

# Estimating the overall population health effects of uniform pricing, indication-based pricing, and alternative commercial arrangements for new pharmaceuticals in the UK NHS

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# Executive summary

## Background

There has been much debate internationally about the merits of moving from a uniform price across uses of a new pharmaceutical to a price for each use of the product, i.e., indication-based pricing (IBP). IBP offers the potential to improve access, and innovation, but is also expected to increase pharmaceutical expenditure with associated health opportunity costs.

In this report we compare the long-term overall population health effects of three policies:

- Uniform pricing whereby the same price applies for all indications;
- ‘Pure IBP’ whereby there is a separate price for each indication; and
- Commercial flexibility, which is a hybrid policy which applies uniform pricing as standard but allows IBP for those indications that would not be launched under uniform pricing. This policy reflects provisions within the 2019-2023 Voluntary Scheme and the 2022 Commercial Framework for new medicines.

This research is topical as the recently agreed 2024 Voluntary Scheme commits NHS England to an update to the Commercial Framework, including clarification of the commercial flexibilities offered for products used in multiple indications.

## Methods

We simulate the effects of each policy through a series of numeric examples using different product value profiles i.e., the pattern of QALY gains and patient population sizes across indications, and scenarios that reflect features of the pricing landscape and medicines market. Unless otherwise stated, uniform pricing and IBP are implemented with an approval norm of £30,000/QALY for all indications, and commercial flexibility is implemented with an approval norm of £30,000/QALY for the uniform pricing policy component and £20,000/QALY for indications requiring commercial flexibility, to reflect current policy.

## Results

- IBP can improve access to, and the health benefits associated with, new medicines compared to uniform pricing; however, due to the large increase in medicines expenditure, IBP reduces overall population health at current approval norms due to the health opportunity costs of additional expenditure.
- These findings were observed across value profiles including when estimates of potential effects on innovation were included (innovation effects estimate effects of payment on the number of drugs developed and number of indications developed per drug).
- IBP would need to be implemented alongside an approval norm of £20,000-25,000/QALY or below (depending on value profile, no innovation effects scenario) across indications for this policy to improve overall population health compared to uniform pricing with an approval norm of £30,000/QALY.
- The only circumstances where IBP was found to increase overall population health under current approval norms occurred where innovation effects were included, and high approval norms or high-cost comparators were relevant in a subset of indications.

- Approval norms that maximise overall population health accounting for innovation effects (i.e. 'dynamically efficient' approval norms) would be £11,500-£15,000/QALY (depending on value profile) under uniform pricing and £9,000-£11,000/QALY (depending on value profile) under IBP. IBP with dynamically efficient approval norms can generate higher population health and higher manufacturer revenue than uniform pricing with dynamically efficient approval norms.
- Application of the quantitative framework to two multi-indication case study drugs (nivolumab and pembrolizumab) found that introduction of IBP at current approval norms would be expected to increase medicines expenditure for those products by approximately double without improving access to medicines.
- Commercial flexibility offers the same improvements in access and health benefits from new medicines as IBP, but with lower medicines expenditure than IBP. However, commercial flexibility, as currently specified, reduces overall population health compared to uniform pricing (no innovation effects scenario).
- Commercial flexibility would need to be implemented using an approval norm of £15,000/QALY or below for the indication where commercial flexibility is required (and £30,000/QALY otherwise) if this policy is to improve overall population health compared to uniform pricing with an approval norm of £30,000/QALY. Commercial flexibility with an approval norm of £15,000/QALY would also improve manufacturer revenue compared to uniform pricing with an approval norm of £30,000/QALY.
  - When innovation effects are accounted for, commercial flexibility results in equivalent or higher overall population health than uniform pricing in most, though not all contexts. Commercial flexibility incentivises product launch and promotes innovation whilst preserving the benefits of uniform pricing in controlling pharmaceutical expenditure in those indications which don't require commercial flexibility.
- In all contexts commercial flexibility was associated with higher overall population health than IBP.
- Introduction of any IBP policy including commercial flexibility introduces operational challenges due to the need to measure or forecast usage in individual indications and link this information to payment. Application of commercial flexibility introduces the additional challenge of assessing whether the policy applies for a particular drug and indication. Careful policy design is therefore required to integrate commercial flexibility within HTA, pricing and funding processes.

## Conclusion

Introducing IBP or commercial flexibility requires careful specification to prevent large increases in medicine expenditure, which would impose health opportunity costs that outweigh the benefits of improved access, and therefore reduce overall population health. For IBP to improve population health compared to uniform pricing it would need to be implemented with a lower approval norm, of approximately £20,000/QALY, across all indications (no innovation effects scenario). For commercial flexibility to improve population health compared to uniform pricing an approval norm of £15,000/QALY would be required for those indications where commercial flexibility is applied (no innovation effects scenario).

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# 1. Introduction

There has been much debate internationally about the merits of moving from a uniform price for a new pharmaceutical to a price for each use of the product, i.e., indication-based pricing (IBP).<sup>(1-3)</sup> IBP is a form of price discrimination. Price discrimination is observed in many markets as it allows more revenue to be extracted by firms. It can offer benefits by incentivising firms to expand the number of customers they serve, but with the risk of firms achieving prices that reduce consumer surplus to zero. Careful evaluation of price discrimination in the market for new pharmaceuticals is important as there is a need to balance the potential benefits of improved access to medicines under price discrimination with higher overall medicines expenditure and the consequent impact on others' health care and outcomes (health opportunity cost).

In the context of the market for new pharmaceuticals, uniform pricing may reduce access to some lower value indications, if launching the drug within these indications would require a price reduction that reduced total manufacturer revenue and therefore made launch commercially unattractive to manufacturers. As well as disincentivising launch and therefore reducing access, there are also concerns that uniform pricing could disincentivise innovation in those indications which offer low or no opportunity for increased revenue under uniform pricing. IBP offers the potential to ameliorate these incentive effects as price is determined by value within each indication. Under IBP, if an innovation offers benefits (i.e., net health benefits) over existing forms of care within an indication, a positive price will be paid, and the manufacturer will increase their revenue by developing and launching the indication. However, IBP also allows prices in early high value indications to be maintained throughout the period of intellectual property protection (IPP) and may therefore increase expenditure on branded medicines.

Although the nature and direction of the effects of IBP have been discussed in the literature, there have been relatively few attempts to quantitatively compare IBP and uniform pricing. A number of studies have found access, quality adjusted life-years (QALYs) <sup>(4-7)</sup> and healthcare costs <sup>(4, 7)</sup> to be higher under IBP than uniform pricing. However, none of the studies attempted to summarise the overall population health impact e.g., by using a measure of health opportunity cost to calculate net health effects. In addition, the studies were limited in scope. For instance, none of the studies accounted for the timing of approvals in different indications, reflected value delivered in the post-IPP period, or considered potential effects on innovation.<sup>(8, 9)</sup>

A comprehensive evaluation of IBP is important as a number of countries have begun to implement forms of IBP, <sup>(1, 6)</sup> and expenditure on multi-indication drugs is becoming increasingly important as new types of products such as immunotherapies show activity across a wide range of cancer tumour types.<sup>(10, 11)</sup> In this paper we focus on the UK which has historically pursued a uniform pricing approach with confidential discounts agreed at the product level via the National Institute for Health and Care Excellence (NICE) Patient Access Scheme (PAS) process. For multi-indication products price discounts may need to be increased to ensure access in later indications, or manufacturers may choose not to launch or accept a restricted recommendation to preserve price.<sup>(10-12)</sup> To mitigate the effects of uniform pricing on patient access, 2024 Voluntary Schemes for Branded Medicines

Pricing, Access and Growth (henceforth the Voluntary Scheme), its 2019 predecessor,(13, 14) and the 2022 NHS commercial framework for new medicines (henceforth the Commercial Framework) (15) allow for commercial flexibility if introducing an additional indication is expected to reduce overall manufacturer revenue under uniform pricing. This effectively allows a different price to be agreed for the additional indication, subject to some restrictions. This research is particularly topical in the UK, as the recently agreed 2024 Voluntary Scheme (14) commits NHS England to an update to the Commercial Framework, including clarification of the commercial flexibilities offered for products used in multiple indications.

In this study we set out a general framework for comparing IBP and uniform pricing policies in terms of their overall population health effects, accounting for (a) both the health gains associated with access to medicines and the health opportunity costs associated with policy-driven changes in health care expenditure; (b) the impacts of each policy in the IPP and post-IPP period; and (c) potential impacts of different pricing policies on innovation. We illustrate our findings using evidence relevant to the UK, but the framework and qualitative findings are likely to generalise to other contexts and health care systems.

## 2. Overview of report

Across the report, three policies are compared: uniform pricing, IBP and commercial flexibility. The main outcome of interest is overall population health impact (i.e., net health effects) which account for both the health gains from using a new drug and the health opportunity costs associated with the additional costs of funding it.

- In Section 3-4 we consider the effects of each policy on overall population health using a series of worked numeric examples. In Section 4 we show findings for six alternative drug value profiles which characterise a range of patterns of QALY gains and population sizes across indications.
- Sections 5-6 consider the potential implications of broader effects of pricing policy. Section 5 quantifies the potential impact of each policy on manufacturers' decisions to invest in developing new drugs or new indications for existing products (i.e. innovation or "dynamic" effects). Section 6 considers how the policies may influence manufacturers' decisions about the order in which to launch different indications, and the implications of this for the overall population health associated with the policies.
- Section 7 examines the likely robustness of the findings to different features of the medicines market.
- Section 8 applies the framework to two case study multi-indication drugs.
- Section 9 summarises findings from a workshop held to understand the operational considerations associated with implementing differential pricing by indication.

