innovators and payers will need to establish how it will be determined if a product is (a) fully reimbursed following a temporary funding decision; (b) recommended for another round of temporary funding; (c) not recommended for full reimbursement following the data collection period.

The AAR also is considering how the framework will need to be funded, resourced, and co-ordinated. Establishing the role of each of the stakeholders, and putting in place the required resources to support new capabilities, will be critical to successful implementation.

Any negotiated pricing and reimbursement scheme will need to remain confidential

The selection of an appropriate pricing and reimbursement scheme will be crucial in establishing a mutually beneficial commercial arrangement between innovators and healthcare payers. This will be facilitated by open, early dialogue between the relevant stakeholders that will establish which organisation is responsible for proposing a selection of pricing and reimbursement schemes and whether the relevant stakeholders will be reactive or proactive with regards to the schemes. Under either approach, to reach consensus, there will be the need for negotiation around the applicable schemes. Our recommendation would be to maintain the HTA body's independence from negotiations and affordability discussions but identify and build the right capabilities within the NHS to do this.

The selection of an appropriate scheme will be facilitated if schemes can be incorporated as part of the HTA performed by bodies such as NICE. This could allow for the HTA body to begin to suggest prices at which the products under review become cost-effective, giving innovators greater clarity around the value assessment and potentially reducing the length of time required for decisions to be made on products (e.g., rather than a product requiring the development of a patient access scheme). Fundamental to these negotiations will be the need for confidentiality on net pricing, which innovators have expressed the need for in light of international reference pricing. The NHS and DH will need to confirm to what extent this is possible in the context of the EU Transparency Directive although we know that commercial confidential agreements are already in place in the UK and other EU countries.

The selection of an appropriate pricing and reimbursement scheme will be crucial in establishing a mutually beneficial commercial arrangement between innovators and healthcare payers.

Tendering remains a requirement for many classes of medical technologies given EU procurement regulations and thresholds

Tendering is included as a potential scheme because for any NHS organisations procuring goods or services over the value of €134,000 (or £111,676) EU law provides rules concerning the tender process that should be followed. This is particularly true for medical devices, diagnostics, and digital products where often there are multiple apparently equivalent products. In addition, the Commercial Medicines Unit (CMU), part of the Department of Health which administers tenders, - strictly interprets EU law and tenders for products within unique suppliers. Tendering is time-consuming and difficult for SMEs who cannot always meet some of the stringent tender requirements e.g., three years of financial records, or case studies of similar service provision.

Having the right RWD collection and analytics platforms will be critical for success of the flexible pricing and reimbursement framework

Data is a fundamental enabler of many of the pricing and reimbursement schemes outlined in the framework. Many public and private initiatives are focused on improving and embedding the way that data is collected as part of routine care in the NHS. We have explored the need for the collection for Real World Data in a later chapter in this report. Having the right infrastructure will also go some way to simplify managing these schemes which could otherwise be time consuming to administer for the NHS.

As the UK healthcare ecosystem gains experience with these flexible pricing and reimbursement schemes, it will be important to review their success and to build on what has and hasn't generated benefits for patients, the industry, and NHS.

As the UK healthcare ecosystem gains experience with these flexible pricing and reimbursement schemes, it will be important to review their success and to build on what has and hasn't generated benefits for patients, the industry, and NHS.

Exhibit 14

Implementation considerations for pricing and reimbursement schemes

Scheme	Implementation considerations	
<i>Tendering and negotiations at scale</i>	<p>Tendering at Scale may offer the NHS and NHSE the <i>opportunity to leverage its power as a single payer</i>, but the <i>complexity of existing commissioning structures</i> are seen as a barrier for innovators, particularly where the routes to market are not clear.</p> <p><i>Tender processes are already implemented</i> within the UK, particularly when goods are valued >about £110k, for medicines, medical devices, and digital products. (See section on Tendering Excellence.)</p> <p>Innovators have stressed that tendering specifications will need to <i>recognise the value of their products</i> and not include large baskets of comparators into the tender. This may require tendering organisations to develop new capabilities to establish the scope of new tenders.</p>	<p><i>Contracts lengths</i> will need to be such that the NHS isn't locked into anti-competitive agreements, particularly where product iterations are short (e.g. for medical devices and digital products).</p> <p>SMEs may find it <i>challenging to meet the requirements</i> for tendering e.g., historical experience meeting tenders, financial history etc.</p>
<i>Price-volume agreements</i>	<p>PVAs can be applied under existing tendering frameworks and should give payers and innovators greater security around the cost of products and price respectively.</p> <p>Broadly, innovators of medicines view PVAs as a <i>second product-level cap on spend</i> when applied under the existing PPRS.</p>	<p>The application of PVAs doesn't necessarily correlate with increased uptake of products in the market. Innovators may <i>desire a commitment on driving uptake</i> of products in greater volumes when proposing a price-volume framework.</p> <p>For product-level PVAs to be more widely implemented within the UK, there will be a need to <i>track uptake of products at regular intervals</i>, which may be challenging for some medical devices. There also will be a feedback mechanism so that cumulative discounts can be calculated and reflected.</p>
<i>Outcomes-based payments</i>	<p>The use of outcomes-based payments <i>aligns with the direction of travel</i> for rewarding innovators for the impact of their products on patient outcomes.</p> <p><i>Endpoints will need to be agreed upon</i> between the contracting parties for performance to be measured against. NHS stakeholders are more likely to agree on contracts that are based on clinical endpoints. For some diseases this can be challenging to measure.</p> <p><i>Data collection infrastructure</i> will need to be in place for measurement of performance against the standards set in the agreement. Such data infrastructure does exist for some disease areas (e.g., SACT for cancer) and may therefore be well suited to pilot initial outcomes-based payment schemes.</p>	<p>When considering success-fee schemes, innovators may seek to <i>limit the amount of time over which outcomes data is collected</i> (e.g., to 6 months). Shorter collection periods will help innovators with <i>revenue recognition concerns</i> and the <i>cost of capital</i> associated with providing product up-front. Moreover, innovative SMEs may not be in the position to provide product for free for extended periods of time. Shorter data collection periods will, however, necessitate that only indications where meaningful endpoints can be gathered in shorter periods of time are covered.</p> <p>There are also some concerns that companies may raise their prices to adjust for the risk associated with outcomes-based payments although, to date, this doesn't seem to be the case with outcome-based payments in other countries e.g., France with Sovaldi.</p>

Exhibit 14 (continued)

Scheme	Implementation considerations	
Conditional reimbursement	<p>Conditional reimbursement schemes will give innovators an opportunity to collect a variety of data sets (clinical, economic, social) to support future submissions, while providing patients with earlier access to game-changing products.</p> <p>For conditional reimbursement schemes to be successfully implemented, there will need to be agreement between the innovator and payer regarding the terms of the data collection period. The terms will include: the length of time over which data is collected, the types of data to be collected (including agreement over endpoints), who will be responsible for collecting and funding the collection of data, how data collection will be monitored, how success will be measured, and the criteria for decision-making following the collection period (i.e. under what conditions will full reimbursement be given, how will products be de-listed, and can the data collection period be extended if all the data collection conditions are not met).</p>	<p>For innovators there is also a desire that any decision made around a price for a product under the conditional reimbursement period is subject to review and updated following the data collection period.</p> <p>Innovators have expressed a desire to own the data collected during conditional reimbursement periods, particularly where that data can support data submissions beyond the UK.</p> <p>As with outcomes-based payments, data infrastructure will be crucial to the successful implementation of a conditional reimbursement scheme. Innovators and the NHS will likely need to partner to pilot and establish this infrastructure, particularly in indications where existing capabilities are lacking.</p>
Deferred payments	<p>Deferred payment models are only likely to be applied to products where there is a clinical imperative to identify or treat patients as quickly as possible. Accelerating access to treatment will increase short-term costs but may lead to downstream cost-savings if the product reduces later care costs or reduces unnecessary treatments in the case of a more definitive diagnosis.</p> <p>Innovators are likely to enter into a deferred payment scheme only where financial intermediaries can be used to provide an additional return on investment, given the higher cost of capital when compared with government</p>	<p>Current budget structures in the NHS are not well suited to a deferred payments scheme as they are annualised and siloed across different care settings. Where products that receive a deferred payment scheme are cost-saving in the long term it is likely that savings will be realised across a variety of care settings (primary, secondary and social) and there is no current system for linking these savings.</p>
Indication-based pricing	<p>Indication-based pricing potentially represents the best mechanism through which to recognise the value of products at specific indications. This could deliver value for the healthcare system, where highly effective indications are priced accordingly and less effective indications discounted.</p> <p>There are multiple ways in which indication-based pricing could be implemented within the UK, either as a weighted average price, calculated on the price at individual indications, or as separate list prices for each indication. There are some concerns that in most cases indication-based pricing will be cost-additive although it is currently used by the Cancer Drugs Fund.</p>	<p>There are concerns that indication-based pricing is not implementable in the UK, particularly as schemes of this nature are technically available at the moment but not implemented.</p> <p>Further challenges to implementation include the complexity of arranging multiple net prices for different indications behind a single initial list price and the necessary rebate and data collection structures that would need to be in place to support this.</p> <p>However indication-based pricing is implemented, there would be clear need for each indication to be considered cost-effective, priced at, or below, the cost-per-QALY threshold.</p>

Exhibit 14 (continued)

Scheme	Implementation considerations
<i>Product-Service Bundling</i>	<p>Product-service bundling may be a particularly attractive opportunity for diagnostics, medical devices, and digital products, where multiple products and services are likely to be used in combination (e.g., where implementation of a medical device would incur a large change in a clinical pathway or workflow and thus require process re-engineering support).</p> <p>Concerns have been raised around the price transparency of individual products that are procured as part of a product-service bundle, as well as the potential for anti-competitive behaviours arising from single manufactures providing multiple products or services.</p> <p>Although implemented widely in other industries product-service bundling is not typically applied as a direct pricing and reimbursement scheme for medical technologies.</p> <p>For implementation, a framework for procurement of bundles will need to be developed that addresses these issues. Further consideration could be the development of a services agreement based on outcomes, under which a provider is tasked with managing health outcomes through the provision of any relevant products or services.</p>

The schemes can be applied to innovative products on the horizon from cell therapies, to cancer companion diagnostics, to a digital support community

To illustrate how the flexible pricing and reimbursement framework could be applied to products on the horizon we have explored some products in detail. (See Appendix D.) We have considered which pricing and reimbursement schemes could be selected from the framework for a particular class of product, depending on the product attributes.

Please note that we have not developed the criteria that would be applied to products to determine their eligibility for different schemes, but we have considered what product attributes would lend themselves well for application under a certain scheme. The scheme applicability criteria will need to be given careful consideration both by the AAR team, as well as members of the National Innovation Partnership.

To illustrate how the flexible pricing and reimbursement framework could be applied to products on the horizon we have explored some products in detail.

