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RESEARCH ARTICLE

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Achieving dynamic efficiency in pharmaceutical innovation: Identifying the optimal share of value and payments required

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Abstract

It has been argued that cost-effectiveness analysis of branded pharmaceuticals only considers static efficiency, neglects dynamic effects and undermines incentives for socially valuable innovation. We present a framework for designing pharmaceutical pricing policy to achieve dynamic efficiency. We develop a coherent framework that identifies the long-term static and dynamic benefits and costs of offering manufacturers different levels of reward. The share of value that would maximise long-term population health depends on how the quantity and quality of innovation responds to payment. Using evidence of the response of innovation to payment, the optimal share of value of new pharmaceuticals to offer to manufacturers is roughly 20% (range: 6%–51%). Reanalysis of a sample of NICE technology appraisals suggests that, in most cases, the share of value offered to manufacturers and the price premium paid by the English NHS were too high. In the UK, application of optimal shares would offer considerable benefits under both a public health objective and a broader view of social welfare. We illustrate how an optimal share of value can be delivered through a range of payment mechanisms including indirect price regulation via the use of different approval norms by an HTA body.

KEYWORDS
analysis of health care markets, dynamic efficiency, government policy, pharmaceutical pricing, public health, regulation, static efficiency

JEL CLASSIFICATION
I11, I18

1 | INTRODUCTION

Policy makers, payers and the pharmaceutical industry have long debated how to price new pharmaceuticals to provide value to the health system, while incentivising manufacturers to invest in the development of new products. Health technology assessment (HTA) bodies, however, have tended to focus on whether or not a new treatment is cost-effective compared to some stated or implied approval norm, or cost effectiveness 'threshold', which represents the maximum additional cost per QALY gained that is deemed acceptable. This serves as a form of indirect price regulation since manufacturers generally set prices or

offer discounts to ensure the cost per QALY of their product is equal to the stated or implied 'threshold' during the remaining period of intellectual property protection (IPP). However, the long-term value of the product post IPP (if and when prices fall with generic entry) and evidence of how the quantity and quality of innovation responds to payments offered is generally not considered (Neumann et al., 2022).

This has led some to argue that cost-effectiveness analysis, and the decisions by HTA bodies that it informs, tends to focus on static efficiency, neglects dynamic effects and undermines incentives for socially valuable innovation (Jena & Philipson, 2008; Moreno & Ray, 2016). Others have drawn on Nordhaus' theory of innovation (William D. Nordhaus, 1969a, 1969b) to argue that insofar as manufacturers face the full cost of research and development they should also be rewarded with the full benefits; and that this can be achieved (at least within the remaining period of IPP) by adopting a cost effectiveness threshold that reflects the consumption value of health based on evidence of individual willingness to pay (Danzon et al., 2015; Jena & Philipson, 2008; Lakdawalla, 2018; Lakdawalla & Sood, 2012; Vernon et al., 2009). This does not, however, directly address what the level of reward ought to be as it implicitly assumes that the period of IPP is already optimal. Others have considered the global dynamics of pharmaceutical pricing, the implications of price controls and the implications of strengthening IPP, all from a similar perspective (Bennato & Giulietti, 2019; Chu, 2008; Council of Economic Advisers, 2019; Egan & Philipson, 2013; Filson, 2012; Gigi, Emma van, Jennifer, & Jeffrey, 2017; Goldman et al., 2011; Lakdawalla et al., 2008; Santerre & Vernon, 2006). Some have argued that it is evidence of the health opportunity cost associated with health care expenditure, rather than individual willingness to pay, that represents the maximum price that health care systems can afford to pay for the benefits of an innovation during IPP, while acknowledging that this is only dynamically efficient if the period of IPP is already considered optimal (Claxton, 2007; Claxton et al., 2008). Others have suggested that approval norms should be set to maximise net health effects, taking account of the health opportunity costs associated with health care expenditure but have not accounted for the longer term value in the post IPP period if and when prices fall with generic entry (Pandey et al., 2018), or have not accounted for the dynamic effects of payment on innovation (Paulden, 2023).

None of this literature has attempted to incorporate the growing body of evidence of how the quantity and quality of pharmaceutical innovation responds to payment (Acemoglu & Linn, 2004; Adams, 2021; Bennette et al., 2019; Blume-Kohout & Sood, 2013; Cerda, 2007; Dubois, de Mouzon, Scott-Morton, & Seabright, 2015; Finkelstein, 2004; Myers & Pauly, 2019; Rake, 2017; Toole, 2012) to identify the optimal level of reward to manufacturers which accounts for the long-term value beyond IPP, while carefully distinguishing the consumption value of health and the health opportunity costs associated with health care expenditure. Equally, the empirical literature has not estimated the likely effect of payment on health outcomes, or other welfare arguments, to identify what level of payment might be optimal and evaluate which pricing policies or approval norms would deliver this payment.

The purpose of this paper is to develop a coherent and evidence-based approach to pharmaceutical pricing policies and payment mechanisms to achieve dynamic efficiency which: (i) accounts for the long-term value of pharmaceuticals beyond IPP; (ii) incorporates the evidence of how the quantity and quality of innovation responds to levels of payment; and (iii) distinguishes approval norms, the willingness to pay for health benefits and the health opportunity costs associated with health care expenditure (Claxton et al., 2015). We show how this analysis can be generalised to other aspects of benefit beyond health, including the implications of accounting for potential value associated with any producer surplus (manufacturers' super normal profits) that might be retained.

We apply this framework to a previously published sample of technology appraisals undertaken by NICE (Woods et al., 2021). We show how it can be used to identify the optimal share of the long-term value of a new pharmaceutical which should be offered to manufacturers, conditional on judgements about the empirical evidence. We show how the optimal share of value can be translated into an overall payment to manufacturers. An optimal payment can be delivered in a number of ways. For example, it could be delivered by modulating approval norms applied by HTA bodies during IPP, changing the length of IPP, securing commitments to lower prices beyond the period of IPP, as well as subscription models where limiting early widespread use may be important (e.g., new antimicrobials). Although we illustrate the implications using UK data as a case study, the principles developed are generalisable across jurisdictions and types of health care system.

2 | EVIDENCE OF HOW INNOVATION RESPONDS TO LEVEL OF PAYMENT

A systematic review was conducted to identify papers quantifying the effects of payment on innovation (see Supporting Information S1). This identified 29 papers quantifying the effect of payment (via price, market size or patent duration) on innovation outputs (quantity and quality of pharmaceutical innovation) or inputs/activity (R&D expenditure or number of clinical trials). Nine studies were considered to be particularly relevant to the research question as they estimated a plausible or robust causal

effect according to the criteria specified in Supporting Information S1 and used measures of innovation outputs rather than measures of inputs or activity which are not easily quantitively related to innovation outputs.

