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REVIEW ARTICLE

A Framework for Considering the Role of the Public Sector in R&D of Health Technology

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Abstract

The development of health technologies involves complex, costly, and risky investments, with significant contributions from both public and private sectors. Recent EU pharmaceutical directives propose transparency on public funding to aid pricing negotiations and affordability. However, questions remain regarding how public investments should be measured and their influence on pricing and reimbursement (P&R) decisions. In this paper, we characterise public sector institutions as "payers," "R&D investors," and "regulators". Through a myriad of agencies and decisions, these institutions directly, indirectly or sometime unexpectedly influence risk and return on private research and development (R&D) through P&R, direct investments, and regulatory policy. P&R decisions by payers for innovative therapies influence risk and expected return of future R&D. Value-based pricing offers a more reliable signal of payers' priorities than cost-plus or (international) reference pricing. For greatest impact, public R&D investment should be directed to areas where markets are deficient, such as basic science, translational research, real-world studies, and towards emerging fields like AI and gene editing that will play an increasing role in healthcare and drug development. Applied R&D should be conducted on a financially sustainable basis. Licensing arrangements can be used to recover those investments, while promoting spillover benefits to wider society. Market access regulators are aware of the need for scrupulous transparency and neutrality, but other public sector actors (payers and R&D investors) also must recognise their policies affect the level playing field.

Key Points

Through a myriad of entities, public-sector institutions directly, indirectly or sometimes unexpectedly influence risk and return on private research and development (R&D) through pricing and reimbursement decisions, direct investments, and regulatory incentives.

For greatest impact, public R&D support should be directed to areas where markets are deficient, such as basic science, translational research, real-world studies, and towards emerging fields like AI and gene editing.

Public applied R&D aimed at supporting development of specific therapies should be conducted on a financially sustainable basis, and consider recovering the investment by retaining intellectual property rights.

Value-based pricing offers a more reliable signal of payers' priorities than cost-plus or international reference pricing, and payers should be aware of the importance of maintaining a level playing field that encourages new entrants.

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1 Introduction

The development of new health technologies is a long, uncertain and costly process. Estimates vary but cost per approved medicine, including the costs of capital and of failures, could range from US$0.16 billion to US$4.54 billion [1, 2]. Total global investments in medicine research and development (R&D) from all sources were estimated to be US$300 billion in 2020 [2]. About 25% of this expenditure originates from public and philanthropic sources [3], and between 25% [4] and 50% [3] of new medicines approved are associated with public-sector institutions or spin-offs.

An argument raised is that the public sector pays twice for some health technologies, first when public institutions invest in R&D and again when public health services purchase the innovation [5]. The EU pharmaceutical directive proposal contains a requirement for marketing authorisation holders "to publish all direct financial support received from any public authority or publicly funded body for the R&D of the medicinal product, irrespective of the legal entity that received that support… More transparency on public funding received by pharmaceutical companies will support national authorities in price negotiations with these companies and help make new medicines more affordable" [6].

However, a series of questions arise. Guidance would be needed around what kind of direct public investments into medical R&D are relevant [3], and how they could be measured [7], and how they should be considered in pricing and reimbursement (P&R) decisions [8]. There are many actors involved in health technology R&D, and any attempt to recover the costs of public-sector R&D support through lower prices for a final product could have repercussions (expected or unexpected) on incentives for future private-sector investment. Alternative financing mechanisms for public-sector and non-profit R&D support are available, including licensing, royalties, crowdfunding, social bonds, etc. [9]. Likewise, the boundary between the "public" and "private" sectors is increasingly fluid in medical R&D, including public-private collaborations, academic spin-offs, and non-profit actors [3, 10].

Research and development R&D are two separate but related activities; research (the generation of knowledge about causes of diseases and potentially effective therapies) and development (the use of that knowledge to produce tangible technologies that improve the health of the population). The lifecycle of medical technologies can be characterised by distinct steps (Discovery, Development, Launch and Post-Launch Evidence) [11], recognising differences for medicines and for devices [12, 13] (Fig. 1).

The objectives, motivations and incentives faced by public-sector actors will vary. In this article we characterise these roles as "public-sector R&D investors and developers" (ministries, state R&D funding agencies and to some extent institutions such as universities and hospitals who engage in R&D), "regulator" (agencies who grant marketing authorisation, Health Technology Assessment (HTA) agencies who assess the benefit and 'value' of new medicines, and patent offices), and "payers" (various institutions who make P&R or purchase decisions about healthcare) [14]. The policies, decisions and incentives provided by these entities may not necessarily be directly concerned with the impact on future R&D and innovation. For example, a payer's primary objective may be to decide on the price of existing therapies based on results of clinical studies, cost-effectiveness analysis and/or budget impact ("static efficiency"). Nevertheless, these decisions influence the economic returns (expressed as expected net present value [eNPV]) of innovations and so will be scrutinised by potential developers and, collectively, will influence private R&D decisions ("dynamic efficiency") [15].

In this article, we aim to produce a theoretical framework to guide researchers and policy makers on the potential impact (expected or unexpected) of public-sector policies, decisions and incentives at distinct points on a product's life cycle on future R&D. For example, the draft EU legislation [6] suggests that transparency about public funding of R&D will help make new medicines "more affordable". This indirectly suggests that companies that have benefited from public-sector R&D investments should charge lower prices to health system payers, presumably compared with a hypothetical similar product that did not receive public support for R&D, and that regulators can help realise this outcome by requiring transparency about these financial flows. Health service payers in some countries, such as Italy and France, already require companies to declare any public R&D funding received [7, 16], although there is little evidence available assessing the impact of these policies or how they impact pricing decisions [3]. This article should help explain how public policies such as those (and others) might bring about expected or unexpected outcomes (Fig. 1).

This work aims to identify the main theoretical approaches that have been used to explain the role of the public sector in medical R&D, either directly or in shaping the actions of private actors. A literature review was conducted, followed by a series of consultations by videoconference, email exchange, and feedback on early drafts with leaders from academic, policymaking, health technology assessment and medicine discovery fields (see Acknowledgements).

