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PRACTICAL APPLICATION

Alternative Payment Models for Innovative Medicines: A Framework for Effective Implementation

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Abstract

Scientific advancements offer significant opportunities for better patient outcomes, but also present new challenges for value assessment, affordability and access. Alternative payment models (APMs) can offer solutions to the ensuing payer challenges. However, a comprehensive framework that matches the spectrum of challenges with the right solution, and places them within a framework for implementation, is currently missing. To fill this gap, we propose evidence-based steps for the effective selection and implementation of APMs. First, contracting challenges should be identified and mapped to potential APM solutions. We developed a decision guide that can serve as a starting point to articulate core problems and map these to APM solutions. The main problem categories identified are: budget impact and uncertainty, value uncertainty, and the scope of value assessment and negotiation. Sub-categories include affordability, uncertainty of effectiveness, and patient heterogeneity, which map onto APM solutions such as outcome-based agreements, instalments, and subscription models. Just as important are the subsequent identification and assessment of the feasibility of potential solutions as well as collaboration to reach agreement on the terms of the APM and lay the groundwork for effective implementation. We adduce recent examples of APM implementation as evidence of how commonly cited implementation barriers can be overcome by applying pragmatic design choices and collaboration. This step-by-step framework can aid payers and manufacturers in the process of effectively identifying, agreeing on, and implementing APMs to advance patient access to cost-effective medicines, while at the same time providing appropriate incentives to support future innovation.

1 Introduction

Rising costs and growing demands on healthcare systems due to demographic shifts and epidemiological factors have contributed to continuing calls for cost containment. However, these same factors also reinforce the need for new medical innovations that can support the more efficient use of healthcare resources and better patient outcomes. What and how we pay for new medicines can impact which therapies are developed, adopted, and accessed. Scientific advancements offer opportunities for better patient outcomes, but they also present new challenges for value assessment and decisions related to pricing, reimbursement, and access.

While stakeholders across the healthcare system have differing remits, objectives, and constraints, the cause that unites them is the advancement of patient care and outcomes in a meaningful and sustainable way. Contracting for pharmaceutical innovations raises joint challenges for payers and manufacturers that are related to payment structure, uncertainties, and incentives for innovation. There is growing interest in the potential for alternative payment models (APMs) to address these issues [1, 2], but there is a lack of a comprehensive framework that articulates the broad spectrum of challenges that APMs could address and can map these to potential solutions and an implementation framework.

Various taxonomies of APMs have previously been proposed for specific types of payment models. Among existing taxonomies, a distinction is commonly made between

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Key Points for Decision Makers

Payer challenges around budget impact, value uncertainty, and the scope of value assessment and negotiation are becoming increasingly common as the landscape of innovative medicines shifts towards high-cost, targeted and/or personalised drugs with potentially uncertain benefits.

We develop pragmatic steps for effective implementation of alternative payment models (APMs), combining a decision guide for finding the right APM solution with examples of how to assess and overcome implementation barriers.

The effective selection and implementation of APMs can advance patient access to cost-effective and high-quality medicines, while at the same time providing appropriate incentives to support future innovation.

financial-based schemes and outcome-based schemes [3–11]. Distinctions are also made between schemes which establish conditions on the population-level versus patient-level [7] as well as between those which do or do not entail risk sharing [9]. Several authors have developed more detailed taxonomies of specific APM-types, such as the numerous available taxonomies of performance-based risk-sharing agreements [5, 10, 12].

Previous literature has mapped a narrower scope of payment models to the challenges they address, or vice versa. For example, Andersson and colleagues map types of uncertainty to the type of risk-sharing mechanism used to address this uncertainty [13]. The mapping focuses on a narrow scope of risk-sharing agreements and only considers existing schemes implemented in Sweden. Kolasa et al. created a decision guide to help manufacturers and payers to identify APMs that address one or more problems encountered when contracting for drugs [14]. They identify three main motives for using an APM: uncertainty of clinical benefit; affordability and budget impact; and external price referencing. Grimm and colleagues provide examples of how managed entry agreements can mitigate issues surrounding value uncertainty in health-technology assessment (HTA) [15]. Whittal and colleagues map pricing and the reimbursement risks frequently faced for innovative therapies to several types of managed access agreements and provide a procedural framework for how payers and manufacturers can reach agreement on the terms of an APM to mitigate these risks [16]. Last, Ardito and colleagues performed a scoping review that maps 70 unique pricing and payment schemes for health technologies, proposing a flexible classification framework to assist decision makers in selecting appropriate schemes based on objectives and key characteristics [17].