## 3. A quantitative framework for estimating the value of multi-indication drugs under different pricing policies

We measure value using overall population health impact (i.e., net health effects) which account for both the health gains from using a new drug and the health opportunity costs associated with the additional costs of funding it. Costs to the health system can be expressed as health forgone using a measure of health opportunity cost,  $k$ . For example, if  $k$  is £15,000/QALY, this implies that for every £15,000 of health care resources used to fund a treatment, 1 QALY of health is forgone elsewhere in the health system. We describe the framework for contexts where pricing and reimbursement decisions are based on cost-effectiveness, and technologies are assessed as cost-effective if their incremental cost-effectiveness ratio (ICER) is below an approval norm,  $\lambda$  (often referred to as a cost-effectiveness threshold). The approval norm represents the health system's stated maximum willingness to pay for a QALY, and in the UK is set via a process of negotiation between the pharmaceutical industry and the Department of Health and Social Care.(13, 14) The approval norm differs from the measure of health opportunity cost  $k$ , which is a property of the health system and can be empirically estimated as the marginal productivity of health care expenditure.(16)

As in Woods *et al.*,<sup>(8)</sup> the total potential population health gain generated by a new medicine (i.e., the net health effects that would be available if it were sold at the cost of production) within a single indication is:



$$T_{b,i} = \sum_{t=t_{0,i}}^{\infty} \frac{n_{t,i}}{(1+r)^t} \left( \Delta h_i - \frac{\Delta npc_i}{k} - \frac{\Delta mc_i}{k} \right) \quad [1]$$

This is a function of the launch time for indication  $i$  ( $t_{0,i}$ ), the number of patients presenting for treatment in year  $t$  within the indication ( $n_{t,i}$ ), the annual discount rate ( $r$ ), the additional health benefit of the product to patients within the indication ( $\Delta h_i$ ), the health opportunity cost associated with additional non-product costs ( $\frac{\Delta npc_i}{k}$ ), and the health opportunity cost associated with additional manufacturing costs i.e. the cost of producing the drug ( $\frac{\Delta mc_i}{k}$ ). The corresponding product-level total potential population health gain is the sum of the indication-level values across all indications that are developed and receive regulatory approval:

$$T_b = \sum_{i=1}^I T_{b,i} \quad [2]$$

The realised overall population health impact will depend on  $T_{b,i}$ , the price paid in each indication and whether the manufacturer is incentivised to launch the indication within the UK. We assume that the manufacturer will be incentivised to launch if launch increases product revenue. Initially we reflect only static effects and exclude any potential dynamic (innovation) effects of pricing on the number of drugs or indications developed. Focusing on static effects is appropriate if UK pricing policy (as a small driver of global revenue) is not expected to influence drug R&D decision making and the UK's primary policy objective relates to UK population health. Dynamic effects are included in Section 6.

We assess the implications of three policies: pure IBP; uniform pricing and the current commercial flexibility afforded by the UK Voluntary Scheme.

Under IBP, the price (defined here for simplicity as the total incremental drug price<sup>1</sup> per patient) for a given indication is:

$$\Delta p_{IBP,i} = \Delta h_i \cdot \lambda - \Delta npc_i \quad [3]$$

Indications are assumed to be launched if this incremental price exceeds the incremental cost of production and supply ( $\Delta mc_i$ ). The revenue received by the manufacturer in a given year under IBP is therefore:

$$R_t = \sum_{i=1}^I \Delta p_{IBP,i} n_{t,i} \quad [4]$$

Under uniform pricing, the price ( $\Delta p_{UNI,t}$ ) and the number of patients who receive the product ( $N_t^{UNI}$ ) depends on which indications are launched. We assume that at any point in time,  $t$ , the manufacturer selects to launch the set of indications,  $I_t^{UNI}$ , to maximise revenue:

$$\max R_t = \Delta p_{UNI,t}(I_t^{UNI}) \cdot N_t^{UNI}(I_t^{UNI}) \quad [5]$$

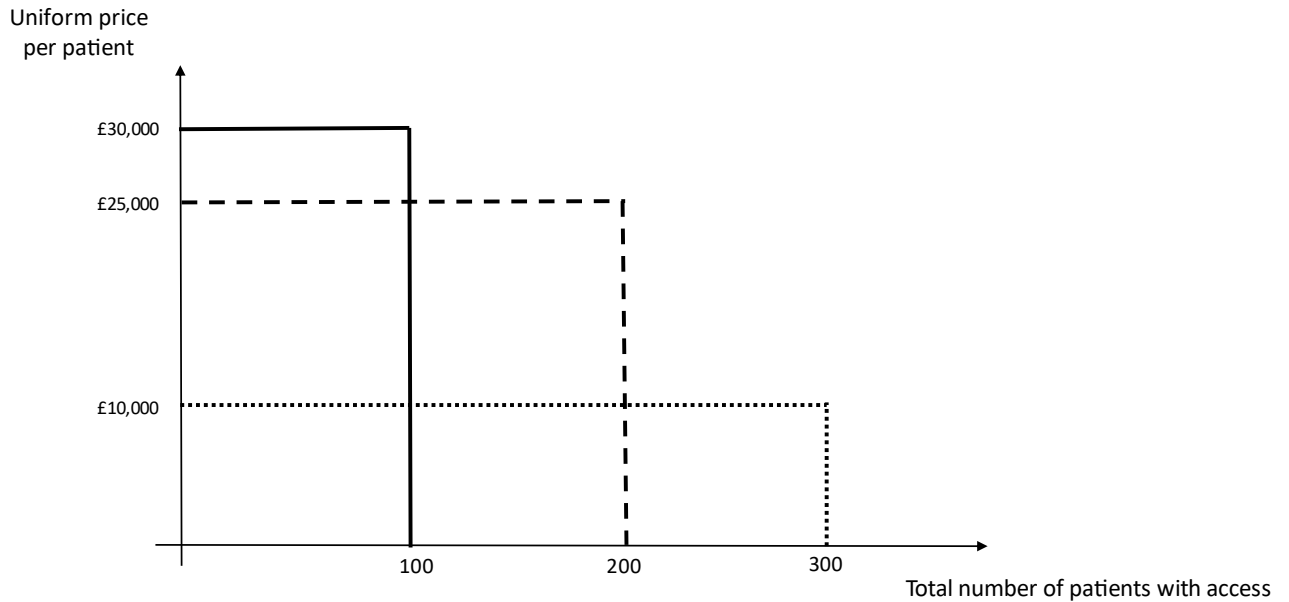
This is expressed formally in the equations in Appendix 1.

We illustrate the revenue maximisation problem faced by the manufacturer graphically in Figure 1 for an example drug with three indications. For each indication the maximum achievable price is equivalent to the price under IBP,  $\Delta p_{IBP,i}$ , which in this example is £30,000, £25,000 and £10,000 per patient for indications 1, 2 and 3. Each indication is expected to have a patient population size of 100

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<sup>1</sup> We work with incremental prices and incremental revenue which is equivalent to assuming that the comparator cost is zero or similar across indications. If the comparator cost differs across indications this could modify the study results as it will change the actual revenue received by the manufacturer. We explore this in Section 7.

patients. The manufacturer faces the choice between launching indication 1 and achieving a price of £30,000 and revenue of £3 million, launching indications 1 and 2 and achieving a price of £25,000 and revenue of £5 million, and launching all three indications achieving a price of £10,000 and revenue of £3 million. In this example the revenue maximising price is to launch indications 1 and 2 but not 3.



**Figure 1: Illustration of revenue maximisation problem faced by the manufacturer under uniform pricing.**

*Legend: The area within the solid line represents the revenue available if only indication 1 is launched, the area within the dashed line represents the revenue available if indications 1 and 2 are launched and the area within the dotted line represents the revenue available if all indications are launched.*

The realised overall population health effects include those accruing in the IPP and post-IPP periods. Under IBP the following overall population health effects accrue:

$$T_b - \sum_{i=1}^I \sum_{t=t_{0,i}}^{T=t_p} \frac{n_i}{(1+r)^t} \left( \frac{\Delta p_{IBP,i}}{k} - \frac{\Delta mc_i}{k} \right) \quad [6]$$

where  $t_p$  is the total duration of IPP. The realised overall population health effects are therefore equal to the total potential population health gain minus the incremental price paid above the cost of production within the patent period.

Under uniform pricing the realised overall population health effects are:

$$T_b - \sum_{t=1}^{T=t_p} \sum_{i \in I_t^{UNI}} \frac{n_i}{(1+r)^t} \left( \frac{\Delta p_{UNI,t}}{k} - \frac{\Delta mc_i}{k} \right) - \sum_{t=1}^{T=t_p} \sum_{i \notin I_t^{UNI}} \frac{n_i}{(1+r)^t} \left( \Delta h_i - \frac{\Delta n p c_i}{k} - \frac{\Delta mc_i}{k} \right) \quad [7]$$

The realised overall population health effects under uniform pricing comprise the total potential population health gain minus the incremental price paid above the cost of production within the patent period for those indications with access, minus the potential benefits associated with any indications that are not launched under uniform pricing.

