

EXPERT CONSENSUS PROGRAMME:

Payment Models for Multi-indication Therapies

CONSULTING | REPORT
NOVEMBER 2021

Amanda Cole
Margherita Neri
Graham Cookson

ohe.org

OHE has developed this report commissioned and funded by AstraZeneca



NOVEMBER 2021

EXPERT CONSENSUS PROGRAMME:

Payment Models for Multi-indication Therapies

Amanda Cole

Office of Health Economics, London

Margherita Neri

Office of Health Economics, London

Graham Cookson

Office of Health Economics, London

Please cite this report as:

Cole, A., Neri, M. and Cookson, G., 2021. Expert Consensus Programme: Payment Models for Multi-Indication Therapies. OHE Consulting Report, London: Office of Health Economics. Available at: <https://www.ohe.org/publications/payment-models-multi-indication-therapies>

Corresponding Author:

Amanda Cole
acole@ohe.org

For further information please contact:

Professor Graham Cookson

Chief Executive, OHE
Honorary Visiting Professor in Economics at City, University of London

Tel +44 (0)207 747 1408

Email gcookson@ohe.org



About OHE Consulting Reports

Many of the studies OHE Consulting performs are proprietary and the results are not released publicly. Studies of interest to a wide audience, however, may be made available, in whole or in part, with the client's permission. They may be published by OHE alone, jointly with the client, or externally in scholarly publications. Publication is at the client's discretion.

Studies published by OHE as OHE Consulting Reports are subject to internal quality assurance and undergo external review, usually by a member of OHE's Editorial Panel. Any views expressed are those of the authors and do not necessarily reflect the views of OHE as an organisation.

Funding

This consulting report was commissioned and funded by AstraZeneca.

Acknowledgements

Project Steering Committee

The authors would like to acknowledge and thank the project's steering committee, whose expertise and guidance supported the project planning phase as well as the final report write-up stage: Ain Aaviksoo, Jens Grueger, Luca Pani, Pedro Pita Barros, Adrian Towse and Durhane Wong-Rieger

Expert Panel

Insights were gathered from a broad group of international stakeholders, who contributed their time and expertise to the key themes described in this report. While the content of the final report is the sole responsibility of the report's authors, we would like to thank all of the individual experts for their unique and insightful contributions to the content: Ain Aaviksoo, Anne D'Andon, Lieven Annemans, Jean-Francois Bergmann, Johann-Matthias Graf von der Schulenburg, Jens Grueger, Richard Hoey, Dipak Kalra, Michael Mayne, Luca Pani, Pedro Pita Barros, Oriol Sola-Morales, Adrian Towse, Jürgen Wasem, Claudia Wild and Durhane Wong-Rieger. It should be noted that individuals' participation in the Expert Panel was as subject experts rather than representatives of their respective organisations. Expert Panel members received payment for their participation.

The study team and AstraZeneca

The authors would like to thank colleagues who contributed to early phases of the work: Dimitrios Kourouklis, Jia Pan and Fred McElwee. We would also like to thank Alison Horsfield and Karen Coulton from AstraZeneca and Minxian Congé (previously AstraZeneca) for their input and guidance throughout the project, and their AZ colleagues for helpful suggestions on earlier drafts of this report.

Table of Contents

Executive Summary	iv
1 Introduction	1
1.1 Background and remit	1
1.2 Our starting point.....	1
<i>The theory</i>	1
<i>The practice</i>	2
1.3 Process: Expert Panel framework of interaction	3
1.4 Elicitation of experts' views	4
<i>Expert Panel engagement: an adapted Delphi methodology</i>	4
1.5 Payer survey	5
1.6 This report.....	6
<hr/>	
2 Framing the problem	7
2.1 Objectives of pharmaceutical pricing	7
2.2 Adequacy of an inflexible uniform price in meeting these objectives	10
2.3 Identifying the symptoms of the problem.....	12
2.4 Summary: Defining the problem.....	15
<hr/>	
3 Principles of the solution	16
A note on value-based pricing.....	17
3.1 Impact of value-based differential pricing	18
3.2 Recognising differential value in payment models: was there consensus?.....	21
<hr/>	
4 Articulating the evidence gaps and investigating the potential benefits	22
4.1 Why has value-based differential pricing not been broadly adopted to date?	22
4.2 Demonstrating improved outcomes for patients and health systems	23
4.3 Modelling exercise: Implications for patient access and financial sustainability for payers	24
<hr/>	
5 Implementation	29
5.1 Models of VBDP	29
<i>Different brands or different list prices for each indication</i>	29
<i>"Blended" price, or weighted average of the prices and volumes appropriate to each indication</i>	30
<i>Single list price with payment adjustments to achieve indication-specific net prices</i>	30
5.2 Data archetypes: <i>what data on clinical value and usage at the indication-level enable VBDP?</i>	33
<i>Country experiences by data archetypes and VBDP models</i>	35
<hr/>	
6 Conclusions and Recommendations	41
7 References	46

Executive Summary

Innovation in drug development is evolving at pace. Increasingly, individual medicines are found to benefit patients in a range of indications, within or across diseases, at different stages of disease, as monotherapy or in combination with other therapies as part of treatment regimens. For a multi-indication medicine, the scale of patient benefit may vary significantly between indications, as would its value-for-money if there is a single, fixed price. In the absence of indication-level payment negotiations or adjustment, this can be problematic for patient access to new treatment indications (for example, if the prevailing price represents poor value for money in a new indication), and/or could fail to incentivise treatment development (for example, if the prevailing price is too low to offer a return on its testing and development in a new indication).

Perspectives on treatment innovation differ across stakeholders. First and foremost, patients (and their treating clinicians) want access to the most effective treatments. Optimising patient access must be considered the overriding objective that unifies all stakeholders, but each works within their own remit and constraints. Payers have accountability for enabling access within the context of the resources and treatment options that are available today. Health care systems more broadly strive to make effective and affordable treatments available *and* to foster an environment that encourages and incentivises the development of those treatments. Those responsible for discovering, developing and bringing innovation to market are motivated by advancing patient care while maintaining a sustainable business model. No stakeholder can act alone, and only by considering all of these distinct perspectives can we make progress.

To drive a deeper understanding of the issues and solutions relating to access to multi-indication therapies, we convened [a multi-stakeholder panel](#) of 16 international experts from 11 countries, with whom we engaged using an [adapted Delphi methodology](#) through a survey, virtual meeting, and structured asynchronous discussions over an online platform. This engagement was complemented by a [payer survey](#) and supplementary research to address the evidence gaps.

Our approach and line of questioning were guided by [previous research](#), which suggested that accounting for indication-level value in payment models could improve patient access, optimise incentives for R&D and put downward pressure on prices through increased competition. While this starting point influenced our approach and line of questioning, our objective was to take the Expert Panel back to first principles: what should payment models for pharmaceuticals aim to achieve, are they being achieved for multi-indication medicines, and can we do better?

The Problem

“Solutions” are unlikely to be found or implemented if the “problems” they seek to address are not recognised. The objectives of pharmaceutical pricing are many, are complex, and can act in opposing directions. The Expert Panel considered the most important objectives to be (in order of importance): protecting the financial sustainability of payers, optimising incentives for innovation, optimising patient access, and increasing value for money and competition. When asked specifically to consider which objectives may not be successfully achieved with an inflexible uniform price, the Expert Panel ranked ‘optimising incentives for innovation’ and ‘optimising access for patients’ as being most problematic.

The inherent difficulty in evidencing that there is a problem is demonstrating the counterfactual: would moving away from uniform pricing bring about more treatment options and more patient benefit? While we cannot observe this directly, we identified the potential symptoms: physical

differentiation/dual branding; off-label use; strategic launch sequencing; withdrawal of indications / unrealised benefit of existing therapies; and the issue of problematic reimbursement for combination therapies. The resulting key question is: Can value-based differential payment help improve incentives and access without compromising financial sustainability?

Principles of the solution

Payment models that recognise value at the indication-level were seen as an important part of the solution for multi-indication therapies by most of the Expert Panel.

The principle that price should reflect a treatment's (clinical and patient) value was supported by most of the Expert Panel. While there was a range of views on how to measure value and how exactly it should relate to price, there was majority consensus among Expert Panel members that permitting payments to account for different value in different indications more directly connects the price paid to the patient benefit realised; this can serve to enable the reimbursement of (and therefore incentivise the development of) cost-effective drugs in all indications of expected patient benefit. In other words, while there were some divergent views on the "value-based" part of the equation, there was broad alignment on the need for "differential payment" of some form to optimally incentivise and provide access to multi-indication therapies.

Supporting evidence

In discussing why value-based differential payment has not been broadly adopted to date, we reviewed the key evidence gaps: evidencing the benefits of implementation and understanding the implications for financial sustainability.

Although data to support a comparative analysis were limited, we identified several examples of how price flexibilities (or lack thereof) have influenced the availability of therapies in individual countries. For example, in the UK, the inability to pursue a differential net price is a leading reason for no submission for national reimbursement approval of follow-on indications; this – and the acknowledgement that patients were missing out as a result – was also a driving factor in Belgium's reforms toward more flexible recognition of indication-based value. Estonia has leveraged routine electronic health records to enable value-based differential pricing to improve access to innovative therapies within a constrained health care budget. There is also evidence from the routine use of risk-sharing arrangements in Italy – an example of a flexible pricing arrangement that can vary by indication – that these lead to quicker access to medicines for patients. These examples suggest that better recognition of value at the indication-level may be associated with improved breadth and speed of access for approved therapy uses with marketing authorisation.

Less tangible and observable is the impact of flexible payment models on incentives to innovate, but we demonstrated through an illustrative modelling exercise that payment models which account for differential value across indications better incentivise innovation and lead to expanded patient access and health benefit (in our example: two further indications unlocked, leading to 509 extra quality-adjusted life years gained). The budget impact depends on how the new indication-level value is reflected in the payments/rebates. Extra (short-term) investment may be needed to support broader patient access, but in practice, payers/health systems could benefit through increased competition and more granular value-based budget management at the indication level.

Implementation

Value recognition at the indication-level can be achieved in multiple ways, and countries have different starting points and enabling infrastructure. Implementation relies on the ability to identify value and usage at the indication level and can be achieved via a single list price with adjustments to

achieve net prices for each indication, or a blended price with weights based on actual or expected usage. Different brands or different list prices per indication are only appropriate under specific circumstances (e.g., physical differentiation of brands justified by safety profile or administration method). Outcomes-based and other forms of dynamic payment model – whereby net price may vary between indications or even between individual patients – are likely to become more relevant as innovative therapy development becomes increasingly targeted and personalised.

Experiences of countries that enable value recognition at the indication-level demonstrate that multiple payment models are possible and with variations to suit the country processes and infrastructure. Current experience also highlights sometimes inconsistent/suboptimal use of the available data to achieve indication-level value recognition.

Conclusions & Recommendations

The outcome of our Expert Panel consensus programme can be summarised by the following five conclusions and associated recommendations for stakeholder action:

1. Inflexible uniform pricing does not optimally support innovation and access. The most important consequence is lost treatment opportunities for patients.

Efforts should be made to work **across all stakeholder groups** to recognise and evaluate the broad and varied clinical and other benefits of individual therapies. Payment models should ensure that the treatment options that are of value to patients and health systems are appropriately incentivised and supported to reach patients in a timely manner.

2. The potential health system and patient benefits of better recognising indication-level value through payment models are tangible.

Industry should continue to work towards maximising the treatment opportunities offered by existing and pipeline therapies, working with **patients** and the **scientific community** to ensure that innovation is driven by and centred on patient need within the context of a system that appropriately incentivises and rewards innovation.

Payers should strive to provide the right incentives for innovation, applying value-based decision making to best service population health needs and maximise health system efficiency. In order to realise the full benefits of medical innovation, **health systems** should reflect on the adequacy of current payment models in realising the full potential of existing therapies, working toward better recognition of differential value to maximise that potential in the longer term.

Payment models that recognise value at the indication-level can provide payers with more granular information to support a negotiation process that is better tailored to specific patient populations. **Payers** and **industry** should collaborate in the pursuit of value-based budget management, which for multi-indication medicines should operate at the indication-level. This would allow payers to maximise opportunities to incentivise and provide access to cost-effective treatments in all those patients that could benefit, thus optimising patient access and health benefit across the health system.

3. Value recognition at the indication level can be achieved in multiple ways; countries have different starting points and enabling infrastructure

To improve willingness to engage in indication-level payment models, **payers** and **industry** could collaborate in piloting programmes at regional or disease level, exploring and agreeing together on those cases that will achieve the highest impact.



Countries have different starting points in terms of payment models. There are different routes to advance value-based differential payment in line with the evolving science of precision medicine. System change should always be considered in terms of the benefits as well as the costs of change.

4. Data infrastructure (the ability to track and access data on real-world usage and/or outcomes) is a frequently cited “barrier” to change. Investing in and/or making better use of health data represents a major opportunity for better monitoring and enabling value-based health care.

The broad benefits of investment in better health data need to be recognised by **health systems**, and the use of those data should be supported by **patients** and by **payers** to enable better and more informed decision-making in health care. Where improved data collection is required to facilitate indication-level payment models, investment in sustainable data generation needs to be considered. In some cases and where the infrastructure is currently sub-optimal, **industry** has a role to play in contributing to the cost of putting in place the data collection and reporting capabilities within a health system to support patient access to a therapy.

5. The focus of further research and action should be at the country-level, to understand and work towards the realised benefits of more flexible payment models

There is a need for **cross-stakeholder collaboration** at the **country-level** to better understand how the opportunities for more flexible value-based payment models can be realised.

1 Introduction

1.1 Background and remit

In recent years, we have witnessed a proliferation of innovative drugs with multiple approved indications. Each approved indication corresponds to a different “use” of the drug; for example: in different diseases, at different stages of the same disease, at different points of the treatment regimen, or in combination with other therapies. Multi-indication medicines have long been available in oncology. For example, the first tyrosine-kinase inhibitor (TKI) to be approved for Chronic Myeloid Leukaemia (CML) was imatinib (Glivec) in 2001; over the following 12 years, the drug was approved in 8 further indications, either within the treatment pathway for CML or in other conditions. In 2018, 75% of oncology drugs were used in multiple indications (IQVIA, 2018). More recently, other therapeutic areas have seen significant expansion of the number of indications per drug, such as diabetes drugs (EMA, 2020) as well as respiratory and immunology therapies, for example, risankizumab (developed to treat plaque psoriasis) and lenzilumab (developed to treat cytokine storm) being repurposed to treat COVID-19 (Rubin, 2021).

The concept of aligning or evaluating a medicine’s price in accordance with the value it provides (over alternative treatments) to patients and the health systems is generally well accepted. This approach, known as value-based pricing, aims to maximise the efficiency of health care investments by rewarding innovation that most benefits patients (EXPH, 2017).

Medicines have historically been priced on a per-pill or per-vial basis. In the case of drugs with multiple indications, a fixed single price fails to align price to differential value across indications. Countries have addressed this problem in different ways, with some offering more flexibility than others. The challenge for health systems is to ensure the reimbursement landscape provides the right signals and a facilitative framework to attract and support clinically beneficial treatment options for patients, which also offer good value for money.

To drive a deeper understanding of the issues, the solutions, and to co-create the way forward, we facilitated a multi-stakeholder discussion of **the problem** posed by multi-indication medicines and the payment models currently available to pay for them, **the principles of the solution**, and practical recommendations for **implementing** the solution, recognising the existence of different enabling factors across contexts. Whilst the relevance of the work is global, the focus of the practical examples in this report are Australia, Belgium, Canada, Estonia, France, Germany, Italy, Spain, and the UK.

1.2 Our starting point

The programme of work described in this report builds on a strong foundation of research on this topic by OHE over recent years. The content and outputs are briefly described in this section.

The theory

The OHE has led an extensive programme of work on innovative payment models for drugs with multiple indications (Towse, Cole and Zamora, 2018; Cole et al., 2018; Mestre-Ferrandiz et al., 2015; Cole, Towse and Zamora, 2020). In particular, OHE’s work has explored the potential of health care systems to support value-based pricing at indication level. This idea typically goes by the name of

indication-based pricing (IBP), although other denominations, such as multi-indication pricing (MIP), indication-specific pricing (ISP) or non-uniform pricing, can also be found in the literature.

At its heart, the use of payment models that reflect multi-indication value is value-based pricing applied comprehensively.

We prefer avoiding the terminology IBP, MIP and ISP in favour of a more neutral notation to avoid misconceptions or association with a specific model of pricing. Through our interaction with the Expert Panel, we often used the notation '**value-based differential pricing (VBDP)**' or payment models with '**value recognition at the indication-level**' to refer more broadly to pricing models that recognise differences in value across the approved uses of a drug.

The main areas of research explored by the OHE to date, with references to the relevant publications, have been:

- [A summary](#) of the key contributions from the literature on value-based differential pricing, as well as a description of the status-quo for the pricing of multi-indication medicines in Europe and the US (Towse, Cole and Zamora, 2018).
- The [theory of value-based differential pricing](#). Based on a review and critique of the economic and grey literature, the OHE has laid out the potential benefits and drawbacks of value-based differential pricing, both in the short- and long term (Towse, Cole and Zamora, 2018; Cole et al., 2018) – a succinct [discussion paper](#) by Cole et al. (2019) summarises the main findings of the earlier papers
- The views of health care system stakeholders on the benefits and drawbacks of value-based differential pricing and on the enablers of and barriers to its implementation. This subject was first explored from a [UK-specific perspective](#) (Mestre-Ferrandiz et al., 2015) and later broadened to capture the opinions of health care [stakeholders globally](#) (Cole, Towse and Zamora, 2020).