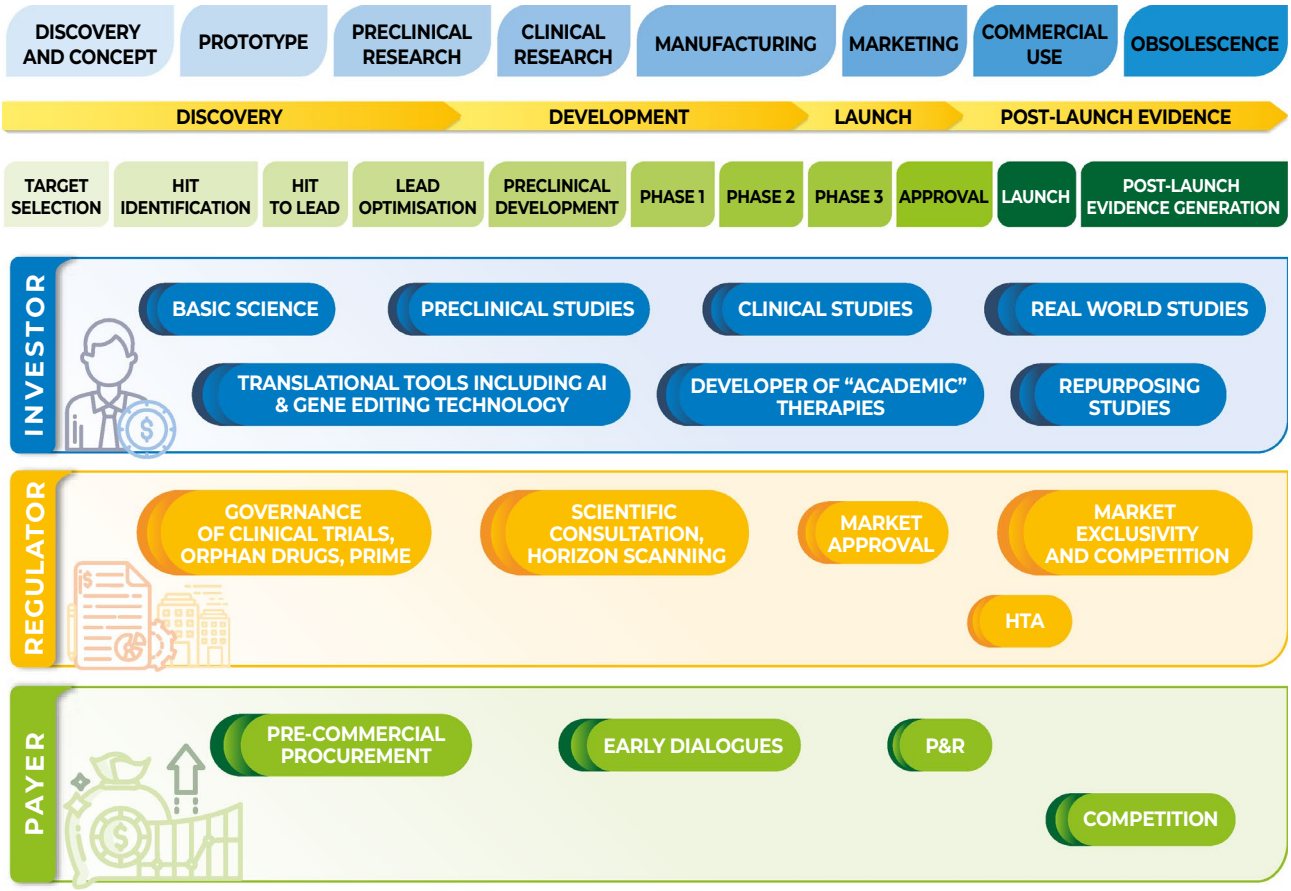

Fig. 1 Research, development and evidence generation over the lifecycle of a medical device (blue) or medicine (green), alongside the potential roles of the public sector as payer, regulator or investor at distinct stages. Source: Produced by authors, based on their interpretation of the literature P&R pricing and reimbursement. *HTA* Health Technology Assessment, *P&R* pricing & reimbursement, *PRIME* priority medicines, *R&D* research and development

2 Literature Search Strategy

As the academic literature is large and diverse, a targeted approach was used. Papers describing theoretical approaches were searched for in each of these categories: (1) The idea that scientific knowledge is a global public good, and the free-rider problem; (2) Approaches that explain the motivations of public-sector investors, regulators or payers (principal-agent theory and public choice theory); (3) Models for regulation of prices (static and dynamic efficiency, value-based pricing, cost-plus pricing, external reference pricing, capturing appropriate share of value); (4) Models used by investors to measure costs and returns to R&D (risk adjusted net present value, public-sector contribution to R&D, and measures of the efficiency of R&D effort); (5) Models for optimal market regulation (market access regulation, intellectual property, competition policy, and the Entrepreneurial State) (see Supplementary Material for methods and included items).

3 Theoretical Approaches to Explain the Role of the Public Sector in Medical R&D

3.1 Knowledge as a Global Public Good

Knowledge is "non-rival" (able to be used by everyone simultaneously) and so open access to the results of science confers positive externalities (any firm can develop innovations based on those findings, promoting advancement of science and technology generally, possibly in unexpected ways) and spillovers (strengthening the industrial base, human capital, etc.) [17, 18]. However, if a firm tries to make these results exclusive (blocking or monetising publication), then the externality value is lost. On the other hand, if the knowledge is non-exclusive (freely accessible to everyone), there is a "free rider" problem, meaning there are few incentives to conduct the research if the entity cannot benefit from the rewards.

3.1.1 Basic Science

Basic research in the life sciences discovers the processes that underlie living organisms and provides the scientific basis for subsequent phases [19]. In pharmaceutical fields, in general only a few compounds progress to the preclinical stage (often lasting 2–3 years) during which the best molecules are selected using various experiments (hit to lead, optimisation, pharmacokinetic studies, toxicity testing, efficacy testing) [20]. In parallel, the firm will develop manufacturing at scale and quality control. Once a candidate molecule is selected, the first clinical studies can start in humans to assess safety, dosing, efficacy and relative efficacy, with the aim of generating the evidence base to present to regulatory bodies (focusing on quality, safety and efficacy) and HTA bodies (focusing on additional clinical benefit and other non-clinical domains to support price and reimbursement decisions).

The classic argument for public-sector support in the basic life sciences focuses on Stiglitz's insight of the potential for knowledge to generate positive externalities and spillover benefits, for example, to spur unexpected new lines of enquiry, or to reduce financial and scientific risk for other actors to undertake further work [17, 21]. However, the value of basic science is unpredictable and may not become apparent for some time. Many scientific discoveries are by chance, but R&D successes do not occur purely at random. Scientists can only learn from the work of others if they have access to this material. Open access promotes validation, reproducibility, transferability, and good governance. Publication of both positive and negative results allows others to build on success and rule out unpromising lines of inquiry [22]. The public sector can also support science by allowing or encouraging open access to anonymised healthcare data for secondary (research) purposes [23, 24]. Furthermore, spillovers arise when R&D benefits other sectors of the economy, such as enhancing productivity or strengthening the education sector. The R&D spillovers are thought to be enhanced by interdisciplinary network and cluster effects [19, 25].

Private actors often have weak incentives to conduct basic science. Patent intellectual property (IP) is not generally granted for discoveries of laws of nature or molecules found "raw" in nature [26]. Even where the IP from a basic science project can be registered, there is a low probability that this investment would eventually result in a tangible commercial product, let alone a positive return for the investor. Basic science is most likely to generate positive externalities and spillovers when the knowledge is a non-exclusive and non-rival public good [18]. Hence, the classic model is for governments to fund basic science, with no conditions (such as fair price clauses, royalties and so on) placed on the use of the knowledge it generates. Such conditions or monetary barriers could end up blocking dissemination of that knowledge, or disincentivising other researchers from using those results and hence stifling the realisation of these benefits. Notwithstanding, there are some open science models of R&D with extensive private sector participation such as campus models and consortium models that promote sharing of results among subscribers while protecting against free-riders [19, 27].