Equations [6] and [7] show that, within the IPP period, realised overall population health effects differ between IBP and uniform pricing due to potential differences in the set of launched indications and differences in pricing. In the post-IPP period, the policies are associated with the same realised overall population health effects. Access to generic versions of the products is expected across all licensed indications including any that were not launched, and generic pricing is assumed to be independent of the pricing policy applied during the IPP period.

The current commercial flexibility afforded by the UK Voluntary Scheme is equivalent to uniform pricing if all indications that have been developed are launched under uniform pricing. If this is not the case, then for the indications that would not be launched under uniform pricing, IBP applies, and the policy is associated with additional (though not necessarily positive) overall population health effects within the IPP period:

$$\sum_{t=1}^{T=t_p} \sum_{i \notin I_t^{UNI}} \frac{n_i}{(1+r)^t} \left( \Delta h_i - \frac{\Delta n p c_i}{k} - \frac{\Delta p_{IBP,i}}{k} \right) \quad [8]$$

The realised overall population health effects associated with commercial flexibility is therefore the sum of equations [7] and [8].

## 4. Static effects of alternative pricing policies

We now illustrate this framework using a simple numeric example with three indications and data as shown in Table 1. For simplicity, the same number of patients is eligible for treatment within each indication per year. We initially model a value profile whereby the health gain is highest for the first indication and lowest for the third. This reflects a typical launch pattern for many products.(17, 18) We explore alternative value profiles at the end of this section.

We use approval norms of £30,000/QALY for the pure IBP and uniform pricing policies, reflecting the upper end of NICE's stated range of approval norms.(19) Under current commercial flexibility, an approval norm of £30,000/QALY is applied in general, but for indications in which commercial flexibility is used, an approval norm of £20,000/QALY is applied to reflect the Voluntary Scheme requirement for "*value propositions at or below the lower end of the standard NICE cost effectiveness threshold range*".(13, 14)

For simplicity and in line with previous literature (20), we assume that treatment dosing, regimen and duration are the same across indications, so that a uniform price at the product level corresponds to a uniform price at the patient level. More realistic assumptions are explored in the case studies in Section 7.

**Table 1: Parameters used in numeric example for value profile 1**

Parameter	Value
Timing of launch for indications 1/2/3 in years	0/2/4
Population treated in each year (per indication)	100
Incremental health gain for indication 1/2/3 (in QALYs)	1.0/0.6/0.3
Incremental non-product costs associated with intervention	£0
Measure of health opportunity cost (expenditure to gain one QALY)	£15,000 <sup>a</sup>
Patent duration in years	13 <sup>b</sup>
Annual discount rate for costs and health outcomes	3.5% <sup>b</sup>
Time horizon in years <sup>b</sup>	100 <sup>b</sup>

<sup>a</sup> Assessment of the marginal cost of producing a QALY to the NHS according to Department of Health and Social Care.(21)

<sup>b</sup> For further discussion of these parameter values see Woods *et al.*(8)

Under IBP, the product is launched in all indications and priced at £30,000, £18,000 and £9,000 per patient treated in indications 1, 2 and 3. Under uniform pricing, the product is launched at £30,000 per patient and this drops to £18,000 per patient (across indications) when the second indication is launched at year 2. The third indication is not launched as this would require a reduction in price across all indications that would reduce manufacturer revenue. Under the commercial flexibility policy, the first two indications are priced as for uniform pricing, and access to the third indication is facilitated via an IBP of £6,000 per patient.

Table 2 shows the outcomes associated with each policy. All cost and QALY results are discounted. Compared to uniform pricing, IBP and commercial flexibility expand access and increase QALYs gained from using the new drug as under these policies all indications are launched. IBP and commercial flexibility increase NHS expenditure on branded medicines, though commercial flexibility less so as the uniform pricing component of the policy facilitates a lower price in indication 1 from year 2 and the commercial flexibility component uses a lower approval norm for indication 3. The QALY gain associated with access to indication 3 under IBP and commercial flexibility is relatively small. This is because, under all policies, patients in indication 3 can access the generic/biosimilar version of the product in the post-IPP period. Realised overall population health is 36% lower under IBP than uniform pricing and 3% lower under commercial flexibility than uniform pricing.

**Table 2: Results of numeric example for value profile 1**

Outcome	Policy		
	Uniform pricing with £30,000/QALY approval norm	IBP with £30,000/QALY approval norm	Commercial flexibility with £20,000/QALY approval norm for flexible component
Proportion of patients with access during IPP	73%	100%	100%
QALYs gained through use of new drug <sup>a</sup>	5,001	5,206	5,206
NHS expenditure on branded medicines <sup>a</sup>	£37,208,293	£53,820,402	£41,325,312
Health foregone due to payments to manufacturer <sup>a</sup>	2,481	3,588	2,755
Net health effects <sup>a</sup>	2,520	1,618	2,451
Share of value to NHS	48% <sup>b</sup>	31%	47%
Share of value to manufacturer	48% <sup>b</sup>	69%	53%

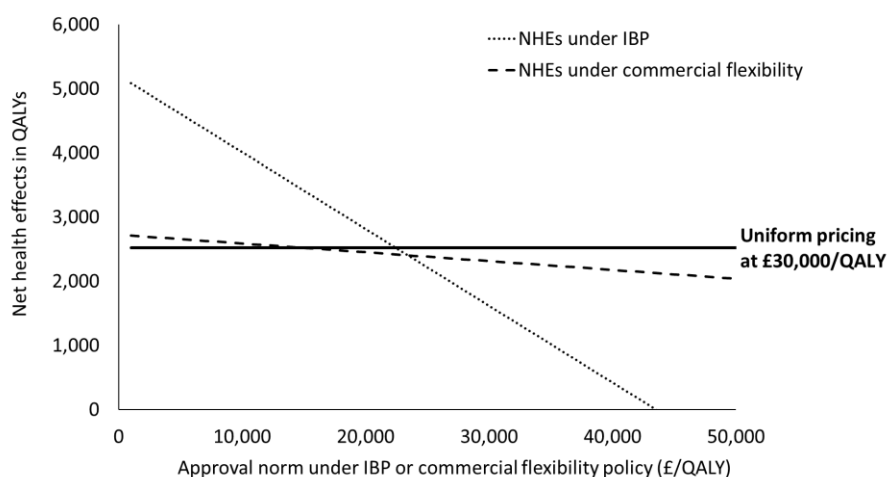
Abbreviation: IPP, Intellectual Property Protection; NHS, National Health Service; QALY=quality-adjusted life year.

<sup>a</sup> Discounted value.

<sup>b</sup> Under the uniform pricing policy the value shares don't sum to 100%. During the IPP period, the value associated with indication 3 that is not launched does not accrue to either the NHS or the manufacturer.

Figure 2 shows how the realised overall population health effects associated with introducing IBP or commercial flexibility vary when these policies are implemented using different approval norms. For this numeric example and value profile, IBP would have to be implemented with an approval norm of £22,000/QALY or below across all indications for this policy to increase realised overall population health compared to uniform pricing at an approval norm of £30,000/QALY. At approval norms of £21,000-22,000/QALY, IBP would benefit both the manufacturer (through higher revenues) and increase realised overall population health compared to uniform pricing at £30,000/QALY, though benefits to both parties are small (less than 7% increase in health benefits and revenue compared to uniform pricing).

Commercial flexibility would have to be implemented using an approval norm of £15,000/QALY or below to improve realised overall population health relative to a uniform pricing policy at £30,000/QALY. At any approval norm below £15,000/QALY, commercial flexibility would also benefit the manufacturer compared to a uniform pricing policy, though benefits to both parties are small (less than 8% increase in health benefits and revenue compared to uniform pricing).



**Figure 2: Population health implications of introducing IBP and commercial flexibility with different approval norms compared to uniform pricing with a £30,000/QALY approval norm.** IBP=indication-based pricing. NHE=net health effects. QALY=quality-adjusted life year. Within the commercial flexibility policy, the approval norm is varied only for the indication to which commercial flexibility applies.

We present results for six alternative value profiles of QALY gains and population size across indications (see Table 3). This reflects different launch patterns, as companies may not always prioritise the highest value indications for earlier launch.

For value profiles where uniform pricing does not disincentivise launch (value profiles 2, 3 and 6), access and QALYs gained from the new drug are the same for all policies and commercial flexibility is not required. The only effect of IBP is to increase expenditure on branded medicines resulting in a decrease in overall population health of 803 (value profile 6) to 1,931 (value profile 3) QALYs compared to uniform pricing.

For value profiles where uniform pricing disincentivises launch (value profiles 1, 4<sup>2</sup> and 5), IBP and commercial flexibility are associated with improved access and QALYs gained from the new drug, as well as increased pharmaceutical expenditure. IBP reduces realised overall population health by 799 (value profile 5) to 2,553 QALYs (value profile 4) compared to uniform pricing. Commercial flexibility reduces realised overall population health by 34 QALYs (value profile 5) to 229 QALYs (value profile 4) compared to uniform pricing.

For IBP to improve realised overall population health compared to uniform pricing (at an approval norm of £30,000/QALY) it would need to be implemented using an approval norm of £20,000-25,000/QALY or below, depending on the value profile. Commercial flexibility would have to be implemented using an approval norm of £15,000/QALY or below.