The key takeaways from this work are summarised in the blog posts that accompanied their publication:

- [Should Drug Prices Differ by Indication? The Debate on Indication-based Pricing](#)
- [What are the Economic Implications of Moving Away from Paying a Single Price for a Single Drug?](#)
- [Indication-Based Pricing: Are We All Onboard?](#)

Taken together, findings from the OHE's research so far have demonstrated that value-based differential pricing may offer an improvement over traditional drug reimbursement models, primarily through improving breadth and speed of patient access, optimising incentives for R&D, and the longer-term consequent potential for downward pressure on prices as a result of increased competition at the indication-level.

The practice

Many contextual factors – arising from the variety of current payment models and data capabilities in tracking usage/outcomes of therapies across countries – may enable or hinder the practical adoption of alternative payment models for drugs with multiple approved uses, such as value-based differential pricing. Some countries are ahead in offering a more flexible reimbursement environment that accounts for differential value. For example, in Estonia, a single price is visible, but different risk-sharing arrangements are implemented at the indication-level, making use of electronic prescribing

data. In Australia, a new form of pricing agreements that allow multiple confidential net prices on top of the published list price through indication-based rebate arrangements are becoming increasingly common. A core part of the work described in this report is to establish what the **best solutions** are and how their **implementation might differ** by health system depending on the available infrastructure.

In a previous consultation on IBP open to anyone with an interest (Cole, Towse and Zamora, 2020), some respondents expressed scepticism about the true benefits of value-based differential pricing, and there is little evidence of it being a policy priority among health care systems. More work is therefore required to better understand the main issues or problems associated with the status quo and the perspectives and concerns of different stakeholders while developing consensus on whether and how better recognition of value at the indication-level could provide a useful and implementable solution.

1.3 Process: Expert Panel framework of interaction

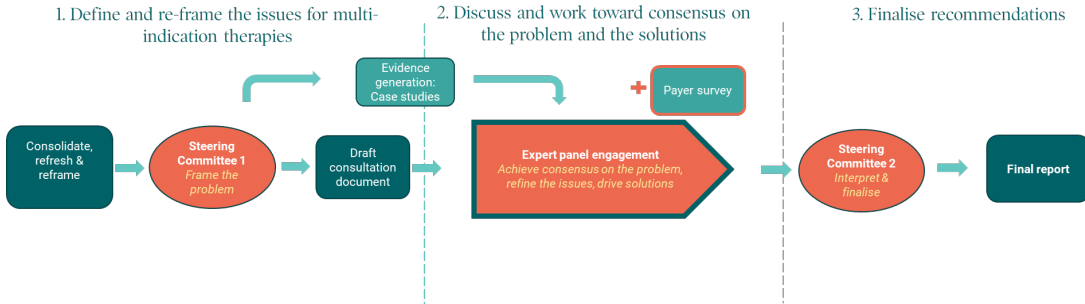
The OHE led this programme of work under the guidance of a Steering Committee, who were a subset of a broader Expert Panel of leading international experts (Figure 1).

FIGURE 1 EXPERT PANEL AND STEERING COMMITTEE



The interaction with the project’s Expert Panel was supported by the use of an online virtual engagement platform, ‘Within3’. The platform facilitates the sharing of resources and participation in topic conversation threads. The flow of activities is represented in Figure 2 and described in more detail in [Appendix 1](#).

FIGURE 2 PROJECT ROADMAP



1.4 Elicitation of experts' views

In recognition of the varied and multiple perspectives relevant to payment models for pharmaceuticals, we convened a group of 16 international experts representing multiple stakeholder groups and 11 individual countries as well as a pan-European perspective, summarised in Figure 3.

FIGURE 3 MATRIX OF STAKEHOLDER AND COUNTRY REPRESENTATION: EXPERT PANEL

	France (2)	Germany (2)	Italy (1)	Spain (1)	UK (2)	Austria (1)	Switzerland (1)	Portugal (1)	Belgium (1)	Estonia (1)	Canada (2)	Pan-EU (1)
Payer/Commissioner/HTA (2)	👤👤	👤	👤			👤						
Patient (1)											👤	
Regulator (1)			👤									
HCP/Clinician/Scientific research (2)	👤		👤		👤							
Academic / pricing expert / Policy-maker (7)	👤	👤	👤	👤	👤			👤	👤		👤	
Data expert (2)			👤		👤					👤		👤
Industry (1)							👤					

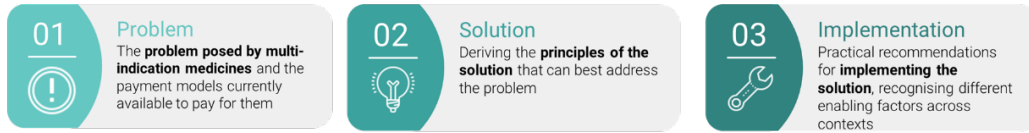
Note: The matrix represents experts' primary field of expertise (👤). Many panellists had multiple perspectives, which they brought to bear, based on multiple current or previous affiliations or roles; where these were significant, we have represented in the matrix with (👤).

Expert Panel engagement: an adapted Delphi methodology

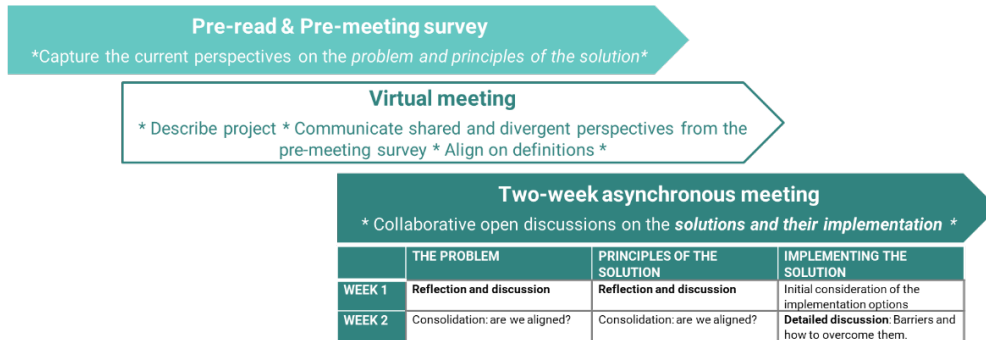
The primary objective of the project was to elicit the views of a broad range of stakeholders and work toward consensus on the problem, the principles of the solution, and practical recommendations on implementation. We adopted an adapted Delphi methodology, outlined briefly in Figure 4 below and described in greater detail in [Appendix 1](#). We used the three phases of engagement as an opportunity to (a) receive individual feedback from each panellist on the relevant topics [pre-meeting survey], (b) play back the overall results and insights to the whole group [virtual meeting], and (c) facilitate a discussion by re-visiting the topics as a group to reflect on commonalities and differences [two-week asynchronous meeting]. The goal was to reduce the range of responses and arrive at something closer to consensus on the key benefits, challenges and proposed policy advancements.

FIGURE 4 FRAMEWORK OF EXPERT ENGAGEMENT: OBJECTIVES AND METHODS

OBJECTIVE: To elicit expert views and work toward and multi-stakeholder **consensus** on:



EXPERT PANEL ENGAGEMENT



It should be noted that our approach and line of questioning for the Expert Panel was guided and influenced by our previous research on this topic, described earlier in this section. Through this programme of work, our aim was to start at first principles to achieve a shared understanding of the problems that are driving research on this topic in order for the solutions to be better informed and more appropriately defined. However, our line of questioning and framework of interaction was undeniably influenced by our pre-conception that (a) payment for health care should optimally be linked with the value that it generates and (b) if value differs by indication, then this warrants some form of differential payment or adjustment. Through our open discussions, some of these core principles were discussed and debated.

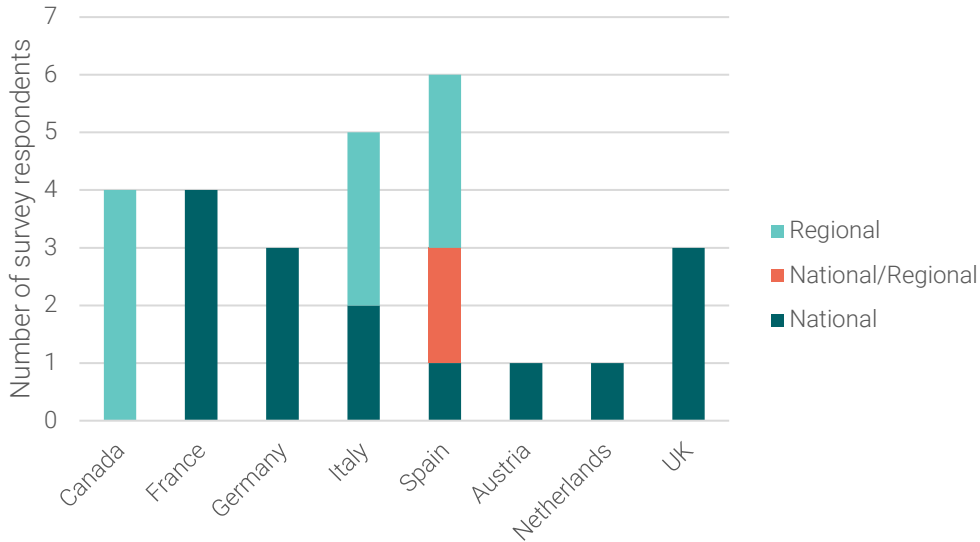
1.5 Payer survey

In recognition of the key voice of payers on the subject of flexible payment models, we carried out a separate survey to gain a deeper understanding of payer experience and perceptions of payment models that address multi-indication therapies and to collect country-specific views from payers at the national and regional levels. This builds on a previous consultation that found payers to be among the stakeholder groups least convinced about indication-based pricing (Cole, Towse and Zamora, 2020).

Anonymous survey respondents were payers (i.e. current or recent former members of HTA or contracting bodies, at the national and regional levels) from several EU countries and Canada (n=27)¹. The distribution of country representation and regional/national level expertise is summarised in Figure 5.

¹ Survey [AZ market research number 7811] conducted using an online platform where respondents receive a fee for their response. Respondents were aware that the research was sponsored by a pharmaceutical company.

FIGURE 5 SUMMARY OF PAYER SURVEY SAMPLE



The line of questioning for the payer survey followed a similar format to the Expert Panel's pre-meeting survey (see [appendix 1](#)). Where relevant, we present the results of the payer survey alongside the main summary of results in the results sections to follow.

1.6 This report

This report describes the main findings from this programme and supplementary research to investigate and evidence the issues. Sections 2 to 5 summarise the main results, organised by (2) Principles of the problem, (3) Principles of the solution, (4) Articulating the evidence gaps and investigating the potential benefits and (5) Implementation models. In section 6, we highlight the main conclusions and recommendations.

2 Framing the problem

“Solutions” are unlikely to be found or implemented if the “problems” they seek to address are not recognised. Therefore, a key part of this project was to see whether a consensus view could be achieved on the *problem(s)* posed by current payment models for medicines serving multiple indications and how these manifest for patients, payers, industry and society more broadly. The Expert Panel discussion, therefore, followed the following line of questioning:

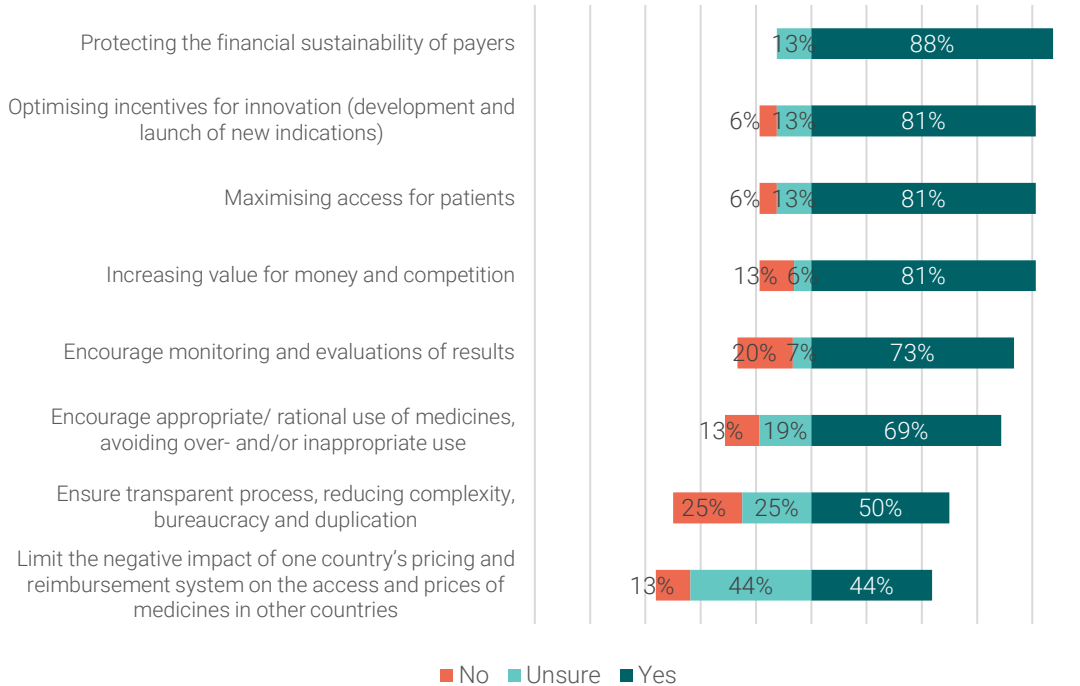
- a) What should be considered the main objectives of pharmaceutical pricing?
- b) Does a uniform, inflexible price optimally meet these objectives?
- c) Can we observe any *symptoms* of the problems identified in (b)?

2.1 Objectives of pharmaceutical pricing

In order to inform a discussion of the problems, it is pertinent to consider what the pricing of pharmaceuticals should aim to achieve. The main criteria commonly used to assess the success of pharmaceutical pricing are the **optimisation of patient access**, the **optimisation of the incentives for innovation** and the **protection of the financial sustainability of payers**. Additional criteria to assess the optimality of pricing models at the national level have been recommended by leading international organisations such as the European Commission Expert Panel on effective ways of investing in health (EXPH), the World Health Organisation (WHO) and the Organisation for Economic Co-operation and Development (OECD) (Mestre-Ferrandiz et al., 2018). These include: **Increase value for money and competition**, via prices which reflect relative value; **Encourage monitoring and evaluation of medicine performance**, via a dynamic pricing system which allows flexible pricing of indications and over time; **Encourage appropriate/ rational use of medicines**, avoiding over- and/or inappropriate use; **Ensure transparent process, reducing complexity, bureaucracy and duplication**; and **Limit the negative impact** of one country’s pricing and reimbursement system on the access and prices of medicines in other countries.

These ‘objectives’ were described in the pre-read report, and Expert Panel members were asked whether they agreed with these in the pre-meeting survey. The level of agreement with each is summarised in Figure 6. Those with the greatest level of agreements were: protecting the financial sustainability of payers, optimising incentives for innovation, maximising patient access and increasing value or money and competition.

FIGURE 6 EXPERT PANEL PRE-MEETING SURVEY: “DO YOU AGREE WITH THE OBJECTIVES OF PHARMACEUTICAL PRICING DESCRIBED IN THE PRE-READING?” (N=16)



PAYER SURVEY BOX 1 – PRICING OBJECTIVES

Through the payer survey, respondents were similarly asked to consider the most important **objectives**, for “pricing and access models for drugs with multiple indications”.

Like the Expert Panel, payer respondents (n=27) agreed that ‘**protecting the financial sustainability of payers**’ (85%) and ‘**maximising access for patients**’ (85%) should be considered the most important priorities. However, there was *less* agreement among payers that ‘optimising incentives for innovation’ (59%) and ‘increasing value for money and competition’ (56%) should be considered important objectives of pharmaceutical pricing. In addition, *fewer* payer respondents agreed with the objectives of monitoring results (44%) and limiting impact on other countries (26%); importance of ensuring a transparent and simple process received a similar level of agreement between the payer survey respondents (56%) and the Expert Panel.

Whilst there appears to be a marked difference between the Payers and the Expert Panel on the importance of (a) incentivising innovation and (b) increasing value for money and competition as important objectives of pharmaceutical pricing, this may reflect that payers are simply more (naturally) focussed / attuned to the end product (patient access and financial sustainability) rather than how we get there (innovation incentives and value for money).

The list of objectives was broadly considered by the Expert Panel to be comprehensive. It was discussed and agreed that the patient access objective should – in recognition of limited budgets – be to *optimise in terms of health benefit*, rather than simply to maximise overall volume treated. To reflect this comment, discussion of it for the remainder of the Expert Panel interaction was modified to ‘Optimising patient access’.

There were several recurring themes in the discussion of the ‘objectives’ of pharmaceutical pricing, both in the Expert Panel’s pre-meeting survey as well as during the asynchronous meeting. These are briefly summarised below.