All nine studies provided plausible or robust causal evidence that related payment to the quantity of innovation (see Supporting Information S1: Table 1). Six of the studies (Acemoglu & Linn, 2004; Cerda, 2007; Dubois et al., 2015; Myers & Pauly, 2019; Rake, 2017; Toole, 2012) estimated elasticities by examining the relationship between demographically-driven variations in market size (argued to be plausibly exogenous) and new molecular entities over time, and by disease area. Three studies (Bennette et al., 2019; Blume-Kohout & Sood, 2013; Finkelstein, 2004) examined the effects of policies, which were expected to have differential effects by disease area, on new molecular entities and drug approvals in those disease areas. As shown in Supporting Information S1; the studies results exhibit a very high degree of heterogeneity and funnel plot asymmetry (i.e., those studies with the widest confidence intervals around the elasticity estimates also have the highest point estimates). The reason for this is unclear but could relate to publication bias, reporting biases, or methodological quality. In these circumstances any meta-analysis may be considered inappropriate, and the use of regression-based methods to adjust for potential biases is only recommended when there is a larger number of studies (Higgins et al., 2022).

Given these concerns, we present our results for a range of elasticities that have been referenced in the recent policy debate around appropriate pharmaceutical pricing. As our central estimate, we use the recent Congressional Budget Office (CBO) analysis of the potential impact of the Lower Drug Costs Now Act (H.R. 3) (Adams, 2021). The CBO provides independent analyses to support the US Congress's budget process. The CBO report uses a simulation model of drug development calibrated using confidential Medicare drug expenditure data and published data on pharmaceutical R&D costs. The model predicts the impact of H.R. 3 on phase I, II and III drug development decisions and how this influences the number of drugs entering the market over time. The findings are consistent with a long-run average elasticity of 0.45 relating the number of drugs entering the market to changes in global revenue (i.e., a 1% increase in global revenues increase the number of drugs entering the market by 0.45%).

We also test the implications of using a lower and a higher elasticity. A lower elasticity of 0.23 is based on Dubois et al. (2015) which was included in our review. Among those studies included within the review, this study was particularly relevant as it uses revenue data (rather than estimated market size) and considers the effect of global revenue. The potential for reverse causality, whereby payment is a consequence of innovation, is addressed via instrumental variables based on income and demographic data. A higher elasticity is based on the value used by Philipson and Durie (Philipson & Durie, 2021) in their analysis of H.R.3. The authors use a base case value of 1.5 based on an unweighted average of elasticities taken from a selection of published studies which relate changes in revenue to changes in new drugs or R&D expenditure.

Only one study identified via the review provided evidence of the effect of payment on the quality of innovation (Bennette et al., 2019). Bennette et al. estimated the effect of a change in payment through the passage of Medicare Part D on both the number of new oncology medications approved and their quality, measured as expected improvements to median survival. This study indicated that, for every 1% increase in the quantity of innovation due to payment, the quality of innovations (survival gains) falls by 0.56% on average. This direction of effect is consistent with diminishing returns to research and development efforts on average at a point in time for a given level of technology.

Given the limited evidence on quality and that the only study identified was restricted to cancer, our primary analysis does not assume any decline in quality (or increase in manufacturing costs) as the quantity of innovation increases with payment. The evidence on quality is incorporated as a sensitivity analysis, where evidence from the CBO report is combined with the evidence on quality from Bennette et al. to estimate an elasticity relating health effects to payment of 0.20 (see Supporting Information S1 for derivation). This estimate implies that a 1% increase in payment increases the QALY-gains associated with new medicines by 20%, assuming (in the absence of alternative evidence) that life-year gains are a reasonable proxy for QALY gains (Soares et al., 2020). Given the heterogeneity in the evidence relating payment to innovation quantity, and the limited evidence relating to quality and manufacturing costs, the key results within this paper are presented for a range of elasticity estimates.

3 | ESTIMATING STATIC AND DYNAMIC BENEFITS AND COSTS

Establishing the optimal share of total value to offer to manufacturers, and the payment needed to deliver it, requires a quantitative framework to trade-off the static (current) and dynamic (future) health benefits, and the health opportunity costs, of different levels of payment. This can be achieved by combining an estimate of the value of innovation elasticity with a measure of the scale of the static and dynamic benefits. In this section we define static and dynamic benefits and in the following sections we show how they can inform an assessment of optimal share under different policy objectives.

If a new pharmaceutical product is brought to market, which is effective relative to existing comparators, it will offer the potential for long-term net health benefits (T_b). This reflects the health gains associated with using the product net of the health opportunity cost associated with the manufacturing cost (mc) and any other non-product costs (npc) (Woods et al., 2021):

$$T_b = \sum_{t=1}^{\infty} \frac{n_t}{(1+r)^t}\left(\Delta h - \frac{\Delta \text{npc}}{k} - \frac{\Delta \text{mc}}{k}\right) \tag{1}$$

The static benefit is a function of the number of patients presenting for treatment in a given year (n_t), the annual discount rate (r), the additional health benefit of the product to patients (Δh), the health opportunity cost associated with non-product costs $\left(\frac{\Delta \text{npc}}{k}\right)$, and the health opportunity cost associated with any additional manufacturing costs $\left(\frac{\Delta \text{mc}}{k}\right)$,[1] where k reflects the marginal productivity of the health care system. The time horizon of these static benefits is unbounded because the value of the product persists, even if no longer used, so long as the value (and price) of future pharmaceuticals are judged relative to generic versions of the product being evaluated. Dynamic benefits associated with future innovations are defined in the same way: as a function of health benefits and the health opportunity costs of non-product and manufacturing costs.

Some share (s) of this static benefit is foregone if the healthcare system pays more than manufacturing costs to provide incentives for innovation. This represents a static health opportunity cost because the additional health care resources required to make this payment could have been used to improve health elsewhere. If the share was zero, the healthcare system would capture the whole static health benefit as no payment in excess of the manufacturing cost would be made. Payment can be expressed as a cost in terms of health ($s.T_b$) or expressed as the healthcare system resources that would be required to generate the same health benefits ($k.s.T_b$) (i.e., in monetary terms).

Incurring static costs in excess of manufacturing costs can be justified to incentivise the development of new pharmaceutical products in the future. These products are associated with a dynamic benefit (T_d), measured in the same way as static benefit. The share of static benefit offered to manufacturers must be regarded as a credible long-term policy commitment that will drive revenue expectations and, therefore, the R&D decisions that determine T_d. Pricing policies that are expected to deliver only a temporary payment for static benefits, rather than a long-term commitment, are unlikely to offer dynamic benefits.[2] Therefore, we consider pricing policies which offer a long-term commitment, where the same share of the dynamic benefits will be foregone through payments to manufacturers and this constitutes the dynamic health cost ($s.T_d$).

4 | ESTABLISHING THE OPTIMAL SHARE OF VALUE TO OFFER TO MANUFACTURERS

Focusing initially on a public health objective, an optimal share will maximise the total (static and dynamic) health benefits ($T = T_b + T_d$) less the total health costs ($s.T$). The optimal share (s^*) will take some value between 0 and less than 1, because if the share is equal to one then not only is the full static benefit foregone but the full dynamic benefits as well.