<sup>2</sup> In the case of value profile 4, uniform pricing incentivises withdrawal of indication 1 from the market once indications 2 and 3 have been launched. Under the commercial flexibility policy, once it becomes unattractive for the manufacturer to continue to supply indication 1, commercial flexibility is applied to this indication (and uniform pricing applied to indications 2 and 3) thus avoiding the withdrawal of indication 1 from the market.

**Table 3: Results for numeric example using alternative value profiles (static results).**

Value profile number	Population treated in each year for indication 1/2/3	Incremental health gain for indication 1/2/3 (in QALYs)	Proportion of patients with access during IPP with uniform pricing*	Total potential population health available			NHS expenditure on branded medicines (£ million)			Net health effects (QALYs)			Approval norm at which policy is equivalent to uniform pricing at £30,000/QALY	
				Uniform	IBP	Commercial flexibility	Uniform	IBP	Commercial flexibility	Uniform	IBP	Commercial flexibility	IBP	Commercial flexibility
1	100/100/100	1.0/0.6/0.3	73%	5,001	5,206	5,206	37	54	41	2,520	1,618	2,451	22,000	15,000
2	100/100/100	1.0/1.3/1.6	100%	10,299	10,299	10,299	79	99	79	5,055	3,710	5,055	23,000	-
3	100/200/400	1.0/0.6/0.3	100%	9,040	9,040	9,040	59	88	59	5,104	3,173	5,104	20,000	-
4	100/200/400	1.0/1.3/1.6	87%	24,993	25,679	25,679	183	232	197	12,794	10,241	12,565	25,000	15,000
5	100/ 75/ 50	1.0/0.6/0.3	83%	4,331	4,434	4,434	33	47	35	2,112	1,313	2,077	22,000	15,000
6	100/ 75/ 50	1.0/1.3/1.6	100%	7,447	7,447	7,447	62	74	62	3,324	2,521	3,324	25,000	-

\* Access is 100% for IBP and commercial flexibility for all value profiles. IPP=intellectual property protection.

## 5. Incorporating dynamic effects

By changing overall payment levels and the way in which payments are distributed across indications, the pricing policies considered have the potential to influence manufacturers' decisions about whether to invest in developing a new drug, or a new indication for an existing product. In this section we model these effects. These results are relevant if either a global multilateral policy for rewarding innovation is in place; or individual countries such as the UK give equal weight to health benefits that accrue to populations within and outside the UK.(9)

We reflect two mechanisms through which pricing policies can influence R&D. Firstly, IBP and commercial flexibility may increase the number of indications which are developed and receive regulatory approval per drug, as these policies provide a value-based payment in some indications where uniform pricing would not offer the opportunity to increase manufacturer revenue. Dynamic effects on the number of indications developed determine whether patients will have access to the product in both the IPP and post-IPP period (unlike launch decisions in the static analysis, where access was expected to be available in the post IPP period across pricing policies).

We assume that the cost of developing an additional indication is relatively small so a pricing policy that provides any positive revenue for an indication will result in that indication being developed. The realised overall health effects associated with IBP are therefore as shown in equation [6] and the realised overall health effects associated with commercial flexibility are the sum of the effects of uniform pricing (see below) and the additional health implications of using commercial flexibility as shown in equation [8].

Under uniform pricing, indications that are not launched are also not developed and therefore not available in the post-IPP period. The realised population health effects under uniform pricing accounting for these innovation effects are therefore equal to those available under the static scenario (see equation [7]) minus the following term which reflects the population health benefits during the post-IPP period for those indications that are not developed:

$$\sum_{i \notin I^{UNI}} \sum_{t=t_p+1}^{T=\infty} \frac{n_i}{(1+r)^t} \left( \Delta h_i - \frac{\Delta n p c_i}{k} - \frac{\Delta m c_i}{k} \right) \quad [9]$$

where  $I^{UNI}$  denotes the full set of indications that are launched and developed and represents the union of the sets of indications  $I_1^{UNI}, I_2^{UNI}, \dots, I_{t_p}^{UNI}$ .

We refer to the overall health benefits associated with each drug that has already been developed as  $T_b$  and those corresponding to each drug that is yet to be developed as  $T_d$ . We assume that the effect of pricing policy on indication development, and therefore the overall health benefits associated with each drug, is the same for existing and future drugs (i.e.  $T_b = T_d$ ). This reflects the expectation that indication development and approval is relatively quick and that a shift in pricing policy could therefore modify which indications are developed for existing as well as future products.

The second mechanism through which the pricing policy can influence R&D is via the number of drugs developed (quantity,  $Q$ ). IBP and commercial flexibility offer a higher payment per drug which



would be expected to increase the number of drugs developed in the future.(22-24) The quantity of drugs developed in the future per drug developed today,  $Q_d$ , will depend on payment level which will depend on policy. We estimate  $Q_d$  as in Woods *et al.* (25) as:

$$Q_d = \alpha \cdot k^\epsilon \cdot s^\epsilon \quad [10]$$

where

$$\alpha = \frac{\gamma}{k^\epsilon \cdot s^{0^\epsilon}} \quad [11]$$

and the ratio of dynamic to static benefits,  $\gamma=2.3$ ; the elasticity of drug approvals with respect to payment,  $\epsilon=0.45$ ; and the current share of value offered by the health system,  $s^{0^\epsilon}=0.50$ . Payment influences the quantity of drugs developed in the future via the share of value paid by the health system to the manufacturer,  $s$ . This differs across policies and reflects the share of all potential value (i.e., reflecting the potential indications available across all policies) such that  $s$  is proportional to payment.

The total potential health effects associated with each policy accounting for innovation effects can be calculated as:

$$T_b + Q_d T_d \quad [12]$$

where  $T_b$ ,  $Q_d$  and  $T_d$  are policy specific. The first term reflects the total potential health effects associated with an existing product and the second term reflects those associated with future products.

Results for the six value profiles incorporating dynamic effects are shown in Table 4. For value profiles where uniform pricing does not disincentivise launch (value profiles 2, 3 and 6), commercial flexibility is not required. IBP increase expenditure on branded medicines, however even when the potential effects of these higher payments on innovation are accounted for, IBP reduces overall population health by 2,230 QALYs (value profile 6) to 4,754 QALYs (value profile 3) compared to uniform pricing.

For value profiles where uniform pricing disincentivises launch (value profiles 1, 4<sup>3</sup> and 5), IBP and commercial flexibility are associated with improved access and (for value profiles 1 and 5) the development of indication 3, which is not developed under uniform pricing. However, these benefits are more than offset by the opportunity costs associated with higher drug expenditure and introduction of IBP reduces realised overall population health by 521 QALYs (value profile 1) to 5,719 QALYs (value profile 4) compared to uniform pricing (with an approval norm of £30,000/QALY for both policies). Commercial flexibility improves overall population health by 191 QALYs (value profile 4) to 1,795 QALYs (value profile 1) compared to uniform pricing. The health system receives greater value from the existing and new drugs developed under commercial flexibility than under a pure IBP policy, as under commercial flexibility many indications continue to be priced according to uniform pricing.

For IBP to increase realised overall population health, a reduction in the approval norm to £20,000 (value profile 3) to 28,000/QALY (value profile 1) would be required. When invoked, commercial

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<sup>3</sup> In the case of value profile 4 uniform pricing incentivises withdrawal of indication 1 from the market.

flexibility increases overall population health compared to uniform pricing at approval norms up to £21,000/QALY (value profile 4), £68,000/QALY (value profile 1) and £70,000/QALY (value profile 5). The benefits of the commercial flexibility policy are less sensitive to the choice of approval norm used for the commercial flexibility component of the policy, as even at high approval norms commercial flexibility can drive innovation that remains valuable to the NHS, as this will be mostly priced according to the uniform pricing component of the pricing policy (which uses a £30,000/QALY approval norm).

The analysis above assesses the approval norm required for IBP to deliver equivalent population health effects to uniform pricing at an approval norm of £30,000/QALY.<sup>4</sup> Table 5 shows the choice of approval norm that would maximise long-term health outcomes accounting for the effects of payment level on innovation, for each of the pricing policies. This shows that the long-term health maximising approval norm would be £11,500-£15,000/QALY (depending on value profile) under uniform pricing and that this would increase realised population health by 2,126 to 8,559 QALYs (depending on value profile) compared to use of a £30,000/QALY approval norm. Under IBP the long-term health maximising approval norm is £9,000-11,000/QALY (depending on value profile). IBP with dynamically efficient approval norms further improves population health compared to uniform pricing with dynamically efficient approval norms by up to 1,759 QALYs. By facilitating the development of additional indications, IBP increases the health generated by new products, and with a dynamically efficient approval norm the health system ensures that it retains a proportion of this additional value as overall population health gains. Although the dynamically efficient approval norms for IBP are lower than those for uniform pricing, manufacturer revenue is the same or higher under IBP.

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<sup>4</sup> Results are not presented for the commercial flexibility policy with a dynamically efficient approval norm, as this is equivalent to IBP with a dynamically efficient approval norm.