Incentives for innovation

There was some discussion among experts about what type of innovation should be incentivised. For example, one expert commented that incentives for innovation should be optimised in terms of *direction* (i.e. toward high-value innovation) but also *intensity* of R&D across research areas (i.e. R&D efforts also committed to areas of unmet need). Another challenged the implicit link between income from pricing and more/better innovation, particularly recognising the role of the public sector in research and innovation.

Pricing is just one tool among many

What and how we pay for therapies is not the only tool that enables the achievement of the broad set of objectives outlined. Rather, pricing should be considered as one tool among many (which include market exclusivity mechanisms, tax incentives, etc.). By the same token, we cannot expect a single payment model to address all objectives.

Not all should be considered “objectives” of pharmaceutical pricing

Several experts commented that some objectives listed, such as “encouraging outcomes monitoring” and “ensuring a transparent process”, should not be considered objectives in themselves, but rather as the (potential) means or pre-conditions to achieve them.

Inherent trade-offs

*“All these objectives are fair but **are they compatible?**”*

Clearly, these objectives may act in opposite directions, and there are trade-offs to be made. In economics, the concepts of welfare maximisation and surplus distribution² are used to explain how these objectives can be balanced. Most economists argue that pharmaceutical pricing maximises social welfare (i.e. it is efficient) when patient access and R&D incentives are optimised. To maximise the health benefit derived from patient access, pricing should guarantee that the finite resources of the health care system are allocated to the more cost-effective interventions, considering the opportunity costs of that investment in the short and longer term. This ensures that total health increases over time because new treatments and interventions add more health gain than is lost through displacement.

The Expert Panel described and discussed the balancing of objectives and the inherent trade-offs that this requires, for example:

² *The concepts of social welfare and surplus are closely linked. Social welfare is the total benefit available to society from an economic transaction, and it corresponds to the sum of the producer and consumer surplus. Consumer surplus is derived from the difference between the price a consumer is willing to pay and the price they pay in practice. Producer surplus is the private benefit to producers, derived from the difference between the minimum price they would be prepared to supply for, and the price they receive in the market.*

- Between maximising patient access and payer financial sustainability (although when the patient access objective is re-framed as 'optimising' patient access, then the payer budget is rightfully recognised as a constraint rather than a conflicting objective per se).
- Between short-term payer financial sustainability and long-term incentives for innovation (static versus dynamic efficiency). The optimal trade-off (i.e., surplus distribution) may vary when the public sector is investing in the research that supports the development of a medicine.
- Between price transparency and payer financial sustainability and patient access. Favourable deals are achieved via confidential agreements; in the context of international reference pricing and trade, price transparency could lead to a convergence of prices across countries, raising prices in lower-income countries and thereby limiting patient access in those countries.

The topic of transparency was discussed at length, with a clear distinction drawn between transparency of *process* (the principles upon which prices are assessed or negotiated, for which there was widespread support) and transparency of *price* (for which there was some disagreement, but with most experts emphasising the importance of net price confidentiality as a way to help health systems achieve more favourable agreements and maintaining access for lower-income countries in the face of international reference pricing from high-income countries (Berdud et al., 2019)). The objective to 'limit the negative impact of one country's pricing and reimbursement system on the access and prices of medicines in other countries' also relates to this issue, particularly in the context of some countries recognising indication-level value and others not; there was a broad spread of agreement/disagreement by the Expert Panel with this objective, which may reflect some ambiguity in its definition.

The question of competing objectives being representative of the competing perspectives of stakeholders was also raised. For example, one expert view that:

"Payers have accountability for treating patients with what is available [resources and treatment options] but no responsibility for encouraging innovation."

This aligned with the payer survey finding that only 59% of payer respondents (versus 81% of the Expert Panel) agreed that payment models should have the objective of incentivising innovation; this finding could also reflect that individual payers, particularly in smaller countries, may feel they have limited impact on overall innovation efforts.

The objectives of pharmaceutical pricing are many, are complex, and can act in opposing directions. The key question is: how well is the balance achieved by payment models that do not recognise indication-level value, and can we do better?

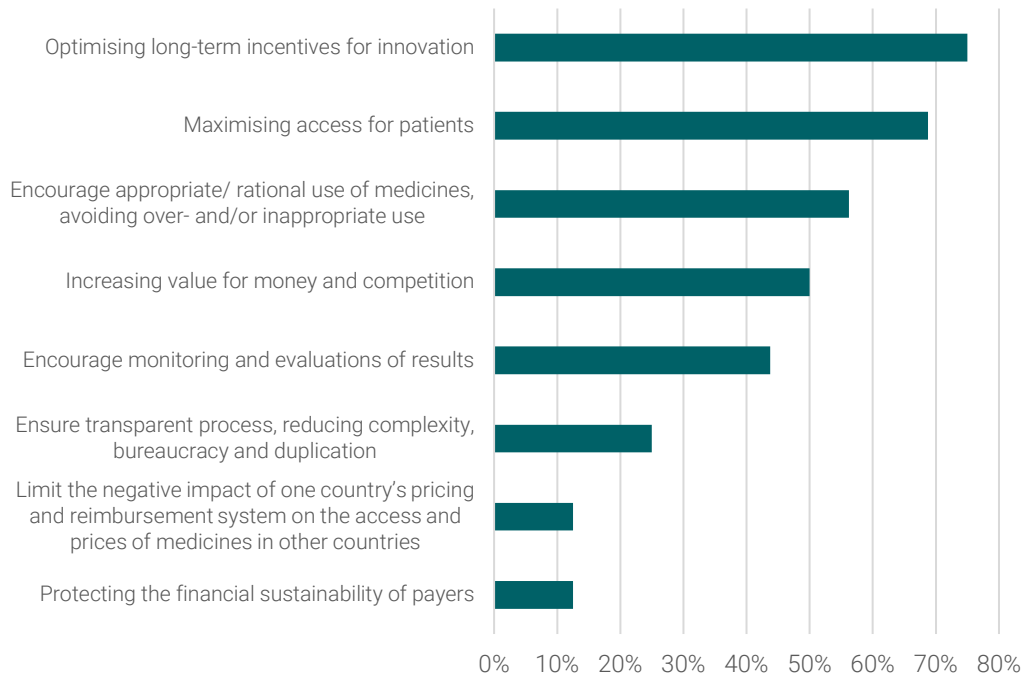
2.2 Adequacy of an inflexible uniform price in meeting these objectives

Expert Panel members were asked in the pre-meeting survey: "Does uniform pricing pose any problems in the case of drugs with multiple indications?". 13 respondents said "yes"; 3 said "no". Of those that said uniform prices did pose a problem, most described incentives for innovation: how a single (fixed) price set at a lower level disincentivises innovation and research incentives by industry, whereas if the medicinal price is calibrated on the basis of a higher-value indication, this may limit use for a potentially more common, relatively lower-value indication, irrespective of its clinical value.

The three respondents who indicated that a uniform price does *not* pose any problems in the case of drugs with multiple indications mainly referred to the successful way in which a uniform price can adapt to the value of successive indications, using a blended ('weighted-average') price model (as used in France, for example). This actually represents one potential model of better recognising value at the indication level, thus anticipating a potential solution rather than considering the principles of a single inflexible price scenario. Given this divergent understanding of the term 'uniform price' in these answers, we subsequently modified our language in later interactions (virtual meeting and asynchronous meeting) to describe an 'inflexible uniform price' or 'price that does not adequately reflect value at the indication-level'.

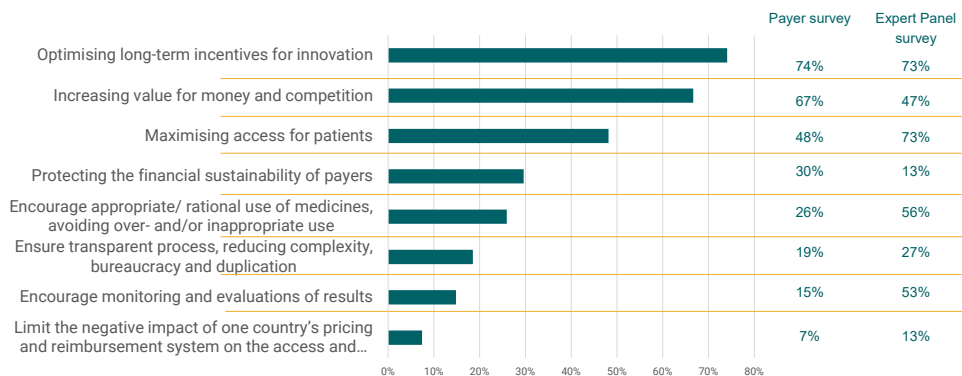
When asked specifically to consider which objectives may not be successfully achieved with a uniform price, the Expert Panel ranked 'optimising incentives for innovation' (75%) and 'optimising access for patients' (69%) as being most problematic.

FIGURE 7. EXPERT PANEL PRE-MEETING SURVEY: "IN THE CASE OF DRUGS WITH MULTIPLE INDICATIONS, WHICH OBJECTIVES MAY NOT BE SUCCESSFULLY ACHIEVED UNDER UNIFORM PRICING PER UNIT OF MEDICINE??" (N=16)



PAYER SURVEY BOX 2 –LIMITATIONS OF UNIFORM PRICING

The Payer survey respondents were asked the same question as the Expert Panel: “In the case of drugs with multiple indications, which objectives may not be successfully achieved under uniform pricing per unit of medicine? They gave the following responses:



Notable differences between payer respondents and the Expert Panel included that *more* payers thought that increasing value for money and competition (67%) and protecting financial sustainability of payers (30%) were not adequately met by uniform pricing for multi-indication medicines, compared with Expert Panel members. Many payers described a situation where an initial uniform price is agreed in a relatively high value indication with small patient numbers; when subsequent indications are associated with greater patient numbers, inability to reduce price limits affordability, and thereby reduces access and competition. Respondents also described this scenario in terms of innovation incentives, whereby inflexible uniform prices lead to a launch sequence that prioritises the earlier launch of indications that grant higher prices (i.e., small population, high added clinical benefit).

2.3 Identifying the symptoms of the problem

A key limitation of traditional uniform pricing for drugs that can service multiple indications is the potential for *suboptimal patient access*. In other words, a drug that could potentially service an unmet medical need in a particular group of patients (indication) may not be available due to the inflexibility of payment models to appropriately signal demand. This may be because there is no financial incentive (or, indeed, there may be a disincentive) to develop, license, launch, or negotiate reimbursement for that indication. All other objectives (including incentivising innovation and being affordable) are tied intrinsically with this overriding objective of optimising patient access (for example, adding indications for an existing drug may increase the number of treatment options for that additional indication, disease or therapeutic class resulting in more competition and ultimately lower prices for payers).

Despite the above argument, the inherent difficulty in evidencing that there is a **problem** is demonstrating the counterfactual. *Would moving away from uniform pricing bring about more treatment options and more patient benefit?* While it is difficult to observe this directly, we can consider the potential symptoms of the problem.

Below we describe three scenarios, along with some indicative examples.

Physical differentiation / dual branding

In some cases, where an existing drug is found to be beneficial for a completely different indication, its use involves an alteration of the drug or its method of delivery. In these cases, the physical differentiation of the drug for the different licensed indications prevents arbitrage³, and differential pricing is possible. An example is the active substance denosumab, licensed under the brand name Prolia® for the treatment of osteoporosis and under the brand name Xgeva® for the prevention of bone fractures in people with cancer (NICE, 2021). The two indications are associated with different strengths and doses of the drug (with their differentiation therefore motivated by safety concerns) and are associated with different prices (Xgeva® for the oncology indication has a higher price, given its dosage regimen). In Europe, Xgeva® required significant discounts to secure access, which was possible because of the dual branding.

Despite containing the same active substance, the distinct pricing and positioning of dual brands is usually reflective of the two very differentiated indications that they serve, in the same way, that any drug is generally priced in a way that reflects the treatment's value in the patient population under consideration, acknowledging the need to incentivise and allow the recouping of costs for developing and testing a drug for that patient population. This being the case, *should it not also be the case for therapies where physical differentiation is not appropriate?*

Off-label use

Where a drug is considered or predicted to be of benefit in an unlicensed indication, medical professionals may decide to use the drug *off label*⁴. There are important safety concerns associated with off-label use, with potentially higher risks to patients without the due diligence of a robust development programme. In addition, it can raise difficulties for payers who cannot appropriately predict or manage their budgets.

Off-label use could be considered in some cases to be a symptom of indications *not* being pursued for regulatory approval due to inflexibility of price and, therefore, an unsupportable business case for investment in development. For example, permitting price to vary by indication could incentivise research and development into the use of existing drugs for rare and untreated disorders which may otherwise fail to provide a return on investment at the prevailing price. For example, anakinra (brand name Kineret®) was approved for use in the EU for rheumatoid arthritis in 2002, and it took over ten years for its use to be approved in the rare autoinflammatory condition Cryopyrin-Associated Periodic Syndromes (CAPS), during which time it was used off-label in that condition (Kapur and Bonk, 2009). *Could the approval in the new indication have been expedited if more flexible pricing could have permitted a higher price and, therefore, stronger incentives for R&D?*

Strategic launch sequencing

Clinical development is influenced by many factors, including the scientific discovery process and consideration of which indications are likely to generate clinical trial results most quickly. However, an important signal of the problem with inflexible uniform prices, which was alluded to by experts at multiple points through the period of Expert Panel engagement, was around strategic launch sequencing. It was suggested that some companies might incorporate business case evaluations before investing in new molecules, for which trade-offs between different indications (and impact on profitability) can lead to deliberative sequencing of indications (launching higher value indications first) or potentially not even developing certain indications.

³ Arbitrage would likely involve the use of the drug in a high-value indication at the price of a lower-value indication.

⁴ AZ does not, under any circumstances, promote its products for off-label or unapproved uses

“Launch sequencing (manipulation) is an indication that something is wrong (with the current model). If a product of our (the Expert Panel programme) activity means launch sequencing is more in line with patient needs, then that would be a profit (benefit) of this project.”

Withdrawal of indications or unrealised benefit of existing therapies

The best evidence of a “problem” with payment models that do not reflect differential value of indications would be to find groups of patients that *could* benefit from a drug but currently do not due to pricing considerations in another indication. An extreme example could be that an indication is not reimbursed because the established price is too high in that context, or a company doesn’t launch/withdraws an indication from the market if it undermines the value-based price that could be achieved in another higher value indication.

Alemtuzumab was originally developed by Genzyme (and acquired by Sanofi) under the brand name Campath® to treat B cell chronic lymphocytic leukaemia. In 2012 Sanofi launched the monoclonal antibody under the trade name Lemtrada® (a lower dose, at a higher price) for multiple sclerosis (MS), where clinical trials demonstrated very high value. In order to *avoid* the risk of volume-related discounts while trying to obtain a price commensurate with the higher value of the MS indication (the cheaper and lower value), Campath® was withdrawn from the market before Lemtrada® was launched (McKee, 2012). Assuming that arbitrage could be prevented, *could a system that enabled differential pricing per indication have prevented the withdrawal of Campath® from the market?*

It is difficult to evidence the unrealised benefit of existing drugs, but one class of medications with multiple indications, whose access across indications may be constrained by inflexible pricing structures, could be an innovative class of cardiovascular drugs, the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. In particular, evolocumab (under the brand name Repatha®) and alirocumab (under the brand name Praluent®) were approved for use as adjuncts to diet and maximally tolerated statin therapy for patients with familial hypercholesterolemia (FH), and those with clinical atherosclerotic cardiovascular disease (ASCVD), requiring a greater reduction in LDL-C levels. Later, the labels of evolocumab and alirocumab were expanded to adult patients with other cardiovascular conditions (Goldman et al., 2018), but payers imposed coverage restrictions, and the uptake of these drugs has been low in the first years of their approval. Whilst there are likely to be other factors at play in this example, *would a more flexible pricing structure, where differential payments by indication could reflect the differences in efficacy and/or certainty of the evidence base across those indications expand access?*

Other anecdotes offered by the Expert Panel in relation to the potential unrealised benefit of existing drugs due to price inflexibilities include that only a small proportion of adult cancer drugs are currently licensed for children, which (as speculated by the Expert Panel member) could be a result of the limited patient numbers and inability to recoup the cost of R&D for their testing in children, or dosage modifications altering the relationship between price and value.

The issue of combination therapies

A key problem area of unrealised benefit of existing drugs is the difficulty in finding a solution to paying for drugs used in combination. This relates to the counter-intuitive scenario whereby the use of a clinically beneficial combination drug therapy is challenged in demonstrating cost-effectiveness (in extreme cases, even at price zero). This arises when the on-patent ‘backbone’ drug is priced at or near the limit of cost-effectiveness, and the combination therapy regimen involves extending treatment duration. This is particularly problematic when there are two distinct developers of the constituent drugs of the combination therapy. Latimer et al. (2021) propose that the most feasible way forward to address the challenge of combination therapies in the near future is to adjust the price of both constituents of a combination to reflect the value they offer when used in that

combination. Assuming that the constituent drugs were not developed solely for use in that indication, this would only be possible if multiple prices (or payment levels) for the individual drugs were permitted.