Therefore, establishing the link between the share of benefit foregone by the healthcare system (s) and the impact on dynamic benefit (T_d) is critical. As discussed in Section 2, the literature has analysed the closely related question of how the number of new products developed (and to a lesser extent their quality) responds to payment through estimation of a value of innovation elasticity (ϵ). We assume that the quantity and average quality measures that underpin these estimates are a reasonable proxy for dynamic benefit and that the elasticity is constant with level of payment.[3] This allows dynamic benefit to be expressed as a power function of payment:

$$T_d = \alpha.p^{\epsilon} \tag{2}$$

where α determines scale (on which more later) and p denotes payment in monetary terms (i.e., $k.s.T_b$).

Dynamic benefit can therefore also be expressed as a power function of share:

$$T_d = \alpha.(k.T_b)^{\epsilon}.s^{\epsilon} \tag{3}$$

Dynamic benefit will be increasing in share so long as the elasticity is positive; and increasing at an increasing rate with share if the elasticity is greater than one, but at a decreasing rate if the elasticity is less than one.

The optimal share can be defined as the one that maximises the difference between total benefit and total cost.

$$s^* = \underset{s\in\Omega}{\text{argmax}}(1-s).(T_b + T_d) \tag{4}$$

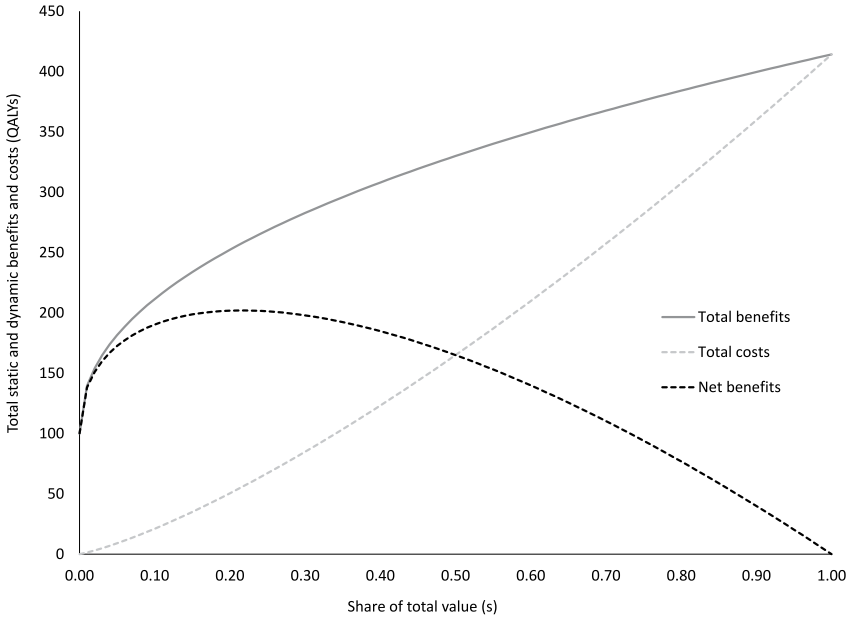

FIGURE 1 Total static and dynamic benefits, costs, and net benefits in health terms. Scale of static benefit is, for illustration, set at a value of 100 QALYs*, $T_b = 100$; value of innovation elasticity, $\epsilon = 0.45$ from the CBO simulation model; marginal productivity of the health care system, k = £15,000/QALY based on evidence from the UK[5]; ratio of dynamic to static benefits, $\gamma = 2.3$ based on ratio of the value of products expected to be developed in the future to products already developed but still within IPP; and the share of value at which this ratio of dynamic to static benefits is observed, $s^0 = 0.5$ based on evidence from a sample of NICE appraisals. This implies a constant, $\alpha = 0.52$. *Note that the choice of value for T_b influences the scale of the predicted outcomes though not the estimated optimal share or other conclusions (see footnote 4).

Taking the derivative of Equation (4) with respect to share:

$$\frac{d(1-s).(T_b+T_d)}{ds} = \left(1-s^*\right)\frac{dT_d(s^*)}{ds} - (T_b+T_d) = 0 \tag{5}$$

There is no general solution for s^*, but it is possible to obtain the optimal share numerically for given parameter values (see Supporting Information S2). The optimal share will depend on the current relative scale of static and dynamic benefit as well as how dynamic benefit is expected to respond to payment (i.e., the elasticity of innovation) but not on the level of T_b, T_d or k.[4]

In order to quantify how T_d responds to a long-term change in share using Equation (3), it is necessary to estimate the scale parameter, α. If we have an understanding of the ratio of dynamic to static benefits under the current policy environment (γ) then we can rearrange Equation (3) to calculate α as:

$$\alpha = \frac{\gamma.T_b}{(k.T_b)^{\epsilon}.s^{0^{\epsilon}}} \tag{6}$$

where $s^{0^{\epsilon}}$ is the share of value currently offered. A 50% share is used to reflect a plausible share of value currently offered to manufacturers, based on evidence from a sample of NICE appraisals (Woods et al., 2021). The relative scale of static and dynamic benefits at the current share of value offered to manufacturers is not directly available from the literature. The static benefits of relevance to this analysis derive from drugs that remain subject to IPP, which, based on available patent duration data (Copenhagen Economics, 2018), would be drugs developed in the last 12 years. Assuming a constant supply of new drugs over time with no change in the scale of benefits they offer (as predicted by the CBO simulation model in their baseline scenario (Adams, 2021)) implies a ratio of dynamic to static benefits of 2.3 when these are discounted at 3.5% per annum.

For these (or any other) chosen parameter values it is now possible to plot the total benefits, total costs and net benefits against share of value given to the manufacturer as in Figure 1 where values are expressed in terms of health. If zero share is offered to manufacturers, the health care system receives only the static net health benefit, since there are no incentives for innovation and no dynamic benefits. At a share equal to 1 there are considerable dynamic benefits as well, but all benefits (static and dynamic) are just offset by the static and dynamic costs, so the net health benefits are zero. In Figure 1, health benefits are maximised at an optimal share of $s^* = 0.22$. The values of T_b and k rescale the graph but do not change the optimal share. They