Product case studies

We use four distinct medical technologies to describe how the accelerated access pathway in conjunction with the pricing and reimbursement framework could work in practice

A biologic cancer medicine which targets a specific tumour mutation and increases survival by 10 months compared to standard of care

Following early dialogue, the product would be deemed as breakthrough and be offered access to the accelerated pathway. On the basis of Phase I clinical trial data, the MHRA would designate it as a PIM which will act as a signal to downstream UK stakeholders and investors in the company that the product could gain rapid access post-MA. In addition, the innovator would apply for a PRIME designation to gain support from the EMA as its development progresses. Once the Phase II data read out confirms Proof of Concept of the product, the innovator submits the latest regulatory dossier to the MHRA where it obtains a Scientific Opinion. The innovator can apply for funding pre-MA to obtain a flat fee contribution towards the costs of manufacturing and distributing this high cost biologic product. The product is then available through EAMS in selected cancer centres to manage access and collect Real World Data (RWD) whilst completing further clinical trials (most likely Phase IIb and Phase III studies) in this indication and others. In line with its global strategy, the innovator will file for centralised review by the EMA and request conditional regulatory approval.

Draft HTA guidance (FAD) will correspond with the conditional Marketing Authorisation approval so the product is available for prescription in the NHS and uptake can begin as soon as the license is in place. HTA review with new data can take place at a later stage using RWD e.g., from an evolved SACT database connected to other healthcare databases to re-determine the product's value in a real world setting.

Given the rapid progression of this product through clinical trials, the product receives a temporary funding decision where the following pricing and reimbursement schemes are applied:

Given the rapid progression of this product through clinical trials, the product receives a temporary funding decision.

- *Conditional reimbursement* - An agreement is made that the product is reimbursed at a discounted initial reimbursement level on the condition that further data is collected on the primary indication in real world settings. Further pre-MA clinical trials also are launched investigating the clinical efficacy of the product in a second cancer indication.
- *Outcomes-based payments* - Preliminary evidence indicates that the product increases measurable survival of patients by 10 months in the primary indication. To support the initial reimbursement period, a rebated outcomes-based scheme is applied. The innovator receives payment for the product up-front but rebates the cost of treatments that don't demonstrate an agreed upon level of improvement in progression-free survival.

Following a two-year data collection period, a new evidence dossier is submitted, which includes both the newly collected Real World Data for the primary indication and clinical trial data for a second indication. Following review of the new evidence, full reimbursement at both indications is granted under an Indication-based Pricing scheme. A price ceiling is established for the product and rebates are provided at the two different indications in the market. Should the product not live up to its promise then the price will need to be revised to reflect the new evidence and the product may need to be delisted.

A companion diagnostic product for a cancer medicine

At the stage of early R&D, the CDx innovator engages with academia and NHS clinicians to identify new biomarker targets aligned to pipeline drugs and clinical priorities in the UK. These pre-competitive collaborations are supported by existing platforms and initiatives such as the MRC/EPSRC pathology nodes, AHSNs, and the Precision Medicine catapult which support the innovator to test the biological feasibility of the product. Then the CDx innovator engages with the medicines innovator to co-develop a drug-device combination, and the CDx innovator would file for a CE mark certification before Marketing Authorisation submission.

The HTA body and the CDx innovator agree on a cost-effective price for the product which will automatically be the maximum price for the procurement exercise. Draft guidance will provide a funding mandate for the medicine-device pairing but will not recommend a specific brand of CDx for uptake. Post HTA, and to accelerate access to the companion diagnostic and reward the investment in being “first to market”, the procurement process will start as soon as the product is launched. Three months later, the in-house tests and other commercial diagnostics

Should the product not live up to its promise then the price will need to be revised to reflect the new evidence and the product may need to be delisted.

tests will be available on the market, but the innovator will now have a strong market share and can compete on price given the volume uptake.

Following HTA, the medicines and CDx innovator enter into a commercial agreement which enables the medicines innovator to respond to a tender for the medicine and diagnostic as part of a product-service bundle. Because the diagnostic effectively stratifies patients according to their genotype, an outcomes-based scheme is also agreed upon, under which payments for medicine where the treatment is not effective are rebated back to the payer.

Implantable pancreatic medical device to assist glycaemic control in patients with insulin dependent diabetes mellitus

Upfront dialogue provides the innovator with early feedback from end users on the specification required from the device to enable safe and effective use. It is expected that this product would be considered breakthrough and it is likely to be considered for a promising device designation. This would provide the product with a greater level of regulatory and HTA support during the development process. In addition to clinical studies, the innovator tests the product in a real world setting by forming strategic partnerships with chosen “test bed” centres, enabling ongoing collection of RWD and refinement of the product to meet the needs of patients.

Uptake also will be encouraged through simultaneous regulatory and HTA decisions which speed up decision making around the most appropriate mechanism for reimbursement.

Given the wide applicability of the product, the expected cost of supplying the patient population, and the requirement for tendering under EU procurement law, a tendering process is applied for the device. Evidence from the business case developed for HTA indicates that uptake of the product will change the clinical pathway for patients. Patients will no longer have to self-inject insulin and the new workflow pattern will require nurses to fit the device. To support the implementation of these changes (e.g., the required re-engineering of the clinical pathway) the product is tendered as part of a product-service bundle. The innovator is provided with support regarding the information required to tender as part of the relationships that were established during early dialogue, including the selection of a partner service provider to meet the tender. Upon successful completion of the tender, a price-volume framework is established between the innovator and the NHS, given the relatively predictable patient population.

Upfront dialogue provides the innovator with early feedback from end users on the specification required from the device to enable safe and effective use.

A digital support tool for people suffering from mental health conditions

The digital innovator reads NHS-published product specifications on desired products and uses this to develop a product prototype to meet provider needs. Then, the innovator engages in the National Information Boards four-step endorsement process. This process includes an initial stage of self-evaluation followed by a community evaluation on the potential of the product for NHS uptake. The last two stages include the development of a business case and an impact assessment of the products clinical efficacy and cost effectiveness. Evidence is generated throughout the process via pilots with local providers and this is submitted for HTA.

The HTA body assesses the business case using the pilot data and provides a recommendation on cost-effectiveness for nationwide rollout. The recommendation is attached to a funding mandate and may be connected to a scheme or set of schemes from the flexible pricing framework. Uptake of the product will subsequently be gathered by AHSNs and fed into national level tracking to support and spread further adoption.

This product would be procured under a tender that could be combined with a product-service bundle. The bundle could apply to the provision of the app and additional counselling services.

Evidence is generated throughout the process via pilots with local providers.

Potential benefits of the accelerated access pathways

As described earlier in the report there are many challenges that need to be addressed within the UK healthcare, clinical research, and medicines ecosystem. However, should the relevant stakeholders be able to evoke the necessary change, we believe that many stakeholders stand to benefit, from industry to the UK government. The changes are imperative for the UK to be seen as leading in the EU in terms of life sciences and innovation uptake.

Patients, the NHS, industry, HTA bodies, Regulators, and the UK government all benefit from the accelerated access pathways

In line with the principles outlined for the accelerated access pathways, the proposed pathways deliver benefits across the different stakeholder groups: patients, the NHS, industry, HTA bodies, regulators, and the UK government.

Patients remain centre stage from the start of the pathway, illuminating areas of need. They receive medicines pre-MA and rapidly post-MA after the final HTA guidance is issued so that they receive seamless care as the product progresses through its development. Over time, the standard of care in the UK will increase to match that of the other major markets. The assessment performed by the MHRA, resulting in the Scientific Opinion (SO), provides reassurance to patients that based on current evidence there is a net positive benefit-risk assessment. Robust processes to manage safe prescribing, whether in primary or secondary care, together with an effective framework for collecting, reporting, and analysing safety information provides confidence to the public that despite early access, the quality of medicines is not compromised. Patients also benefit from earlier and more extensive piloting and adoption of innovative medical devices and digital products following national mandates post-HTA for funding. The robust economic data collection processes provide confidence that the value of medical devices in delivering patient outcomes and potentially cost savings is maintained throughout the lifecycle of the medical device/digital products.

As described earlier in the report there are many challenges that need to be addressed within the UK healthcare, clinical research, and medicines ecosystem... The changes are imperative for the UK to be seen as leading in the EU in terms of life sciences and innovation uptake.

The NHS (providers, procurement, local payers) benefits from support and, if relevant, incentives to uptake innovation across the groups of medical technologies. The NHS (England and devolved administrations) is involved early on to define the areas of UK unmet need and support the HTA body as it works with industry to select the appropriate pricing and reimbursement schemes. The NHS then acts as partner to develop the medical technologies using existing infrastructure to support clinical and economic evidence supplemented by RWD (including patient-reported outcomes). The schemes deliver value to the NHS and the maximum ceiling price for tenders, where relevant, is set by the HTA process. This makes tendering simpler, whether at national or local level, since the value assessment has been completed centrally and the procurement organisation can focus on price and the overall service offering.

Industry benefits from a streamlined infrastructure that is clearly signposted, ready to support innovative clinical trial designs across multiple therapy areas, and able to leverage the power of new technologies such as genomics. As such, innovations can benefit from a faster route to access by up to six years post-MA for transformative medicines. (See Exhibit 15, next page.) This acceleration could bring additional revenues per product, of between £11 million for niche orphan products to £525 million for more mainstream medicines mostly available in primary care. In the case of products which do not match the target product profile, products can fail quicker, allowing industry to reduce futile costs and increase portfolio efficiency.

Pilots to improve the RWD infrastructure also will benefit the industry: industry will be able to access the data and perform its own analyses to support regulatory submissions and pricing and reimbursement across the UK and eventually across the rest of the EU. We estimate that by focusing the RWD studies predominantly in the UK, companies could save up to £80 million per product by reducing the number of centres and studies elsewhere in the EU. Funding at the relevant parts of the accelerated access pathways pre- and post-HTA will allow the industry to accrue additional revenues, and much earlier on in the lifecycle of the product. In addition, the collaborative environment that the NHS and AHSNs will foster between industry and key UK stakeholders, including the NHS, will provide clarity to industry early on around areas of unmet need, of upcoming evidence requirements, and about what price the NHS can afford for a particular medical technology.

The NHS (providers, procurement, local payers) benefits from support and, if relevant, incentives to uptake innovation across the groups of medical technologies.