**Table 4: Results for numeric example using alternative value profiles (dynamic results).\***

Value profile	Population treated in each year for indication 1/2/3	Incremental health gain for indication 1/2/3 (in QALYs)	Total potential population health available from developed drugs and indications			NHS expenditure on branded medicines (£ million)			Net health effects (QALYs)			Approval norm at which policy is equivalent to uniform pricing at £30,000/QALY	
			Uniform	IBP	Commercial flexibility	Uniform	IBP	Commercial flexibility	Uniform	IBP	Commercial flexibility	IBP	Commercial flexibility
1	100/100/100	1.0/0.6/0.3	14,503	19,041	17,491	121	197	139	6,440	5,919	8,235	28,000	68,000
2	100/100/100	1.0/1.3/1.6	34,183	36,767	34,183	261	353	261	16,777	13,243	16,777	23,000	-
3	100/200/400	1.0/0.6/0.3	28,576	32,421	28,576	187	316	187	16,134	11,380	16,134	20,000	-
4	100/200/400	1.0/1.3/1.6	81,168	89,849	85,305	594	810	653	41,551	35,832	41,742	25,000	21,000
5	100/ 75/ 50	1.0/0.6/0.3	13,409	16,330	14,917	110	172	119	6,082	4,835	6,989	25,000	70,000
6	100/ 75/ 50	1.0/1.3/1.6	25,380	26,875	25,380	211	267	211	11,327	9,097	11,327	25,000	-

\* Access with the IPP period is as per Table 3 and therefore not repeated in this table for brevity.

**Table 5: Implications of applying dynamically efficient approval norms.\***

Value profile	Population treated in each year for indication 1/2/3	Incremental health gain for indication 1/2/3 (in QALYs)	Net health effects under uniform pricing at an approval norm of £30,000/QALY	Dynamically optimal approval norms (£/QALY)		Net health effects at dynamically efficient approval norms (QALYs)		Revenue to manufacturer at dynamically efficient approval norms (£ million)	
				Uniform pricing	IBP	Uniform pricing	IBP	Uniform pricing	IBP
1	100/100/100	1.0/0.6/0.3	6,440	11,500	9,500	8,643	10,517	35	44
2	100/100/100	1.0/1.3/1.6	16,777	12,500	10,000	20,803**	20,804**	84**	85**
3	100/200/400	1.0/0.6/0.3	16,134	15,000	10,000	18,260	18,260	76	76
4	100/200/400	1.0/1.3/1.6	41,551	13,000	11,000	50,109**	51,868**	202	220
5	100/ 75/ 50	1.0/0.6/0.3	6,082	11,500	9,000	8,011	8,956	32	36
6	100/ 75/ 50	1.0/1.3/1.6	11,327	11,500	10,000	15,042**	15,042**	61**	64**

\* Access with the IPP period is as per Table 3 and therefore not repeated in this table for brevity.

\*\* Values differ between uniform pricing and IBP due to limitations in precision of the model.

## **6. Strategic optimisation of launch order**

Pharmaceutical companies may respond to pricing policies by changing their launch order to maximise revenue. This is reflected in the following analysis where, under each policy, pharmaceutical companies are modelled as choosing launch order to maximise revenue, where revenue is discounted at 10.5% per annum (26) to reflect the cost of capital. As shown in Table 6 and Table 7, strategic indication launches reduce overall population health benefits across policies due to higher medicines' expenditure. However, these impacts were generally similar across policies as the optimal order was similar across policies, and therefore did not change the relative performance of the policies under both the static and dynamic analyses.

**Table 6: Implications of strategic optimisation of launch order: static results (results with no change in launch order shaded grey)**

Value profile	Population treated in each year for indication 1/2/3	Incremental health gain for indication 1/2/3 (in QALYs)	Net health effects without launch order optimisation			Net health effects with launch order optimisation		
			Uniform	IBP	Commercial flexibility	Uniform	IBP	Commercial flexibility
1	100/100/100	1.0/0.6/0.3	2,520	1,618	2,451	2,520	1,618	2,451
2	100/100/100	1.0/1.3/1.6	5,055	3,710	5,055	4,827	3,481	4,827
3	100/200/400	1.0/0.6/0.3	5,104	3,173	5,104	5,065	3,097	5,065
4	100/200/400	1.0/1.3/1.6	12,794	10,241	12,565	10,962	8,188	10,733
5	100/ 75/ 50	1.0/0.6/0.3	2,112	1,313	2,077	2,112	1,313	2,004
6	100/ 75/ 50	1.0/1.3/1.6	3,324	2,521	3,324	3,324	2,521	3,324

**Table 7: Implications of strategic optimisation of launch order: dynamic results (results with no change in launch order shaded grey)**

Value profile	Population treated in each year for indication 1/2/3	Incremental health gain for indication 1/2/3 (in QALYs)	Net health effects without launch order optimisation			Net health effects with launch order optimisation		
			Uniform	IBP	Commercial flexibility	Uniform	IBP	Commercial flexibility
1	100/100/100	1.0/0.6/0.3	6,440	5,919	8,235	6,440	5,919	8,235
2	100/100/100	1.0/1.3/1.6	16,777	13,243	16,777	16,334	12,612	16,334
3	100/200/400	1.0/0.6/0.3	16,134	11,380	16,134	16,086	11,169	16,086
4	100/200/400	1.0/1.3/1.6	41,551	35,832	41,742	31,702	30,166	37,788
5	100/ 75/ 50	1.0/0.6/0.3	6,082	4,835	6,989	6,082	4,835	6,785
6	100/ 75/ 50	1.0/1.3/1.6	11,327	9,097	11,327	11,327	9,097	11,327

## 7. Influence of features of the medicines market on policy performance

A series of analyses was conducted to explore features of pricing policy and the medicines market which were expected to influence the relative performance of the policies. Each analysis was conducted for all value profiles in Table 3.

### *a. Static results*

Across all analyses which did not consider innovation effects, IBP and commercial flexibility result in equivalent or higher levels of access (Figure 3 panel (a)) but equivalent or lower net health effects (Figure 3 panel (b-c)) compared to uniform pricing. The magnitude of net health effect losses associated with implementing IBP or commercial flexibility depend on the value profile and the features of the medicines market, however the losses associated with IBP are consistently higher than those associated with commercial flexibility.

**Higher approval norms for specific indications:** We considered how the policies would perform if a higher approval norm of £100,000/QALY<sup>5</sup> applies to the first indication. Higher approval norms for specific indications may be relevant if indications are considered within the Highly Specialised Technologies programme or severity decision modifiers are considered to apply within the NICE Technology Appraisal programme<sup>6</sup>. (27) The higher approval norm for indication 1 disincentivises launch of subsequent indications under uniform pricing for value profiles 1, 3, 5 and 6, resulting in lower access under uniform pricing than under IBP or commercial flexibility. Nonetheless, net health effects remain higher under uniform pricing than IBP or commercial flexibility as these policies facilitate access within the patent period at an approval norm that exceeds the measure of health opportunity cost. For value profiles 2 and 4 uniform pricing has minimal effects on access and offers lower pharmaceutical expenditure compared to IBP as IBP effectively “ringfences” the first indication from price erosion, which results in high population health losses associated with IBP. IBP and commercial flexibility also generally increase manufacturer’s incentives to seek higher approval norms as these policies allow the manufacturer to “ringfence” the first indication from price erosion (see Appendix 2).

**Generics and biosimilar markets:** We explored the impact of using more realistic parameter values to reflect the generics and biosimilars market. We include more realistic assessments of the incremental costs of generics/biosimilars and account for the time taken from the end of IPP for generic/biosimilar products becoming available using evidence from Woods *et al.*(8) When using evidence reflecting the biosimilars market, the overall population health losses associated with moving from uniform pricing to IBP increase. This is because the drug prices permitted by IBP are effective for longer, due to the delay to biosimilar entry.

**High-cost comparators for specific indications:** We also explored the impact of a higher cost (e.g., branded) comparator being available for one of the indications at a price of £10,000 per patient. This doesn’t change the value associated with the new product or how it is shared between the NHS and

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<sup>5</sup> The lower bound of the approval norm applied within the NICE highly specialised technology programme.

<sup>6</sup> Although severity modifiers are operationalised by multiplying incremental QALYs by a factor, this is equivalent to multiplying the approval norm by the same factor.

manufacturer, however it does change the revenue optimisation problem faced by the manufacturer who is now able to achieve a higher absolute price for those indications where they supplant a high-cost incumbent, with consequent implications for launch decisions under uniform pricing. The scenario may increase or decrease the impact of IBP on population health. For example, for value profile 4, if there is a high-cost comparator in the second indication, then this incentivises withdrawal of indication 1 to preserve a higher price under uniform pricing. This reduces the difference in net health effects between IBP and uniform pricing. In contrast for value profile 4 if there is a high-cost comparator in the third indication, the manufacturer is not incentivised to alter their launch decision under uniform pricing and their price is therefore constrained by the price in indication 2. Under IBP, the manufacturer can capture both the cost of the incumbent and the additional value-based price for this indication. In this case the difference in net health effects between IBP and uniform pricing is larger when a high-cost comparator is relevant.