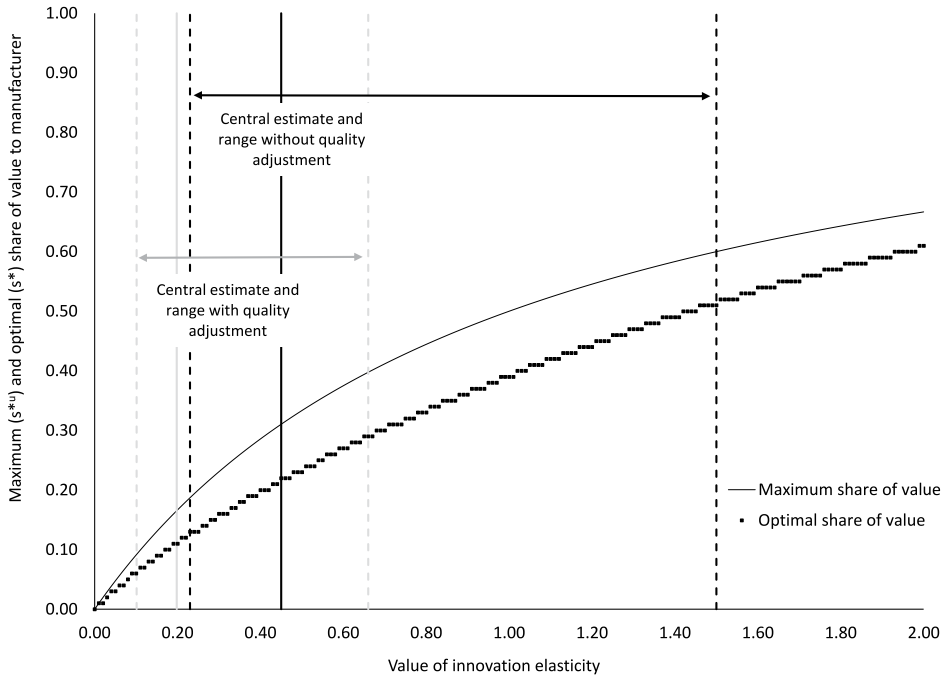

FIGURE 2 Maximum (s^{*U}) and optimal (s^{*}) share of value for a range of value of innovation elasticities.

do however, alongside s^{*}, determine the payment level commensurate with this share as discussed in detail in Section 5 of this manuscript.

Given the uncertainties around the relative contribution of static and dynamic benefits, we also estimate optimal share under the extreme assumption that dynamic benefits are unbounded relative to static benefits (which then become negligible). This maximum share (s^{*U}) is 0.31 using the parameter values described above (see Supporting Information S1 for derivation). Figure 2 illustrates the possible range of maximum and optimal shares of value to offer manufacturers, given a range of estimates of the value of innovation elasticity. This suggests an optimal share of value to offer to manufacturers of 22% (range: 13%–51%) when the evidence of how quality changes with quantity of innovation is excluded. When the available evidence on quality effects is included, the optimal share would be lower (11%: 6%–29%). The corresponding maximum shares are 31% (19%–60%) when quality effects are excluded and (17%: 9%–40%) when quality effects are included.

5 | PAYMENT, APPROVAL NORMS AND APPLICATION TO NICE APPRAISALS

The optimal overall payment (p^{*}) to manufacturers is the optimal share of the static health benefit expressed as the additional healthcare resources that would be required to generate the same health benefits ($p^{*} = s^{*}.k.T_b$). Once established, this payment could be delivered in a number of ways: most obviously via the transaction price paid during IPP (e.g., by modulating the approval norms applied by HTA bodies). Equivalently the length of IPP could in principle be modulated at a fixed approval norm, or commitments to lower post IPP prices could be secured. Subscription models are another possible mechanism, where limiting early widespread use may be important (e.g., new antimicrobials) (Rothery et al., 2018).

In this section we show how, once the optimal payment level has been identified, this can be translated to a specific pricing policy. For illustration, we show how an optimal approval norm can be determined assuming that other aspects of policy (e.g., IPP, and generics/biosimilar policies) remain constant. Importantly this is only one, and not necessarily the best, way to deliver the payments required for dynamic efficiency. Nonetheless, we choose to illustrate the implications for this particular mechanism of payment as the question of appropriate approval norms has been widely discussed in the HTA literature (Brouwer, van Baal, van Exel, & Versteegh, 2019; McCabe et al., 2008; Wouterse, van Baal, Versteegh, & Brouwer, 2023).

HTA bodies such as NICE commonly compare the incremental cost-effectiveness ratio (ICER) of a new product to some approval norm (λ) or 'threshold', which represents their maximum acceptable ICER, and this regulates manufacturers' price setting or offers of confidential discounts. We refer to the actual price paid by the health system, reflecting any discounts and

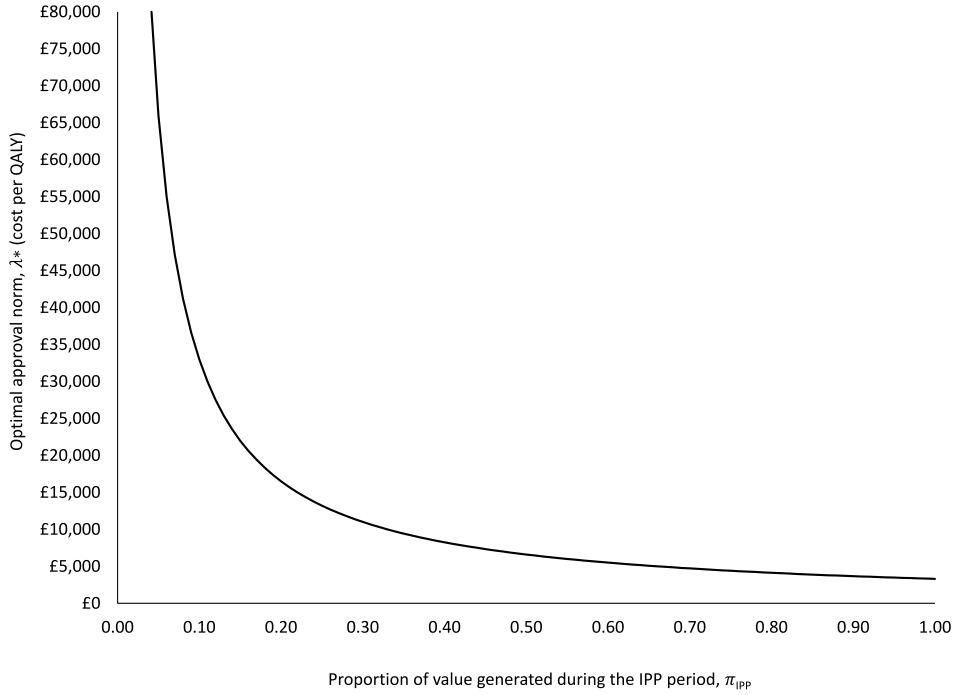

FIGURE 3 Relationship between optimal approval norm and proportion of value generated during IPP. Optimal share, $s^* = 0.22$; other parameter values as per Figure 1.

rebates as the transaction price. Manufacturers will potentially only receive this transaction price for their product during the period of IPP.[6] Assuming no changes in IPP, even for products with the same benefits (T_b) and therefore overall payment level (p^*), the 'optimal' approval norm (λ^*) will differ based on the proportion of value that is generated during the IPP period (as well as for different manufacturing and non-product costs).