3.1.2 Development of Science, Technology, Engineering and Mathematics Applications

Advances in AI, image recognition, genome sequencing, gene editing, materials science and other science, technology, engineering and mathematics (STEM) areas are generating technologies that are not in themselves a specific medical therapy but are increasingly instrumental in life sciences [19]. Given the large expected spillover on medical R&D, the impact of such instrumental technologies would be maximised if they were made open source, affordably priced and non-exclusive [28]. The challenge for the public interest is to reconcile these two apparently conflicting objectives: to ensure appropriate investment in developing new technology of this kind, and at the same time ensure that the technology is affordable and widely available to stimulate other researchers to use it to develop new healthcare therapies (see case study: CRISPR).

3.1.3 Case Study: CRISPR

CRISPR (a gene editing tool) has been finding applications in development of cell and gene therapies and diagnostic tools, as well as other fields such as agriculture and bioenergy. CRISPR was developed in 2012 by researchers at Massachusetts Institute of Technology (MIT) and was spun off with private investor funding. The CRISPR example highlights that bodies that supposedly have an overarching non-profit educational and public-knowledge mission (such as universities) also may have commercial motivations that can undermine the public-interest mission, especially if they need to find additional sources of income. The MIT university sold exclusives to develop CRISPR therapies to the start-up founded by their own researchers. This exclusivity, along with ferocious patent disputes and an unclear licensing situation, has made access to this technology difficult for small and medium enterprises [29].

Spin-offs from academia need external (usually private) investment to grow and continue R&D (Table 2). These investors expect a return that corresponds to the risk they take, with the academic partner providing the underlying science and ensuring that the collaboration retains some strategic public-interest mission, and the private sector providing

growth capital, translational science, experience of regulatory issues or commercial acumen.

It would seem then that technologies such as CRISPR require a particular technology transfer model to realise their potential for spillover benefits. The case for public-private partnerships or social enterprise that combine the best attributes of public and private enterprise is particularly strong in these areas (the "collaborative approach" described in Table 2). This kind of conditionality or reciprocity suggests an "entrepreneurial" public-sector R&D policy/strategy, along the lines proposed by Mazzucato [30].

3.1.4 Development of "Publicly Owned" Therapies

Some public hospitals, in specialist fields such as advanced therapy medicinal products (ATMPs), are acting as a developers. Hospitals in the EU can develop custom-made therapies for named patients where no other option is available under special "hospital exemption" regulations. Some hospitals are taking this a step further and seeking centralised marketing authorisation, for example, ARI-0001, a gene therapy developed in a Spanish public hospital [31, 32]. The stated justification for the public sector taking a leading role or co-owner as a potential marketing authorisation holder for ATMPs is two-fold: to provide a therapy for populations where there are no or few other options [33], and at a price lower to the NHS than a for-profit developer would charge [32]. Nevertheless, there are counter-arguments. The argument that the publicly owned therapy will be provided "at cost" begs the question of how this cost has been calculated. For example, the methodology published by the Spanish Ministry of Health supposes that cost comprises the direct marginal cost of manufacturing the medicine, plus a percentage mark-up of between 1% and 5% for "incentives" [34]. It does not mention the R&D cost incurred, nor a compensation for the risk of R&D failures (sunk costs), nor a compensation for the cost of capital. Each of these elements contribute to the opportunity cost, and would be required in the price of a private-sector commercial product. A price of a therapy that does not include those elements assumes that capital is free, and only acknowledges the upside benefits of successful R&D but not the downside risks of failures (see Sect. 3.2, on the motivations of actors, and Sect. 3.4, on the cost and returns to R&D). A developer that commercialises a medicine at a price that excludes elements of full economic cost could be undercutting fair competition [35]. The government is also regulator of the market, and as such, has a duty to enforce a level playing field. There is a concern that the imperatives of the public-sector payer to pay low prices, working together with a public-sector developer keen to invest in new therapies, could conflict with the market regulatory role of the public sector (see Sect. 3.5, on the role of the public sector as a regulator) (Table 1).

3.1.5 Translational Studies

Incentives for private sector investors are weakest in the "translation gap" from basic science to preclinical phases [10] (Fig. 3). For non-orphan medicines, risk-adjusted eNPV is negative at these stages [10]. Hence, private sector investment in these very early stages, if undertaken at all, tends to be financed by investors with a high appetite for risk, variously termed seed capital investors, angel investors, venture capital and so on. Within "translational" technological transfer models (Table 1), risk-seeking early investors often aim to take a discovery to the preclinical stage and sell the IP to mainstream corporations (merger and acquisition, M&A).

The private venture capital industry is a very specialised sector, and there are likely to be many promising emerging technologies that do not get this kind of support. Moreover, venture capitalists will expect a high and rapid rate of return to compensate the high risk, which, alongside the substantial legal fees and commissions involved in M&A, filter through into higher prices. Hence there may be here an economic justification for public-sector or non-profit support for promising technologies to help bridge this "translational gap".

Although research at this stage has a low probability of commercial success (Table 2), it is conceptually and qualitatively distinct from basic science. Translational research is applied science, meaning that it is oriented towards producing a specific therapeutic product that has a readily available or creatable market. In the case that these data have a potential commercial value, companies have an incentive to invest, although they will be aiming to keep the IP exclusive. This suggests that the public sector should only consider investing scarce research capital in translational research (and later applied stages) if there is a clear public interest that cannot be met by the market.

3.1.6 Real-World Studies and Repurposing Studies

Even after a product obtains market approval, further studies on the use of the therapy in the real-world setting may have value to practitioners and health systems (in addition to the usual pharmacovigilance). Doctors may be able to optimise the duration or dose of therapy, identify the most effective subgroups, or mitigate environmental damage from residues. However, the marketing authorisation holder has weak economic incentives to voluntarily conduct post-marketing studies that would lead to lower revenues (for example, that might occur if a study showed a lower dose is as safe and effective as a higher dose and price depends positively on strength). Repositioning or repurposing is the use of existing medicines in new indications after expiry of intellectual property rights (IPR) [36]. Likewise, there can be few incentives for either the originator brand or generic manufacturers to conduct the necessary clinical studies to