In other words, combination therapies face challenges in the recognition of value by indication, as do multi-indication therapies. The implementation of prices that suitably recognise the value of combination therapies relies on specific factors which deserve separate consideration from the case of multi-indication therapies and were beyond the scope of this project.

2.4 Summary: Defining the problem

By facilitating a discussion with the Expert Panel around the primary *objectives* of pharmaceutical pricing and the extent to which these are met by inflexible uniform price, we were able to observe a converging view of the crux of the problem, which is summarised below.

What are the main objectives of pharmaceutical pricing?	Does uniform pricing address the objective?
1. Protecting financial sustainability of payers (88%)	YES
2. Optimising incentives for innovation (development and launch of new indications) (81%)	NO
3. Optimising access for patients in terms of health outcomes (81%)	NO
4. Increasing value for money and competition (81%)	?

Of the four highest-ranked objectives of pharmaceutical pricing, *optimising incentives* for innovation and *optimising access* for patients are not well met by inflexible prices that do not recognise value at the indication-level.

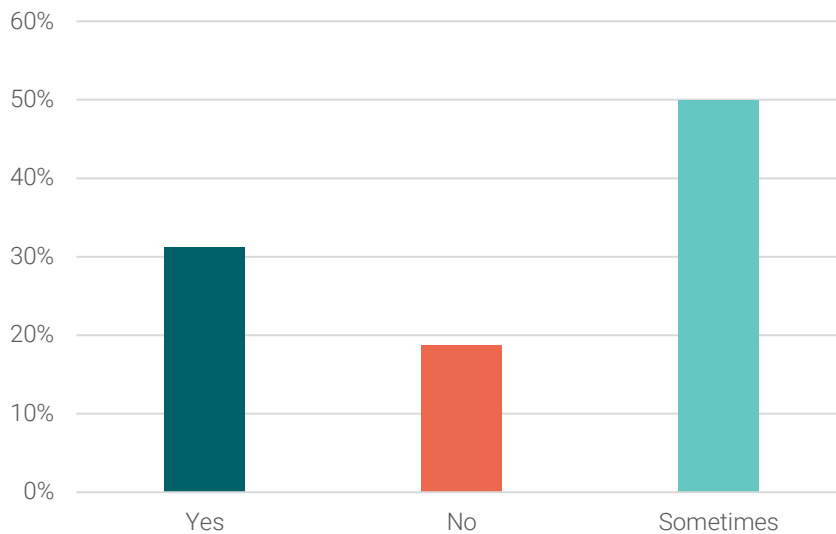
We have also observed the symptoms of the problem, which include physical differentiation, off-label use, strategic launch sequencing, withdrawal of indications, and most significantly (but also most difficult to demonstrate): unrealised benefit. Combination therapies, especially of high-value therapies such as in oncology, present a particular challenge, especially when the components are from different manufacturers and systems cannot assign contribution of value to the two components or apply isolated discounts to therapies when used in combination vs monotherapy.

Given the overall comfort of many stakeholders in a status quo uniform price scenario, and its perceived compatibility with financial sustainability, the key question therefore is: Can value-based differential pricing help improve incentives & access without compromising financial sustainability?

3 Principles of the solution

Payment models that recognise value at the indication-level were seen as an important *part* of the solution for multi-indication therapies by most of the Expert Panel.

FIGURE 8. EXPERT PANEL PRE-MEETING SURVEY: "DOES VALUE-BASED DIFFERENTIAL PRICING OFFER AN APPROPRIATE RESPONSE?" (N=16)



Reasons to support those that answered "yes" (n=5) included:

"For drugs with multiple indications with different value, then it allows more patient access."

"We would also see many more indications being developed rather than deprioritized due to indication sequencing."

"It is near impossible to make a coherent decision on the justified price of such drugs if the different indications are not factored into the assessment."

Those that answered 'no' (n=3) or 'sometimes' (n=8) could be split into three groups according to the motivations for those answers:

1. **Misunderstanding of the terminology/comparison.** A misunderstanding that a blended price is a form of the counterfactual 'uniform price' scenario, rather than actually being one of the potential implementation models of value-based differential pricing (as envisaged and described in section 5 of this report).
2. **Value-based differential pricing is just *part* of the solution.** It is too bold to regard it as a solution in itself but rather a tool to build solutions in the context of broader initiatives or recognition of benefits. Similarly, some experts explicitly referenced the optimal use of risk-sharing initiatives to account for differences in outcome in conjunction with (or as part of) the payment models under discussion.

3. **It depends on the context.** As well as depending on the implementation, there was also commentary that – whilst value-based differential pricing could be regarded as an ideal solution – there are implementation challenges in some small countries with highly regionalised health systems.

A note on value-based pricing

In setting out the considerations relevant to “value-based differential pricing”, it is easy to take for granted a shared understanding of the term “value” and the merits of linking this with payment for pharmaceutical innovation. However, during the asynchronous meeting of the Expert Panel, there was much discussion and debate on what ‘value’ means, how it should be measured, and to what extent it should be recognised or incentivised in payment models. This is a helpful reminder that the concept of “value” is broad and understandably holds different connotations for different stakeholders. Given the intrinsic importance of this concept for the payment model discussion, we elaborate briefly on the points here.

For a health economist, “value” captures the impact of introducing a new health technology in terms of its clinical and other benefits over and above the standard of care as well as implications on costs and resource use. Central to our understanding of “value” is making sure that we capture the most important and relevant outcomes that matter to patients. The impact of a treatment on a patient’s quality and length of life is an integral part of the treatment benefits captured and evaluated through health technology assessment. But our understanding of patient outcomes, patient preferences, and how these should be captured and measured continues to evolve. Any discussion of value-based care and value-based pricing should encompass and incorporate the patient’s perspective in defining that value.

In order to provide the right incentives for future R&D, pricing should reward the development of drugs that deliver larger clinical, patient and economic benefits (Mestre-Ferrandiz et al., 2015). To meet this objective, it has been argued that prices should permit R&D costs to be recouped⁵. Some suggest that price should be set at a level defined by the consumer’s willingness to pay (WTP) for the drug’s value (i.e. the implicit or explicit cost-effectiveness threshold) to ensure that there is a reward for innovation and a future incentive for further innovation. However, the concept of value-based pricing can be applied more broadly and beyond those health systems that have a quantitative basis for calculating value-based prices using thresholds.

Depending on the reimbursed price of the drug (i.e. proximity of price to the maximum consumer’s WTP), the economic “surplus” is captured by or shared between the producer and the consumer (or payers, as in the case of publicly funded health care systems). The optimal share of surplus that producers and consumers should appropriate to balance optimal R&D incentives and the health system’s financial sustainability is a matter of debate in the literature⁶. This topic was also a matter of debate among Expert Panel members. In addition, there was commentary on how the appropriation of “surplus” could be managed in an optimal way, for example, through a two-price reimbursement model that starts with a high price for initial doses (guaranteeing that profits can be realised upfront) and low continuation prices (limiting potential financial liability of payers in the face of uncertain patient numbers) (Chassang et al., 2018).

⁵ We assume that the length of patent period, during which producers are able to price above marginal cost of production and to capture the surplus, is such that it provides optimal R&D incentives (Danzon, Towse and Mestre-Ferrandiz, 2015). We are aware that the optimal length of patents and their role in stimulating optimal R&D is the subject of debate in the literature (Health Action International (HAI), 2016). The discussion of this aspect is considered beyond the scope of our project.

⁶ Some researchers have argued that to foster R&D incentives, the industry should appropriate all the surplus (by setting a price equal to or just below the maximum consumer’s WTP) (Danzon, Towse and Mestre-Ferrandiz, 2015). Other researchers have argued that surplus should be shared between producers and consumers (by setting prices below the maximum consumer’s WTP) to protect the financial sustainability of the health system (Claxton, 2007; EXPH 2017).

Various perspectives were exposed on how price should reflect value, what value means, and who should be “rewarded” for it. As well as fundamental concepts of whose value we should measure and to what extent this should reflect societal preferences or go beyond health care, there was also some debate on what signal payment models send in this regard.

In the context of multi-indication medicines, one Expert Panel member questioned whether relatively “low value” innovation (relating to the clinical benefit over and above the standard of care in a given indication) should be incentivised at all, suggesting that payers may choose simply to reject this rather than be willing to pay lower prices. Other experts disagreed, asserting that *relative* value must, of course, differ between indications, and the pricing should incentivise the development of all valuable innovation no matter the relative level of benefit (within reason) or prevailing value-based price (which relates to both the clinical benefit offered and the prevailing price benchmark in a given indication).

“If it is lower value, then health systems will pay less than if it is higher value [...]. Innovation does not always come in giant steps; often, it is the smaller steps (easier administration, fewer side effects, etc.) that drive population benefit through broader uptake.”

Over the last 20 years, value-based pricing has received more traction, recognising that it can drive value-based competition and ultimately improve outcomes for patients. The development of disease-modifying and even curative drugs is a testament to the strong signals sent by a value-based pricing approach. However, the issue that interventions can be value-based but unaffordable represents a conflict, and there are some that call for changes to the way drugs are valued and reimbursed.

The Expert Panel group felt that the evolving discussion accurately reflected the diverging views between different stakeholders. The discussion on value relates to how we price drugs in general, which then has implications for how we use value-based differential pricing for drugs with several indications.

3.1 Impact of value-based differential pricing

In the pre-read document, we summarised some working principles and expected effects of value-based differential pricing as a *potential solution*. Value-based differential pricing consists of applying value-based pricing at the indication level to recognise differences in clinical and/or economic value across indications. This concept can be operationalised in multiple ways, which we discuss in detail in section 5.

The impact of value-based differential pricing on patient access, R&D incentives, and payers’ affordability largely depends on the scenario under consideration compared to uniform pricing and how the uniform price is set. Under uniform pricing, the price tends to remain anchored to the value of a single indication, often the first to be launched⁷. Therefore, the implications of value-based differential pricing will differ according to the relative value of new indications compared to the anchor indication (the one determining the single price). Below we summarise the short- and hypothesised longer-term effects of value-based differential pricing. In the *short-term*:

- **Patient access may expand** if indications – that would not otherwise be reimbursed with uniform pricing – can now be priced at a value-based level for that indication (e.g., lower clinical value indications or combinations of therapies with high additive price). As a natural consequence of increased patient access, **overall spend may increase** in the short term. However, it makes sense

⁷ Some countries have tried to accommodate differential value across indications by implementing a single price based on a weighted average of value across indications. This will be discussed further in the implementation section.

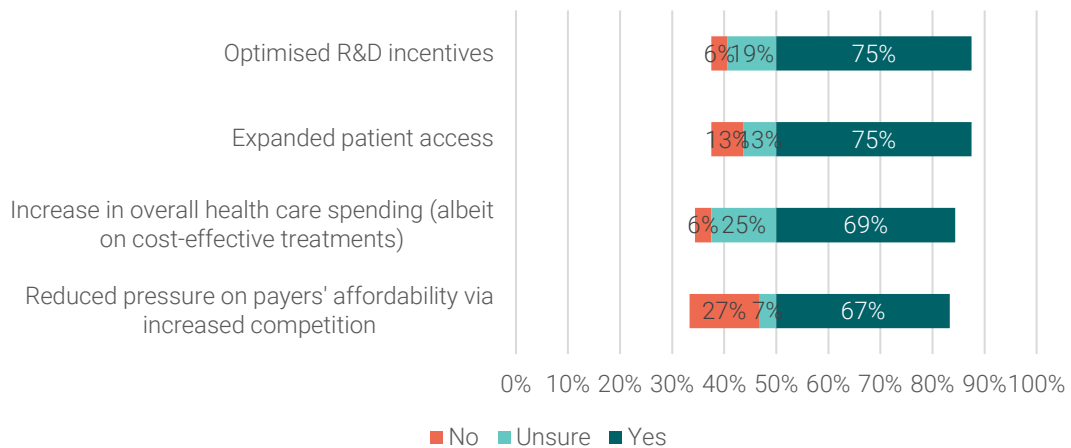
to reimburse the additional indication (at a value-based price) because this would represent a good use of health care resources, the assessment of which encompasses the whole treatment pathway and cost offsets, as well as broader societal value where this can be captured.

Set against the potential near-term spend increase, we may observe a trade-off in the *longer term*, where:

- **Incentives for R&D are optimised (or at least better aligned with social value)**, in contrast to uniform pricing, which fails to recognise and therefore incentivise the R&D of medicines for some indications. This would thereby lead to further innovation and expansion of patient access.
- **Reduced pressure on payers' affordability through competition:** Cole et al. (2018) argue that improved R&D incentives will increase competition by incentivising an expansion in the number of indications serviced by each drug, and therefore leading to a greater number of therapies available for any given indication. More competition at the indication-level would put downward pressure on price, thereby driving price below the consumer's maximum willingness-to-pay⁸.

Ideally, these would be acknowledged in the reimbursement review, although evaluating the magnitude and speed of these effects is a difficult exercise: examples of pure value-based differential pricing are rarely observed in practice, and – critically – there is no 'counterfactual' scenario to compare. The level of agreement of the Expert Panel on the effects described is summarised in Figure 9.

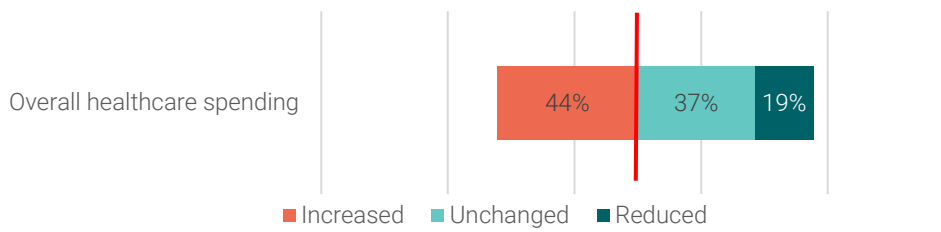
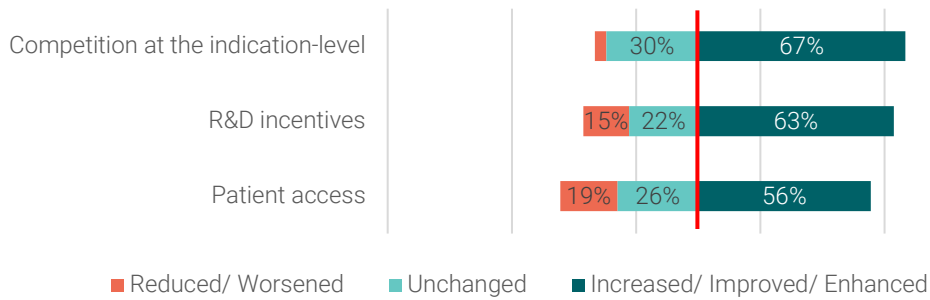
FIGURE 9 EXPERT PANEL PRE-MEETING SURVEY: "DO YOU AGREE WITH OUR DESCRIPTION OF THE SHORT- AND LONG-TERM EFFECTS OF VBDP?" (N=16)



⁸ This would lead a re-distribution of economic surplus from the producer to the consumer.

PAYER SURVEY BOX 3 – IMPACTS OF VALUE-BASED DIFFERENTIAL PRICING

When payers were asked about the possible (or realised) impact of value-based differential pricing, their responses were as follows:



Only 44% of payer survey respondents believed that overall health care spending would increase as a result of implementing value-based differential pricing; 37% believed it would remain unchanged, and 19% believed it would be reduced.

Overall, potential advantages of better value-recognition at the indication-level were cited by the Expert Panel to be:

- Increases the number of therapeutic options per indication or in new target groups of patients
- Encourages providers to use the therapies that are most likely to achieve the best outcomes for patients
- Reduces off-label use of drugs
- Improves clinical information on efficacy and safety relying on evidence-based data

Potential disadvantages were highlighted as being:

- Risks distorting prescribing incentives of providers (arbitrage)
- Challenging and complex implementation (particularly for highly decentralised health systems), with high information requirements
- Uncertain overall impact on health care bill

3.2 Recognising differential value in payment models: was there consensus?

Did the Expert Panel think that they were aligned?

"This is a complex problem which we all see from different perspectives and with different emphases. I do not sense us disagreeing with each other, but we focus on different aspects of this issue depending on our expertise."

There are various perspectives on how price should reflect value, what value means, and who should be "rewarded" for it. The key question is: when a drug serves more than one indication, is it more efficient for the price-value relationship to be determined at the indication level, rather than to base it on the launch indication only (as is the case in systems that do not recognise value at the indication-level)? While the group represented different perspectives, divergent views were mainly on the "value-based" part, which complicated discussion on the "differential pricing" for multi-indication therapies, for which there was broad alignment.

Given the accepted need to recognise different uses of a drug in our payment models, a discussion of the "implementation models" makes sense. There was a majority consensus among Expert Panel members that permitting price to account for different value in different uses more directly connects the price to the patient benefit; this can serve to enable the reimbursement of (and therefore incentivise development of) cost-effective drugs in all indications of expected patient benefit.