Calculation of the optimal approval norm requires estimation of the per patient incremental costs associated with the optimal payment $\left(\frac{\mathrm{p}^*}{N_{\mathrm{IPP}}} + \Delta\mathrm{npc} + \Delta\mathrm{mc}\right)$ where N_{IPP} is the net present value of the number of individuals treated with the new product within the IPP period.[7] It also requires calculation of per patient benefits in health (QALY) terms $\left(\Delta h = \frac{T_b}{N} + \frac{\Delta\mathrm{npc}}{k} + \frac{\Delta\mathrm{mc}}{k}\right)$ where N is the net present value of the number of individuals treated with the new product in the IPP and post–IPP periods and is calculated as in Equation (1) as $\sum_{t=1}^{\infty} \frac{n_t}{(1+r)^t}$. The ratio of per patient incremental costs associated with the optimal payment to per patient incremental QALYs gives the optimal approval norm:

$$\lambda^* = \frac{\frac{\mathrm{p}^*}{N_{\mathrm{IPP}}} + \Delta\mathrm{npc} + \Delta\mathrm{mc}}{\frac{T_b}{N} + \frac{\Delta\mathrm{npc}}{k} + \frac{\Delta\mathrm{mc}}{k}} \tag{7}$$

If additional manufacturing and non-product costs are zero then this simplifies to:

$$\lambda^* = \frac{\frac{\mathrm{p}^*}{N_{\mathrm{IPP}}}}{\frac{T_b}{N}} = \frac{\mathrm{p}^*}{\pi_{\mathrm{IPP}}.T_b} = \frac{s^*k}{\pi_{\mathrm{IPP}}} \tag{8}$$

where π_{IPP} is the proportion of value that is generated during the IPP period.[8] Although this proportion does not affect the overall payment during the IPP period, it does influence the payment at the patient level and the approval norm which would need to be applied. For example, a lower proportion of value generated during the IPP period, means that the optimal payment must be "loaded" on to fewer patients (Figure 3), and this would require a higher optimal approval norm.

The optimal approval norm may be more or less than k, depending upon the proportion of value that is generated during IPP. For example, if the proportion of value generated within IPP was relatively low (e.g., 10%), as might be observed for an antimicrobial which is held in reserve to treat emergent resistant infections, then the approval norm would be £33,000/QALY $\left(\lambda^* = \frac{s^*k}{\pi_{\mathrm{IPP}}} = \frac{0.22*15{,}000}{0.10}\right)$. If the proportion of value generated within IPP was relatively high (e.g., 60%), as might be observed in a chronic condition with high prevalence and low incidence, then the optimal approval norm would be £5500/QALY. If a

TABLE 1 Optimal price premium and approval norms for a sample of NICE technology appraisals.

	Current policy			Optimal analysis				
Product (ordered by ICER)	ICER (£ per QALY) for the IPP period	Implied price premium[a] (£)	Estimated share of value to manufacturer	Share to manufacturer	Optimal implied price premium[a] (£)	Optimal approval norm (£ per QALY)	Optimal implied price premium with commitment to generics policy[a,b] (£)	Optimal approval norm with commitment to generics policy[b] (£ per QALY)
Nalmefene	1110	322	9%	22%	784	7910	1036	10,521
Vortioxetine	2970	49	7%	22%	157	9234	198	11,657
Rivaroxaban	5622	309	6%	22%	1136	12,519	1689	16,378
Thalidomide	9174	10,862	19%	22%	12,565	10,570	16,590	13,801
Adalimumab	19,328	26,725	114%	22%	5143	−3,632[c]	8090	−2,586[c]
Vedolizumab	21,620	2328	144%	22%	357	10,671	698	9207
Enzalutamide (pre-chemotherapy)	32,985	27,590	79%	22%	7687	−6820[c]	8955	−4,550[c]
Pembrolizumab (NSCLC)	44,490	22,756	260%	22%	1928	10,120	3500	12,039
Cabazitaxel	45,159	10,703	118%	22%	1993	8407	2403	10,137
Enzalutamide (post-chemotherapy)	45,626	11,022	168%	22%	1442	8782	1685	9471
Pembrolizumab (melanoma)	46,662	36,953	243%	22%	3347	8902	5800	10,815
Olaparib	46,973	34,883	148%	22%	5181	9845	6339	11,099

Abbreviations: ICER, incremental cost-effectiveness ratio; IPP, intellectual property protection; QALY, quality-adjusted life year.

[a]Price premium is the additional price paid by the health system above and beyond the existing comparator, net of additional manufacturing costs.

[b]Generics policy involves immediate availability and full uptake of generic/biosimilar products at patent expiry alongside a price reduction of 25% from current levels.

[c]Negative approval norm arises due to substantial cost savings. Only 22% of the value generated by the cost savings is retained by the manufacturer so the numerator in Equation (7) is negative.

new product is expected to be associated with additional manufacturing or non-product related costs, or offers savings in these costs, then this will modify the optimal approval norm, and may even result in a negative approval norm.[9]

An appropriate measure of health opportunity cost, k, should be used when calculating the optimal payment level ($p^* = s^*.k.T_b$) to ensure the optimal payment level (and associated optimal approval norm, derived using Equation (7)) delivers the desired optimal share of value to the manufacturer. Suppose instead, for illustration, that the long-term health benefit ($T_b = 100$) was multiplied by a consumption value of health based on evidence of individual willingness to pay ($v = £70{,}000$)[10] and that 22% of this was given to the manufacturer. This payment would be 4.67 times higher, at £1,540,000. The resulting health foregone from this payment would be determined by k (and not v), and would be 103 QALYs $\left(\frac{£1{,}540{,}000}{£15{,}000 \text{ per QALY}}\right)$. In this case, the share of value to the manufacturer is 103% rather than 22%. Reimbursement of the product at this payment level would result in net health losses of 3 QALYs. This static loss would also apply to the dynamic effects because future innovations, which also attract this share of value, will also impose net health losses. This would deliver fewer health benefits than if a zero share was assigned, dynamic benefits were foregone and only static benefits accrued. Such a pricing policy would also deliver fewer health benefits than if the product had not been offered to the health care system at all. In general, if the measure of health opportunity cost, k, is less than the consumption value of health, v, then using v to calculate payment will reduce health outcomes overall, and this loss will be larger at higher values of the innovation elasticity.

A recent analysis estimated the share of value given to the manufacturer for a sample of 12 NICE technology appraisals (Woods et al., 2021). The share of value given to the manufacturer varied between 6% and 260% (Table 1). This share is determined by current levels of IPP, the functioning of the generics and biosimilars market and regulatory and reimbursement processes. The strongest driver of differences in share for this sample of appraisals is the ICER associated with using the product within the period of IPP. In general, manufacturers are incentivised to set a transaction price such that the ICER equals the approval norm (i.e., £20,000-30,000/QALY for products appraised by NICE, with a higher norm of £50,000/QALY applied for products that are considered to be life-extending end-of-life treatments[11]), though other factors such as local price sensitivity and uniform pricing across indications may also influence the revenue-maximising price and, therefore, the ICER.