There is also a need to advance the dialogue further to articulate what is needed to support the effective implementation of APMs based on previous experience. In this paper, we propose a framework to enhance the effective selection and implementation of APMs in an efficient manner that balances access, affordability, and innovation.

2 Methods

We conducted a pragmatic literature search on Google Scholar of articles published between 2010 and March 2024 using keyword strings including ‘taxonomy’, ‘typology’, ‘pricing models’, ‘payment models’, pharmaceutical’, ‘managed access agreements’, and ‘performance-based risk-sharing agreement’. Articles were screened for their relevance to classifications of innovative payment models and the problems they address. ‘Snowballing’ and ‘pearl-growing’ techniques were used to identify citations of/from seminal articles and publications from the grey literature.

Case studies were selected to represent a spectrum of APMs that have been implemented. The framework was created by synthesising learnings from the case studies and broader literature on experiences across a variety of APM types and implementation stages.

We focus on challenges in pharmaceutical contracting relating to payer coverage decisions for medicines. Only product-specific payment models for medicines between industry and healthcare systems were considered; contracts between other stakeholders, e.g., payers and provider networks, were excluded. We excluded price referencing because it was not intrinsically a ‘contracting issue’. Government initiatives exclusively intended to incentivise innovation and/or improve provider incentives, such as prize funds or delinked payments to address market failures in antibiotic research and development (R&D), were also excluded because they are not contracting problems that can be implemented at the payer-manufacturer level.

While we designed the framework to be broadly applicable, the likelihood that certain contracting problems arise and the manner in which they manifest will differ between health systems with different characteristics (multiplicity of payers, how healthcare is financed, etc.) For example, problems associated with insuree churn are more likely to arise in multi-payer systems like in the USA than single-payer systems like the UK NHS. The framework accommodates a broad range of problems and is not limited to those faced universally by every health system.

We selected five APM case studies on the basis that sufficient publicly available information was available in English

about the rationale for the APM and about the implementation process.

3 Framework for Effective APM Implementation

A comprehensive yet problem-focussed and practical framework for the implementation of APMs involves the following steps:

1. *Articulate the core problem:* Identify critical issues related to budget impact, uncertainty, or the scope of value assessment and negotiation that the APM should overcome.
2. *Map problems to potential solutions*: By design, what types of APMs can overcome these specific problem(s)? If several problems are present, can APMs be combined to address them?
3. *Assess feasibility of implementation:* Consider legal, administrative, and IT-hurdles that may challenge APM implementation and, where available, draw on best practice examples to overcome those hurdles.
4. *Payer-manufacturer collaboration:* Multiple contracting options and designs may be available. The parties must work together to find a feasible 'win-win' solution.

We explain each of these steps in detail in the following sections.

3.1 Step 1: Articulating the Core Problem

Core problem 1: Budget impact and uncertainty: The budget impact of a pharmaceutical product refers to the financial consequences of adopting that product within a specific healthcare setting or system. Budget impact analysis (BIA) predicts the financial consequences of adopting a new intervention by considering both the costs of introducing the new drug and the changes in expenditures on existing treatments or related healthcare resources. Because utilisation, and therefore budget impact, is uncertain, both the point estimate and the distribution of expected expenditure matter.

The 'affordability' problem refers to situations where the medicine is difficult to fund because its estimated budget impact is large. Healthcare budgets are finite, meaning that a medicine may be deemed unaffordable even if it is considered cost effective [18, 19]. For example, if a high-priced drug is expected to be used widely, it could strain the resources of a payer or healthcare system, leading to potential challenges in maintaining other services [20].

A separate but related affordability problem involves how costs are distributed over time and how this aligns with the budget cycles of payers. A product which is just entering the market may create extraordinary financial strains on the health system in the short term while it accommodates a 'surge' of pent-up demand immediately after the medicine is made available [21]. In such cases, payers face budget cycles that can create financial pressures which make a product unaffordable in the short term, even if the product is affordable and cost effective in the long term [22].

Beyond the level of budget impact, uncertainty surrounding that impact leads to budget risk for payers. Budget risk refers to situations in which utilisation of the medicine in the health system is uncertain, which could introduce risks around the estimated level of expenditure that make it difficult for payers and manufacturers to predict and plan expenditures and revenues, respectively. As a result, both parties may be averse to budget risk and seek to manage these uncertainties [23–26].