Table 1 Seven possible archetypes of potential development routes to launch

Model	No.	Actors	Source of asset	Stage
Do it alone	1	Big biopharma in-house	Asset: discover internally lead compounds, including repositioning of medicines	From internal R&D to launch
	2	Biotech/SMEs	May discover asset, may be a big-biopharma carve-out, repurposed medicine, or an academic/PRG discovery	From internal R&D to launch
Translational	3	In-licensing or acquisition of assets	Transfer of asset ownership during R&D via asset in-licensing or acquisition of assets Various asset origins are possible in this route	Most in licensing deals happen earlier in the process than company M&A, i.e., in medicine discovery or the preclinical-development phase
	4	Company mergers and acquisitions (M&A)	Asset ownership is transferred to big biopharma during the R&D process via company M&A The acquired company may, for example, be a big-biopharma carve-out or an academic/PRG spin-out	Most M&A occurs at the preclinical development phase and in phase 2
Collaborative	5	Industry-industry collaboration	All asset origins are possible Share product development responsibilities and costs with another industry player to access capabilities and reduce the development-cost burden on the originator	From internal R&D to launch
	6	Industry-academic collaboration	The asset originates from an academic medicine discovery or spinout in this route	While early medicine-development stages may be pursued internally by academic institutions, capital requirements often necessitate the involvement of an industry collaborator
	7	Industry-PRG/not-for-profit collaboration	The asset originates from a PRG discovery or PRG spin-out in this type of collaboration	Like academic institutions, the PRG typically needs an industry partner for later-stage development

The table illustrates seven possible ways that a new discovery might be brought to market

Source: Kalindjian et al. [10]

M&A merger and acquisitions, *PRG* public research groups, *R&D* research and development, *SMEs* small and medium-sized enterprises

Table 2 Risk of failure, out-of-pocket costs and capitalised costs along the life cycle

	Target to hit identification	Hit to lead	lead optimisation	Preclinical	Phase 1	Phase 2	Phase 3	Approval	Cumulative total
Phase success PoS	80%	75%	85%	69%	63%	31%	58%	85%	
Cumulative PoS to launch	3%	4%	6%	7%	10%	15%	49%	85%	
Attempts per launch	29.5	23.6	17.7	15.1	10.4	6.5	2	1.2	
Cost per attempt	1	3	12	6	20–40	40–60	150–210	49	Out-of-pocket $1235–1695 m
Total phase cost per approved medicine (2020 USD m)	30	71	213	90	208–415	202–393	304–426	58	
Years (timing)	1	1.5	2	1	1.5	2.5	3	1.5	
Cost of capital	10%								Total capitalised $2370–3160 m

The table shows (for illustrative purposes) a method for calculating the risk-adjusted total capitalised cost per approved medicine, including out-of-pocket cashflows, cost of capital and costs of failures. Illustrative conversion rate: $1 = 0.866 euros (xt.com 14/5/2025)

Source: Kalindjian et al. [10]

PoS probability of success

obtain market approval for the potential new indication after loss of market exclusivity. There may be an a priori justification for public-sector or non-profit investment to conduct real-world and repurposing studies, whose results may lead to cost savings and/or benefits to patients.

3.2 The Motivation of Public-Sector Actors

The public sector, even within a single country, is not monolithic but acts through multiple entities with different objectives, degrees of independence and sources of finance (Fig. 1). Public Choice theory suggests that the actions of all actors, public and private, are shaped by the institutional context and incentives, and its institutions can be captured by special interests [37, 38]. The State is unlike other bodies, in that it requires citizens to be members, and imposes obligations (such as paying taxes and/or obeying regulations) on private individuals and businesses. Hence, checks and balances are essential to ensure that government actions do not favour public-sector or private-sector special interests without good reason [39].

Public investment in R&D is likely to have the greatest potential societal impact when it addresses a clear market failure or can springboard private-sector investment [40]. The ex ante justification for public-sector engagement might be weaker where the aim of the R&D is to commercialise a specific therapy (for example, phase 2 or 3 studies, Fig. 1). Recognition should be made of the possible trade-offs or unintended consequences of this action. Public-sector applied research may compete with the private sector, and State Aid should not result in unfair competition, or crowd-out private sector incentives. Because the State has the power to meet debt obligations by increasing taxation, the cost of borrowing for the public sector is usually lower than for commercial companies, but this does not mean the public sector is better placed to take on high risk R&D [14, 41]. The cost of capital should recognise that public funds invested in R&D might displace expenditure in other public services or require higher taxes.

Hence, an important element of governance in public R&D is to carefully justify, ex ante, the expected societal benefits and opportunity costs, and take steps to mitigate the risks and unintended consequences. If the public sector chooses to engage in applied R&D, this activity should be justified, financially sustainable and transparent. Research and development is inherently risky, and failures are inevitable and costly. This suggests public applied R&D should not be ad hoc ("individual project by project"), but conducted as part of coherent strategy. These considerations may justify public-private collaboration [42, 43]. The partner might offer commercial management expertise such as setting achievable objectives, capital and tools to measure and manage the risks. The entity should enjoy the legal autonomy to own IPR, use the IPR to generate revenues, to retain and reinvest financial surpluses, be able to reward success and learn from failures, and be subject to accounting rules that require prices fully reflect all the opportunity costs, including the costs of capital and the costs of R&D failures.

Nevertheless, the entity or collaboration should have a public interest mission, rather than profit-maximising. In the case of a STEM technology such as gene editing tools, it seems in the societal interest that such a collaboration sells

non-exclusive rights to use the technology to any interested third party at an affordable price. This would allow access to this technology by small and medium-sized enterprises, who are the type of actors who would be most adept at seeking out multiple ways of exploiting it to produce innovations that could benefit patients. An unconditional spin-off or acquisition of the technology by a large corporation is more likely to result in exclusivity, limiting the potential benefits. The CRISPR example (Sect. 3.1.3) illustrates that it cannot be assumed that academic and public research groups automatically adhere to a public-interest mission. It is not clear how such institutions could be persuaded, incentivised or obliged to take a "benevolent" societal perspective [38]. There is a case for reconsidering how academic spin-offs should be governed and capitalised. Crowd funding or social bonds may offer potential mechanisms (Fig. 2).

3.3 Models for Regulation of Prices

For new medicines and health technologies, payers often use HTA to evaluate the evidence and guide P&R decisions. Essentially, payers are aiming to establish whether the technology offers positive "net benefit" or value for the health service, and so should be adopted at the price offered by the manufacturer [44]. However, there is no clear consensus about how this value should be defined, measured [45], and ultimately shared between the payer and the developer [46]. The concept of the "value-based price, VBP" represents the maximum price that the payer would be willing to pay for the technology, and this should set the upper limit for decision making about actual prices and reimbursement policy.

A few countries formally express net benefit as a formula (Eq. 1). For example, in the UK health is measured in terms of the quality adjusted life year (QALY), and costs in terms of the resources used by the national health service; λ represents the opportunity cost of health that might be displaced by adopting a new intervention (or "threshold"). For countries using this methodology, the value-based price represents the (theoretical) price that will make the net benefit exactly equal to zero:

$$\text{Net benefit} = \text{Incremental health} \times \lambda - \text{incremental cost}. \quad (1)$$

It has been frequently suggested that the value-based price provides a (theoretical) equilibrium between the demands of the payer (higher prices displace health care and health from other patient groups) and the objectives of developers and investors (higher prices encourage future investment in those therapeutic areas) [7, 15, 47]. If a health service payer wishes to encourage development of new therapies in certain areas (such as unmet need, rare diseases, etc.) this can be signalled in the framework of Eq. 1 by declaring a higher value of λ for these areas than other cases [48, 49].