Based on the results in this paper, it is possible to estimate the optimal approval norm for each product. As discussed above, this will differ based on the proportion of value generated during IPP and the scale of manufacturing and non-product costs. This reanalysis suggests that, in most cases, under current approval norms, the share of value offered to manufacturers and the price premium paid by the NHS was higher than would have been optimal (Table 1), in many cases leaving the NHS with negative long-term value. If modulation of an approval norm is the only policy tool available then achieving the optimal payment level requires an approval norm that varies from product to product. This indicates that the application of a single approval norm is unlikely to deliver overall dynamic efficiency or incentivise innovation appropriately across indications. These analyses reflect the evidence-based estimates of entry, use and pricing of generic medicines used by Woods et al. (2021) We also present the optimal price premium if commitments could have been made to ensure generic entry at the point of IPP expiry, no use of the originator brand beyond this point and that generic prices reflect manufacturing costs. The optimal price premium with credible commitments of this type in place is between 16% and 96% higher than under more realistic empirically based assumptions.

This sample of appraisals was also reanalysed to assess the scale of net health effects under current and optimal payment levels. Across the products considered, manufacturers currently accrue approximately 50% of value. If we consider this share of value to provide a signal of expected reward for all product types (i.e., observed variation in shares across products is random) then we can compare the static and dynamic benefits expected to arise from the current share of value, to those we would expect under optimal payment levels. Moving from current to optimal payment levels for this set of products would create static and dynamic benefits of 146,297 QALYs, a 24% increase in net health benefits from the status quo (calculations shown in online Supplementary Excel File, Supporting Information S2).

Alternatively, the observed *variation* in shares across products may be interpreted as a long-term signal of how share will vary across products in the future. If this is the case then R&D is expected to focus on those product types allocated a higher share, which will therefore accrue higher dynamic benefits (T_d). The dynamic *net* benefits expected to arise from current payment levels will be lower in this context as there will be both static and dynamic losses from those types of products where reward exceeds long-term value (i.e., the value share exceeds 100%). Under this scenario moving from current to optimal payment levels for this set of products would create static and dynamic benefits of 445,074 QALYs (a 144% increase from the status quo).

6 | OTHER ASPECTS OF VALUE

Static benefit (T_b) does not need to be expressed as health or include heath as the only welfare argument. For example, the static and dynamic benefits and costs could be expressed as consumption based on a consumption value of health (v) chosen to reflect the social welfare effects or individual willingness to pay. Irrespective of the value chosen, the only effect is to rescale the Y axis of Figure 1. The optimal share of value, now expressed as consumption rather than health, and the payment of health care resources required to deliver it, are unchanged.

There may be indirect effects of innovations on wider social benefits beyond health, and on other socially valuable attributes of health not captured by currently used measures of health (e.g., QALYs). For example, there may be preferences about how health effects are distributed by current health status, income or other characteristics. Reflecting these considerations does change how T_b is measured, but does not necessarily change what share of this value should be offered to manufacturers. Whether or not such considerations increase or reduce the appropriate payment level depends on: (i) the range of attributes offered by a new pharmaceutical product; (ii) the relative weights assigned to these attributes; (iii) the marginal productivity of health care expenditure in providing them and (iv) how this modified definition of dynamic benefit responds to payment.

Rather than focusing on a public health objective, or one modified by other attributes of value (but still focused on consumer surplus), an alternative objective could be to maximise the sum of consumer and producer surplus. Assessing the implications of different payment levels for net benefit in welfare terms requires two additional assessments; an assessment of the proportion of the payment to the manufacturer that is retained as producer surplus, and, an assessment of the marginal value of health care funds (which weights health expenditure relative to private super normal profits). The extent of any producer surplus that might be retained after the costs of research and development, commercialisation, competition for temporary monopoly rights, and the effects of competitive capital flows are accounted for, is not clear.[12] For drugs already developed the research and development costs are sunk, so a greater share of payment made for static benefits might be reasonably expected to be retained as producer surplus (manufacturing costs are already accounted for in the calculation of T_b). However, the payment for dynamic benefits cannot be regarded as producer surplus as the research, development and other costs for these subsequent innovations (and all other related products that failed to reach the market to achieve these successes) have not been accounted for. Therefore,

interpreting the payments made, net of manufacturing costs, as producer surplus would be a form of double counting by counting the benefits of innovation without subtracting the costs of achieving it, that is, treating the costs as if they were a benefit too.

Consumer surplus (CS), producer surplus (PS) and net benefit in welfare terms (NB(W)) can be expressed as:

$$\mathrm{CS} = \upsilon.(1-s).(T_b + T_d) \tag{9}$$

$$\mathrm{PS} = \phi_b.s.k.T_b + \phi_d.s.k.T_d \tag{10}$$

$$\mathrm{NB}(W) = \mathrm{CS} + \mathrm{PS} \tag{11}$$

where ϕ_b and ϕ_d refer to the proportion of payment for static and dynamic benefit that is retained as producer surplus. Equations (9)–(11) indicate that welfare, and the optimal share, will also depend on the value of health care resources (k) relative to private consumption (υ). Theoretical considerations and empirical evidence suggests that the marginal cost of (raising) public funds (MCPF) is likely to be greater than one (Claxton et al., 2019; Dahlby, 2008; Ruggeri, 1999) and therefore the marginal value of public funds (MVPF) is also likely to be >1 (Finkelstein & Hendren, 2020). Conditional on the welfare function used to estimate MCPF and MVPF, public funds are expected to be raised and those resources allocated such that MVPF = MCPF>1. This applies to health care resources, whether they are publicly or privately financed. Again for good theoretical and empirical reasons one would expect health care resources to be more valuable than private consumption so the marginal value of health care funds $\left(\frac{\upsilon}{k}\right)$ is likely to be greater than 1, because the marginal costs of health care funds will be greater than 1[13] (Claxton et al., 2019). As a consequence, any payment that is retained as producer surplus is less valuable than the equivalent amount of health care resources because it is a transfer of resources from within the health care system to private consumption. The marginal cost of health care funds is expected to exceed 1 due to several distortions including the welfare losses associated with raising funds for health care. In the context of a collectively funded health care system, welfare losses result from socially acceptable forms of taxation and social insurance. In a private insurance system, welfare losses occur due to market failures resulting from asymmetric information, moral hazard and imperfect agency (Arrow, 1963). In addition, in a democratic system, the marginal value of health care funds may exceed 1 if funds are obtained (and regulations devised) on the basis of median preferences over health and consumption, as opposed to mean preferences, due to the skewed distribution of individuals' consumption value of health (Phelps, 2019). Empirical evidence from the UK[14] and US[15] suggests a marginal value of health care funds of 4.67 $\left(\frac{\upsilon}{k} = \frac{£70{,}000}{£15{,}000}\right)$ and 2.5 $\left(\frac{\upsilon}{k} = \frac{\$250{,}000}{\$100{,}000}\right)$ respectively. As a consequence, including consideration of any producer surplus that might be retained has a modest impact on the optimal share of value. For example, assuming that all payment associated with static benefit, and 20% of the payment associated with dynamic benefit, is retained as producer surplus ($\phi_b = 1$; $\phi_d = 0.2$) would increase the optimal share to 0.24 using UK evidence on the marginal value of health care funds $\left(\frac{\upsilon}{k} = 4.67\right)$. Using the US evidence $\left(\frac{\upsilon}{k} = 2.5\right)$ the optimal share increases to 0.27.