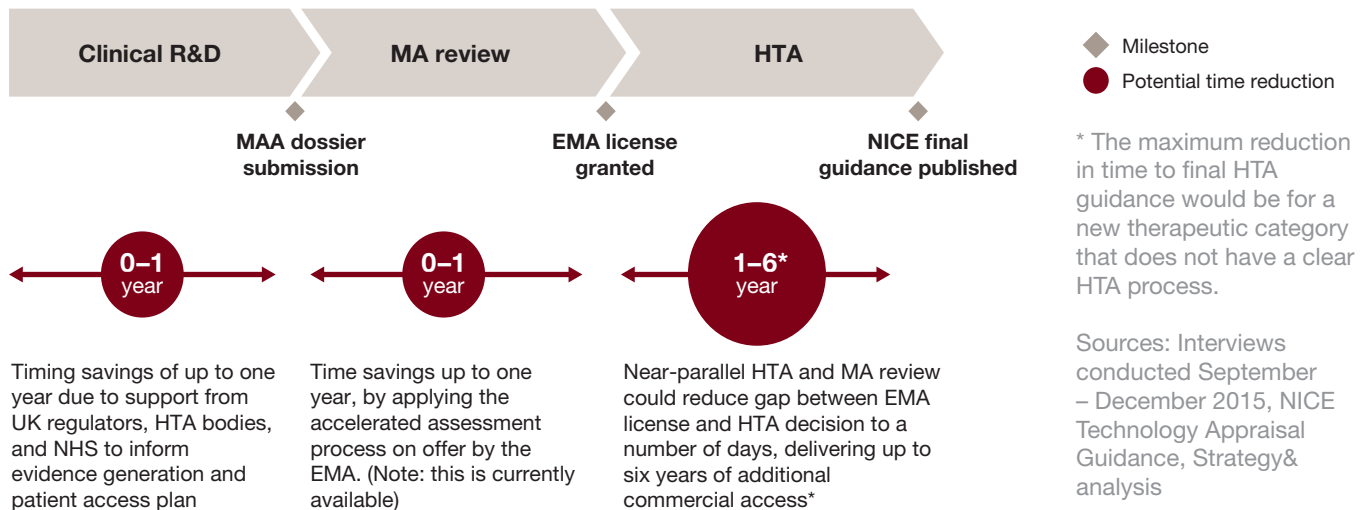
Size of potential benefits for medicines development

Via interviews with industry members and research organisations, we estimated the potential benefits of the accelerated access pathway for three different medicines. The information was obtained directly from companies and supplemented by desktop research and independent analysis to estimate the time- and patient access- impact of the early access pathways for these products.

Exhibit 15

Potential benefits for medicines development

Accelerating development, regulatory, and HTA timelines for medicines



Delivering earlier and greater patient access in conditions with high unmet need

<p>Case 1. Cell therapy for cartilage replacement</p> <p>600–1,500 additional patients treated over six years (based on an estimated addressable market of up to 500 patients per year, over 6 years of additional commercial access)</p> <p>£11 million–£28 million in additional revenue*</p>
<p>Case 2. Oncology immunotherapy for an orphan indication</p> <p>Up to 150 additional patients treated over 3 years (based on an incidence of 80 patients eligible for treatment per year.)</p> <p>£11 million in additional revenue*</p>
<p>Case 3. Novel mainstream primary care product</p> <p>Up to 15,000 additional patients treated over 14 months (based on a large addressable market with more serious disease treated first, assuming a likely uptake of roughly 12 percent based on competing products and market dynamics)</p> <p>£525m additional revenue*</p>

*Revenue estimates are based on list prices.

Sources: Interviews conducted September – December 2015, NICE Technology Appraisal Guidance, proprietary forecast data from biotech and pharmaceutical companies, EvaluatePharma Strategy& analysis.

Strategy& view

Through adoption of the accelerated access pathways, we see a clear opportunity for industry to achieve earlier patient access for potentially transformative products in the UK post-MA. The increased revenues do not take into account use pre-MA but were noted to be significant for all three companies who worked with us on the case studies (percentage of total revenues could not be shared due to commercial sensitivities). To note that although some reduction in time to access is possible, this is the result of a faster HTA process. Given that industry is still experimenting with new clinical trial designs and how to use RWD in the context of their global development plan, it is not envisaged that there are cost-savings pre-MA during development. However, if the UK was able to provide support and infrastructure with RWD collection, we estimate that overall cost of their Phase IV / RWD trials could be lower by approximately £80million per product for a mainstream product. Further analysis will be necessary to confirm these benefits with further types of products and other medical technologies.

A comparison of the access journey for a mainstream product in England and other EU markets

Taking one exemplar mainstream product—we examined the potential future patient access route using the accelerated access pathway and compared this to the paths the product took in England, France, Germany and Spain. This case study was developed in conjunction with a Pharma company based on the experience of their European market access team and has been supplement by independent analysis and research by Strategy&.

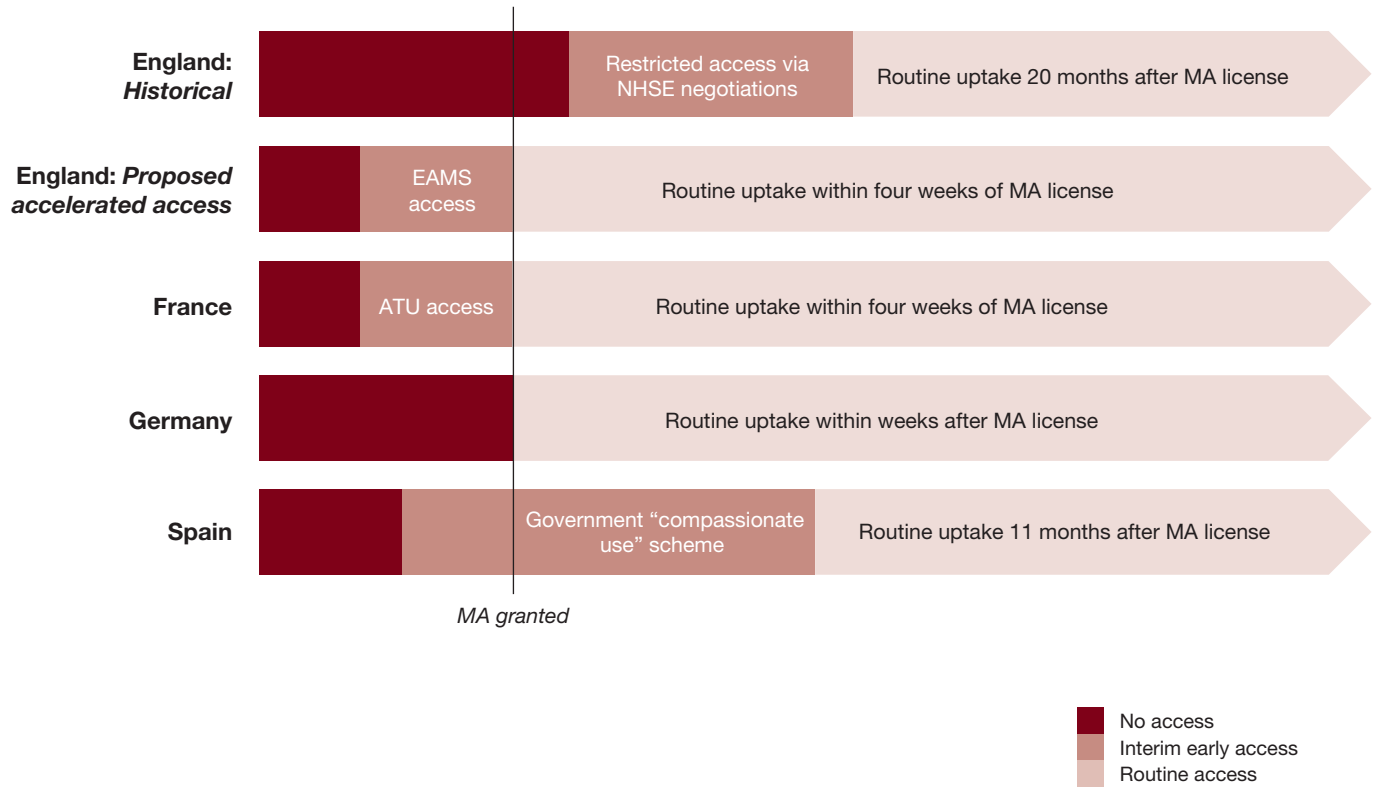
Time taken to achieve routine patient uptake for mainstream product across the EU

In England, patients did not receive full, routine uptake until 20 months post-MA license due to the time taken for NICE HTA assessment and NHS adoption of the recommendation. In comparison, France and Germany offered significantly faster routes to access. Via the future UK accelerated access pathway, it is envisaged that routine patient access can occur shortly after the MA license is granted and is supported by additional patient access pre-MA via the EAMS. It is up to the English system to differentiate itself via its RWD capabilities.

Through adoption of the accelerated access pathways, we see a clear opportunity for industry to achieve earlier patient access for potentially transformative products in the UK post-MA.

Exhibit 16

Comparing the access pathway for England versus that of other EU markets



Sources: Company interviews conducted September – December 2015, literature review, Strategy& analysis

HTA bodies and UK regulators will benefit from being able to provide input earlier on to innovators to guide their evidence gathering efforts, contributing to the overall evidence package that is required across other EU markets. For HTA bodies, changes to their remit and the scope of their decisions will enable them to support more evidence-based use of medical technologies, therefore improving patient outcomes. They will be seen as facilitators of uptake whilst maintaining product quality. For the MHRA, the accelerated access pathway enables the regulator to play a greater role in shaping the clinical development of innovative medicines, companion diagnostics, and medical devices. The pathways encourage innovative clinical trial designs, and encourage regulators to consider together with industry how to best apply RWD to its assessment. Their considerations can then feed into the EU dialogue on how RWD can be used.

Finally, the UK government will have successfully improved patient outcomes and will have started to re-establish the UK as the place for innovators to partner with the whole system to develop and launch their products. This will eventually result in a net positive economic benefit for the UK economy as clinical research flourishes and creates additional opportunities for life sciences graduates. We expect that this, in turn, will incentivise additional companies to invest more broadly in the UK economy, rebuilding commercial organisations within the UK to take advantage of the opportunities to collect globally-relevant RWD and patient experience data well in advance of other markets in order to inform the global development plan, as appropriate. Ultimately this will position the UK as leading across the EU in advising innovators on product development either directly or via the activities of the MHRA within the EMA.

The pathways encourage innovative clinical trial designs, and encourage regulators to consider together with industry how to best apply RWD to its assessment.

Overview of enablers

Patients are a key enabler for the accelerated access pathways in addition to novel clinical trial designs

The *Exhibit 17, next page* summarises some of the key enablers of the accelerated access pathways including the flexible pricing and reimbursement framework. Patients are one of the main enablers as their data is being collected every day by the NHS – they are also a key stakeholder in defining areas of UK unmet need and public health interest early on in the pathway.