Value-based price is a normative concept, not a description of a particular methodology. It recommends that health services should estimate its maximum willingness to pay for a given therapy according to the "therapeutic utility" it provides to patients, and perhaps other beneficiaries (such as carers) or even beyond health care if a societal perspective is adopted.

Few countries calculate incremental net benefit by cost-effectiveness analysis (CEA) with a published value for λ. Countries such as Sweden conduct CEA but do not publish λ. Nevertheless, a signal can be tacitly observed through the approval/rejection decisions of the P&R process. France and Germany *de facto* apply a VBP concept by estimating comparative clinical effectiveness using a rigorous methodology, which then determines the boundaries for price negotiation.

Value-based price has two important corollaries for R&D. First, if a developer wishes to charge more than the value-based price, the payer should reject that application and precisely indicate the reasons. The negative decision provides a meaningful signal to future developers about the priorities in that country's health service. Second, value-based prices are not determined by the cost incurred by the developer. That is, health services must not be lured into paying high prices "because new therapies are costly to develop" [50]. This reverse-thinking would imply a form of "cost-plus" pricing. Cost-plus pricing can be distorted by information asymmetry between developer and payer. Moreover, the method does not provide efficient dynamic signals to guide future R&D as it creates incentives for the industry to pursue innovations with high development or manufacturing costs rather than focusing on providing high health benefits. Likewise, external reference pricing disassociates the price of a therapy from its therapeutic impact [51]. For example, Singh notes a tendency for developers to pursue biologic therapies based on their high expected reimbursement price, rather than consider small molecule therapies that might have a similar incremental therapeutic benefit but see payers usually reimbursed at lower prices [19]. Value-based pricing sends a signal that the industry must only bring therapies with costly R&D to market where it can demonstrate commensurately large therapeutic benefits.

Nevertheless, there are several ways that value-based pricing signals only imperfectly convey payers' interests and priorities. One reason is information asymmetry between the developer and the payer. The developer chooses which molecules to investigate; the timing of clinical studies; and proposes the key parameters of the estimand [52] (in HTA usually referred to as PICO: population, intervention, comparators, outcomes). Second, there are many payers (given medicines are usually developed to serve multiple countries and regions), and any individual payer's influence on R&D through its pricing decisions depends on the value of the

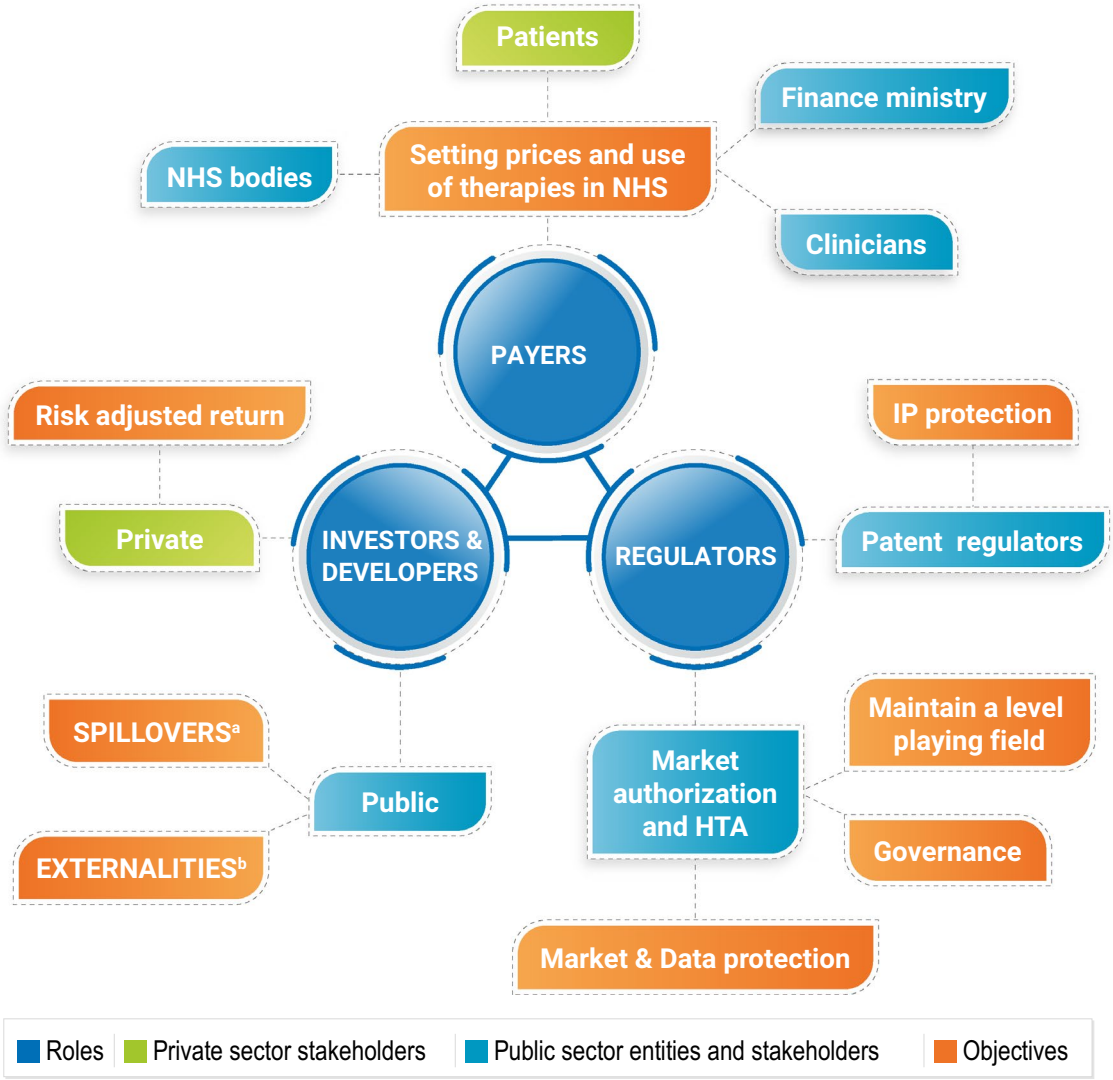

Fig. 2 Objectives of R&D activity and policies. Source: Produced by authors, based on their interpretation of the literature. a. Examples of spillovers: sustainable R&D environment, employment, productivity; b. Examples of externalities: diffusion of knowledge, advancement of science. *HTA* Health Technology Assessment, *R&D* research and development

market. Because of the long timelines from laboratory to market, developers will be most responsive to coordinated, durable and predictable price signals [46]. Third, healthcare regulators also set policies and provide incentives that impact on revenues and costs of developers, such as accelerated access for unmet need or orphan medicine status (including the Orphan Drug Act and the Orphan Drug Legislation) [53]. While these measures have stimulated investment in orphan medicines [54], they can also provide opportunities for gaming. Developers of a new therapy could exploit loopholes in these regulatory incentives to engage in market differentiation to extract the maximum consumer surplus, for example, positioning the first indication for the therapy as an orphan medicine, and once established in the market with a high launch price, gradually engage in other clinical studies to open up further indications. Some authors have expressed concern that there are now "too many" incentives for orphan medicines in Europe [10].