7 | DISCUSSION

This framework offers a coherent and evidence-based approach to designing pharmaceutical pricing policies and payment mechanisms to achieve dynamic efficiency. Based on the available evidence linking payment to innovation, the optimal share of the long-term value of new pharmaceutical products to offer to manufacturers is approximately 20% (range 6%–51%). Reanalysis of a sample of NICE technology appraisals suggests that, in most cases, the share of value offered to manufacturers and the price premium paid by the UK NHS were higher than would have been optimal and, in many cases, left the NHS with less than zero share of long-term value. These effects will be exacerbated if future R&D investment focuses on those areas where shares are highest. A payment and pricing policy based on evidence of how the quantity and quality of innovation responds to payment would offer considerable benefits under both a public health objective and a broader view of social welfare. While the most obvious application of these results would be through price regulation, either directly or indirectly through HTA processes (or both), the appropriate share of value could be delivered through a range of alternative payment models. These might include subscription models, commitments to limit IPP and sell branded medicines at lower prices beyond the IPP period, or through national rebate schemes at portfolio rather than product level, such as the UK voluntary scheme for branded medicines pricing and access.

These conclusions about the optimal share are not sensitive to assumptions about the relative scale of static and dynamic benefits; whether value is expressed in monetary terms based on willingness to pay or health terms; or inclusion of additional attributes of value including taking a broader social welfare perspective by including producer surplus. The optimal share is also insensitive to the marginal productivity of the health care system, though this does influence the appropriate payment level.

Our conclusions differ from previous studies. A number of authors have concluded that optimal rewards to manufacturer can be achieved by using an approval norm equal to the consumption value of health, at least within the remaining period of IPP (Danzon et al., 2015; Jena & Philipson, 2008; Lakdawalla, 2018; Lakdawalla & Sood, 2012; Vernon et al., 2009). The current study shows that there is no reason for this to be the case, and that an optimal approval norm will depend (primarily) on the responsiveness of innovation value to payment, the marginal productivity of the healthcare system (k) and the proportion of value generated during the period of IPP. Other studies have concluded that raising pharmaceutical payment levels through prices or IPP extensions are likely to improve consumer surplus (Council of Economic Advisers, 2019; Filson, 2012; Gigi et al., 2017; Goldman et al., 2011; Lakdawalla et al., 2008; Santerre & Vernon, 2006). These studies did not, however, consider the health opportunity costs associated with higher payments.

Our findings also appear to differ from the wider economics literature relating to the economics of innovation (Gilbert & Shapiro, 1990; Green & Scotchmer, 1995; Loury, 1979; Matutes et al., 1996; William D. Nordhaus, 1969a, 1969b; William D. Nordhaus, 1969a, 1969b; O'donoghue et al., 1998). This literature tends to take the perspective of the firm, with and without a temporary monopoly, deciding whether to invest in an innovation when facing an expected market demand curve signalled by the choices of fully informed individual consumers. Since the firm is unable to perfectly price discriminate, some consumer surplus is retained even at the temporary monopoly price but a dead weight loss is incurred. The optimal scale of IPP (length, breadth and width) attempts to balance these welfare benefits and costs, including the benefits associated with any producer surplus that might be retained. Importantly, in these circumstances extending IPP will increase deadweight loss but will never eliminate the benefits of innovation as some consumer surplus will always be retained. Therefore, this literature implies an optimal share below 1 rather than solving for the optimal share.

The context for health care, whether financed from collective public funds or private insurance, is quite different (Arrow, 1963). Consumers are not fully informed so rely on (imperfect) agents to signal their demand. Nor do they face the full marginal costs of their choices. For this reason we focus on the perspective of a social decision maker (with potential monopsony power) considering what level of payment to offer to firms. They seek to maximise welfare (whether defined as health, the consumption value of health or some more complete welfare function) but do not control the level of collective or private health care expenditure. They are, however, able to set pricing policy (choose s*), mindful of how firms are likely to respond to payment by observing their past behaviour (based on the econometric and other evidence discussed previously). Therefore, they fully account for potential dynamic benefits of their policy choice despite their monopsony power. The social decision maker or their agent (e.g., HTA bodies) is effectively able to perfectly price discriminate, because all those for whom access is expected to improve health ($T_b > 0$ or $T_d > 0$) can be granted access (as patients do not face their marginal cost at the point of access) at an average price that could eliminate the deadweight loss but could also offer all or more of long term value to the manufacturer (Claxton, 2007; Claxton et al., 2008). For this reason, we focus on solving for the optimal share of value to be offered to manufacturers taking the decisions of firms as being empirically reflected in the econometric and other evidence. Therefore, the wider literature attempts to solve for IPP and implies an optimal share below 1. Here we solve for the optimal share directly which means we can express the optimal payment required and examine pricing policies where the scale of IPP is either regarded as fixed or as a decision variable.

There are, however, other differences. For example, we account for the evidence that the marginal value of health care funds is greater than 1. We also examine different perspectives for the objectives of a social decision maker and by implication different definitions of welfare. We also apply the same consumption value of health to all health effects whether they are dynamic benefits or dynamic health costs. This appears a reasonable normative position in a collectively funded health care system (it is one of the reasons cited for collective funding). It may also be a reasonable positive assumption at the margin in a privately funded health care system, although it would also be plausible to assume that the individual willingness to pay for those displaced by higher insurance cost (the dynamic health cost) is lower than those that gain (the dynamic health benefit) (Phelps, 2019; Vanness et al., 2021). Whether or not this positive observation should be given normative significance for policy choice in health care is for others to judge (e.g., citizens in a social democracy).

We conducted a systematic review of studies reporting a plausible or robust causal effect of payment on innovation in order to understand the dynamic benefits associated with higher payment levels. Given the heterogeneity in innovation elasticities across the identified studies we present key results for a range of elasticities. Our central estimate does not include the limited evidence of a decline in quality, or assume an increase in manufacturing costs, as the quantity of innovation increases with payment. This reflected the paucity of evidence on both of these effects. This analysis is therefore likely to overestimate the responsiveness of innovation value to payment, and therefore overestimate the optimal share, as the theoretical and empirical literature supports a negative effect of payment on product novelty with higher payments tending to encourage "me-too" products with limited incremental value (Dranove et al., 2014, 2020; Adams, 2021; Blume-Kohout & Sood, 2013). Higher payments are also likely to encourage the development of medicines that are more expensive to produce.