Novel clinical trial designs can enable faster decision-making on progression of development

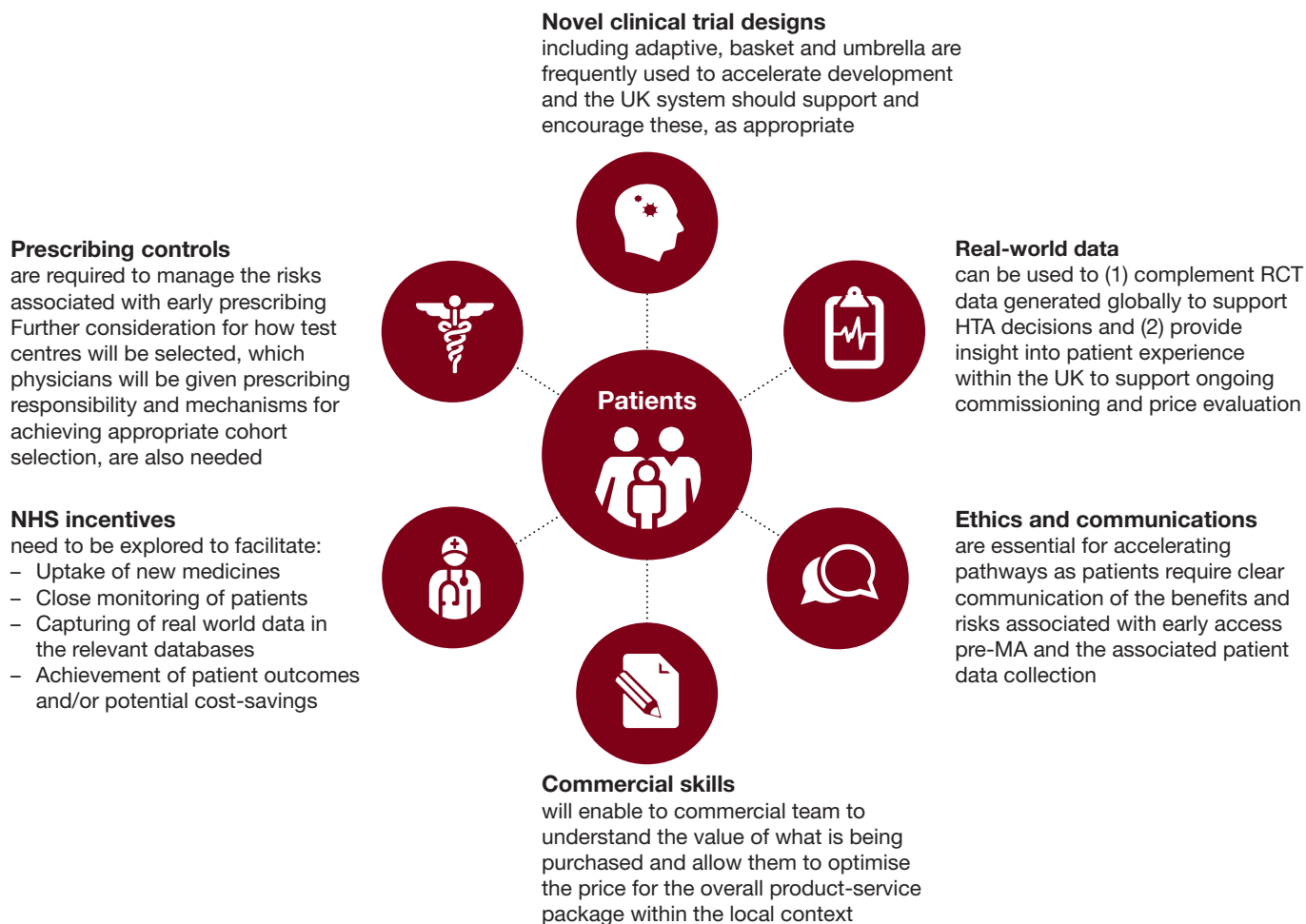
Over the last decade, the number of novel clinical trial designs has increased as a result of new technology, such as next generation sequencing, and as a result of the focus on stratifying patients to better target treatment. This is particularly true in cancer where multiple clinical trial designs for new medicines are now commonplace. (See *Exhibit 18, page 72.*)

In addition, in our discussions with industry and the NHS, we have heard that the traditional sequential phases of clinical trials are increasingly rare, as companies blend phases together. Blurring clinical research and practice is also commonplace, particularly where cocktails of medicines are used, or medical devices or digital products are being piloted within the NHS.

Patients are one of the main enablers as their data is being collected every day by the NHS – they are also a key stakeholder in defining areas of UK unmet need and public health interest early on in the pathway.

Exhibit 17

Key enablers for pathway acceleration



Source: Strategy& analysis

Exhibit 18

Exemplar clinical trial designs being used in cancer medicines clinical trials

Type of clinical trial	Key features	Example trials
<i>Adaptive</i>	Uses advanced statistical methods (such as Bayesian statistics) to adjust design over time based on accumulating clinical data. For example, investigators will stop unsuccessful initiatives or build on successes.	recAP (recombinant human Alkaline Phosphatase) in sepsis-associated acute kidney injury
<i>Basket</i>	Tests a single treatment across different types of disease variations; it is more efficient in that it replaces multiple phase I/II trial with one overarching study	Programmed cell-death ligand 1 in multiple cancers
<i>Umbrella</i>	Tests the impact of several treatments on different molecular variations within a specific type of disease	– Signature trial – National Lung Matrix study
<i>In-life</i>	Merges clinical practice with clinical research	Stand Up to Cancer initiative for melanoma
<i>Pragmatic</i>	Conducted in a real-life setting to assess co-morbidities, polypharmacy, and adherence	Salford Lung study
<i>Virtual</i>	Investigators recruit patients electronically and patients submit data via e-diaries. (Some trial designs use e-diaries in a traditional clinical trial setting.)	REMOTE trial*; Insomnia study

* Although this trial failed to recruit sufficient patient numbers, it demonstrated the value of e-diaries in capturing patient-reported outcomes

Source: Strategy& analysis

Whilst reducing costs is always welcome, most companies focus on new trial designs to either speed up recruitment or to improve the clarity of the risk-benefit data and, therefore, the product's value proposition. In addition, it is equally important to consider the patient view of what outcome measures may be useful to them and how they could contribute to the evidence base.

“Novel clinical trial designs are often necessary when there is some difficulty in recruiting the right patients - this could be because the study is for a paediatric product, for an ultra-orphan indication, or because a specific sub-population of patients is desired for a personalised medicine. In all these cases, the ability to quickly recruit patients is critical to success.” - MHRA

If the UK could support multiple novel trial designs, then principal investigators could act as expert advisors to industry on which approach to select, given the data needs identified early on by UK stakeholders. In order to enable multiple novel trial designs, better incentives need to be in place to encourage NHS staff to partake in clinical research amongst their other duties. There is perceived need for multiple novel trial designs. We have heard from regulators, HTA bodies, and the NHS that often industry shies away from more complex clinical trials that incorporate other data sources e.g., RWD. For medicines, the trials would help achieve seamless passage through the UK pathway via EAMS, and would enable faster EMA approval and potentially market access in EU countries where clinical superiority is critical e.g., Germany and France. These trials could be conducted in parallel to capturing data in real-life use via the RWD infrastructure.

To successfully continue to support novel clinical trial designs, following capabilities should be nurtured:

- *Fast-cycle collection and data analytics* to facilitate adaptive tailoring of trials
- *Seamless integration of the different data types e.g., genomics data, data captured in Electronic Data Capture (EDC) systems for industry, patient reported outcomes, and in particular for medical devices and digital products, economic data to support their business case*
- *Ability to leverage patient registries for more rapid patient identification, stratification, and trial recruitment*
- *Biostatisticians to conduct and analyse complex novel clinical and RWD trials*
- *Early multi-stakeholder input into evidence generation sources, trial design, and definition of endpoints and outcomes*

If the UK could support multiple novel trial designs, then principal investigators could act as expert advisors to industry on which approach to select, given the data needs identified early on by UK stakeholders.

Novel clinical trial designs have multiple benefits for the accelerated access pathway:

- Potential to speed up process of drug development, or to allocate resources more efficiently
- Ability to tailor an ongoing trial test a new hypothesis or to focus on the arm with positive
- ‘Fail fast or file fast’ by accessing data earlier to enable product development decisions
- Smaller sample sizes, shorter trial duration, and a more resource efficient development process
- More informative dose-response information
- Prospective and retrospective stratification, where a specific population can be identified for targeted therapy improving the benefit-risk profile for the stratified population
- Reduce costly (approximately \$500K cost per amendment, Tufts, 2013) and time-consuming (about 60 days to implement, Tufts, 2013) protocol amendments by pre-planning approach to trial modifications

Real-world data can complement clinical trial data to demonstrate real-life clinical effectiveness and outcomes

We don't expect that RWD collection (*see Exhibit 19, next page*) would replace clinical trials in providing the pivotal confirmatory proof of positive risk-benefit for regulatory and HTA approvals, but it could be complementary, particularly with patient reported outcomes, such as quality of life and incidence of adverse events. RWD addresses the limitations of clinical trial interventions, which limit the selection of patient cohorts and typically exclude those with co-morbidities and extensive concurrent medication.

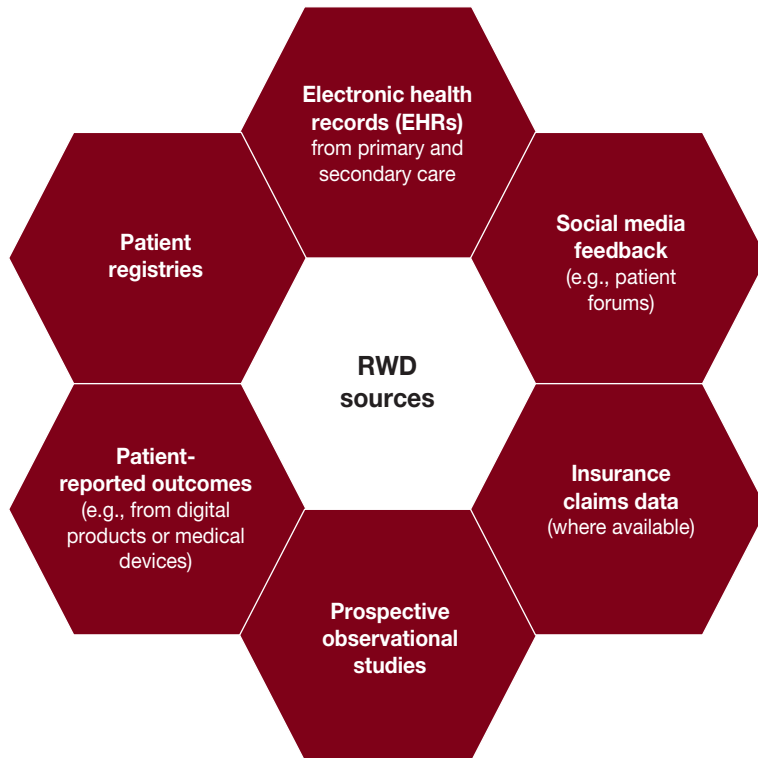
In the nearer term, it is unlikely that RWD can be used to understand product efficacy, but regulators shared with us that they remained keen to consider how RWD could support this end.

For repurposed medicines with long-term established use, regulators are used to seeing analyses of observational data to support efficacy claims.

In the nearer term, it is unlikely that RWD can be used to understand product efficacy, but regulators shared with us that they remained keen to consider how RWD could support this end.