A criticism sometimes levied at the VBP concept is that developers will set prices up to the VBP, and so the developer will accrue all the value, and the health service will get none. This criticism does not consider that prices tend to fall over time, because of entry of other therapeutic alternatives during the IP protection period, and generic or biosimilar competition afterwards [55]. Hence, it is possible for prices of new branded medicines to be set at the VBP at launch, and for both parties to share the value over the lifetime of the therapy [46]. If, as is quite common, prices are set above the VBP, the value for the health service can be negative [46].

Furthermore, these high prices attract more investment in those areas and therefore will be dynamically inefficient.

Another misunderstanding about monopoly profits from innovations is that they provide the funds for future R&D by the same company. Industrial sectors with higher concentrations are usually not more R&D intensive [56]. Monopoly power can make firms defensive rather than efficient, and the firm may choose to return profits to shareholders rather than invest [14]. Large, liquid capital markets should be able to allocate funds to projects with greatest risk-adjusted expected returns. Traditionally in the pharmaceutical sector, large, diverse firms have been better placed to absorb the high sink costs per individual R&D project and take advantage of economies of scale [56], but recently other models have been successful, particularly in small populations and ATMP [57].

3.4 Models to Measure Costs and Returns to R&D

Profit-seeking manufacturers and investors measure the value of the technology in terms of the financial return it can generate, or expected net present value (eNPV, Eq. 2). Other factors may also influence the firm's decisions, such as building a diversified or synergistic portfolio or being first-in-class:

$$\text{eNPV} = \sum_{t=0}^{T} \sum_{m=1}^{M} (p_{mt} q_{mt} - c_t)/(1+r)^t. \quad (2)$$

In Eq. 2, p_{mt} is the price in country 'm' at time 't', q_{mt} is the absolute market size for the product in country 'm' at time 't', c_t is the risk-adjusted R&D and manufacturing cost at time 't', and 'r' is the cost of capital of the firm. The time horizon 'T' will include time both with and without market exclusivity, highlighting that the market dynamics before and after generics/biosimilar entry can be very different [46]. The developer's expectations about cost (Table 2) and revenues will enable an estimate of future eNPV at any given stage on the life cycle (Fig. 3), and thereby guide the company's strategic investment decisions (Table 2).

Table 2 shows how a private firm might calculate the fully capitalised economic cost of R&D per approved product. These estimates are shown for illustration of the underlying concepts, as the numbers vary across sources [1, 10], depending on the data and sample of medicines included. The private firm must take account not only of "out-of-pocket" expenses of R&D (i.e., the direct cash outlay incurred for that product) but two further "non-cash" elements that can be difficult to estimate: (a) the sunk costs of abandoned or failed R&D projects and (b) the cost of capital [7, 58]. The sunk costs already incurred up to time t should not be considered in a stop-go decision about an ongoing R&D project. However, sunk costs from abandoned or failed projects can only be recovered by sales of other, successful therapies and so it is important for the solvency of the company that successful therapies are priced and generate revenues with this in mind. This is the idea of the "risk-adjusted" eNPV [59]. Multiproduct pharmaceutical firms hold an evolving portfolio of existing and developing products. Because the firm must ensure that it is overall financially solvent in the long run, "costs" comprehend both those directly attributable to the successful product at each R&D phase, and also a share of the costs incurred by the R&D failures.

The second "non-cash" element is the cost of capital. This represents the cost to the firm of the investment capital required to finance the R&D project. It is an "opportunity cost", rather than a cash expenditure, because it takes account of the returns that could have been generated by

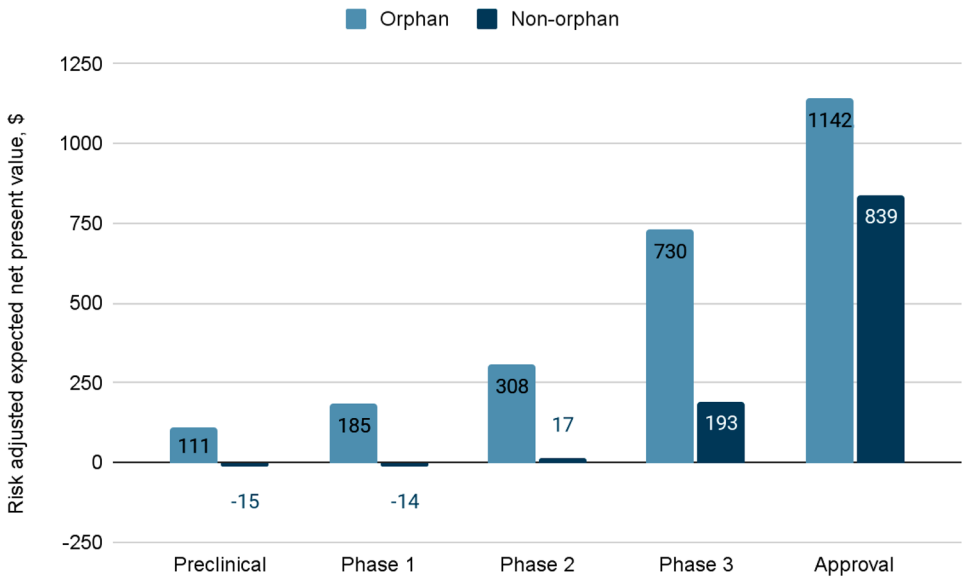

Fig. 3 Estimated risk adjusted expected net present value for non-orphan and orphan medicines, at each phase of research. Source: Kalindjian et al. [10]. *eNPV* expected net present value. Illustrative conversion rate: \$1 = 0.866 euros (xt.com 14/5/2025)

alternative projects. As shown in Table 2, the cost of capital can be a substantial portion of overall R&D cost, because firms need to sustain substantial capital outlays in R&D over many years to gain approval before the product can begin to generate revenue. The 10% cost of capital shown in Table 2 is illustrative but broadly consistent with the figure used in many of the studies [1, 10]. For a commercial firm, "*r*" (in Eq. 2) is called Weighted Average Cost of Capital (WACC) [60]. Firms finance investment either by debt (issue of bonds) or equity (money raised from shareholders or from internal re-investment of previous earnings). The WACC is specific to the firm and is complex to calculate. It depends on how investors perceive the ability of the firm to generate cash to service its financial obligations, which in turn will depend on the conditions in the sector it operates in, its existing portfolio of approved products and projects, and its plans for investment. DiMasi et al estimate a 1-point increase in the WACC rate adds over one hundred thousand dollars to the predicted R&D cost per approved medicine [61]. Interest rates are also affected by macroeconomic tax and fiscal policies including overall spending on health services. Hence the "public sector" (represented by fiscal and monetary authorities) can also influence overall R&D investment by macroeconomic levers and effect on business confidence.