The framework presented is necessarily a simplification of the complex process through which payment drives innovation and associated health and welfare effects. We have assumed that either a global multilateral policy for rewarding innovation is in place or that individual countries such as the UK, in acting unilaterally, take full account of the dynamic benefits that accrue to others outside their jurisdictions.[16] The optimal share would be substantially lower if only the domestic dynamic benefits are considered or are given greater weight, as is recommended in the UK central government guidance on appraisal and evaluation (HM Treasury, 2022). We also assume that the innovation elasticities reflect the effects of payment on innovation mediated solely through private investments in R&D, and do not reflect the effects of public sector R&D efforts. To the extent that public sector R&D was controlled for in the underlying empirical studies this may be a reasonable assumption. However, the optimal share should only be applied to the portion of static and dynamic benefits that are attributable to private investment. Therefore, insofar as public sector R&D contributes some portion of these benefits the optimal share of total static and dynamic benefits to assign to the manufacturer would be expected to be lower.

In line with the empirical literature on which this paper draws, we assume a constant elasticity relationship between payment and innovation value. We made this assumption in the absence of any basis to inform an alternative specification; however, application of a constant elasticity may not be appropriate for non-marginal changes in payment. In addition, we assume that those who could benefit from a new drug will have access to it. Where payment level influences price and the costs faced by patients, as may be the case in predominantly private insurance-based systems or where payment influences usage through other mechanisms, a higher share will imply a higher price and therefore lower access. Health opportunity cost will therefore rise more quickly with share as fewer individuals who stand to benefit from the intervention receive it. Accounting for these effects would, therefore, be expected to reduce the optimal share. There may also be heterogeneity in the responsiveness of innovation to payment across different types of product (Dubois et al., 2015; Myers & Pauly, 2019). If this could be robustly estimated, then it may be appropriate to offer different shares for products in different therapeutic areas.

This framework of analysis offers a coherent, evidence-based and feasible way to set payment levels to achieve dynamic efficiency. The most appropriate mechanism by which to deliver the optimal payment level is, however, likely to depend upon the mechanisms available to determine pricing and deliver payment levels within individual countries. As an illustration we show how optimal payment levels could be delivered for a set of NICE appraisals through the use of product-specific approval norms. Regardless of how payment is operationalised, the approach to estimating the optimal payment level has a number of informational requirements. An assessment of the value of the product is needed, which is not far removed from what is conventionally captured in cost-effectiveness analysis and relies on the same inputs, plus estimates of patient numbers over time (this is often calculated when estimating budget impact). It also requires an estimate of manufacturing cost and the expected behaviour of the medicines market beyond the IPP period, which can be estimated using a similar approach to Woods et al. (2021). Estimates of k are available for the NHS and are already required for impact assessment by the Department of Health and Social Care (Department of Health and Social Care, 2020), estimates for other countries are also available (Edney et al., 2022; Ochalek et al., 2018; Vanness et al., 2021). Plausible estimates of other parameters that are required, such as the value of innovation elasticity can be obtained from this paper.

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CONFLICT OF INTEREST STATEMENT

Beth Woods is a member of the York Health Economics Consortium Board of Directors, she receives no renumeration for this role. The authors report no other conflicts of interest in relation to this manuscript.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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ENDNOTES

[1] The term manufacturing costs is used to refer to the overall cost of producing and delivering an already developed product to the health system.

[2] This is consistent with the evidence of the elasticity of innovation with respect to payment as much of this empirical literature is based on long-term changes in the potential market, that is, this evidence of the responsiveness of innovation to payment relates to long-term commitments rather than temporary ones.

[3] This assumption of constant elasticity is consistent with the specifications used in estimating the innovation elasticity in much of the econometric literature as shown in Supporting Information S1: Tables 2 and 3 and references.

[4] This can be shown by substituting Equation (3) (and it's derivative with respect to share) into Equation (5):

$$\epsilon.\alpha.(k.T_b)^{\epsilon}.(1-s^*).s^{*\epsilon-1} - \alpha.(k.T_b)^{\epsilon}.s^{*\epsilon} - T_b = 0.$$

Substituting Equation (6) into the previous equation and simplifying:

$$\gamma.\epsilon.(1-s^*).s^{*\epsilon-1} - \gamma.s^{*\epsilon} - s^{0^{\epsilon}} = 0$$

Which demonstrates that $s^{*\epsilon}$ does not depend on T_b, T_d or k.

[5] Assessment of the marginal cost of producing a QALY to the NHS according to Department of Health and Social Care (Department of Health and Social Care, 2020).

[6] Prices well above manufacturing cost may persist beyond the period of IPP if generic versions of products are not developed or take time to enter the market, or if the use of branded products persists even when generic drugs enter the market (Woods et al., 2021).

[7] Which can be calculated as $\sum_{t=1}^{T=t_p} \frac{n_t}{(1+r)^t}$ where t_p denotes the duration of IPP.

[8] We assume per patient net health benefit is constant over time.

[9] When $\frac{s^*}{\pi_{IPP}}$ is less than 1, the optimal approval norm is higher in the presence of these costs whereas when $\frac{s^*}{\pi_{IPP}}$ exceeds 1, the optimal approval norm is lower in the presence of these costs. Cost savings will lower the optimal approval norm when $\frac{s^*}{\pi_{IPP}}$ is less than 1 and increase the optimal approval norm when $\frac{s^*}{\pi_{IPP}}$ exceeds 1. The optimal approval norm can be negative if the incremental cost associated with introducing a product is negative in the IPP period. This can occur if there are relatively large cost savings and $\frac{s^*}{\pi_{IPP}}$ is less than 1 so these cost savings are not fully passed on to the manufacturer. It can also occur if there are relatively large additional costs and $\frac{s^*}{\pi_{IPP}}$ exceeds 1, in this context a manufacturer would need to offer a price lower than current standard of care to offer value to the health system.

[10] This is the consumption value of health according to the UK Treasury's Green Book (HM Treasury, 2022).

[11] These are the approval norms applied by NICE at the time of these appraisals.

[12] There is a substantial literature on research and development costs ((DiMasi et al., 2016) However, these estimates tend to reflect the costs of the average, rather than the marginal product that is required for this analysis.

[13] Whether or not more resources should be allocated to health care when $v/k > 1$ depends on whether the observed empirical estimate of v/k is greater than the marginal cost of health care funding. Therefore, observing $v/k > 1$ does not necessarily imply that too little is being spent on health care. That requires a comparison of v/k with the marginal cost of health care funds, which is likely to differ under different types of health care finance, for example, collective financing through taxation or through private insurance.

[14] The consumption value of health according to the UK Treasury's Green Book is £70,000 per QALY (HM Treasury, 2022) and the marginal cost of producing a QALY to the NHS is £15,000 per QALY according to Department of Health and Social Care.

[15] The mean consumption value of health is estimated at $250,000 per QALY calculated using estimates of the ratio of willingness to pay for a QALY by income (21) alongside data on the US individual income distribution. The marginal cost of producing a QALY in the US healthcare context is estimated as $100,000 per QALY based on Vanness et al. (Vanness et al., 2021).

[16] This 'internalisation' of external effects would be equivalent to a multinational policy if the rest of the global market already offered the optimal share of value or if all internalised the external effects of their pricing policy.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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