4 Articulating the evidence gaps and investigating the potential benefits

4.1 Why has value-based differential pricing not been broadly adopted to date?

We asked Expert Panel members why value-based differential pricing had not been broadly adopted to date and the related question of what evidence would be needed to support its adoption. The Panel members referred to and discussed various obstacles and constraints, which differed by country. The main issues arising are summarised in the table below, along with considerations of the evidence gaps:

Why has value-based differential pricing not been broadly adopted to date?	What evidence is needed to support adoption?
<ul style="list-style-type: none"> • Payers' inertia and/ or scepticism • Inadequate data infrastructure and/or data governance issues • Complex implementation • Adverse legislative framework • Lack of public understanding and awareness • Lack of conceptual framework to determine/demonstrate benefits and suitability of VBDP use 	<p>Data</p> <p>Data on real-world usage of therapies at the indication-level, and/or real-world outcomes data (if relevant)</p> <p>Making the case</p> <ul style="list-style-type: none"> • Evidence that lack of differential pricing led to access delays for patients • Evidence of undeveloped indications when the indications' value is not recognised • Framework to assess benefits and suitability of VBDP use • Pilots showing benefits to all stakeholders



In the separate payer survey, respondents were similarly asked about the reasons why value-based differential pricing had not been broadly adopted to date; Payers raised similar themes as the Expert Panel, but with more emphasis on inadequate access to use/outcomes tracking data infrastructure and the complexity of implementation.

In response to the evidence requirements articulated, and in order to provide complementary insight to support the findings of this project, the project team investigated how these evidence gaps could be filled, seeking input and discussing interpretation with the Expert Panel. These relate primarily to the questions articulated under "Making the case" in the table above, while considerations of data barriers and enablers are reserved for the implementation section of this report.

In the following subsections we seek to address: ***Can value-based differential pricing solve the problem of constrained or delayed patient access to multi-indication therapies whilst mitigating payer concerns over budget impact?***

4.2 Demonstrating improved outcomes for patients and health systems

By pursuing this line of enquiry, we sought to **evidence the benefits of implementation:** *Can we find evidence of increased price flexibility at the indication-level leading to more/faster indication launches, and therefore increased patient access? (Or the converse: access delays from lack of differential pricing).*

Ideally, we would perform an analysis where we would categorise/group countries according to the level of price flexibility, and observe the number of indication launches (and speed) by country, to see if we could detect any systematic relationship between price flexibility and treatment availability within countries. Whilst experts agreed that this would be a worthwhile exercise, in theory, such an analysis would be limited by the complexity of factors associated with launch decisions and a lack of suitable sources for comparable data. However – with support from Expert Panel members – we identified several useful anecdotal examples of how price flexibilities (or lack thereof) have influenced the availability of therapies in individual countries.

Restrictions on access to therapies in some authorised indications are observable in the real-world.

A manufacturer may choose not to submit indications for reimbursement consideration in a specific country for a number of reasons. For example, there may be a lack of clinical demand, or clinical data may be too immature. Another reason could be the anticipation that it would not be found to be cost-effective or that the discount required across indications (in price-inflexible countries) would make the case unsupportable. A survey issued by the UK's pharmaceutical trade association (Association of British Pharmaceutical Industries: ABPI) to member companies investigated the reasons for non-submission of evidence for reimbursement decisions in England. The top reason (34% of the sample of 29) was "Lack of flexibility to pursue differential net pricing or complex schemes, with consequent risk to previously approved indications"; the second most selected reason was "Unable to present a cost-effective case due to pricing of other medicines in the combination" (24% of the sample), which represents a related problem (ABPI, 2021).

Reforms toward more flexible recognition of indication-based value in Belgium were motivated by a recognition that patients were missing out.

According to an expert panel member, an analysis was undertaken in Belgium to evaluate the local reimbursement status of EMA-approved indications between 2010 and 2013. At that time, a linear price decrease was imposed for all new indications. The analysis found that a significant proportion of new indications were not reimbursed in Belgium and that most of these were due to non-submission by the pharmaceutical company. The analysis also demonstrated the magnitude of the opportunity for improved patient access in Belgium to multi-indication therapies, which informed and drove the reforms in Belgium, led by the Ministry of Health. The "PACT of the Future" – a commitment signed by the Belgian Pharmaceutical Industry and the Belgian Minister of Public Health – states that *"In order to continue to guarantee patients' access to innovation, the industry is encouraged to submit dossiers for the extension of indications for market authorisation and reimbursement. To this end, an innovation-stimulating method will be developed that will help foster a more objective pricing, related to the product's clinical value and the number of patients treated"* (De

Block, 2015, p.8). This has led to the more value-based algorithm now in place in Belgium, which considers and incorporates value at the indication-level.

Estonia has leveraged routine electronic health records to enable value-based differential pricing to improve access to innovative therapies within a tight health care budget.

In Estonia, the pricing of innovative medicines has evolved, with routine electronic health records able to capture use by indication and the health system adopting differential prices by indication set ex-ante. An OECD study published in 2020 evaluated access to oncology medicines across 22 OECD/EU countries (OECD, 2020). Based on the total sample of 109 therapy/indication pairs, 62% had “approved and covered” status in Estonia, which, although low amongst the countries studied (17th out of 22), has been achieved in the context of a *lower* pharmaceutical spend per capita than any of the countries that ranked below Estonia on the list (OECD, 2021). Whilst indication-based pricing alone should not be considered the panacea to all problems, it can be a way to improve patient access to innovative therapies whilst maintaining/limiting budget impact, with “*new opportunities for agreements between manufacturers and payers*” which “*certainly can improve also access to medicines for patients. There is no guarantee VBDP will deliver it on its own, but it certainly does not automatically cause harm*”. The panel member also stated that ex-ante indication-level prices are used to lower the total cost to the payer.

Lessons from Italy indicate that the use of real-world data to support risk-sharing agreements achieves quicker access to medicines for patients.

In a study by Russo et al. (2010) of time to patient access for oncology therapies across regions in Italy between 2006 and 2008, the authors found that the overall mean time required before patient access was 2.3 years. However, oncology therapies authorised with a risk-sharing agreement were associated with a mean shortening of time to patient access of 256 days relative to those authorised without a risk-sharing agreement.

This demonstrates that the use of Italian registries to secure cost-effective access to therapies in specific sub-populations may also have the benefit of speeding up that access.

The anecdotal examples presented above go some way to suggesting that better recognition of value at the indication-level is associated with improved breadth and speed of patient access. However, this relates to individual countries making therapies available that have already been developed and received marketing authorisation. Perhaps even more important but also less tangible is the impact of flexible payment models on incentives to innovate. How many potential drug uses were never developed because there was no positive business case at the prevailing uniform price? In the absence of an empirical analysis, in the next section, we describe a modelling exercise that simulates the potential indication expansion path of a multi-indication therapy, outlining the business case for each sequential development and the implications for patient access and health benefit where they are or are not pursued due to the reimbursement environment. It also illustrates the relevant considerations and budget impact for payers.

4.3 Modelling exercise: Implications for patient access and financial sustainability for payers

To address payer concerns of protecting financial sustainability whilst supporting better patient access through value-based pricing, we built a framework to consider the impact of value-based

differential pricing from the perspective of the payer as well as to illustrate how value-based differential pricing could impact the incentives for innovators to bring more indications to market.

An Expert Panel member summarised a challenge to understanding the potential benefits of better recognising value at the indication-level in payment models as being the difficulty in observing indications that may never have been developed due to the lack of appropriate incentives:

"I think pricing models need to provide stronger incentives for innovation and stronger support to make the results of innovation available to as wide a population of patients as will derive benefit. It is frustrating that currently some highly innovative products are only made quite narrowly available because there is little incentive for pharmaceutical companies to take them forward in new indications,"

Our modelling exercise – for which the assumptions and data are described in more detail in [Appendix 2](#) – shows the indication-expansion journey of a hypothetical drug and compares the outcomes associated with uniform vs differential pricing for:

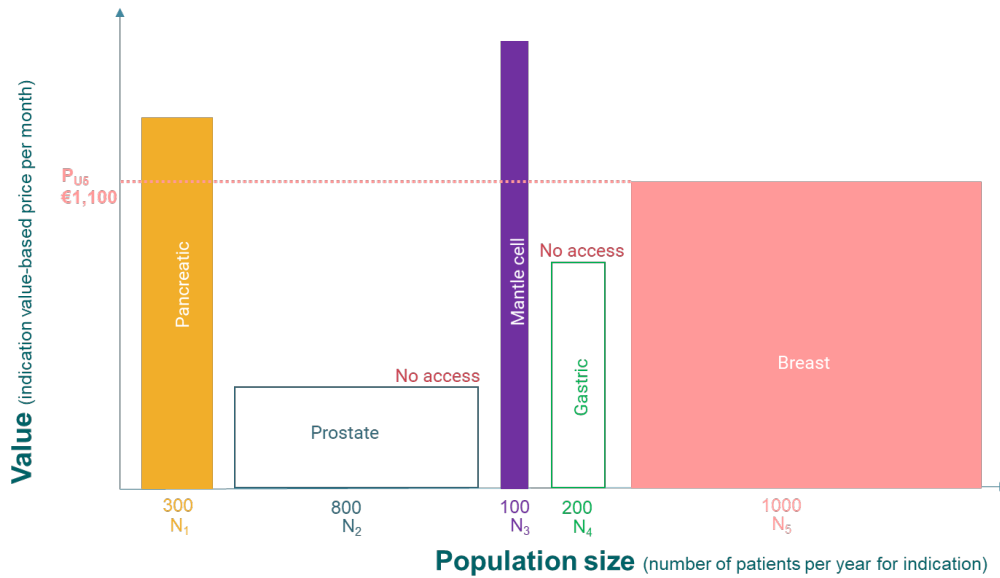
- Patient access & benefit
- Budget impact for payers
- Incentives for innovation

Illustrative assumptions are applied around value-based reimbursement decision-making by payers, assuming a fixed cost-effectiveness threshold that guides reimbursement decisions in a uniform pricing world and the level of the value-based price “ceilings” in a differential pricing world. While we use an illustrative threshold as a quantitative basis for calculating the value-based prices, the example and lessons arising are transferable to settings that use an alternative basis for the assessment/determination of price.

We demonstrate the anticipated budget impact of each scenario based on the indications that are (incentivised and therefore) brought to market and reimbursed. The model demonstrates that companies are not always able to support the case for investment in the R&D for all clinically beneficial indications, where payment models do not account for differential value. This, therefore, impacts the number of indications available to patients, which is wider for more flexible payment models that account for indication-level value. The main result is summarised in Figure 10 and Figure 11.

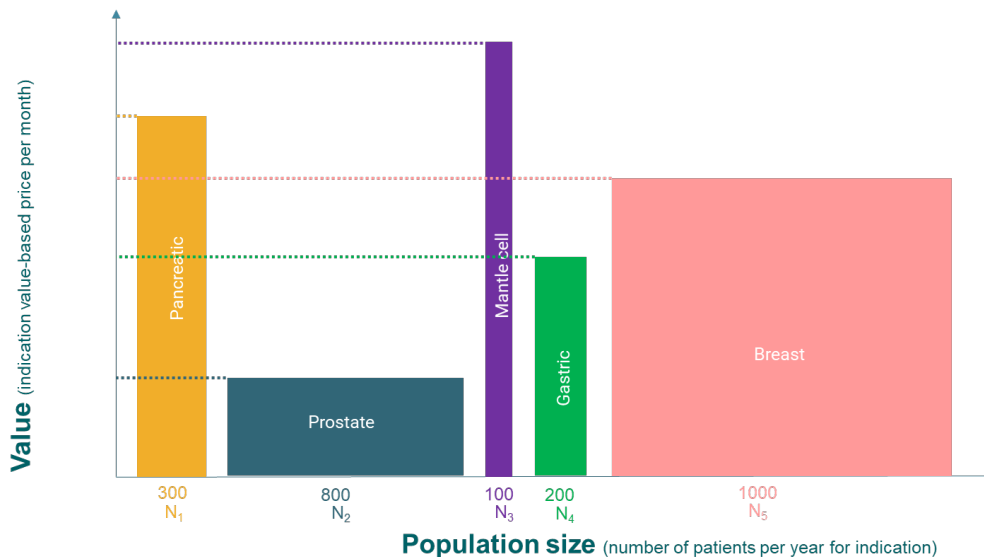
Note: As in the rest of the report, we use the term “value-based differential pricing” to refer to the *concept* of recognising indication-level value within payment models. We do not anticipate or reflect a specific implementation model but rather model a scenario whereby indication-level value *can be* reflected in the payment for a therapy (this could include, for example, the use of a single price with differential confidential adjustments based on indication-level value).

FIGURE 10 UNIFORM PRICE SCENARIO (DISCOUNTS PERMITTED BUT APPLIED ACROSS ALL INDICATIONS): YEAR 10



See [Appendix 2](#) for full description and price evolution over time: price equals the value-based price of the pancreatic cancer indication until year 10, when a discount is applied to bring price in line with the value-based price of the breast cancer indication, to enable its introduction.

FIGURE 11 VALUE-BASED DIFFERENTIAL PRICING SCENARIO (INDICATION-LEVEL VALUE REFLECTED IN PAYMENT MODEL): YEAR 10



Through value-based differential pricing, payers – who are the ultimate decision-maker and tasked with deciding what to fund from a limited budget – are afforded a more granular view of (and influence over) decision-making at the indication-level. By making decisions on the value of each indication separately, payers can consider budget impact alongside the value of each indication, as

well as projected volume (i.e., the size of the relevant patient population). This may simplify the negotiation process by permitting a focus on each indication individually. Overall **budget impact** for payers depends on what level the indication-based payments/rebates are set. If payments are aligned with the indication-level value-based price, this would lead to two further indications being available and require a higher investment of up to EUR 18m for the hypothetical medicine compared with the uniform pricing world with one price over the 10-year time horizon modelled (€62.9m versus €45m under uniform pricing)⁹. This extra investment would be considered a cost-effective use of resources for the payer if the appropriate cost-effectiveness threshold (or another method to determine cost-effectiveness) is applied, but all economic “surplus” would be retained by the manufacturer.

However, in practice, the value-based level is likely to be considered a price “ceiling”. Where prices are set below these ceilings (either naturally via the impact of increased competition – a plausible side-effect of permitting VBDP – or through more directive payer procurement, negotiation, and budget management at the indication-level), then the patient benefit from expanded patient access can be maintained, with both payers and manufacturers being better off.

The modelling exercise demonstrated that, versus the non-flexible uniform pricing scenario, value-based differential pricing was associated with:

- **Potentially short-term higher budget impact for payers:** the magnitude of the budget impact depends on what level the indication-based prices are set
- Payers have a **more granular view**/budget control at the indication-level (both of indication-level payment and volume)
- **Greater patient access & benefit:** 509 extra QALYs gained (2096 under VBDP scenario; 1587 under uniform pricing)
- **Better incentives for innovation:** Two further indications unlocked (access under the un-flexible uniform price scenario limited to three indications, due to a positive business case for investment not being supported at the prevailing price for two indications, despite the positive clinical benefits)

The modelling exercise uses “value-based differential pricing” to represent a flexible pricing model that permits recognition of differential value across indications, which in practice could be through the use of a single list price with confidential adjustments (up or down). An alternative model of implementation, applied in many countries such as Germany and France, is a “blended” price which represents an average weighted price across all reimbursed indications (to be elaborated in further detail in the upcoming ‘Implementation’ section). The results, in terms of the evolving level of the blended price as further indications are reimbursed, are presented in [Appendix 2.1](#).

In the blended price modelling scenario, we assume that access is enabled for all five clinically beneficial indications, and therefore the results (in terms of access, health benefit and budget impact) are in line with the scenario described in Figure 10. However, how the blended price is determined in practice, as well as how sensitive prescribers are to the prevailing price of the therapy, have important implications for what the outcomes would be in practice.

⁹ See [appendix 2](#) for further details and assumptions, including the timings that the indications are launched, and the price evolution of the medicine over those 10 years in the uniform price scenario (for which the price of EUR 1,100 represents the price at the end of the 10 year period following the introduction of the breast cancer indication, before which there was a higher price: EUR 1,450, which was the value-based price associated with the pancreatic indication)

There are two ways in which blended pricing can be implemented: first, a blended price determined ex-ante based on expected relative usage, and second, one determined (or adjusted) ex-post based on realized relative usage. The ability to implement a blended pricing model is dependent both on the type of blended price in question ('ex-ante' or 'ex-post') as well as the structure of and incentives built into the health system.

When a blended price is set ex-ante, one critical factor to consider is whether the medicine is still prescribed for relatively lower-value indications for which the medicine is not cost-effective at the blended price. Even if a national HTA body endorses a drug for a set of indications with a blended price, if the coverage/prescribing decision is in the hands of local budget holders or value-conscious providers, those decision makers may still restrict coverage for indications considered to be 'low-value for money' even if the therapy is the best option for that population. As a result, the success of 'ex-ante' blended pricing in fragmented systems depends on the sensitivity of local budget holders/providers to value-for-money at the indication-level.

When there is no price sensitivity among local budget holders or prescribers, and/or the blended price is adjusted to recognize realized usage ex-post, a blended price has the same expected budget impact and covers the same number of patients as value-based differential pricing. Price sensitivity is not an issue when there is an adjustment of the relative usage assumptions ex-post because, on the margin, the price of treating a patient for a certain indication is equal to the value-based differential price for that indication.