Exhibit 19

Potential sources of real-world data (RWD)



Source: Strategy& analysis

“RWD is collected from patients with very severe forms of the disease who often also have many other complications and co-morbidities. As such, it must be recognised that the outcomes generated from these studies are likely to be poorer than via clinical studies and this should be reflected in HTA and commissioning procedures.” - Large Pharma

For the most part however, RWD can support:

1. *Understanding natural disease progression* at baseline without any interventions applied. This has already been applied to study the impact of innovative medicines on rare diseases but also can be used to capture clinical outcomes associated with medical devices (pre- and post-process flow changes).
2. *Regulatory safety assessment, particularly post-MA for medicines or post-CE mark for medical devices and companion diagnostics.* For example, in:

- identifying adverse effects, particularly those with less frequent incidence that would not have been identified within the limited population size of a randomised controlled clinical trial
- selecting the most appropriate dose of a new product in a given patient cohort
- identifying the most appropriate class of drugs in patients with co- morbidities
- understanding the safety implications of switching from one product to another

“There is great potential for RWD collection in the UK. We have a structured healthcare system which allows us to join up the various data sources to get a long-term view of patient outcomes. Whilst this is far from being an easy task, projects are already under way to do this.” – Government stakeholder

3. *Confirming real-world clinical effectiveness* by measuring long-term outcomes over many years in patients with multiple co-morbidities and other treatments. This could include patient-reported outcomes including on patient Quality of Life.
4. *The HTA process in linking economic and clinical outcomes* and in reviews where a temporary funding decision was made for a medical technology with a limited evidence base.
5. *Reinforcing the value of medical technologies at local level for NHS commissioners post the initial pilots at a local level and post-HTA* to confirm the business case and cost-effectiveness demonstrated at a national level.
6. *Identifying new patient cohort groups and new applications for existing medicines as well as assessing the level of uptake of a particular product within the NHS.*

Much of the required data already exists but is captured in disconnected EHR systems and databases across primary and secondary care. Furthermore, bringing disparate datasets together is complex. Unique patient identifiers need to be matched, with data cleansed to remove duplicates and/or to capture the most up-to-date data where there are multiple inputs for a specific data field. Industry also has commented that they are not completely clear on what data fields are collected. Experience has indicated that the data sets are often incomplete, even when the data fields have been clear, particularly when data is entered manually.

Much of the required data already exists but is captured in disconnected EHR systems and databases across primary and secondary care.

“Other European countries e.g. Sweden and Italy are a little further advanced in their disease-based registries which have good coverage across the patient population and captures longitudinal outcomes data.” – MHRA

Feedback from NHS and industry stakeholders indicated that the Systemic Anti-Cancer Therapy (SACT) database is a good example of linked real world data in England with all of the 144 chemotherapy providing Trusts submitting data about patients receiving cancer treatment at any given time. (See below for more details.)

The SACT database collects data from hospital e-prescribing systems and is linked to the Cancer Outcomes and Services Database (COSD), the Radiotherapy Data Set (RTDS), and three diagnostic databases

“SACT is one of the most advanced databases I’ve come across in the UK and would act as a good starting point from which pilot RWD studies can be run.” – Biotech

The SACT database is underpinned by data collection predominantly from hospital electronic prescribing systems, with central collation at the Chemotherapy Intelligence Unit (CIU) within Public Health England where data quality and assurance checks take place. Data varies from Trust to Trust, and SACT has been developed to accept data with different levels of detail.

Where electronic prescribing systems are available (about 70% coverage across the NHS in 2013, Plos One), it is possible to collect chemotherapy regimen / cycle details as well as a record of when drugs have been administered. However, input into the e-prescribing system is often still a manual process which is what has led to its limited utility so far for industry that have had access to it beyond being able to track the number of patients on a specific regimen for a specific cancer.

Based on a published analysis of cancer inequalities for the elderly (NHSE, 2013), SACT currently can capture:

- Patient demographics e.g., age
- Cancer type and stage
- Performance status e.g., bedbound, symptomatic, asymptomatic
- Number of chemotherapy courses

Data varies from Trust to Trust, and SACT has been developed to accept data with different levels of detail.

The database does not currently capture actual outcomes nor treatment patterns/intensity.

It is also evident that information on treatment intent and the performance status of patients is not captured in its entirety, and that SACT dataset significantly under-records the use of endocrine therapy. The under-representation of endocrine therapy is because this is often prescribed and dispensed in primary care and so not captured on hospital e-prescribing systems. Finally, currently there is no formal mechanism for industry to access the data which is collected by SACT. Only a few companies with medicines on the Cancer Drugs Fund or on the EAMS have limited access.

SACT is linked to two other databases enabling analysis across:

- The COSD which records tumour type, treatment options, and treatments undertaken. COSD is also used for 2/3 of cancer audits e.g., the National Lung Cancer Audit.
- The RTDS which collects consistent and comparable data of all radiotherapy treatments provided across all NHS acute providers in England.

Where data from all three of these sources is available for a patient, it is possible to track back to identify exactly which interventions led to particular outcomes and thereby attribute value to an intervention, based on outcome rather than activity.

Treatment databases in SACT are also linked to three *diagnostic* databases which provide information on imaging, endoscopy results, and blood/biomarker details.

Based on discussions with NHS and industry stakeholders, we propose that going forward, RWD databases capture a broader set of information in a consistent manner by appropriately incentivising system users to better capture the data. The UK Cystic Fibrosis (CF) Registry collects data on 99% of people with CF — of their 10,583 registered patients, 89% have annually updated complete data sets, which are then entered manually via a pro-forma form into their database⁴. The form captures information such as procedures patients have undergone, including transplantation, physiotherapy, blood tests, and treatment.

The information needed for medical devices is often more complex. For medical devices, clarity on the range of medical devices that have been used for a particular intervention, patient process flow, and procedure need to be captured to allow for a complete evaluation on causality in

Based on discussions with NHS and industry stakeholders, we propose that going forward, RWD databases capture a broader set of information in a consistent manner by appropriately incentivising system users to better capture the data.

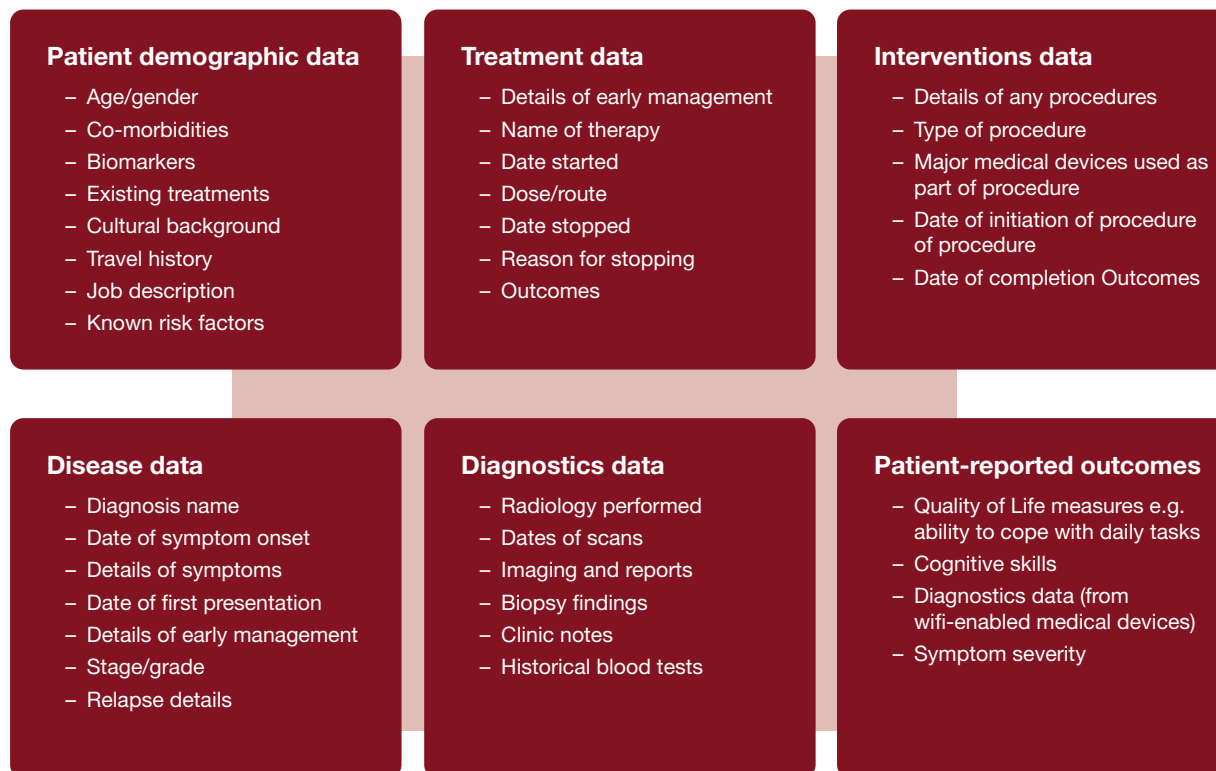
relation to patient outcome. *Exhibit 20* summarises the key data fields, some of which are currently captured in existing databases such as SACT, and some of which are not. In all cases, the data should be collected and owned by the NHS with access given to industry and other stakeholders so that they can perform their own analysis. The analysis then should be shared with the NHS and other key stakeholders, such as regulators and/or HTA bodies in order to adjust recommendations for clinical use and/or funding. Patients would need to give consent for their data to be used in this way, and likely would, according to patient groups.

“From an industry perspective, we would also like to note that the UK must offer the necessary support to industry before mandating its collection.”
 - Trade Association

Exhibit 20

Recommended list of data fields to capture within RWD sources

Patient level information, linked and traceable to an anonymised individual with a unique patient ID across databases, EHR and other data sources



Source: Strategy& analysis

In order to facilitate RWD collection, analysis, and use we propose:

- Upfront investment into a data infrastructure system by the NHS which links the patient-level information described above across primary and secondary care with current reimbursement status, and allows for further linkages with other data sources such as genomics data from Genomics England.
- Establishing standards of diagnostic testing and disease management to harmonise the quality of data collected into databases.
- Collaboration between HTA, regulators, patient groups, and industry to define the questions that RWD could be used to answer in the nearer term in order to validate its utility.
- Development of technological solutions to anonymise data at source to maintain patient confidentiality, yet be able to trace back to a unique patient identifier to allow data mining and analysis across the different connected databases.
- Creation of unique access platforms for the NHS, industry, and any other stakeholders e.g., patients, so that each group only has access to data which is relevant and appropriate to the analysis being undertaken.
- Defining leading practices for analysing and interrogating RWD for specific research questions.
- Addressing the cultural mind set of industry, regulators, and HTA bodies in order to embrace the potential of RWD, given the well-established hierarchy of evidence.
- Instituting incentives across the whole system so that all stakeholders participate in question definition, data collection, data cleansing and analysis, data aggregation, and the use of data to make decisions.

In addition, we recommend that further work should be completed to:

- Understand the full capabilities of the UK RWD sources, including CPRD and other patient registries.
- Describe how a pilot with SACT could be implemented to test how RWD can be used and whether the data fields recommended capture the necessary data for robust analyses.

- Understand how to connect clinical RWD with economic data across the healthcare system and eventually social care and other care settings.
- Highlight what should be in place to implement RWD within the NHS in a consistent way, including incentives for data collection and the overall upfront investment required to complete the gaps in the current data infrastructure.
- Understand where standards of care vary dramatically from that of the other EU5 and the US to address these gaps which will impact the quality of data generated and the ability of the data to be used outside the UK context.