**Figure 3: Heat maps describing the influence of features of medicines market on policy performance across value profiles (static results)**

(a) Access under uniform pricing

		Value profile					
		1	2	3	4	5	6
Features of medicines market	Standard	73%	100%	100%	87%	83%	100%
	High app norm	39%	94%	18%	100%	50%	50%
	Sm mol generics	73%	100%	100%	87%	83%	100%
	Biologic market	73%	100%	49%	87%	50%	100%
	High cost comp1	39%	100%	100%	100%	50%	100%
	High cost comp2	73%	73%	49%	85%	83%	100%
	High cost comp3	100%	100%	100%	87%	100%	100%

(b) Net health effects of IBP compared to uniform pricing

		Value profile					
		1	2	3	4	5	6
Features of medicines market	Standard	- 902	- 1,345	- 1,931	- 2,553	- 799	- 803
	High app norm	- 728	- 3,441	- 1,867	- 5,184	- 494	- 1,397
	Sm mol generics	- 1,099	- 1,668	- 2,397	- 3,162	- 969	- 991
	Biologic market	- 1,568	- 2,436	- 2,731	- 4,613	- 858	- 1,439
	High cost comp1	- 728	- 470	- 2,511	- 1,705	- 494	- 264
	High cost comp2	- 322	- 964	- 939	- 961	- 219	- 1,238
	High cost comp3	- 742	- 1,803	- 879	- 4,383	- 719	- 1,032

(c) Net health effects of commercial flexibility compared to uniform pricing

		Value profile					
		1	2	3	4	5	6
Features of medicines market	Standard	- 69	-	-	- 229	- 34	-
	High app norm	- 243	- 80	- 622	-	- 165	- 466
	Sm mol generics	- 69	-	-	- 229	- 34	-
	Biologic market	- 69	-	- 274	- 229	- 165	-
	High cost comp1	- 243	-	-	-	- 165	-
	High cost comp2	- 69	- 229	- 274	- 290	- 34	-
	High cost comp3	-	-	-	- 229	-	-

	Gain in NHEs of >1,000 QALYs compared to uniform pricing
	Gain of 1-1,000 QALYs compared to uniform pricing
	Loss of 1-1,000 QALYs compared to uniform pricing
	Loss of >1,000 QALYs compared to uniform pricing

*b. Dynamic results*

When dynamic effects are reflected the picture is more complex, as shown in Figure 4. IBP is associated with lower net health effects than uniform pricing in most contexts, and the losses associated with implementing IBP are considerably higher when more realistic features of the small molecules and biosimilars markets are reflected within the analysis. However, there are conditions under which IBP is associated with higher net health effects than uniform pricing. This occurs when there is a particularly high price associated with early indications due to a combination of higher numbers of QALYs being generated within these indications and price being elevated by high approval norms and/or high-cost comparators. In these circumstances, uniform pricing disincentivises launch and R&D for the later indications, effects which are avoided by IBP. Commercial flexibility is associated with gains in net health effects compared to uniform pricing in a wider set of contexts as the costs of the policy are lower due to the retention of uniform pricing for indications where commercial flexibility is not required. The policy option that offers the highest net health effects is either uniform pricing or commercial flexibility across all contexts considered.

**Figure 4: Heat maps describing the influence of features of medicines market on policy performance (dynamic results)**

(a) Access under uniform pricing

		Value profile					
		1	2	3	4	5	6
Features of medicines market	Standard	73%	100%	100%	87%	83%	100%
	High app norm	39%	94%	18%	100%	50%	50%
	Sm mol generics	73%	100%	100%	87%	83%	100%
	Biologic market	73%	100%	49%	87%	50%	100%
	High cost comp1	39%	100%	100%	100%	50%	100%
	High cost comp2	73%	73%	49%	85%	83%	100%
	High cost comp3	100%	100%	100%	87%	100%	100%

(b) Net health effects of IBP compared to uniform pricing

		Value profile					
		1	2	3	4	5	6
Features of medicines market	Standard	- 521	- 3,534	- 4,755	- 5,719	- 1,246	- 2,231
	High app norm	3,040	- 13,691	8,269	- 16,216	1,991	6,086
	Sm mol generics	- 1,671	- 5,225	- 7,067	- 9,105	- 2,205	- 3,235
	Biologic market	- 6,734	- 10,480	- 11,127	- 19,753	- 2,470	- 6,375
	High cost comp1	3,655	- 1,325	- 5,737	- 4,434	2,456	774
	High cost comp2	1,051	- 1,981	5,112	- 1,817	348	- 3,270
	High cost comp3	- 2,092	- 4,538	- 2,414	- 9,343	- 2,041	- 2,793

(c) Net health effects of commercial flexibility compared to uniform pricing

		Value profile					
		1	2	3	4	5	6
Features of medicines market	Standard	1,795	-	-	191	907	-
	High app norm	5,724	- 196	13,860	-	3,932	10,581
	Sm mol generics	1,607	-	-	- 154	812	-
	Biologic market	- 57	-	- 355	- 874	304	-
	High cost comp1	5,075	-	-	-	3,454	-
	High cost comp2	1,816	52	6,974	- 9	919	-
	High cost comp3	-	-	-	460	-	-

	Gain in NHEs of >1,000 QALYs compared to uniform pricing
	Gain of 1-1,000 QALYs compared to uniform pricing
	Loss of 1-1,000 QALYs compared to uniform pricing
	Loss of >1,000 QALYs compared to uniform pricing

## 8. Case studies

The framework developed was applied to two multi-indication drugs: nivolumab and pembrolizumab, as data on key parameters were available from a previous study.(5) As in Cole and colleagues, we included all the indications approved by NICE up to July 2018 (Table 8). These represent all the indications that had received regulatory approval in the UK at this time.(28)

**Table 8: List of indications approved by the National Institute for Health and Care Excellence (NICE) in the UK for nivolumab and pembrolizumab, up to July 2018 in order of NICE approval.**

Indication	Nivolumab	Pembrolizumab
1	Advanced (unresectable or metastatic) melanoma as monotherapy (TA384)	Advanced (unresectable or metastatic) melanoma after disease progression with ipilimumab (TA357)
2	Advanced (unresectable or metastatic) melanoma in combination with ipilimumab (TA400)	Advanced (unresectable or metastatic) melanoma as monotherapy not previously treated with ipilimumab (TA366)
3	Previously treated renal cell carcinoma (TA417)	Programmed Cell Death Ligand 1 (PD-L1) positive non-small-cell lung cancer after chemotherapy (TA428)
4	Relapsed or refractory classical Hodgkin lymphoma (TA462)	Untreated PD-L1 positive metastatic non-small-cell lung cancer (TA447)
5	Previously chemotherapy treated locally advanced or metastatic squamous non-small cell lung cancer (TA483)	Locally advanced or metastatic urothelial cancer after platinum chemotherapy (TA519)
6	Previously chemotherapy treated locally advanced or metastatic non-squamous non-small cell lung cancer (TA484)	—
7	Recurrent or metastatic squamous cell carcinoma of the head and neck after platinum-based chemotherapy (TA490)	—

Abbreviations. *PD-L1*, Programmed Cell Death Ligand 1.

Table 9 reports the parameters required to populate the model. The annual eligible population comes from Cole et al (5), which retrieved the information from the NICE appraisals or from published literature when required. Where information was not available from Cole et al., (5) additional data (e.g., time to discontinuation) were sought from NICE technology appraisals.(29-40) We prioritised evidence reflecting the Committee preferred assumptions, followed by evidence reflecting the External Review Group preferred assumptions and lastly the manufacturer base-case analysis. When no information was reported in the technology appraisal documentation, we consulted the published literature. Ultimately, assumptions were made to address data gaps. However, we tested key assumptions in sensitive analysis, and the findings do not change qualitatively. Further details on how the parameters were estimated, and data gaps addressed are reported in Appendix 3.

According to the UK Intellectual Property Office,(41, 42) for nivolumab and pembrolizumab, the duration of patent protection is expected to be 14 and 15 years from first indication launch, respectively. To estimate the rate of entry and the cost of generics and biosimilars, we followed the approach and data sources from Woods et al.(8) Uniform pricing was assumed to apply at the level of the product rather than the patient. This meant that equation [5] was adapted to account for the drug and indication-specific treatment regimen and time on treatment when calculating the maximum achievable product price under different launch strategies.

**Table 9: Input parameters required for the case studies**

	Indication number						
Parameter	1	2	3	4	5	6	7
ICER							
Nivolumab	£30,000 (32)	£29,221 (35)	£50,000 (29)	£31,031 (33)	£49,982 (31)	£49,122 (30)	£49,408 (34)
Pembrolizumab	£46,662 (37)	£50,000 (36)	£53,222 (39)	£31,350 (40)	£50,000 (38)	—	—
Incremental QALYs							
Nivolumab	1.72 (32)	1.63 (35)	0.64 (29)	2.80 (43)	0.46 (31)	0.68 (30)	0.40 (34)
Pembrolizumab	1.19 (37)	0.61 (36)	0.52 (39)	0.93 (40)	0.68 (38)	—	—
Incremental non-product cost <sup>y</sup>							
Nivolumab	£6,563 (32)	£2,208 (35)	£5,648 (29)	£0 (33)	£12,537 (31)	£5,222 (30)	£0 (34)
Pembrolizumab	£1,578 (37)	£3,825 (36)	£2,794 (39)	£4,867 (40)	£0 (38)	—	—
Incremental marginal cost of production							
Nivolumab	£4,379 (32)	£1,565 (35)	£2,975 (29)	£3,470 (43)	£1,396 (31)	£4,177 (30)	£1,900 (34)
Pembrolizumab	£1,749 (37)	£1,833 (36)	£1,836 (39)	£2,499 (40)	£2,272 (38)	—	—

Total mg per indication							
Nivolumab	8,110 (32)	1,796 (35)	5,663 (29)	6,532 (33)	2,398 (31)	6,880 (30)	3,576 (34)
Pembrolizumab	1,131 (37)	1,036 (36)	1,053 (39)	1,960 (40)	1,782 (38)	—	—
Annual eligible population							
Nivolumab	550 (5)	550 (5)	800 (5)	50 (5)	950 (5)	350 (5)	240 (5)
Pembrolizumab	600 (5)	561 (5)	2000 (5)	1500 (5)	500 (5)	—	—
Year of NICE approval*							
Nivolumab	2016 (32)	2016 (35)	2016 (29)	2017 (33)	2017 (31)	2017 (30)	2017 (34)
Pembrolizumab	2015 (37)	2015 (36)	2017 (39)	2017 (40)	2018 (38)	—	—

Abbreviations. *ICER*, incremental cost-effectiveness ratio; *QALYs*, quality-adjusted life years.