Another way in which budgetary and value-for-money outcomes of "ex-ante" blended pricing differs from value-based differential pricing is if *realized* relative usage between indications deviates from the *expected* relative usage, which was used as the basis for deciding an "ex-ante" blended price. However, "ex-post" blended pricing accounts for deviations in relative usage and, as a result, has the same budgetary and value-for-money outcomes as value-based differential pricing.

5 Implementation

5.1 Models of VBDP

The discussion on the implementation of VBDP took place around three pricing models, which the Expert Panel agreed represent a comprehensive taxonomy of the main implementation approaches of VBDP. These included:

1. Different brands or different list prices for each indication.
2. A “blended” price, obtained as a weighted average of the prices appropriate to the different indications and the volumes associated with each indication.
3. Single list price with adjustment of net price to align with value-based payment per individual indication.

Below we provide a summary of the main views of the Expert Panel on the advantages, limitations and barriers associated with the implementation of each model.

Different brands or different list prices for each indication

The first model envisages that drugs with multiple indications are marketed under different brands or with different list (published) prices for each indication of the drug, charged at the point of sale. The Expert Panel highlighted multiple limitations of this model when applied to drugs whose indications have similar formulations, routes of administration or dosages.

In these cases, and where the safety profile allows doing so, substitution patterns across indications are highly likely. Budget holders or prescribers would, in fact, have an incentive to purchase the least costly brand (i.e., arbitrage), especially where price differences across indications are significant. High quality data to track the indication of each prescription could solve the arbitrage issues, but as discussed in the following sections, the same type of data would also serve the implementation of other forms of VBDP. Other means to avoid arbitrage include physically differentiating brands, which in turn bears additional costs (e.g., packaging, marketing) and regulatory requirements.

Under these conditions, health care payers and the public are unlikely to accept this model. Additional barriers quoted by the Expert Panel for implementing this model include the lack, in many countries, of legal and regulatory environments that authorise multiple list prices for the same drug.

Different brands per indication have worked adequately when physical differentiation across brands of the same drug was justified on safety grounds, administration methods, or the safety profile did not support substitution across indications. Real world examples of this case are offered by aflibercept (sold under the brand names Eylea® and Zaltrap®) and tobramycin (for example, sold under the brand names TOBI® and Nebcin®), where different routes of administration supported different brand names for use in different therapeutic areas.

Successful implementation of this VBDP model relies on specific conditions which only hold for a limited selection of drugs with multiple indications. For this reason, the Expert Panel considered this model not suitable for a system-wide application to drugs with multiple indications.

“Blended” price, or weighted average of the prices and volumes appropriate to each indication

With the second model, drugs with multiple indications are sold under a single “blended” price, obtained as the average of the prices appropriate to the different indications, weighted by the volumes of prescriptions by indication. Quantification of the latter can be informed by data on either actual usage or estimated usage (e.g., based on epidemiology data), de facto allowing two implementations of the same “blended” pricing approach. The Expert Panel offered considerations on the advantages and disadvantages of both, which we summarise below.

Blended price based on data on actual usage enables a more accurate reflection of value at indication level while requiring more sophisticated data on prescriptions by indication. This approach may add complexity to the reimbursement process due to the need to monitor and regularly recalibrate the volume weights to ensure that they reflect actual usage.

Blended price based on data on estimated usage is more feasible in systems that are unable to track actual usage by indication. However, it introduces a risk that the price will not reflect the correct mix of patients using the drug (where estimated and actual usage differ significantly) and that the budget holder will consequently under- or over-pay. It is worth noting that this risk can also affect an implementation model relying on actual usage data, albeit to a lesser extent. For example, this will be true when the patient case-mix of the local budget holder (e.g., hospital) is different from the one used to calibrate the weights of the single blended price at the national level.

A general limitation of blended pricing, regardless of the method used to define the volume weights, concerns the behaviour of prescribers. Depending on the sensitivity of prescribing decisions to prices, the blended price may lead to over-prescription in indications where the drug delivers high value or, vice versa, under-prescription in indications where the drug delivers lower value. In fact, prescribing decisions are likely to be guided by the blended price rather than the underlying price relevant to the indication of use. However, evaluating the practical impact of this effect is challenging because the underlying prices relevant to each indication are often confidential. The Expert Panel suggested that the price sensitivity problem could be mitigated through separate budgets for the reimbursement of multi-indication drugs. Practical examples of dedicated budgets that facilitate the reimbursement and prescription of differential prices by indication exist in France (e.g., liste-en-sus) or England (e.g. Cancer Drug Fund), but their remit is limited to selected therapeutic areas and specific eligibility requirements.

Single list price with payment adjustments to achieve indication-specific net prices

The third model envisages a single list price with adjustments to the net price of individual indications, achieved via means such as discounts applied upfront or rebates applied ex-post¹⁰.

This approach shares some of the advantages of “blended” price with data on actual usage. At the same time, it avoids one potential distortion of “blended” pricing, namely the risk of over- or under-paying for the multi-indication drug due to the potential misalignment between the prescription volumes by indication that determine the blended price and the patient mix faced by local budget holders. Linking each prescription to a different indication-based price adjustment aligns more closely with the idea of pure differential pricing at the indication level.

The Expert Panel offered mixed views with respect to the often-confidential nature of discounts and rebates that are used to enable differential net prices by indication. On the one hand, the lack of transparency of net prices creates concerns about how prices are determined. On the other hand,

¹⁰ It may be more straightforward for the list price to correspond with the highest value indication, and for use in lower value indications to attract discounts/ rebates to bring the net price in line with its value (Towse, Cole and Zamora, 2018), although the clinical value of the initial and subsequent indications is not generally known until clinical trials report.

confidentiality of net prices may help health systems achieve more favourable agreements and enable value-based differential payment. In fact, a discussion of the appropriate degree of transparency of the level of prices is relevant to all pricing arrangements involving confidential agreements rather than being specific to VBDP.

As noted earlier with blended pricing, a practical issue related to the confidentiality of net prices is the impact on prescription patterns by price-sensitive prescribers. If prescribers do not know the underlying discounts and adjustments, the list price will guide the prescription decision, with an unclear impact on the use of the multi-indication drug.

It is important to distinguish the desire for transparency of prices and payments (implementation) from transparency relating to principles and processes regulating prices (policy). Concerning the latter, members of the Expert Panel argued that VBDP could offer an opportunity to enhance the transparency of the processes that determine prices, regardless of the specific VBDP model in use. VBDP could reassure the public that pharmaceutical funding processes are guided by evidence of value and appropriate use of taxpayer/insured member funds.

While, in principle, VBDP implies a greater degree of complexity of the reimbursement processes, it would also help to build more trust across stakeholders. At present, payers show some resistance to overcome this trade-off.

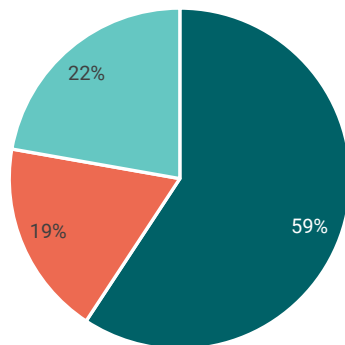
To implement this model, data systems to track the volumes of prescriptions by indication are a key requirement. As scientific innovation results in an increasing number of indications per medicine, which can be prescribed in multiple lines of treatment and for conditions of the same disease area, the quality of data to track indication-specific prescriptions will have to evolve accordingly. Within this landscape, an interesting role to differentiate value by indication may be played by **outcome-based pricing**. Outcome-based pricing relates to agreements between payers and manufacturers whereby the net price (payment) per indication is confidential and is determined ex-post, depending on the observed performance of therapies in terms of patients' outcomes. The primary purpose of outcome-based pricing is addressing payers' uncertainty around clinical value, but applying outcome-based pricing to one indication can, of course, result in differential pricing (or payment) across indications or within indications depending on the outcome achieved by individual patients. The data infrastructure and tracking requirements required to implement outcome-based pricing, therefore, supersede other VBDP models. An in-depth discussion of the implementation of outcome-based pricing was outside the scope of our Expert Panel engagement programme.

A final consideration for implementing a single list price with differential net prices concerns the ex-post reconciliation of adjustments to the list price (e.g., rebates) with sales at the local level. This element should be carefully considered by the more decentralised systems, which are characterised by greater budget segmentation at the local level.

PAYER SURVEY BOX 4 – OPTIMAL PAYMENT MODEL FOR MULTI-INDICATION DRUGS

To supplement the insights into the payer perspective on the models of implementation of VBDP, payers were asked to describe the optimal payment model for multi-indication therapies and discuss the barriers towards implementation.

The pie chart summarises the payers' views in terms of support for VBDP as described by proposed implementation models:



■ Support for VBDP ■ No support for VBDP ■ Unclear preference

The VBDP payment models proposed by the payers surveyed were largely aligned with the taxonomy of models that we discuss in section 5.1 of this report and included: different brand names and dosing across indications (where relevant), differential rebates across indications, differential pricing across indications with managed entry agreements to align prices to specific outcomes. A more innovative proposal was made in terms of differential pricing across indications with a lower cost-effectiveness threshold for multi-indication therapies to reduce the share of surplus captured by the industry.

Another suggestion was limiting the coverage of VBDP to a selection of drugs reimbursed by the health system, such as selected therapy classes (e.g., oncology), hospital drugs, and therapies with large value differences across indications.

Proposals opposing the concept of VBDP focussed on existing price models including a single price to decrease the complexity of reimbursement systems or a price that decreased with the extension of indication and patient population.

In terms of the barriers associated with the implementation of VBDP, these generally aligned with those referenced by the Expert Panel. The barriers most quoted by payers were lack of transparency on differential prices across indications, legal frameworks that veto multiple list prices for the same drug, absence of easy-to-use patient registries to track prescriptions, uncertain evidence on effectiveness during HTA, cultural resistance to new pricing models, and the risk of increasing bureaucracy lack of trust among stakeholders.

5.2 Data archetypes: what data on clinical value and usage at the indication-level enable VBDP?

The Expert Panel highlighted a key role for indication level data on clinical value and usage to implement VBDP. In this section, we further discuss this dimension to show **what models, in theory, are possible to implement given different data capabilities and provide real-world examples of how this is currently achieved in practice across countries**. In other words, we focus on data capabilities and demonstrate how these have been utilised to achieve VBDP through the various available implementation models that these data can support.

To show different indication level data requirements on clinical value and usage that are necessary to implement VBDP, with Figure 12, we introduce a two-dimensional plane. On the plane, the x- and y-axes capture increasing degrees of sophistication to measure indication level clinical value and usage, respectively. On the x-axis, clinical value at indication level is:

Expected	Realised
Based on evidence of effectiveness in the indication relevant population, available at the time of the pricing negotiations*.	Observed, upon treatment, as an average treatment effect in the indication relevant population or through individual patient outcomes.
<i>Examples:</i> RCT data	<i>Examples:</i> real-world evidence (RWE) data, patient clinical registries

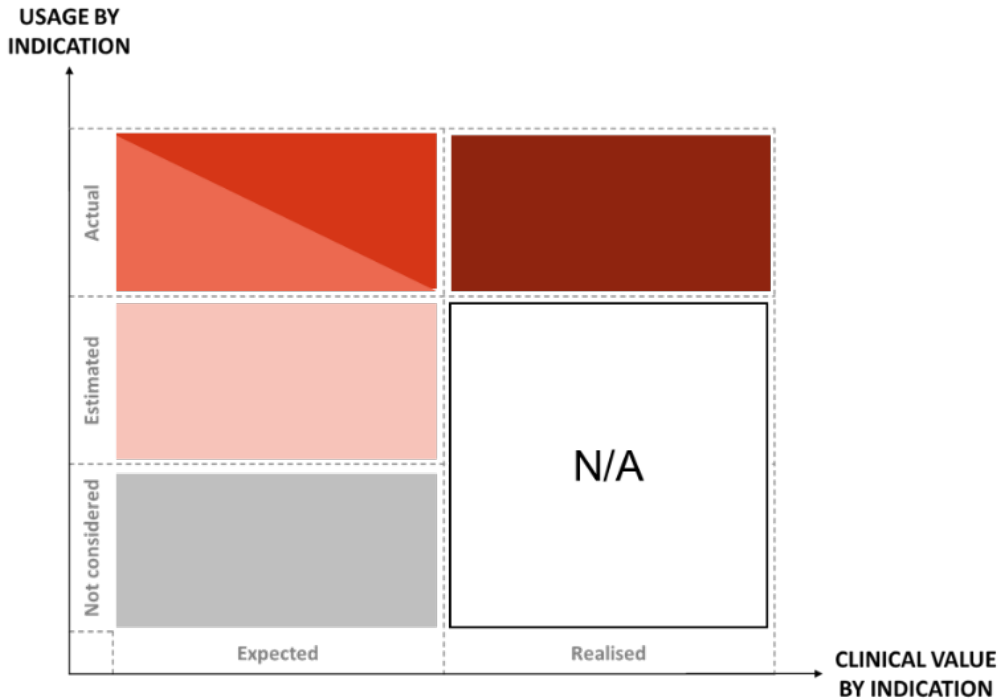
Note: * Evidence of expected clinical value may inform reimbursement decisions on each indication (e.g., based on the cost-effectiveness of the relevant indication) but may not necessarily inform the price negotiations.

On the y-axis, usage at the indication level is:

Not considered	Estimated	Realised
Not tracked.	Based on predicted use in the patient population at the time of the pricing negotiations.	Tracked, based on the actual level of issued prescriptions.
<i>Examples:</i> N/A	<i>Examples:</i> epidemiological data	<i>Examples:</i> sick fund claim data, patient clinical registries

We plot in Figure 12 different payment models for multi-indication drugs, depending on **the minimum data requirements** on usage and value by indication for their implementation. In this representation, we include the models discussed in the previous section, excluding different brands or different list prices for each indication which are not ideal for widescale implementation. Instead, we include outcome-based pricing, which (as explained in the previous section) can result in VBDP if applied to address uncertainties concerning the clinical value of one or more indications of a multi-indication therapy. Figure 12 also highlights the combinations of usage and value data capabilities which do not enable any form of VBDP. The “No VBDP” group thus encompasses a multiplicity of pricing (or payment) approaches where no recognition of value at the indication level takes place (e.g., uniform price based on first launched indication, or uniform price with confidential discounts or rebates permitted based on sale volumes).

FIGURE 12 MINIMUM DATA REQUIREMENTS ON USAGE AND CLINICAL VALUE BY INDICATION



KEY: No VBDP; Blended price, weights based on estimated usage; Blended price, weights based on actual usage; Single list price with adjustments to achieve net prices for each indication; outcome-based pricing; Not applicable, assuming that realised clinical value includes tracking actual usage.

As shown in Figure 12, most payment models for drugs with multiple indications are enabled by a combination of data on usage and value by indication. Table 1 compares archetypes in terms of minimum requirements for the implementation of payment models for multi-indication drugs. It should be noted that even where sophisticated data on usage and value at the indication-level *could* be or *are* collected, less “data-demanding” payment models may, in fact, be used (e.g., countries with data capabilities corresponding with archetype 1 may choose to implement VBDP via a different payment model).

In the following section, we discuss some of the most notable experiences of countries with setting up data systems on usage and/ or clinical value at the indication level and using them to pay for drugs with multiple indications.

TABLE 1 DATA ARCHETYPES

Data archetype	Measurement of value	Measurement of usage	Examples of enabled VBDP model
Archetype 1	Realised	Actual	Outcome-based pricing
Archetype 2	Expected	Actual	Single list price with adjustments to achieve net prices for each indication
			Blended price, weights based on actual usage
Archetype 3	Expected	Estimated	Blended price, weights based on estimated usage
Archetype 4	Expected	Not considered	No VBDP

Country experiences by data archetypes and VBDP models

Archetype 1 combines data on realised clinical value and actual usage, which are the minimum data requirements for the implementation of outcome-based pricing. A real-world example of this data archetype is provided by **Italy**. The Italian data infrastructure leverages nationwide web-based registries for individual drugs, which collect patient-level data about clinical eligibility, supply, dispensing and follow-up. The registries were created in 2006 to ensure prescription appropriateness and economic sustainability based on payment conditional to the clinical outcome. The scope of the registries is hospital drugs, mainly for cancer and rare diseases. Historically, these web-based registries have supported outcome-based (payment by result) and economic risk-sharing (cost-sharing) managed-entry agreements (MEAs). In more recent years, the implementation of outcome-based payments in Italy has declined in favour of simpler agreements based on single list price and confidential net prices. In other words, while Italy would fit under archetype 1 in terms of the available data capabilities, the currently more prevalent approaches to pay for multi-indication drugs do not involve tracking real-world patient outcomes. Rather, the registries are used to identify patient populations to which to apply indication-specific value-based contracts, such as confidential discounts, rebates etc. (i.e., the payment models enabled by data archetype 2). A limiting factor in the Italian experience is AIFA capacity to conduct analyses of registry data and lack of sharing of the data with regions and others in the health system to carry out analyses themselves. Further, due to the significant bureaucratic work associated with filing prescription information, prescribers do not keep registries fully up to date, and a large amount of payback from outcome-based agreements goes unclaimed.

Archetype 2 combines data on expected value and actual usage, which are the minimum data requirements for both single list price with indication-specific net price adjustments, as well as blended price, with weights based on actual usage.