Tax rates and R&D incentives also will affect private return on investment. Many countries also apply clawbacks and rebates on overall profit, and tax-credits and deductions linked to the extent of R&D and manufacturing spending in the country, often aiming to support the broader R&D environment, productivity or employment (Fig. 2) [3, 40]. For example, the Profarma policy in Spain, a programme designed by the Ministry of Industry to stimulate Spain's pharmaceutical sector by offering fiscal incentives to companies that establish production or R&D in the country [45, 62].

Figure 3 illustrates that the out-of-pocket cost of each phase of R&D increases compared to the previous phase, reflecting the increasing size and complexity of the clinical studies. However, it also shows that, because the cumulative probability of success is increasing as the project passes from one phase to the next, risk adjusted eNPV is low at early stages but increases as the project nears marketing approval. Rand Capital Corporation (RAND) estimates that the eNPV for non-orphan medicines is usually negative at the preclinical and phase 1 stages, which means that only investors with a high appetite for risk would consider investment at these stages (see Sect. 3.1 "Knowledge as a public good: translational studies").

3.5 Optimal Market Regulation

3.5.1 Regulator of Intellectual Property Rights

Patents represent an ingenious regulatory solution to a fundamental economic dilemma. Knowledge is best placed at the service of society and the progress of science when it is a public good that is widely and freely available to anyone, but "free-riders" have little incentive to contribute to the cost of its production. Patents are usually administered by national "patent offices", based on international regulations. The solution offered by patents is that the data are placed in the public sphere, and are fully available to anyone, but others cannot commercially exploit this information without the permission of the patent owner.

Patents are usually granted for 20 years [63]. The developer will apply for the patent early in the development process, but due to the long duration of clinical trials and associated uncertainty discussed above, the developer may typically have 8–10 years from marketing authorisation until patent expiry. Hence, in the EU and other jurisdictions, regulators provide extended protections in the form of supplementary patent protection certificates, market exclusivity periods and regulatory data protection (RDP). Companies can also apply for other legal protections, such as trademarks.

The defining (temporary) characteristic of IPR protection is to offer a period of relative market exclusivity to the innovator. While patents and other extended IPRs do not themselves directly set prices (and therefore are sometimes categorised as belonging in the family of "non-price" incentives in the literature [64]), these legal instruments exclude copies and hence indirectly enable the developer to negotiate a higher price than if competition were present. Hence an important feature of IPR is that it allows for decentralised effort and freedom in the discovery process—those who want to pursue a research line can do so in the expectation that the patent will allow them to recover costs without any centralised mechanism. Nevertheless, it is also an example of one public-sector actor (the patent regulator) passing the cost of the policy to another (the payers).

A basic principle of patent law is to oblige the IP owner to publish a full description of the invention in exchange for blocking commercial exploitation of that data. Within the guarantee of market exclusivity, other interested parties can study these data, and use them indirectly to inspire other lines of research (for example, develop different molecules as therapies for the same patient population). Therefore, the patent does not in any way protect the marketing authorisation owner from therapeutic competition from other innovations. Hence the commercial interest of the IP holders are protected while scientific progress can

proceed unencumbered. Furthermore, patents are time-limited. After expiry, other firms can commercialise an off-patent version (generics/biosimilars), potentially driving down prices towards marginal cost and maximising consumer surplus. These attributes mean that while the patent confers a temporary monopoly on the physical product, the underlying knowledge enjoys the attributes of a public good, that is, freely and widely available, which maximises the potential for scientific advance and spillover benefits.

From the inception of patent law, it was also quickly recognised that the patent can be used to block other inventors from improving on the original, and hence stifling the realisation of potential spillovers and positive externalities. A particular product may have multiple patents, covering the active principle, other ingredients, the pharmaceutical formulation, materials, manufacturing processes and so on [65, 66]. Companies sometimes take advantage of overlapping and confusing patent law to delay the entry of potential generic competitors through legal and regulatory lawfare [67]. Regulators aiming to make the generic/biosimilar market as efficient as possible is of course well aligned with the 'payer' incentives of controlling expenditure.

Although the data supporting patent applications are in the public domain, some clinical data used to make regulatory decisions are protected by RDP, stifling their use by others. Some authors propose a "club-goods" arrangement to allow and promote data sharing while maintaining commercial confidentiality [24, 27].

3.5.2 Promote Good Research Governance, Quality and Transparency

The FDA, EMA and other regulators set strict guidelines for the conduct of clinical studies that will be submitted as evidence for commercial authorisation. Regulators are acutely aware that stringent evidence requirements are necessary to guarantee that therapies are safe and effective, but also that such evidence is costly and lengthy to generate and so therapies take a long time to reach patients. In situations of severe diseases with unmet need, regulators may allow "accelerated access" or conditional marketing authorisation (CMA), allowing early access before the phase 3 study has been completed. This regulatory compromise creates uncertainty for HTA, and makes it challenging for payers to estimate a value-based price at the time of launch. Furthermore, the number of pharmaceuticals granted CMA has grown steadily over the last decade. Payers have responded to this uncertainty by introducing conditional reimbursement schemes or payment by results schemes, which aim to link finance to further evidence. Regulators could do more to ensure that early access is only given in exceptional circumstances, and hold manufacturers to account to publish further evidence as agreed. Moreover, it will be important to continue, and build from the on-going collaborations between regulators and HTA bodies to streamline and coordinate the different evidence generation requirements, for example, as is taking place during Joint Scientific Consultations [68].

3.5.3 Regulator/Arbiter of the Level Playing Field

Government agencies play an important role as market regulators. For example, the European Commission (EC) Directorate for competition and national bodies monitor and promote competitive markets and tackle unfair behaviour, whether arising from the actions of private businesses or by other government departments. Ministries of health exercise a role as "healthcare market referees" when they set prices and administer competition between therapeutic options. In this regard, the ministry should be aiming to maintain a level playing field, ensuring that competition is conducted on an objective, impartial and consistent basis, without conflict of interest or improper influence [38, 41].

Many regulatory and HTA agencies maintain neutrality and independence by being legally separated from the executive branch (including patent office, EMA, IQWiG, and NICE, among others). Notwithstanding, there are some instances of potential conflict between the roles of ministries of health as neutral market referees, versus its role as payer or R&D investor. For example, health ministries may give more favourable P&R terms to national producers than foreign producers, which may be contrary to the spirit of the EU single market, or try to achieve lowest prices possible to minimise budget impact.