\*In the model, we assumed that indications 1 to 3 were approved and commercialised in the UK during year 1, while indications 4 to 7 were approved and commercialised during year 2. For pembrolizumab, we assumed that indications 1 and 2 were approved and commercialised in the UK during year 1 whilst indications 3 to 5 were approved and commercialised in the UK during year 2.

<sup>y</sup> Due to lack of evidence in some indications, we assumed an incremental non-product cost equal to £0

Under uniform pricing, the model predicted that the revenue maximising strategy was to launch all indications for nivolumab. For pembrolizumab, the model predicted the launch for only indication 1 during the first period with indication 2 being delayed and launched alongside the other indications in the second period. In general, the model predicts that all indications will be launched, even those indications with relatively low value. For example, during period 1, indication 3 for nivolumab is associated with incremental QALYs of 0.64 which is a relatively low value compared to indication 1 and indication 2. Under the uniform pricing policy, launching indication 3 drives the price down. However, the manufacturer is predicted to launch all three indications as this is the combination of launches that maximizes their revenues. Here, a key driver of revenue is the size of the annual eligible population for indication 3 and this outweighs its lower value.

As no commercial flexibility policy was required<sup>7</sup>, we report the findings for uniform pricing and IBP. For both drugs, uniform pricing has no negative effects on access and therefore implementation of IBP would only modify pharmaceutical drug expenditure. IBP is predicted to approximately double the expenditure on nivolumab (from £748 million to £1,534 million) and pembrolizumab (from £1,180 million to £2,403 million). Under both policies the ICERs exceed the measure of health opportunity cost and, along with the expected relatively high costs and slow entry of biosimilars, this means that introduction of these products is expected to reduce overall population health. However, the reduction in population health associated with introducing the drugs is much higher under IBP due to the higher drug expenditure.

For nivolumab, population health losses of 69,747 QALYs are predicted to be associated with introduction of this drug under IBP compared to losses of 17,333 QALYs under uniform pricing. For pembrolizumab, population health losses of 102,467 QALYs are predicted under IBP compared to 19,603 QALYs under uniform pricing. The share of value assigned to the manufacturer exceeds 100% across all policies but is much larger under IBP. Full results are presented in Table 10. Similar results are observed when dynamic effects are included though the losses in overall population health are higher as they occur for current and future drugs (see Appendix 4).

**Table 10: Comparison of uniform pricing and IBP for nivolumab and pembrolizumab case studies.**

	Nivolumab		Pembrolizumab	
	Uniform price	Pure IBP	Uniform price	Pure IBP
Proportion of patients with access during IPP	100%	100%	97%	100%
Total potential net health effects gained through use of new drugs*	32,551	32,551	57,204	57,751
NHS expenditure on branded medicines	£748,257,149	£1,534,462,581	£1,180,214,657	£2,403,258,291
Health foregone due to payment manufacturers*	49,884	102,298	78,681	160,217

<sup>7</sup> Technically commercial flexibility could have been applied in the case of pembrolizumab, however this would have had minimal impact on the results as it would have facilitated access for only one year for one indication.



Realised population net health effects*	-17,333	-69,747	-19,603	-102,467
Share of value to the NHS	-53%	-214%	-34% <sup>a</sup>	-177%
Share of value to manufacturer	153%	314%	138% <sup>a</sup>	277%

Note. Values with an asterisk (\*) are discounted net health effects in quality-adjusted life years.

Abbreviations. IPP, intellectual property patent; NHS, National Health Service.

<sup>a</sup> Under the uniform pricing scenario, the value shares don't sum to 100%. During the IPP period, the value associated with indications that are not launched does not accrue to either the NHS or the manufacturer.

## 9. Operational considerations when implementing differential pricing by indication

The international literature has emphasised the operational challenges associated with indication-based pricing (IBP).<sup>(1, 2, 5, 6)</sup> We conducted workshops with NHS England and NICE stakeholders to understand the operational challenges associated with current commercial flexibility and any future implementations of IBP within the NHS.

### *a. Current processes*

The current process for establishing whether commercial flexibility applies, and the parameters of any associated contract involves both NICE and NHS England.

An initial assessment is made as to whether commercial flexibility is likely to apply. This is based on an assessment of the revenues associated with existing indications and the revenues expected if the indication under appraisal was also launched. Commercial flexibility may be permitted if these revenue predictions show that a manufacturer would not be incentivised to launch an indication under uniform pricing or would be incentivised to opt for an optimised recommendation under uniform pricing. Criteria requiring the product to offer a “strong value proposition”, “highly differentiated” clinical effectiveness and to address “unmet need” also apply, but there is a lack of clarity about how these additional criteria should be defined or operationalised. As the assessment of eligibility for commercial flexibility requires an understanding of the value-based price for the indication under appraisal, it is often revisited during the NICE appraisal process as the Appraisal Committee’s judgements about the clinical value of a new product evolve.

Once a decision has been made to offer commercial flexibility, NHS England negotiates a contract with the company which may either specify a fixed payment based on forecast drug usage in each indication or link payment to actual usage in each indication. Drug usage data by indication is available from the Blueteq system<sup>8</sup> for High-Cost Drugs (those excluded from the Payment by Results tariff) with additional data available for drugs within the Cancer Drugs Fund.

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<sup>8</sup> Blueteq records intention to treat rather than actual treatment initiation. Blueteq estimates of usage may be combined with overall data on volume from company sales, hospital purchasing volumes or dispensing data to provide a more accurate picture of usage.

High-Cost drugs are pass through costs for local providers. NHS England receives rebates from manufacturers at the national level to ensure that prices paid by the NHS reflect agreed confidential commercial arrangements.

### ***b. Operational challenges with current processes***

Several operational concerns were raised with regards to the current implementation of commercial flexibility.

The current ambiguity around the criteria for accessing commercial flexibility may be contributing to inconsistent decisions about which products and indications should qualify for these more flexible commercial arrangements.

Stakeholders noted that facilitating commercial flexibility requires considerable additional human resource due to the information needs of assessing eligibility, and the need to develop and implement the associated (more complex) commercial agreements.

Commercial flexibility has the potential to increase the number of NICE Appraisal Committee meetings. It may also increase the complexity of decision making by NICE Appraisal Committees, who may be asked to make decisions based on cost-effectiveness in the knowledge that further negotiations on price may occur.

Both uniform pricing and commercial flexibility were noted to be associated with opportunities for strategic revenue maximising behaviour by companies as decisions made for one indication (or subset of indications) have implications for the revenue achievable in other indications. For example, under commercial flexibility companies are more incentivised to achieve a high price for the first launch indication - for example via the NICE Highly Specialised Technologies programme - to access commercial flexibility for subsequent indications.

Workshop participants reported that commercial flexibility may reduce the ability of local decision makers to make efficient use of resources as they are not always fully informed of the prices negotiated under commercial flexibility.<sup>9</sup> Stakeholders also reported that the existence of multiple prices and multiple commercial mechanisms influencing price had at times caused challenges in determining the appropriate price for comparator technologies within NICE appraisals. There may be concerns that use of the actual indication-specific transaction price negotiated via the commercial arrangements process will disincentivise the launch of new products in that indication.

Participants also noted that implementation of any IBP approach in primary care or for drugs prescribed within secondary care that fall within the Payment by Results tariff (i.e., non-High-Cost Drugs) was likely to be challenging due to a lack of data on usage within individual indications, and in the case of primary care a lack of mechanisms with which to ensure appropriate payment flows between NHS England, integrated care boards and GPs. Though it should be noted that similar challenges can occur even for simple confidential PAS discounts in these settings.

### ***c. Recommendations***

The above findings suggest that if the commercial flexibility policy is continued there is a need for more explicit criteria to determine when commercial flexibility will be granted. This would most logically be based on demonstration that the indication has the potential to deliver value to patients and the health system, but that its launch under uniform pricing would lead to a reduction in

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<sup>9</sup> Local payors are made aware of simple Patient Access Scheme (PAS) discounts.

revenue for the manufacturer. This impact on revenue can only be assessed if there is clarity with respect to the health gains and non-product costs expected to be associated with a new indication, both of which are ideally determined via extensive deliberation within the NICE appraisal process.

Within the existing HTA paradigm, decisions about reimbursement are based on cost-effectiveness which is based on the final negotiated price. In this context, the decision about whether commercial flexibility applies is most obviously taken early in the HTA process to allow price negotiations to occur and cost-effectiveness to be assessed. This means that a thorough assessment of non-product costs and QALYs is unlikely to be available, and the decision about whether commercial flexibility applies will rely on preliminary information about value (e.g. from early-stage economic evaluations). An alternative, and potentially more radical, approach would be to assess eligibility for commercial flexibility *after* NICE appraisal. This would shift the focus of NICE Appraisal away from assessing cost-effectiveness and towards assessing the evidence of health benefits and non-product costs associated with new innovations. Pricing decisions and negotiations would then be conducted at the end of the NICE appraisal process, or as a separate process. This could enable more informed decisions about the applicability of commercial flexibility but, perhaps more importantly, would avoid more general challenges associated with negotiating pricing against a backdrop of evolving evidence of value.