A good example of data archetype 2 is **Estonia**, where an advanced data system supports pricing of multi-indication and combination therapies in various therapy areas through one single visible price across indications and confidential risk sharing schemes differentiating net price per indication. For retail medicines, upon agreement of a risk sharing scheme, an algorithm is in place to determine the price per patient (e.g., based on number of packages prescribed and achievement of measured patient outcome, such as disease non-progression). The risk-sharing agreement is entered into the e-prescription system, which is integrated with an electronic medical record (EMR) system, allowing for

tracking indications by prescriptions at hospital level. Through the e-prescription system an automated calculation of the bill is performed and issued to the producer by health insurance fund. In hospitals, risk sharing takes place but is monitored manually by doctors and hospital pharmacists. Work is currently ongoing to build electronic systems for hospital medicines and to capture individual patient real-world outcomes to further support value-based pricing.

Below, we discuss a few examples of countries that oscillate between archetypes 2 and 3 in terms of available data systems and enabled payment models.

In **Belgium**, confidential contracts per indication are possible for innovative medicines. An a-priori reimbursement approval by sick funds is required for prescription, whereby physicians complete a form specifying the details of treatment. The national sick funds (6-8 major sick funds) collect therapy usage data at the indication level on all patients, and the Inter Mutualistic Agency (IMA) provides a central database that collates data from the sick funds. It takes about nine months until the data are available, after which time data access can be granted after submitting an official request (for contract or reimbursement purposes) and paying a small fee. To calculate payback in the framework of confidential agreements, both general sales data (based on annual declaration) in combination with IMA data (on indication level) might be used. In practice, the actual measurement of usage is not always taken into account, in which case the use of blended prices with weights based on estimated usage might be more common.

In **Australia**, VBDP has historically been implemented via a blended price calculated for multi-indication medicines after each indication has undergone separate HTA. Initially, indication-specific prices are weighted using estimated usage data. The company submission provides the initial source of the estimates and is confirmed by an evaluation sub-committee on drug utilization (DUSC). The same committee compares predicted usage versus actual usage after 24 months of listing. Although this review could lead to a change in the weighted price, changes to price weighting do not ordinarily occur in practice. Therefore, blended prices are mostly based on estimated rather than actual utilization. Recently, special pricing arrangements (SPAs) have become more common than blended pricing. SPAs allow multiple confidential net prices through indication-based rebate arrangements. The payment of the SPAs rebates is determined by actual data on usage by indication. Higher quality of data is associated with drugs that require written applications, and therefore higher administrative burden on prescribers, while prescription data on drugs that do not require pre-authorization to prescribe are less reliable. For this reason, SPAs are mainly agreed for medicines and indications requiring pre-authorization, such as high-cost cancer medicines.

France is another country where multiple models are possible to price drugs with multiple indications. Depending on the outcome of the negotiations with the Healthcare Products Pricing Committee (Comité Economique des Produits de Santé, CEPS), either a blended price or single list price with adjustments to achieve net prices for each indication is implemented, although the outcome of these negotiations is usually confidential. When blended price is the chosen option, the negotiations with the CEPS will also determine whether the volume weights are based on estimated or actual usage. In the latter case, an optimal timeframe to review the volume determining the blended price weights is also established. As for the underlying data capabilities to track actual usage, the French payer has access to data on hospital (provided by the Agence technique de l'information sur l'hospitalisation, ATIH) and outpatient prescriptions (provided by the French National Health Insurance Fund, Caisse nationale de l'Assurance Maladie, CNAM). The reasons behind the lack of wide application of the available usage data are unclear but may be due to capacity constraints.

An alternative reimbursement mechanism is available in France to a minority of innovative hospital drugs via the *liste en sus*. The *liste en sus* provides funding on top of the diagnosis-related group (DRG) payments and covers the indications of a medicine that meet specific eligibility criteria,

determined by the level of added therapeutic value (ASMR rating), level of public health interest (ISP rating), and the registration of comparators in the *liste en sus*. To ensure that these drugs are used appropriately, hospitals must report the indication of prescription, or access to the additional funding is not allowed. While recognition of high therapeutic value grants access to additional funding for certain indications, *de facto* prices or discounts do not vary based on the value of individual indications.

In **Germany**, the prevalent payment method for drugs with multiple indications is blended pricing, with weights based on either estimated or actual data. In the former case, weights are informed by prospective epidemiological data, while in the latter, weights are informed by current and historic real-world evidence (RWE) data. RWE data on prescriptions are generally accessible to both payers and manufacturers, while the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) also has access to claims data with a 100% coverage of the statutory health insurance. There are two limitations, however: the data are only available after 9-12 months and only at the ICD-10 level, which is not always sufficiently granular to identify the drug indication. The decision to use RWE or epidemiological data is taken during the negotiation and is determined by a number of factors, including the complexity of identification of the specific indication, the robustness of the chosen identification approach, the likelihood of being successful with this approach in a possible negotiation arbitration board procedure, the quality and timing of access to the chosen data source.

Archetype 4 captures data systems where usage by indication is not considered, while clinical value by indication is based on evidence of effectiveness available at the time of reimbursement (e.g., from clinical trials). In fact, while each indication typically undergoes a separate value assessment, the outcome of this process is not reflected in a new price, therefore leading to payment models which do not differentiate value by indication (i.e., no VBDP). As examples of this archetype, we describe countries whose data systems currently do not support VBDP or only by exception, e.g., at the regional level, or within special time-bound schemes, or possibly for one-off cases.

In **Canada**, a single list price is regulated at the federal level based on the approved indication or use for which the drug offers the greatest incremental therapeutic benefit at the time of introduction into the Canadian market. This will be the maximum price for the drug, and when additional indications are launched, the drug's list price will likely be unaffected (Paris and Belloni, 2014; OECD, 2020). Confidential net pricing may be negotiated with payers and is typically based on a combination of cost-effectiveness and budget affordability. In Canada, obtaining data on actual usage is very difficult due to a regional fragmentation of electronic medical records, and therefore, net pricing is typically applied at the molecule level based on a blend of the different indications in consideration.

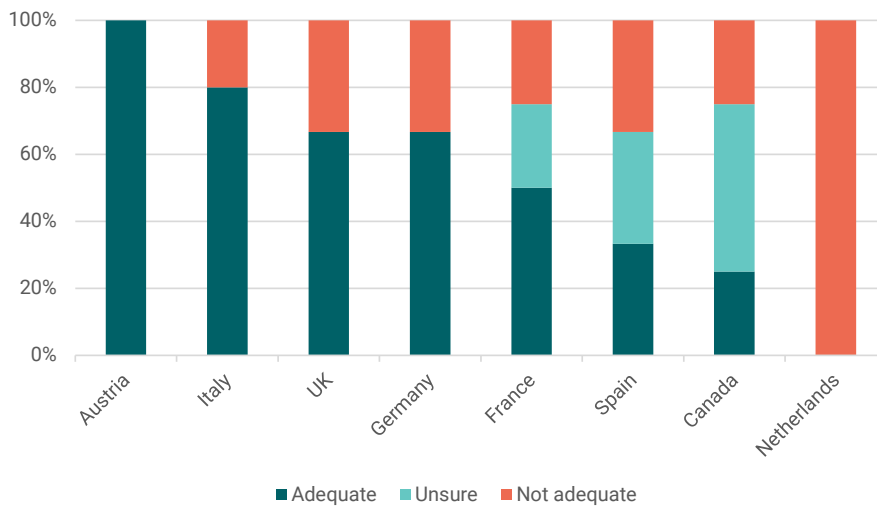
In **England**, all indications must be cost-effective at a single price (sometimes with an undisclosed confidential discount applied) (OECD, 2020). Renegotiation of the net price is possible if new indications are not cost-effective at the existing price. Differential net prices are possible, in principle, with patient access schemes and managed access agreements (MAAs), which are tools designed to manage price and patient access through financial- and outcome-based agreements. To date, MAAs have been most frequently used in the context of the Cancer Drug Fund (CDF) and for "highly specialised technologies" (Marsh, 2018), where very small patient numbers can lead to significant uncertainty in the available evidence of effectiveness. Through the CDF, for example, NHS England and manufacturers reach a commercial access agreement to cover a period of funding for the indication of the drug under review while additional evidence is generated (through the systemic anti-cancer therapy (SACT) dataset and ongoing clinical trials) to resolve uncertainty around clinical and cost-effectiveness. This can result in differential value recognition by indication, enabled by tracking of data use via the authorisation process (a necessary condition for gaining access to CDF drugs). Of note, the scope of the drugs eligible for this funding will be expanded in the future beyond cancer drugs with the Innovative Medicines Fund (NHS England, 2021). More generally, NHS England, in line

with language in the Voluntary Scheme for Branded Medicines Pricing and Access (VPAS) (DHSC, 2018), offers only very limited flexibility for indication-specific pricing.

In **Spain**, at the national level, a single list price is negotiated at the central level and is revised downwards when new indications are launched. Net prices per indication may vary at the decentralized level (i.e., regions or hospitals) through differential discounts or risk-sharing agreements (Campillo-Artero et al., 2020). VALTERMED (an abbreviation for Sistema de Información para determinar el Valor Terapéutico en la Práctica Clínica Real de los Medicamentos de Alto Impacto Sanitario y Económico en el SNS) is government initiative recently set up to measure real world therapeutic value via a defined protocol (Ministero de Sanidad, 2021). The initiative's aims are to improve the evaluation and financing of medicines for a more financially sustainable system. VALTERMED enables outcome-based (indication-specific) payment models in exceptional cases, such as therapies with high clinical value and budget impact. In terms of the tools for tracking usage and billing, at the regional level are available electronic health records and electronic prescription data on a majority of primary and speciality care drugs (Flume et al., 2016).

PAYER SURVEY BOX 5– ADEQUACY OF CURRENT SOLUTIONS BY COUNTRY

To gauge the current desire for improvement of methods to price drugs with multiple indications, payers were asked to provide their perspectives on the adequacy of their country’s current pricing solutions:



Further insights on the payers’ perspectives around the adequacy of current pricing solutions are exemplified by the following quotes. Note: while payers from Austria and the Netherlands were included in this payer survey, research into the pricing systems of these countries were not part of our core investigations for this research project; therefore, we do not further elaborate on the “adequacy” of those pricing systems beyond the results displayed in the above graphic.

Italy “The system has been working well for 12 years.”, “Additional complexity is limited thanks to the existing patient registries, which also guarantee appropriate usage.”, “The additional complexity is limited when patient registries are already in use. The appropriate usage is guaranteed.”

UK “Adequate, given current capabilities (e.g., not all NHS prescribing is currently electronic)”, “Not adequate but there is no obvious solution: drugs are approved earlier and with poorer evidence, and the number of new indications is increasing and beyond the HTA evaluation capacity.”, “The process is rational, transparent, and fair but can be bureaucratic, slow (preventing rapid take up of treatments) and narrow in the definition of value”

Germany “Indications prescribed on-label receive full access and reimbursement.”, “Lack of transparency on implicit prices across indications.”, “Details of the outcomes are confidential and limited data suggest that the price does not correlate with the clinical added benefit assessed in HTA”, “I think the solution we have is sufficient”

France “Adequate compromise to maintain the simplicity of the system for prescribers. So far, it is the easiest approach available.”, “Very complex and not transparent approach. Impossible to know the real net price of a drug in a precise indication.”

Spain *"No incentives for further research to expand indications of existing molecules.", "Clinicians may prescribe some drugs for off-label indications.", "Price discounts in new indications are valuable to make more cost-effective use of the drug.", "The current system avoids the more complicated process of billing and pharmaceutical dispensing"*

Canada *"The current approach is functional from an operational perspective and provides financial relief for the payer, however it is not transparent"*

In sum, payers' views on the adequacy of current solutions vary and are sometimes contrasting. This tends to be the case in particular for the perceived level of access, complexity and transparency guaranteed by current pricing and payment approaches. In this sense, it is important to read the above quotations in consideration of the diversity of solutions currently implemented across countries to pay for drugs with multiple indications, which, as we have demonstrated, vary significantly in the level of value recognition at the indication level.

6 Conclusions and Recommendations

The evolving future of medicine development requires health systems to adapt their payment models in ways that recognise clinical benefits in ever-smaller and multiple population groups. The challenges that this poses across stakeholder groups are broad, but so are the opportunities.

Throughout the report, we have referred to the concept of value recognition at the indication-level under various terms, which we think is appropriate given the broad nature of the concept and its application. At the beginning of the journey, we labelled the concept “*value-based differential pricing*”. At the end of the journey, we prefer the notion of *value-based differential payment*, which better captures the various mechanisms that differential value is or could be recognised through payment adjustments.

The reasons for value-based differential payments not being broadly adopted to date have been outlined in this report. Perhaps most significant is acceptance of the status quo within the context of complex decision-making; payers have a demanding role in optimising health benefits for their constituencies within not unlimited budgets. As summarised by one participant:

“Current pricing models are a composite of interests: manufacturers’ and payers’, and they have settled a status quo where everyone is knowledgeable of the rules. [Value-based differential pricing] is a divergence from that equilibrium, hence the unwritten rules need to be re-defined.”

There was also a sentiment among experts that stakeholders should work together to overcome challenges and to strive for the best outcomes for society:

“We should not shy away from pricing that optimally balances access and innovation just because it is complex.”

Through the research described in this report, we have taken a multi-stakeholder perspective and – along with an international panel of experts – been on a journey to better understand the *need for and opportunities associated with* payment models that recognise value at the indication-level, as well as the challenges associated with their implementation and how they can be overcome. By collaboratively discussing and debating the core principles and objectives of pharmaceutical pricing and payment, we have exposed divergent views on these matters and distilled the issues that are most important for the principles of paying for multi-indication therapies, summarising the majority view on the solutions moving forward. Below we highlight the main conclusions of the project and accompanying recommendations.

1. Inflexible uniform pricing does not optimally support innovation and access. The most important consequence is lost treatment opportunities for patients.

By outlining and achieving broad consensus on the primary objectives for pharmaceutical pricing and how these are achieved in payment models for multi-indication therapies, most stakeholders share the view that incentives for innovation and patient access are not adequately met by an inflexible uniform price. This manifests in two ways: (1) lack of access within certain countries to clinically beneficial therapies due to an inability (anticipated or realised) to negotiate a mutually agreeable price, and (2) lost opportunities within the drug development pipeline for new treatment populations

to benefit from existing therapies, due to inflexible payment models failing to signal the right incentives. Off-label use, withdrawal of indications, and the pursuit of different prices for physically differentiated uses of a therapy can also be seen as symptoms of the problem and evidence that change is needed. Challenges in providing access to combination therapies also represent an important signal of the issue. Given the nature of pharmaceutical R&D and confidentiality of industry-payer negotiations, industry has a role in supporting communication of the challenges arising from inflexible uniform pricing.

Even where opinion diverged on the optimal relationship between price and value – and what “value” should capture – there was an understanding and agreement that that relationship cannot be optimised for multi-indication therapies without accounting for the variable clinical and patient benefit between indications.

Several countries have adapted their payment models to account for this. For example, Belgium – which used to apply linear price cuts for every new indication – now adopts a more flexible and value-based approach to new indication decisions, in recognition of the failures of the previous model to secure timely access for patients to valuable new treatment opportunities.

Recommendation: Efforts should be made to work **across all stakeholder groups** to recognise and evaluate the broad and varied clinical and other benefits of individual therapies. Payment models should ensure that the treatment options that are of value to patients and health systems are appropriately incentivised and supported to reach patients in a timely manner.

2. The potential health system and patient **benefits** of better recognising indication-level value through payment models are tangible.

We demonstrated through an illustrative modelling exercise that payment models which adequately account for differential value across indications better incentivise innovation and lead to expanded patient access and health benefit. The budget impact depends on how the new indication-level value is reflected in the payments/rebates. Extra investment may be needed to support broader patient access, but in practice, downward pressure on those prices may arise from the more directive payer procurement, negotiation, and budget management at the indication-level, or naturally as a consequence of increased competition at the indication-level. This means that payers/health systems can benefit through increased competition and more granular value-based budget management at the indication level.

Regardless of the model of implementation, transparency of the principle of indication-specific value recognition promotes trust that value-based processes guide price-setting and reimbursement decisions.

Recommendation: **Industry** should continue to work towards maximising the treatment opportunities offered by existing and pipeline therapies, working with **patients** and the **scientific community** to ensure that innovation is driven by and centred on patient need within the context of a system that appropriately incentivises and rewards innovation.

Recommendation: **Payers** should strive to provide the right incentives for innovation, applying value-based decision making to best service population health needs and maximise health system efficiency. In order to realise the full benefits of medical innovation, **health systems** should reflect on the adequacy of current payment models in realising the full potential of existing therapies, working toward better recognition of differential value to maximise that potential in the longer term.

Recommendation: Payment models that recognise value at the indication-level can provide payers with more granular information to support a negotiation process that is better tailored to specific patient populations. **Payers and industry** should collaborate in the pursuit of value-based budget management, which for multi-indication medicines should operate at the indication-level. This would allow payers to maximise opportunities to incentivise and provide access to cost-effective treatments in all those patients that could benefit, thus optimising patient access and health benefit across the health system.