Core problem 2: Value uncertainty: We describe two categories of value uncertainty that can provide rationale for an APM. Here, 'value' is defined as 'net benefit', a concept used by health economists to describe the economic surplus that accrues to the payer and the patient population it covers. It is calculated as the difference between the monetary value of health benefits and the net costs of the intervention. While health systems differ in how they define these components used to calculate net benefits, our framework is agnostic to the scope of benefits and costs considered. What is relevant is that these benefits and costs may be uncertain, which contribute to uncertainty of net benefit. 'Value uncertainty' therefore refers to the uncertainty in net benefit which accrues to the payer as a result of deciding to reimburse a medicine.

The first category is value uncertainty within a patient subgroup or clinical indication. This may be because existing trial evidence of the product's efficacy and safety is uncertain. This can stem from statistical uncertainty of the product's efficacy based on trial data, as well as uncertainty about how representative that trial data will be of real-world effectiveness or adherence (e.g., because clinical trials were conducted with a non-representative patient population or comparator standard of care, or did not capture long-term or meaningful endpoints). It can also be due to uncertainties in the modelling process, such as structural uncertainty or uncertain model parameters such as cost inputs.

The other category of value uncertainty concerns the uncertainty of relative use between multiple patient subgroups. In other words, one can predict with a high degree of certainty how well the product works in individual subgroups, but—where effectiveness differs between those

groups—there is a great deal of uncertainty surrounding the composition of the patient population treated.

Core problems 1 and 2: A note on uncertainty and risk: A common core underlying motivation for contracting parties to engage in an APM is the presence of (and aversion to) uncertainty, whether around budget impact or value [27, 28]. Payers and manufacturers hold different attitudes and aversions to budget risk and value uncertainty [22, 29, 30], and a conventional payment model may sub-optimally distribute exposure to these uncertainties between the manufacturer and payer relative to these preferences. When multiple APM solutions are available to address a given problem, the choice of which is preferred may depend on their preferences on how to trade-off and share these risks.

Core problem 3: Scope of value assessment and negotiation: Quite separate from uncertainty, there may be contracting problems which arise from the *scope* of the value assessment by the payer. The first of these manifests in disagreement or incompatibility between the time horizon adopted in the payer's assessment methodology and the duration of treatment effect. For example, in the case of curative medicines, benefits may persist for years, decades, or an entire lifetime. However, much of the health gain and cost offsets may fall outside of the time horizon considered by the analysis used by HTA or payers as the basis of the coverage/reimbursement decision [31]; in some cases, this time horizon is as short as 1–2 years [21], and is < 10 years on average for private US payers [32]. In other words, a product that is cost effective in the long term may not be cost effective within the time-horizon of the relevant decision maker, if the full treatment cost is concentrated in the short term when it is administered [33, 34]. This is fundamentally a payer agency problem, and can also be relevant when the current payer does not internalise all future cost savings when there is insuree churn [28].

The second group of problems may arise if there is (known) heterogeneity of effectiveness between sub-populations or indications and if the negotiation process allows the payer to make stratified decisions conditioned on population- or indication-specific value [35]. When the process only allows negotiation to take place based on one uniform price, sub-optimal decisions or restrictions to patient access may result [36]. This is because, for example, the scale of patient benefit may vary significantly between indications, as would its value-for-money if there is a single, fixed price. In the absence of indication-level payment negotiations or adjustment, this can be problematic for patient access to new treatment indications. An APM that permits cost-effective prices at the individual- or subgroup-level could address this problem.

3.2 Step 2: Mapping Contracting Problems to APM Solutions

As described in the introduction, the relatively narrower scope of APMs considered by existing taxonomies in the literature show that some APMs have already been extensively studied while others have not yet been considered within a broader decision guide. Because our starting point is the range of *problems* to be addressed by payers and manufacturers, and match APMs to overcome those rather than the other way around, our framework also includes relatively less studied APMs.

The APM Decision Guide comprises three broad problem categories and several sub-categories which are described and mapped to potential solutions in Table 1 and shown in the decision guide in Fig. 1. The payment model solutions are defined in Table 2.

Table 3 explains each mapping of problem to solution and provides stylised and real-world examples.