Robust prescribing controls are required around early access to medical technologies so that they are used effectively and safely whilst further data is being collected

A controlled approach should be taken to the uptake of new products to maintain patient safety, particularly where these products are made available pre-MA. We propose:

- Clear selection criteria for identifying centres and clinicians/ prescribers who are suitably qualified and with the appropriate supporting infrastructure e.g. diagnostics and other required medical devices for the particular intervention.
- Developing a short communication and education programme for clinicians and administrators that will come into contact with these innovative products to understand what is required for data collection, patient tracking, and reimbursement. In addition, it should be made clear that the product should be used as the innovator proposes to use it post-regulatory approval and post-HTA.
- Developing guidelines for different types of medical technologies around broad patient inclusion criteria so that patient safety is maintained based on the current safety signals for medicines and risks associated with the use of specific medical devices.
- Establishing clear communication channels across the key stakeholders along the pathway to communicate any concerns, emerging data, and/or findings so that clinical practice and patient safety can be optimised. Clear mechanisms to track product use and procedures to enact a recall will be of paramount importance in case of any issues arising from product use.

A controlled approach should be taken to the uptake of new products to maintain patient safety.

- Agreeing on the level of frequency and extent of patient monitoring and/or support that will be required for the different innovative medicines and procedures/process flows associated with new medical devices and/or digital products.

By carefully thinking through the details of the accelerated access pathways and potential risks to patients, any ethical considerations can be addressed

Inevitably, by accelerating medical technologies development, particularly for medicines, there is a higher level of uncertainty around how the product behaves across the different patient cohorts in real life. This raises a number of ethical concerns around the risk that patients may be exposed to within an accelerated access pathway. In addition, innovators also will have multiple options for making their product available pre-MA, including via clinical trial recruitment, compassionate use, and the EAMS. Each approach has its own risks and benefits which should be clearly communicated to patients so that they can make a well informed decision about the route for accessing innovative medicines. In addition, consideration should be given to concerns from the NHS of its funding ‘unproven’ treatments over ‘proven’ treatments where some patient groups may benefit more than others.

Clear entry criteria for product selection for accelerated access and/or use of a flexible pricing and reimbursement framework and a robust process for managing the entry of these innovative medicines pre- and post-MA will go a long way in allaying fears that patient safety may be compromised. These concerns may come from multiple stakeholders who will need assurance that the pathway has been well-thought through.

The AAR team working in partnership with CASMI are conducting further work in this area which will feed into the final recommendations.

Consideration should be given to concerns from the NHS of its funding ‘unproven’ treatments over ‘proven’ treatments where some patient groups may benefit more than others.

Conclusion

The proposed accelerated access pathways, supported by a flexible pricing and reimbursement framework, play an important role in achieving the Accelerated Access Review's aim of increasing earlier uptake of safe, innovative medical technologies for the UK population. They also seek to make the UK a more attractive location for innovation so that companies consider it an early and critical market for product development, clinical and economic validation, and market access a global context. Beyond the qualitative benefits, we have estimated, using medicinal exemplar products, that the proposed accelerated pathways can provide earlier patient access by one to six years with significant increases in revenues for companies (up to £11-525 million over projections per product), and can help reduce the costs in the longer-term of running multiple large RWD studies across the EU (about £80 million of savings per product). Our recommendations form an important input to Proposition 2 of the Accelerated Access Review: Getting Ahead of the Curve.

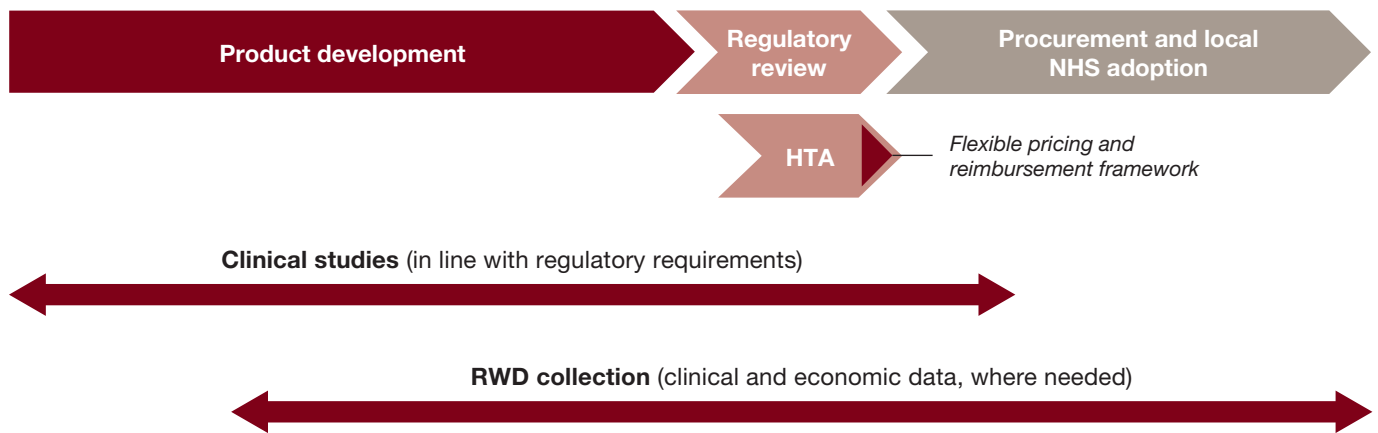
We have developed specific accelerated access pathways for medicines, companion diagnostics, medical devices and digital products, incorporating the views of over 150 stakeholders through surveys, interviews, and co-creation workshops. Implementation of these pathways can reduce the time to patient access and offer earlier post-MA revenue generation for industry. For core components of the proposed pathways across medical technologies (*see Exhibit 21, next page*).

When considering commercial incentives, we recommend a flexible pricing and reimbursement framework be available to all innovators with medical technologies that are considered for accelerated access. The pricing schemes we evaluated within the framework seek to balance affordability and budget predictability with risk-sharing around outcomes and recognition of innovation, all the while remembering that the fundamental goal must be to increase patient access. We recognise that potentially increasing the number of products recommended for funding by HTA bodies would mean that the NHS would need to identify ways to tackle affordability beyond the use of the flexible pricing and reimbursement scheme.

We have developed specific accelerated access pathways for medicines, companion diagnostics, medical devices and digital products, incorporating the views of over 150 stakeholders through surveys, interviews, and co-creation workshops.

Exhibit 21

Proposed core components of the UK accelerated access pathways across medical technologies



Innovators proceeding on the accelerated access pathway will need to consider as early as is feasible which of the pricing and reimbursement framework schemes will help them achieve the required cost-effectiveness during the HTA process. There may be additional pricing schemes that will be product-specific, e.g., for products targeting dementia, ultra-orphan products, and products to treat anti-microbial resistance, and that will need to be agreed upon on a case-by-case basis. Our analysis across the different groups of medical technologies indicates the wide applicability of the different schemes within the flexible pricing and reimbursement framework.

Key to implementation success will be strengthening the enablers for accelerated access. Feedback from stakeholders has confirmed that the UK has set up some positive initiatives that aim to improve clinical trial infrastructure, and better support medical device innovators with business case creation. However, the feedback also reflected that more needs to be done to strengthen infrastructure for data collection across the pathway, whether economic or clinical, for all medical technologies. In addition, stakeholders commented that a seamless pathway to patient access was required across the different stages of the pathway and particularly to incentivise uptake of innovation by the NHS. Although the Strategy& work did not focus on how to incentivise uptake of innovation post-Health Technology Assessment (HTA), the proposed flexible pricing framework should help to facilitate uptake.

Innovators proceeding on the accelerated access pathway will need to consider as early as is feasible which of the pricing and reimbursement framework schemes will help them achieve the required cost-effectiveness during the HTA process.

The Life Sciences industry offers great potential to improve the quality of life of the UK population. Within this context, the Accelerated Access Review should seize the opportunity to implement mechanisms that distinguish the UK, not only as a powerhouse of innovation across Europe and beyond, but also as a healthcare system that places innovative technologies in the hands of its people.

Appendix A: Glossary of terms

AHSN	Academic Health Science Networks	EC	European Commission
AIFA	l'Agenzia Italiana del Farmaco (Italian Medicines Agency)	EDC	Electronic Data Capture
ATU	Autorisations Temporaires d'Utilisation (Temporary Authorisation for Use)	EMA	European Medicines Agency
CASMI	Centre for the Advancement of Sustainable Medical Innovation	EPSRC	Engineering and Physical Sciences Research Council
CCG	Clinical Commissioning Group	EU	European Union
CDx	Companion Diagnostic	FAD	Final Appraisal Determination
CE	CE marking / CE mark	HTA	Health Technology Assessment
CF	Cystic Fibrosis	IPP	Interventional Procedure Programme
CIU	Chemotherapy Intelligence Unit	IRP	International Reference Pricing
CLAHRC	Collaboration for Leadership in Applied Health Research and Care	IVD	In Vitro Diagnostics
CMU	Commercial Medicines Unit	MA	Marketing Authorisation
COSD	Cancer Outcomes & Services Database	MHRA	Medicines and Healthcare products Regulatory Agency
CPRD	Clinical Practice Research Datalink	MRC	Medical Research Council
DAP	Diagnostics Assessment Programme	MTA/ MTAP	Multiple Technology Appraisal Process
DEC	Diagnostics Evidence Co-operatives	MTEP	Medical Technologies Evaluation Programme
DH	Department of Health	NGS	Next Generation Sequencing
EAMS	Early Access to Medicines Scheme	NHS	National Health Service
		NIB	National Information Board
		NICE	National Institute for Health and Care Excellence
		NIHR	National Institute for Health Research

P&R	Pricing and Reimbursement		External Quality Assessment Service
PAD	Peripheral Artery Disease		
PAS	Patient Access Scheme	WT	Wellcome Trust
PHE	Public Health England	ZiN	Zorginstituut Nederland (The Care Institute)
PIM	Promising Innovative Medicine		
PMC	Precision Medicine Catapult		
PoC	Proof of Concept		
PPRS	Pharmaceutical Price Regulation Scheme		
PRIME	Priority Medicine		
PVA	Price Volume Agreement		
QALY	Quality-Adjusted Life Year		
R&D	Research and Development		
RCT	Randomised Controlled Trials		
RTDS	Radiotherapy Data Set		
RWE	Real World Evidence		
RWD	Real World Data		
SACT	Systemic Anti-Cancer Therapy		
SBRI	Small Business Research Initiative		
SME	Small & Medium Sized Enterprise		
SO	Scientific Opinion		
STA/STAP	Single Technology Appraisal		
UK	United Kingdom		
UK NEQAS	United Kingdom National		

Appendix B: Definitions of selected terms

Terms and Definitions

- **Academic Health Science Networks**
Network organisations within NHS England that aim to support economic growth and increase the quality of care for patients within the NHS. There are 15 AHSNs in total, each serving a distinct geographic region within England.
- **Accelerated Access Pathway**
An outline of the typical route a medical technology could take to deliver earlier patient access relative to current processes.
- **Archetype**
Groups of medical technologies categorised based on a series of shared characteristics e.g. mode of action or indication.
- **Arm's Length Bodies**
Public service organisations which operate to varying degrees of independence from the Government. Arm's length bodies include NHS England, the National Institute for Health Care Excellence and the Medicines (NICE) and Healthcare products Regulatory Authority (MHRA).
- **Autorisations Temporaires d'Utilisation (Temporary Authorisation for Use)**
Early access scheme which provides access to medicines pre-marketing authorisation in conditions where there is clear unmet medical need. The ATU is granted by the French ANSM (Agence Nationale de Sécurité du Médicament).
- **Biomarker**
A naturally occurring molecule, gene, or characteristic by which a particular pathological or physiological process, disease, etc. can be identified.
- **Cancer Outcomes & Services Database**
Cancer outcomes and services dataset collected and coordinated by the National Cancer Intelligence Network.
- **CE marking / CE mark**
An abbreviation of Conformité Européene (European Conformity), CE marking serves as the manufacturer's declaration that a product meets the requirement of the Directive 93/68/EEC.
- **Chemotherapy Intelligence Unit**
Part of Public Health England, the Chemotherapy Intelligence Unit provides a repository for cancer chemotherapy data in England.
- **Clinical Commissioning Group**
NHS organisations established by the Health and Social Care Act of 2012 to organise the delivery of NHS services in England. Clinical Commissioning Groups are represented by General Practitioners in the community and are responsible for commissioning most health and care services for patients within a locality.
- **Clinical Practice Research Datalink**
Observational data and interventional research service for NHS England which operates as part of the Department of Health. The Clinical Practice Research Datalink is jointly funded by the National Institute of Health Research and the MHRA.