3. Value recognition at the indication level can be achieved in multiple ways; countries have different starting points and enabling infrastructure

The implementation of payment models that reflect the benefits of drugs across multiple indications relies on the ability to identify clinical and other value and usage at the indication level. Implementation of value-based differential payments can be achieved via a single list price with adjustments to achieve net prices for each indication or a blended price with weights based on actual or expected usage. Outcomes-based pricing applied to one or more indications also enables/results in value-based differential payments.

Different brands or different list prices per indication are deemed unsuitable approaches except when specific conditions are met (e.g., physical differentiation of brands justified by safety profile or administration method).

Current experiences of countries that enable value recognition at the indication-level demonstrate that multiple payment models are possible and with variations to suit the country processes and infrastructure. Current experience also highlights inconsistent/suboptimal use of available data on prescriptions to associate drug usage to individual indications. This seems to be driven by insufficient buy-in to indication-level payment models or a lack of physical resources (e.g., staff) to implement or oversee them.

Recommendation: To improve willingness to engage in indication-level payment models, **payers and industry** could collaborate in piloting programmes at regional or disease level, exploring and agreeing together on those cases that will achieve the highest impact.

When considering the scientific innovation landscape, which is increasingly evolving towards personalised/precision medicine, payment models will need to account for recognition of clinical benefits in ever-smaller and more specifically defined patient groups. This trend requires sufficient sensitivity of usage tracking systems (e.g., when indications are authorised for different lines of treatment of the same disease or different diseases within the same therapeutic area). For therapies with a large number of indications without large variations in value/benefit across indications, such as some immune-oncological therapies, it may be appropriate to consider specific solutions such as grouping comparable indications or applying blended weighted pricing; recently, multi-year multi-indication payment models have been applied whereby one price is agreed and applied to all future indications to enable timely access, with a possibility for adjustments to account for differential value (Lawlor et al., 2021). Following the science of innovation and treatment development of new and more targeted therapies may lead in the long run to the need for more dynamic patient-level payment models – such as outcome-based payment – to accommodate the necessary flexibility in value recognition at the patient level. Any decision guiding the future improvement of payment methods for multi-indication drugs should consider the available enabling factors to strike the right balance between future benefits and costs of change.

Recommendation: Countries have different starting points in terms of payment models. There are different routes to advance value-based differential payment in line with the evolving science of precision medicine. System change should always be considered in terms of the benefits as well as the costs of change.

4. Data infrastructure (the ability to track and access data on real-world usage and/or outcomes) is a frequently cited “barrier” to change. Investing in and/or making better use of health data represents a major opportunity for better monitoring and enabling value-based health care.

The broad discussions across multiple stakeholders that were facilitated by this project, as well as supporting illustrations through modelling and use cases within individual countries, demonstrated that the role of *payment models* within the broad ecosystem of health, health care innovation and health care delivery is complex. As we work toward a better understanding of the health and health needs of the population, as well as how we can best meet those needs, the role of real-world data (on usage and/or outcomes) is amplified. Investment in the infrastructure for collecting those data has implications and benefits well beyond the assessment of or payment for therapy-level value. Data, therefore, should be seen as an **enabler** of value-based health care – including indication-level value for some therapies – rather than a *barrier*. There are numerous multi-stakeholder and multi-national initiatives addressing the improvement of real-world data infrastructure, sources and networks (e.g. EMA’s DARWIN (EMA, 2021) and the IMI European Health Data & Evidence Network (EHDEN, 2021)) and developing recommendations for how real-world data can support decision-making (e.g. EU health data space (European Commission, 2020), RWE4Decisions (RWE4Decisions, 2021), Get Real (GetReal, 2021)) Countries and health systems should actively leverage these opportunities to build and strengthen their data systems.

The use in several countries of indication-level novel payment arrangements demonstrates that it can be done in a way that is compliant with data protection regulations. Optimally, and to minimise additional admin effort, these would be facilitated by data extraction from routinely collected datasets. Where the routine data capture does not exist, experience – for example, in Italy – has shown that it can be done through the creation of dedicated registries.

There is rapid momentum toward enhanced data collection in health care and beyond and – most importantly – using those data to make better decisions. In health care, that means recognising that patient-level experience and benefit varies across patients. The better we can capture that information and use it to inform treatment development and provision of health care, the better we can serve the health care needs of the population. The outbreak and response to the COVID-19 pandemic over the last 18 months has demonstrated that data capabilities and quality can improve rapidly where there is a will to do so, a belief in the benefit, and collaboration across stakeholders to make it happen. Operational obstacles can be overcome. We should make sure that this momentum is not lost and that it is harnessed to improve decision-making and value-based health care across the board.

Recommendation: The broad benefits of investment in better health data need to be recognised by **health systems**, and the use of those data should be supported by **patients** and by **payers** to enable better and more informed decision-making in health care. Where improved data collection is required to facilitate indication-level payment models, investment in sustainable data generation needs to be considered. In some cases and where the infrastructure is currently sub-optimal, **industry** has a role to play in contributing to the cost of putting in place the data collection and reporting capabilities within a health system to support patient access to a therapy.

5. The focus of further research and action should be at the country-level to understand and work towards the realised benefits of more flexible payment models

Through this programme of research, we have investigated and outlined the core principles of payment models for pharmaceuticals and how these manifest for multi-indication medicines. We have also offered a framework for understanding the current options for recognising indication-level value in payment models and how these have been successfully applied in some health systems (or sub-national schemes). By demonstrating data archetypes and how these may lend themselves to the various implementation models, it is possible to observe the routes to better recognition and realisation of value through payment models. The next steps should be to work toward a better country-level understanding of the benefits and resistance to recognising indication-level value through payment models for pharmaceuticals and local considerations and actions for enabling their implementation.

Recommendation: There is a need for **cross-stakeholder collaboration** at the **country-level** to better understand how the opportunities for more flexible value-based payment models can be realised.

We finish with a quotation from a member of the Expert Panel, which encapsulates where we have got to and opportunities for the future:

"As uncertainty seems to be the main barrier (Operational - how difficult/easy it will be? Fiscal and financial - how big will be the shift and in which direction(s)? Health politics - how will it affect the power balance?) the evidence should converge around 1-2 strategic goals [...] Based on the discussions here, the "access within limited resources" seems to be the easiest to find consensus about. Now, as access is usually understood (narrowly) by "making available medicines that have been developed", it omits the important and costliest part of the formula - somehow, the medicines have to be developed first so that the access becomes a meaningful goal. Hence, "motivation to innovate" must be part of the goal-setting. [...] To conclude, I feel that it is possible to build a case backed with the evidence to support the argument that VBDP is the most effective way to balance the short-term fiscal targets with the long term health policy targets."

7 References

ABPI, 2021. *ABPI Member Survey NICE Optimised and Terminated Appraisals | ABPI*. [online] Available at: <https://www.abpi.org.uk/publications/reasons-for-nice-optimised-recommendations-and-terminated-appraisals/> [Accessed 23 Sep. 2021].

Berdud, M., Chalkidou, K., Dean, E., Ferraro, J., Garrison, L., Nemzoff, C. and Towse, A., 2019. *The Future of Global Health Procurement: Issues around Pricing Transparency*. [online] Available at: <https://www.ohe.org/publications/future-global-health-procurement-issues-around-pricing-transparency> [Accessed 24 Aug. 2021].

Campillo-Artero, C., Puig-Junoy, J., Segú-Tolsa, J.L. and Trapero-Bertran, M., 2020. Price Models for Multi-indication Drugs: A Systematic Review. *Applied Health Economics and Health Policy*, 18(1), pp.47–56. 10.1007/s40258-019-00517-z.

Chassang, A., Mantua, V., Snowberg, E., Xoxi, E. and Pani, L., 2018. *Sustainable Reimbursements: Towards a Unified Framework for Pricing Drugs with Significant Uncertainties*. CESifo Working Paper. [online] Available at: <https://www.cesifo.org/en/publikationen/2018/working-paper/sustainable-reimbursements-towards-unified-framework-pricing-drugs> [Accessed 11 Aug. 2021].

Claxton, K., 2007. Oft, Vbp: Qed? *Health Economics*, 16(6), pp.545–558.

Cole, A., Towse, A., Lorgelly, P. and Sullivan, R., 2018. Economics of innovative payment models compared with single pricing of pharmaceuticals. *OHE Research Paper 18*, 4.

Cole, A., Towse, A. and Zamora, B., 2019. *Indication-Based Pricing (IBP) Discussion Paper: Should drug prices differ by indication?* Office of Health Economics.

Cole, A., Towse, A. and Zamora, B., 2020. *Indication-Based Pricing (IBP) Consultation Report*. Office of Health Economics.

Danzon, P., Towse, A. and Mestre-Ferrandiz, J., 2015. Value-Based Differential Pricing: Efficient Prices for Drugs in a Global Context: VALUE-BASED DIFFERENTIAL PRICING. *Health Economics*, 24(3), pp.294–301.

De Block, 2015. *PACT OF THE FUTURE WITH THE PHARMACEUTICAL INDUSTRY*. [online] Available at: https://issuu.com/pharma.be/docs/pact_of_the_future [Accessed 15 Jul. 2021].

DHSC, 2018. *The 2019 Voluntary Scheme for Branded Medicines Pricing and Access*. [online] Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/761834/voluntary-scheme-for-branded-medicines-pricing-and-access-chapters-and-glossary.pdf .

EHDEN, 2021. *European Health Data Evidence Network – ehden.eu*. [online] Available at: <https://www.ehden.eu/> [Accessed 24 Aug. 2021].

EMA, 2020. *ANNUAL REPORT 2019. The European Medicines Agency's contribution to science, medicines and health in 2019*. [online] Available at: https://www.ema.europa.eu/en/documents/annual-report/2019-annual-report-european-medicines-agency_en.pdf [Accessed 24 Mar. 2021].

EMA, 2021. *Data Analysis and Real World Interrogation Network (DARWIN EU)*. [Text] European Medicines Agency. Available at: <https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu> [Accessed 19 Jul. 2021].

European Commission, 2020. *European Health Data Space*. [Text] Public Health - European Commission. Available at: https://ec.europa.eu/health/ehealth/dataspace_en [Accessed 19 Jul. 2021].

Expert Panel on effective ways of investing in health, 2017. *Opinion on Innovative payment models for high-cost innovative medicines*. [online] Available at: https://ec.europa.eu/health/sites/health/files/expert_panel/docs/opinion_innovative_medicines_en.pdf.

Flume, M., Bardou, M., Capri, S., Sola-Morales, O., Cunningham, D., Levin, L.-A., Touchot, N. and Insight, P., 2016. Feasibility and attractiveness of indication value-based pricing in key EU countries. *Journal of market access & health policy*, 4(1), p.30970.

GetReal, 2021. *GetReal Insitute: Homepage*. [online] GetReal Institute. Available at: <https://www.getreal-institute.org/> [Accessed 19 Jul. 2021].

Goldman, D.P., Van Nuys, K., Cheng, W.-H., Hlávka, J.P., Pani, L., Chassang, S. and Snowberg, E., 2018. A new model for pricing drugs of uncertain efficacy. *NEJM Catalyst*, [online] 4(6). Available at: <https://catalyst.nejm.org/doi/full/10.1056/CAT.18.0035> [Accessed 15 Mar. 2021].

Health Action International (HAI), 2016. *Keys to Improving Access & Innovation of Needed Medicines*. [online] Available at: <https://haiweb.org/wp-content/uploads/2016/07/Keys-to-Improving-Access-and-Innovation-of-Needed-Medicines.pdf> [Accessed 21 Mar. 2021].

IQVIA, 2018. *Global Oncology Trends 2018. Innovation, Expansion and Disruption*. [online] Available at: <https://www.iqvia.com/institute/reports/global-oncology-trends-2018>.

Kapur, S. and Bonk, M.E., 2009. Riloncept (Arcalyst), an Interleukin-1 Trap for the Treatment of Cryopyrin-Associated Periodic Syndromes. *Pharmacy and Therapeutics*, 34(3), pp.138–141.

Latimer, N.R., Towse, A. and Henshall, C., 2021. Not cost-effective at zero price: valuing and paying for combination therapies in cancer. *Expert Review of Pharmacoeconomics & Outcomes Research*, 21(3), pp.331–333. 10.1080/14737167.2021.1879644.

Lawlor, R., Wilsdon, T., Darquennes, E., Hemelsoet, D., Huismans, J., Normand, R. and Roediger, A., 2021. Accelerating patient access to oncology medicines with multiple indications in Europe. *Journal of Market Access & Health Policy*, 9(1), p.1964791. 10.1080/20016689.2021.1964791.

Marsh, S.E., 2018. PHP365-TRENDS AND CHARACTERISTICS OF MANAGED ACCESS AGREEMENTS APPROVED BY NICE. *Value in Health*, 21, pp.S212–S213.

McKee, S., 2012. *Sanofi withdraws Campath in US and EU*. [text] PharmaTimes. Available at: http://www.pharmatimes.com/news/sanofi_withdraws_campath_in_us_and_eu_976762 [Accessed 26 Mar. 2021].

Mestre-Ferrandiz, J., Towse, A., Dellamano, R. and Pistollato, M., 2015. Multi-indication pricing: pros, cons and applicability to the UK. Seminar Briefings. Office of Health Economics.

Mestre-Ferrandiz, J., Zozaya, N., Alcalá, B. and Hidalgo-Vega, Á., 2018. Multi-Indication Pricing: Nice in Theory but Can it Work in Practice? *PharmacoEconomics*, 36(12), pp.1407–1420.

Ministero de Sanidad, 2021. *Sistema de Información para determinar el Valor Terapéutico en la Práctica Clínica Real de los Medicamentos de Alto Impacto Sanitario y Económico en el SNS (VALTERMED)*. [online] Available at: <https://www.msbs.gob.es/profesionales/farmacia/valtermed/home.htm> .

NHS England, 2021. NHS England announces new Innovative Medicines Fund to fast-track promising new drugs. Available at: <https://www.england.nhs.uk/2021/07/nhs-england-announces-new-innovative-medicines-fund-to-fast-track-promising-new-drugs/> .

NICE, 2021. *BNF: British National Formulary - DENOSUMAB*. [CorporatePage] Available at: <https://bnf.nice.org.uk/medicinal-forms/denosumab.html> [Accessed 26 Mar. 2021].

OECD, 2020. *Addressing Challenges in Access to Oncology Medicines. Analytical Report*. [online] Available at: <https://www.oecd.org/health/health-systems/Addressing-Challenges-in-Access-to-Oncology-Medicines-Analytical-Report.pdf> [Accessed 12 Mar. 2021].

OECD, 2021. *Health resources - Pharmaceutical spending - OECD Data*. [online] theOECD. Available at: <http://data.oecd.org/healthres/pharmaceutical-spending.htm> [Accessed 8 Jul. 2021].

Paris, V. and Belloni, A., 2014. *Value in pharmaceutical pricing—country profile: Canada*. OECD Country Profiles. [online] Available at: <https://www.oecd.org/health/Value-in-Pharmaceutical-Pricing-Canada.pdf> .

Rubin, R., 2021. *Study Aims to Identify Drugs That Could Be Repurposed for COVID-19 | Infectious Diseases | JAMA | JAMA Network*. [online] Available at: <https://jamanetwork.com/journals/jama/fullarticle/2773252> [Accessed 26 Mar. 2021].

Russo, P., Mennini, F.S., Siviero, P.D. and Rasi, G., 2010. Time to market and patient access to new oncology products in Italy: a multistep pathway from European context to regional health care providers. *Annals of Oncology: Official Journal of the European Society for Medical Oncology*, 21(10), pp.2081–2087. 10.1093/annonc/mdq097.

RWE4Decisions, 2021. *RWE4Decisions - Real World Evidence for Decisions*. Available at: <https://rwe4decisions.com/> [Accessed 19 Jul. 2021].

Towse, A., Cole, A. and Zamora, B., 2018. The debate on indication based pricing in the US and five major European countries. *London: OHE Consulting*.



About us

Founded in 1962 by the Association of the British Pharmaceutical Society, the Office of Health Economics (OHE) is not only the world's oldest health economics research group, but also one of the most prestigious and influential.

OHE provides market-leading insights and in-depth analyses into health economics & health policy. Our pioneering work informs health care and pharmaceutical decision-making across the globe, enabling clients to think differently and to find alternative solutions to the industry's most complex problems.

Our mission is to guide and inform the healthcare industry through today's era of unprecedented change and evolution. We are dedicated to helping policy makers and the pharmaceutical industry make better decisions that ultimately benefit patients, the industry and society as a whole.

OHE. For better health care decisions.

Areas of expertise

- Evaluation of health care policy
- The economics of health care systems
- Health technology assessment (HTA) methodology and approaches
- HTA's impact on decision making, health care spending and the delivery of care
- Pricing and reimbursement for biologics and pharmaceuticals, including value-based pricing, risk sharing and biosimilars market competition
- The costs of treating, or failing to treat, specific diseases and conditions
- Drivers of, and incentives for, the uptake of pharmaceuticals and prescription medicines
- Competition and incentives for improving the quality and efficiency of health care
- Incentives, disincentives, regulation and the costs of R&D for pharmaceuticals and innovation in medicine
- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
- Health and health care statistics