Confidentiality around prices (and pricing mechanisms) that are agreed via commercial flexibility may facilitate pricing levels and/or access that would not otherwise be feasible. However, these benefits should be balanced against the risks that further confidentiality may complicate NICE Technology Appraisals of competitor products with the risk of poorer resource allocation decisions<sup>10</sup> and may compromise local decision makers' abilities to make cost-effective formulary decisions.

Any more extensive application of commercial flexibility or other forms of IBP would require extensive human resource investment, and possibly further investment in appropriate data infrastructure.

## 10. Discussion

This paper sets out a quantitative framework for comparing IBP and uniform pricing policies in terms of their overall population health effects in the IPP and post-IPP periods, accounting for the health gains associated with access to medicines and the health opportunity costs associated with medicines expenditure.

If the UK acts unilaterally and only considers health effects within the UK population when formulating pharmaceutical pricing policy, then effects on innovation are likely to be immaterial as the UK only represents a small part of the global market for new medicines. In this context, we find that when compared to uniform pricing, pure IBP can improve access to, and health benefits associated with new medicines, but reduces overall population health due to the large increase in medicines expenditure. For IBP to improve population health it would need to be accompanied by a reduction in the approval norm for all indications. Commercial flexibility can improve access to new

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<sup>10</sup> The existence of complex confidential pricing for competitor products poses several potential risks to NICE appraisals. Firstly, the existence of complexity raises the risk of human error in the identification and application of the correct prices. Secondly, it reduces transparency thus increasing the risk of poor decision making. Finally, it reduces the ability of the new entrant to identify and offer a cost-effective price when confidential prices may exist at multiple points in the treatment pathway.

medicines and the health gained from these treatments, however it also increases medicines expenditure, and can therefore only improve population health if an approval norm below the measure of health opportunity cost is applied within the indication(s) for which commercial flexibility is relevant.

If a global multilateral policy for rewarding innovation was in place or individual countries such as the UK were to give equal weight to health benefits that accrue to populations within and outside the UK, then effects of UK pricing policy on global pharmaceutical innovation become relevant. When these effects are accounted for, the current commercial flexibility policy may offer improvements to overall population health compared to uniform pricing in some scenarios where it promotes access and therefore innovation. Whether this is the case depends on the value profile and features of the medicines market. Across all context's considered IBP is associated with lower overall population health than commercial flexibility, which improves access and innovation whilst more effectively controlling pharmaceutical expenditure, because uniform pricing continues to apply to most indications.

Previous work (8, 9) has examined the way in which value is shared between manufacturers and health systems for individual drugs in single indications, and the balance of value shares that would be considered optimal from the perspective of maximising population health considering effects on innovation. This work concluded that the share of value offered to manufacturers under current policies is higher than would have been optimal and, in many cases, left the NHS with negative long-term value. Our analysis of two case studies suggests that, even though uniform pricing of multi-indication drugs facilitates price reductions for higher value indications, these are not sufficient to result in a positive share of value for the NHS. This indicates that regardless of the pricing policy approach, population health could be improved by reducing the approval norm. Furthermore, the dynamically efficient pricing policy would involve a form of IBP to provide incentives for the development and launch of all indications in which the product delivers net benefits, alongside a reduction in the approval norm across indications to ensure this additional value is optimally shared to balance innovation incentives with the opportunity costs of higher prices.

One potential criticism of the commercial flexibility policy is that, via the application of a different approval norm, the policy "values" health gains in new indications less than existing ones. This criticism could also be levelled at uniform pricing which ensures the same price is paid per tablet or per vial, but will typically result in a different price per unit of health gain across different indications. Approval norms are generally utilised as a policy tool for assessing cost-effectiveness, rather than representing the value of health gains by decision-makers. This raises the question of whether the application of different approval norms across indications is likely to lead to inequities across indications in access to existing or future medicines. For products already developed this seems unlikely. At approval norms of £15,000/QALY or above, prices should be high enough to cover costs of production and supply, and as R&D costs are already sunk this should be sufficient to incentivise market entry for all indications. However, it is possible that the application of different approval norms would differentially incentivise R&D across indications. Whether this is a core consideration for the UK as a relatively small part of the global pharmaceutical market is discussed above. However, if this is considered important then our analysis suggests that if a health system wanted to equally weight health gains across indications, across existing and new medicines, and across recipients of new medicines and those who forego health in the process of funding new medicines, then the population health maximising policy would be to offer pure IBP with an approval norm in the region of £10,000/QALY.

This research has several limitations. We aimed to provide a broad assessment of the implications of each policy for drugs with different value profiles, and market contexts. However, this is unlikely to have exhausted all possible scenarios. We examined two case studies to show the implications of the framework in a real-world setting. The results from this exercise suggested that the difference between policies may be starker than suggested by the numeric examples due to the application of much higher approval norms for some indications considered (up to £50,000/QALY), and the slow entry and substantive costs of biosimilars. Other products with lower approval norms and/or that deliver higher post-patent value are likely to align more closely with the findings from the numeric examples. The case studies were informed by evidence in the public domain. For some indications, the cost-effectiveness results corresponding to the final NICE Appraisal Committee decision were not available due to commercial confidentiality and had to be proxied with the best available alternative evidence. Finally, our workshop on operational issues focused pragmatically on NHSE and NICE stakeholders. Engaging a broader group of stakeholders including clinicians, other NHS decision makers such as individuals working within integrated care boards, and representatives of the pharmaceutical industry would likely have uncovered additional operational challenges associated with the policies considered.

We considered three policies that were viewed as most relevant to the current policy debate in the UK. It is feasible that additional policy options might offer higher overall population health outcomes. For example, an interesting case is when a valuable subsequent indication makes it more profitable for the manufacturer to withdraw the first launched indication for a product. Within the commercial flexibility model considered within this research, this would be addressed by allowing commercial flexibility to apply to the first indication following launch of the higher value subsequent indication (as occurs for value profile 4 in our analysis). An alternative policy would be a prospective agreement between the manufacturer and health system that a lower approval norm would be applied to the second indication. This would likely deliver higher overall population health and may be attractive to the manufacturer if it increases certainty regarding pricing. Further research would be required to quantify the effects of alternative policy models.

We have not accounted for the potential beneficial effects of additional product launches within an indication on price competition. If price competition occurs, this could increase the overall population health benefits of IBP and commercial flexibility policies when these policies contribute to a larger number of products being available in an indication. Discussion with NHS England, NICE and local commissioners during this project indicated that, in the UK, there are limited mechanisms to promote price competition. However, this may be a more relevant consideration in other jurisdictions. It is also possible that IBP and commercial flexibility may discourage new entrants if a multi-indication incumbent is able to offer a lower price due to the availability of these policies.

We have assumed that under both IBP and commercial flexibility pricing policies, companies will launch their product if the price premium (i.e., additional price compared to the comparator) exceeds any additional cost of production and supply. This seems a reasonable assumption as R&D costs are sunk at the point of the decision to launch, and UK pricing decisions are not expected to influence international prices (e.g., via international reference pricing) due to the application of confidential discounts via NICE PAS or other mechanisms.

The literature on IBP has highlighted a series of operational challenges associated with its implementation including challenges in establishing an appropriate data infrastructure to track product usage at an indication level and the administrative burden associated with recording this data and linking it through to payment, as well as potential incentive issues that may occur where the recorded indication influences the transaction price.<sup>(1, 2, 5, 6)</sup> The commercial flexibility policy

adds another layer of operational challenges as it requires an additional step to determine whether commercial flexibility should be permitted for a given drug and indication.

There is a need for clarity on the criteria for access to commercial flexibility to ensure robust and consistent decision making. Assessing eligibility for commercial flexibility requires an understanding of the value associated with the new indication. This could be established early in the appraisal process via the use of early economic evaluation evidence. Alternatively, this could be assessed after NICE appraisal, with HTAs of new pharmaceuticals shifting their focus to assessing the evidence of health benefits and non-product costs associated with new innovations, with pricing decisions/negotiations conducted at the end of the HTA process, or as a separate process. This could enable more informed decisions about the applicability of commercial flexibility, but perhaps more importantly would avoid the broader challenges associated with negotiating pricing against a backdrop of evolving assessments of value. The feasibility, benefits, and risks of this shift in the role of HTA would require careful evaluation.

## **11. Conclusion and policy application**

Introducing IBP or commercial flexibility requires careful specification to prevent large increases in medicine expenditure, which would outweigh the benefits of improved access and therefore reduce overall population health. For IBP to improve population health, compared to uniform pricing using an approval norm of £30,000/QALY, it would need to be implemented with a lower approval norm of approximately £20,000/QALY, across all indications (no innovation effects scenario).

For commercial flexibility to improve population health compared to uniform pricing, an approval norm of £15,000/QALY would be required for those indications where commercial flexibility is applied (no innovation effects scenario). These findings are relevant both to the upcoming update of the NHS Commercial Framework for new medicines, and to health care systems considering IBP policies internationally.

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