- **Collaboration for Leadership in Applied Health Research and Care**
A collaboration of local providers of NHS services and NHS commissioners, universities, other relevant local organisations and the relevant Academic Health Science Network.
- **Commercial Medicines Unit**
Part of the Medicine, Pharmacy and Industry Group of the Department of Health which looks at supply and procurement of medicines in hospitals.
- **Companion Diagnostic**
A medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product.
- **Department of Health**
Ministerial Department of the UK Government responsible for government policy on health and social care in England.
- **Diagnostics Assessment Programme**
NICE evaluation programme focusing on the evaluation of innovative medical diagnostic technologies.
- **Diagnostics Evidence Co-operatives**
A collaboration between industry and NHS experts, including clinicians, commissioners, researchers and patients, to help generate clinical and cost-effectiveness information for in vitro diagnostic devices. Diagnostic Evidence Co-operatives are funded by the National Institute for Health Research in support of the Government's Strategy for UK Life Sciences.
- **Digital products**
Digital solutions which allow individuals to better track, manage, and improve their health. Within the context of this report, digital products have focused on app-based products as defined by the National Information Board.
- **Early Access to Medicines Scheme**
Early access scheme in the UK seeks to provide early patient access to innovative medicines pre-Marketing Authorisation where there is clear unmet medical need.
- **Engineering and Physical Sciences Research Council**
Publically funded government agency responsible for coordinating and funding research in engineering and the physical sciences.
- **EU Medical Device Directives**
A core legal framework of three directives (Medical Devices Directive 93/42/EEC, In-Vitro Diagnostics Directive 98/79/EC and Active Implantable Medical Devices Directive 90/385/EEC) with which any medical device made available on the European market must comply.
Note: A Directive is defined as a legislative act that sets out a goal that all EU countries must achieve. It is up to the individual countries, however, to devise their own laws on how to reach these goals.
- **EU Transparency Directive**
Directive 89/105/EEC designed to verify that national pricing and reimbursement decisions do not create obstacles to the pharmaceutical trade within the EU's Internal Market.
Note: A Directive is defined as a legislative act that sets out a goal that all EU countries must achieve. It is up to the individual countries, however,

to devise their own laws on how to reach these goals.

- **European Commission**
Executive body of the European Union responsible for proposing legislation, implementing decisions, upholding the EU treaties and managing the day-to-day business of the EU.
- **European Medicines Agency**
European Union agency responsible for the evaluation, supervision and safety monitoring of medicines developed by pharmaceutical companies for use in the EU.
- **Final Appraisal Determination**
The Appraisal Committee's final draft guidance about using a treatment or group of treatments in the NHS (technology appraisal guidance). Consultees can appeal against the recommendations set out in the final appraisal determination. If there is no appeal, or an appeal is not upheld, the final appraisal determination is issued by NICE as guidance.
- **Funding Mandates**
Funding mandates are relevant for certain products following a recommendation by the NICE. They place a requirement on the NHS to provide funding for a product such that the product can be made available to patients.
- **Genomics**
A discipline in genetics that applies recombinant deoxyribonucleic acid (DNA), DNA sequencing methods, and bioinformatics to sequence, assemble, and analyse the function and structure of genomes.
- **Health Technology Assessment**
A systematic evaluation of properties, effects, and/or impacts

of health technology, where health technology is defined as drugs, medical devices, diagnostic techniques, surgical procedures, and other treatments to improve health or prevent ill health. In the UK, health technology assessments focus on clinical effectiveness and cost effectiveness and the outcome of the assessment is used to inform pricing and reimbursement discussions.

- **Horizon Scanning**
Proactively looking into the future to review and assess emerging health technologies that may have a significant impact on patients or the provision of health services in the near future.
- **In-House Test**
In vitro diagnostic tests developed by the NHS within pathology laboratories of individual NHS trusts. In-house tests are exempt from regulation and are not subject to the same requirements as commercially developed tests e.g., the requirement for CE marking in compliance with the In-Vitro Diagnostics Directive 98/79/EC.
- **In Vitro Diagnostics**
Tests that can detect diseases, conditions, or infections. Some in vitro diagnostic tests are used in laboratory or other health professional settings and other tests are for consumers to use at home.
- **International Reference Pricing**
A price control mechanism whereby a Government considers the price of a medicine in other countries to inform or establish the price in its own country.
- **Interventional Procedure Programme**
NICE evaluation programme focusing on the evaluation of

interventional procedures which are defined as those used for diagnosis or treatment that involve incision, puncture, entry into a body cavity, or the use of ionising, electromagnetic or acoustic energy.

- **Marketing Authorisation**

The approval provided by the European Medicines Agency to market a medicinal product as defined by Directive 2001/83/EC and in Regulation (EC) No 726/2004.

- **Medical Device**

An instrument, apparatus, implant, in vitro reagent, or similar or related article that is used to diagnose, prevent, or treat disease or other conditions, and does not achieve its purposes through chemical action within or on the body. Also defined in the EU by the Medical Devices Directive 93/42/EEC, In-Vitro Diagnostics Directive 98/79/EC and Active Implantable Medical Devices Directive 90/385/EEC.

- **Medical Research Council**

Publically funded government agency responding for coordinating and funding medical research in the UK.

- **Medical Technologies Evaluation Programme**

NICE programme to identify medical technologies that could offer benefits to patient or the NHS. Manufacturers notify NICE about possible topics. The Medical Technologies Advisory Committee selects products for evaluation. It may carry out the evaluation itself or refer the topic to be evaluated by another NICE programme - usually technology appraisals, interventional procedures, diagnostics, and sometimes guidelines.

- **Medical Technology**

Also referred to as health technology, these are drugs, medical devices, diagnostic techniques, surgical procedures and other treatments to improve health or prevent ill health.

- **Medicine**

A drug or other preparation for the treatment or prevention of disease. Also defined in the EU by Directive 2001/83/EC.

- **Medicines and Healthcare products Regulatory Agency**

Executive agency of the Department of Health and the UK's regulator for medicines, medical devices, and blood components for transfusion, responsible for ensuring their safety, quality and effectiveness.

- **Multiple Technology Appraisal Process**

A technology appraisal conducted by NICE that assesses several drugs or treatments used for one condition, or a single drug or treatment that is used for several. Single technologies can also be appraised using this process if there are issues complicating the appraisal, such as a complex situation around the comparator treatments.

- **National Information Board**

UK organisation which brings together national health and care organisations from the NHS, public health, clinical science, social care, and local government, along with appointed independent representatives, to develop the strategic priorities for data and technology. Through their work-stream roadmaps, the National Information Board has set out plans to make it easier for the public to access health and care information by improving digital services.

- **National Institute for Health and Care Excellence**
Executive non-departmental body of the Department of Health in the UK responsible for developing national guidance, standards, and information on providing high-quality health and social care and preventing and treating ill health.
- **National Institute for Health Research**
UK organisation funded through the Department of Health which seeks to improve the health and wealth of the nation through research. It is a large, multi-faceted and nationally distributed organisation that coordinates and funds research for the NHS in England.
- **Next Generation Sequencing**
Also known as high-throughput sequencing, next generation sequencing refers to modern sequencing technologies by which DNA can be sequenced at lower cost and within shorter timeframes than previous methods.
- **Notified Body**
An organisation accredited by an EU member state to carry out conformity assessments according to a European Commission Directive e.g., the Medical Devices Directive 93/42/EEC, In-Vitro Diagnostics Directive 98/79/EC and Active Implantable Medical Devices Directive 90/385/EEC.
- **Orphan Product**
A pharmaceutical agent that has been developed specifically to treat a rare medical condition, the condition itself being referred to as an orphan disease.
- **Patient Access Scheme**
A scheme proposed by a pharmaceutical company to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines.
- **Pharmaceutical Price Regulation Scheme**
A voluntary agreement between the Department of Health and the Association of the British Pharmaceutical Industry regarding the supply of branded medicines to the NHS. The Pharmaceutical Price Regulation Scheme was first introduced in 1957 and is generally renewed every five years or so. The current scheme runs for five years from January 2014.
- **Precision Medicine Catapult**
An innovation centre established by Innovate UK to support the development and delivery of precision medicines in the UK.
- **Price Volume Agreement**
An agreed price negotiated between the manufacturer and payer for a product based on a forecast volume of sales, usually as part of a tender. As actual sales volumes exceed the forecast, the discount offered for the product is higher.
- **Priority Medicines Scheme**
Proposed scheme by the European Medicines Agency to optimise the development and accelerated assessment of medicines of major public health interest. Also known as the PRIME scheme, an anticipated launch date has been set for Q1 2016.
- **Promising Innovative Medicine**
The first step in the Early Access to Medicines Scheme (EAMS) application process which gives an indication that the product may be eligible for the EAMS patient access based on early clinical data.

- Proof of Concept**
In medical technologies development this represents a milestone in the development process, marking the transition from exploratory development to confirmatory development. Typically for medicines this is around Phase IIB clinical trials. Proof of Concept demonstrates that the medical technology has performed as intended in diagnosing or treating disease.
- Public Health England**
Executive agency of the Department of Health in the UK with a mission to “protect and improve the nation’s health and wellbeing, and to address health inequalities”
- Quality-Adjusted Life Year**
A measure of the state of the health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One Quality-Adjusted Life Year is equal to one year of life in perfect health. This measure is used by NICE as a measure of cost-effectiveness.
- Radiotherapy Data Set**
Dataset collected by NHS Acute Trust providers of radiotherapy services in England against a nationally defined standard. The purpose of the standard is to collect consistent and comparable data across all NHS Acute Trust providers of radiotherapy services in England, in order to provide intelligence for service planning, commissioning, clinical practice and research and the operational provision of radiotherapy services across England.
- Randomised Controlled Trials**
A study in which a number of subjects matched for demographics are randomly assigned to two (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the intervention e.g., medicine being tested, the other (the comparison or control group) receives an alternative intervention, a dummy intervention (placebo), or no intervention at all. The groups are then followed to assess the effectiveness of the experimental intervention.
- Real World Data**
Data generated prospectively from observational studies in a “real world” setting to provide insight on patient outcomes.
- Real World Evidence**
Analysis and use of real world data, often at a population level, to generate meaningful insights.
- Regulatory Submission Package**
Any documentation or information submitted to a regulator for review, for notification, or in response to a request for additional information related to a healthcare product.
- Salford Lung Study**
A pragmatic, randomised phase III, real-world effectiveness trial in chronic obstructive pulmonary disease, coordinated by the pharmaceutical company, GSK, in Salford, UK.
- Scientific Opinion**
The second step of the UK’s Early Access to Medicines Scheme (EAMS) application process whereby the MHRA describes the risks and benefits of the medicine based on data gathered from the patients who will benefit. A positive Scientific Opinion qualifies the medicine for patient access via the EAMS.