3.5.4 Fair Pricing Models

The proposed EU Pharmaceutical Legislation requires transparency on public funding received by pharmaceutical companies. There are many potential advantages associated with greater transparency, both from developers and payers, about the clinical studies undertaken, and the cost and sources of finance of those studies [7]. This information may address information asymmetry and possibly influence pricing negotiations, as well as understanding by all stakeholders of financial flows in the industry.

In this section, we examine an implicit normative assumption in the Pharmaceutical Legislation (and by other authors), that products that have received public-sector R&D support should have a lower price, compared with products that offer similar added therapeutic value but were brought to market without public-sector support [69]. The argument often made for this approach is that public-sector funders such as National Institutes for Health receive insubstantial

revenues from licencing royalties [5], and that "Fair Pricing" clauses in licensing agreements are unenforceable [8], so it falls on payers to negotiate lower prices.

Even if this could be achieved, and it addresses immediate issues of affordability, there may be unintended consequences for dynamic efficiency if prices are set lower for products that received public support. As argued in Sect. 3.2, current prices guide future private R&D investment, and over the long term, prices that are "value-based" serve to allocate scarce R&D capital to where it is expected to generate greatest therapeutic benefit [46]. If actual prices in a particular field are higher (or lower) than the VBP, future R&D will be misdirected towards (or away from) that field. The development cost or the source of finance is not relevant to calculate the VBP (for special cases such as rare diseases a higher value of λ can be applied [70, 71]). Using prices to recover public R&D investment may also distort competition, and will unintentionally blunt the potential for therapeutic competition to reduce prices during the IP-protected period.

The use of royalties may be a more effective and efficient way to recoup public R&D investments than attempting to claw-back the investment through lower prices. They are more efficient, because a royalty does not distort price signals to future developers or competitors. They are likely to be more effective, because a royalty agreement is settled ex ante, and usually has international legal force, whereas prices are the uncertain and sometimes arbitrary ex post outcome of one-to-one negotiation with individual payers.

Similar arguments apply to prices of therapies discovered in the public sector. If the price of a publicly owned commercialised product (e.g., a hypothetical scenario of an ATMP developed within the public sector that later might obtain a European centralised MA) does not include elements of opportunity cost such as the cost of R&D and cost of capital, then it may not be operating on a level playing field with respect to private competition. In effect, potential competitors could argue that this product received hidden State Aid, and the public-sector payer and regulator would be complicit in this anti-competitive tactic. This is one area where greater clarity on the regulation and greater transparency about cost methodology and cost data from both the public and private sector would be recommended.

3.5.5 Royalties May Be a More Efficient Way to Recoup Public R&D Investments Than Lower Prices

Imagine a country that usually allows a maximum value-based price of €20,000 per patient for a product that generates 1 QALY, that is, λ = €20,000. Imagine a product "A" that generates 1 QALY that was developed with public support that cost €5000 per patient. Imagine that the payer indicates that it will only pay up to €15,000 for this product (that is, less that the value-based price), because of the public-sector R&D investment.

The initial "discount" becomes "baked into" maximum prices of any future potential innovations in that pathology. Imagine that a different developer discovers a new product "B" that provides 2 QALY for the same population as product "A". If A had been priced at its value-based price, "B" would expect to charge €40,000 (that is, €20,000 more than "A"). However, because A was priced at €15,000 "B" will only be allowed to charge €20,000 more than €15,000,that is, €35,000. The discount on the first product has acted to weaken the incentive for the private sector to research and develop future innovative products that might have offered worthwhile incremental benefits.

Alternative mechanisms such as royalties would provide a return on the initial public-sector R&D investment without distorting price signals to future developers. For example, imagine that the public-sector research institute that discovered "A" enters a licensing agreement with the developer such that the developer agrees to pay a royalty of €5000 per patient. If "A" is then reimbursed at the normal value-based price of €20,000, there would be no distortion created in the market for a hypothetical new product "B" in the same population, and the public-sector institution in the country that invested in developing "A" gets a return.

This approach was used by MRC Technology, a UK-based medical research charity who helped develop a leading cancer medicine, pembrolizumab, and retained an IP interest. The agreement left the commercial marketing authorisation holder (Merck Sharp & Dohme) free to negotiate prices with payers. The charity sold the royalty rights to a Pension Fund for $1300 million, and uses this capital to advance further R&D [72].

4 Discussion and Recommendations

This paper has discussed, from a theoretical perspective, the various roles that public-sector agencies take on in promoting and financing medical R&D. Other authors have covered some of the same ground, but we believe this is the first paper to attempt a 360° view, from different perspectives and points in the life cycle of technologies. The paper has tried to include illustrative examples drawn from real life, although many others could be insightful. The paper also has several limitations. The selection of theoretical approaches included here was to a large extend conditioned by the experience and background of the authors. We made considerable effort to gain feedback and comment from a wider group of experts from different fields. Our work leads to a number of recommendations for policy.

The conventional model of health technology R&D assumes a linear progression from discovery, development,

launch and post-launch evidence. In practice, the process may be more iterative and exploratory. Increasingly, developments originating in other STEM disciplines play a key role. The public sector influences R&D through a pantheon of institutions with distinct and overlapping roles. These can be characterised as "R&D investor", "Regulator" and "Payer". These agencies should recognise that influence on R&D may be indirect, but powerful.

The combination of P&R decisions, direct R&D investment and regulatory incentives will steer the R&D ecosystem. A coherent public R&D strategy would require a certain level of coordination between the various public-sector agencies. For example, while support and special incentives are given for orphan medicines, there can be affordability issues limiting their use and uptake. Nevertheless, excessive incentives for one area could misdirect scarce R&D capital away from other areas that might provide greater public health benefit.

Value-based pricing is a normative concept that aims to bring predictability to payers' decisions and, through P&R decisions for current therapies, provide reliable signals to developers about future NHS priorities. It is a principle, rather than a specific formula or a rule. Other pricing mechanisms such as cost-plus or external reference pricing are unlikely to promote dynamic efficiency.

There are several areas where markets are likely to be deficient in providing incentives for private actors to undertake R&D. These include basic research, translational research, real-world studies, and repositioning studies. There is also a strong economic case for the public sector to heavily invest in technologies with widespread potential spillover benefits such as AI and gene editing, and use licensing arrangements that make these widely available and affordable for small and medium-sized enterprises.

Where the public sector conducts in-house development, such as for new gene therapies, this investment should be conducted on a financially sustainable footing, even if not-for-profit. The public sector has a duty as a market regulator to maintain a level playing field, especially if publicly owned therapies could be in competition with the private sector. Public subsidies for applied R&D can be recovered by royalties. This IP instrument is less likely to distort price signals, and more likely to promote R&D in therapeutic alternatives, than attempting to claw back the subsidy by lower prices post-launch.

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Declarations

Data Availability Data sharing is not applicable to this article as no new data were created or analysed in this study.

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