- **Single Technology Appraisal A**
technology appraisal conducted by NICE that assesses the use of a single technology for a single indication.
- **Systemic Anti-Cancer Therapy**
Cancer chemotherapy dataset collected by Chemotherapy Intelligence Unit across acute, outpatient, and community settings against an agreed standard. The standard covers all patients receiving cancer chemotherapy in, or funded by the NHS in, England.
- **Tendering**
A process for acquiring products in which the payer negotiates the lowest price for the product with the manufacturer.
- **Test Beds**
NHS England initiative which enables frontline health and care workers in selected areas to pioneer and evaluate the use of novel combinations of interconnected devices such as wearable monitors, data analysis, and ways of working, which will help patients stay well and monitor their conditions themselves at home. Successful innovations will then be available for other parts of the country to adopt, and will adapt to the particular needs of their local populations.
- **Trade Association**
An industry trade group which is founded and funded by businesses that operate in a specific industry. Trade associations within the pharmaceutical and biotechnology industry in the UK include the Association of the British Pharmaceutical Industry (ABPI), the BioIndustry Association (BIA) and the Ethical Medicines Industry Group (EMIG).
- **Uptake Assessment**
A review of the rate of uptake of medical technologies across the NHS.
- **Wellcome Trust**
An independent global charitable foundation dedicated to improving health through science, research, and engagement with society.
- **Zorginstituut Nederland (The Care Institute)**
An independent administrative authority which ensures that Dutch citizens have health insurance.

Appendix C: Stakeholders engaged via survey and interviews

Insight and viewpoints of the AAR have been gathered through a series of interviews and workshops. In total, Strategy& have held discussions with 68 different organisations. The full list of organisations can be found below:

Pharma and biotech

AbbVie
ARIAD Pharma (UK) Ltd.
AstraZeneca
Atlantic Healthcare
Avillion
Bayer
Bristol-Myers Squibb
Eisai
Eli Lilly
Gilead Sciences
GlaxoSmithKline
Gruenthal
ImmunoCore
Janssen-Cilag
MSD
Napp Pharmaceuticals Limited
Novartis
Pfizer
Roche
Shire

Medical devices and diagnostics

Cambridge Computer Imaging
Device Access UK
EM Imaging
Hitachi Healthcare
GE Healthcare
Glyconics
Lehman Micro Devices
Medtronic
Roche Diagnostics

Digital

Big White Wall
Digital Health & Care Alliance
P1 Vital
SpeakSet
Telefonica

Association groups

Association of British Healthcare Industries (ABHI)
Association of British Pharmaceutical Industry (ABPI)
BioIndustry Association (BIA)
British In Vitro Diagnostics Association (BIVDA)
European Medicines Group (EMG)
Ethical Medicines Industry Group (EMIG)

Innovation centers

Cell Therapy Catapult
Centre for the Advancement of Sustainable Medical Innovation
Precision Medicine Catapult

Government and AAR team

Department of Health
Her Majesty's Treasury
National Institute for Health Research
Office for Life Sciences
Public Health England
Scottish Government
Welsh Government

NHS

Health Innovation Network (South London AHSN)
NHS England
NHS Foundation Trusts
NHS Northern Ireland
NHS Scotland
NHS Wales

Patient advocacy groups

Cancer Research UK
Cystic Fibrosis Trust
Duchenne Children's Trust
Myeloma UK
Patient Voices
Pumping Marvellous
The Brain Tumour Charity

Regulator

Medicines and Healthcare products
Regulatory Agency
British Standards Institution

HTA

All Wales Therapeutics and Toxicology
Centre
National Institute for Health and Care
Excellence
Scottish Medicines Consortium

Appendix D: Reimbursement framework for product archetypes

Product	Indication and mechanism of action	PVAs	Tenders	Conditional reimbursement	Outcomes-based payments	Deferred payments	Indication-based pricing	Product-service bundling
Medicines								
5-HT ₆ antagonists	Alzheimer's disease Blockade of 5-HT ₆ receptors to improve memory and cognition	✓	✓	✓	✗	✗	✗	✗
		The national focus on dementia would warrant the use of regional/national tendering and PVAs to provide the widest access. Products in phases I and II will likely require further data collection under conditional reimbursement schemes.						
Chimeric antigen receptor T-cells	Various cancer indications T-cells collected from patients are modified and re-introduced into the patient to target and kill cancer cells	✗	✗	✓	✓	✗	✗	✗
		Cell therapies are likely to require additional data collection among wider patient populations and thus would be suited to a conditional reimbursement schemes. Outcomes can also be tracked using defined cancer endpoints.						
Protease and nucleoside polymerase inhibitors	Hepatitis C Inhibitors act to prevent virus replication preventing protein and RNA production	✗	✓	✗	✓	✓	✗	✗
		Despite differences in product characteristics, newly launched protease and polymerase inhibitors will likely require tenders. If patients are stratified by genotype, outcomes-based payments could also apply, as outcomes are measureable within a short period (8-24 weeks).						
Anti-CD20/25 antibodies	Multiple sclerosis Monoclonal antibodies are targeted to bind and destroy CD20/25 B cells to reduce the inflammatory respons	✗	✗	✗	✓	✗	✗	✗
		Data-collection infrastructure exists that could support an outcomes-based payments scheme. Relapse rates would need to be assessed over relatively long time periods, making a rebate scheme more attractive to innovators.						
Anti-interleukin 5 antibodies	Eosinophilic asthma Reducing the activity of eosinophils through interactions with IL-5	✗	✗	✗	✓	✗	✓	✗
		Measurable outcomes for asthma make these products suitable for outcomes-based payments. Applicability to COPD/broader asthma indications also opens up the possibility for indication-based pricing.						
Novel antibiotics	Anti-microbial resistance New antibiotics designed to fight community acquired infection	✗	✗	✗	✓	✗	✓	✗
		Given policy priorities, AMR products could use alternative schemes (such as guaranteed revenues). Alternatively, outcomes-based schemes are feasible for acute infections, and indication-based pricing could be applied, depending on the specificity of the new product.						
Neuro-protective compounds	Spinal muscular atrophy Molecule prevents loss of muscle function	✓	✗	✓	✓	✗	✗	✗
		Predictable and identifiable patient populations will facilitate the application of PVAs, while close monitoring of a small patient population will make outcomes-based schemes easier to track and validate.						
Sodium-glucose transporter inhibitors	Diabetes Act to reduce blood glucose and increase excretion of glucose in urine	✗	✗	✗	✓	✓	✗	✗
		Reducing the risk of cardiovascular events could justify the use of a deferred payments scheme. Similarly, outcomes-based payments could apply to patient populations with co-morbidities, though the large size of the applicable population would be challenging to monitor.						

Product	Indication and mechanism of action	PVAs	Tenders	Conditional reimbursement	Outcomes-based payments	Deferred payments	Indication-based pricing	Product-service bundling
B-cell lymphoma 2 inhibitors	Chronic lymphocytic leukaemia Inhibits a protein that leads to cancer cell death	X	X	✓	✓	X	X	X
		Results from phase II trials indicate a good clinical effect for this class of medicine, warranting the use of a conditional reimbursement scheme while further real-world data is collected. Combination with a rebated outcomes-based scheme will safeguard payers against treatments that do not meet the outcomes requirements						
Anti-protein convertase substilin/kexin type 9	Hypercholesterolemia Antibodies that inhibit PCSK9, preventing the inhibition of LDL receptors and a reduction of blood LDLs	X	✓	X	✓	X	X	✓
		PCSK9 inhibitors could be procured as part of a product-service bundle that provides cholesterol testing and other drugs that manage LDLs. Outcomes-based payments are also feasible, provided stakeholders can agree on suitable surrogate endpoints.						
Companion diagnostics								
Anti-CD38 antibodies and CDx	Multiple myeloma Medicine used to treat multiple myeloma and a companion diagnostic	X	✓	✓	✓	X	✓	✓
		CDx can stratify patients and select treatment, with the diagnostic and drug bundled and procured via tender. Given the likely clinical and workflow changes that would arise due to the diagnostic, the tender may also include service required to support the these changes. Anti-CD38 antibodies are also effective at CLL, making it suitable for indication pricing.						
Anti- Aβ antibody and CDx	Alzheimer's disease Non-invasive Dx for Alzheimer's disease based on eye movements and an antibody treatment	X	X	X	X	✓	X	✓
		Given the high societal and financial cost of Alzheimer's disease, a diagnostic that provides an early diagnosis could improve clinical outcomes when patients receive treatment before they begin showing symptoms. In such a scenario a product-service bundle could be tendered for a drug and diagnostic combination, along with a deferred payment scheme to spread the cost of treatments.						
Medical devices								
Smart digital hip protectors	Hip protection from damage Hip protectors reduce impact from falls and integrated sensors collect data to inform carers if a severe falls requires urgent medical attention	X	✓	X	✓	X	X	✓
		Hip protectors would likely be procured via tender and could be combined with a telehealth or emergency service in the case of bad falls. An outcomes-based payment rebate could apply to incidents in which the hip protector did not deliver on a predicted cost reductions to the NHS.						
Artificial pancreas	Diabetes Small devices that monitor blood glucose and are able to administer insulin to tightly regulate blood glucose levels	X	✓	X	✓	X	X	✓
		The device could be used in combination with other interventions designed to assist patients in managing their condition. Outcomes-based schemes could consider blood glucose levels or clinical endpoints associated with cardiovascular disease.						
Digital products								
Online tools and applications	Mental health conditions Online web communities, diagnostics and interventions that assist with the management of mental health conditions	X	✓	X	X	X	X	✓
		Digital products will likely be tendered but—as with many medical devices—could also be procured as part of a product-service bundle. If the digital tool provides a diagnostic function, follow-up counselling services could be provided as part of the bundled package.						

Endnotes

¹ Life Sciences Competitiveness Indicators, March 2015 – Office for Life Sciences

² Medical Technologies Evaluation Programme (MTEP), Diagnostics Assessment Programme (DAP), Interventional Procedure Programme (IPP), Single Technology Appraisal Process (STAP) and the Multiple Technology Appraisal Process (MTAP)

³ <http://amr-review.org/home>

⁴ Cystic Fibrosis, 2013-2015 analysis

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