Notably, payment models and the challenges they address do not map one-for-one, meaning that some challenges can be addressed by multiple models and some models serve as solutions for more than one problem. When multiple models are available to address one problem, the preferences and objectives of the contracting parties will influence the potential solution that is most suitable. Consideration must also be given for the scope of the APMs for multi-indication drugs, as APMs can be implemented at the indication level or across multiple indications, and payers and manufacturers should consider how an APM would affect reimbursement for future indication expansions.

These specific contracting choices are represented by the numbered decision nodes in the proposed decision guide (Fig. 1). In addition to the preferences and objectives of contracting parties, there are critical barriers and enabling factors associated with different payment model solutions which influence applicability.

3.3 Steps 3 and 4: Assessing Feasibility and Collaborating for Successful Implementation

The success of these schemes may depend on context-dependent factors and the specific design of a scheme, which can be tailored to each application [27]. Decisions around APM selection and feasibility hinge on factors such as: costs of contract negotiation and implementation; presence of enabling data/IT infrastructure; structure of the price/contract negotiation process; effects on internal or external reference pricing; compliance with government regulation; and additional product-specific and health system factors.

While the taxonomy mapping allows stakeholders to match contracting problems with fitting APM solutions, this

Table 1 Contracting problems and payment model solutions

Broad problem category	Problem sub-category	Payment solutions
Budget impact and uncertainty	*Affordability*: Drug budgets are constrained, which makes it difficult to accommodate new drugs which are more clinically effective but are also more costly—especially in the short term	SM; instalment; PVA; patient-level dose/cost capping
	Budget risk: Uncertainty of utilisation leads to uncertainty of budget impact, which introduces 'actuarial risk'. This risk makes payer spending less predictable and therefore makes it difficult to budget into the future. From the perspective of the manufacturer, this manifests as revenue uncertainty	PVA; SM; patient-level dose/cost capping
Value uncertainty	*Uncertainty of effectiveness*: Based on existing evidence, there is uncertainty surrounding the effectiveness—and, hence, the value—of the drug in real-world situations. Payers may be averse to this risk and want to find ways to insure against or 'share' it. Alternatively, uncertain evidence can lead payers and manufacturers to come to different beliefs about the value of adopting the technology in the health system and the value of additional research	OBA; CC
	Uncertainty of relative use by indication: Uncertainty of relative usage between different indications or subpopulations leads to uncertainty of the cost effectiveness of the product when contracted at a uniform price	VBDP; OBA; CC
Scope of value assessment and negotiation	*Scope across heterogeneous subgroups*: Effectiveness varies within and/or between specific indications or patient subpopulations, meaning that price is not aligned with value for certain indications or subpopulations from the perspective of the payer	VBDP; OBA; PM, PVA; SM; patient-level dose/cost capping
	Scope across payers and budget cycles: There are benefits of the treatment which fall outside of the time horizon considered by the economic analysis which forms the basis of the coverage/reimbursement decision. This is fundamentally a payer agency problem, where the current payer does not internalise all future cost savings, e.g., when there is insuree churn or when the time horizon being considered by a single-payer is not sufficiently long	Instalment

CC conditional coverage with a fixed price, *OBA* outcome-based agreement, *PM* portfolio model, *PVA* population price volume agreement, *SM* subscription model, *VBDP* value-based differential pricing

is only one piece of the puzzle. All parties need to be confident that the fit-for-purpose APM can be effectively implemented and that the benefits of doing so outweigh the costs.

Barriers to the implementation of certain APMs, such as outcome-based agreements (OBAs) or value-based differential pricing (VBDP), are well-documented. The proposed taxonomy covers a broad spectrum of APMs, for which implementation issues vary [72]. Generalised views about system readiness for APMs as a concept are complicated by barriers and enablers being highly context-specific [73]. Even within a given APM category, implementation barriers can vary widely based on the country, product, and enabling infrastructure [74, 75]. Nevertheless, some commonly cited barriers to their broader use exist.

Inadequate data infrastructure or complexities around data governance is one such challenge, as many APMs require prospective data collection and data linkage [8, 30, 63, 76]. However, routes to advance APM solutions differ depending on data infrastructure and the extent to which surrogate, de novo or re-purposed data or proxies where appropriate can be leveraged to facilitate feasible data collection within a reasonable timeframe. To smooth the pathway to implementation, data collection systems should be accessible, simple, and add little burden to physicians.

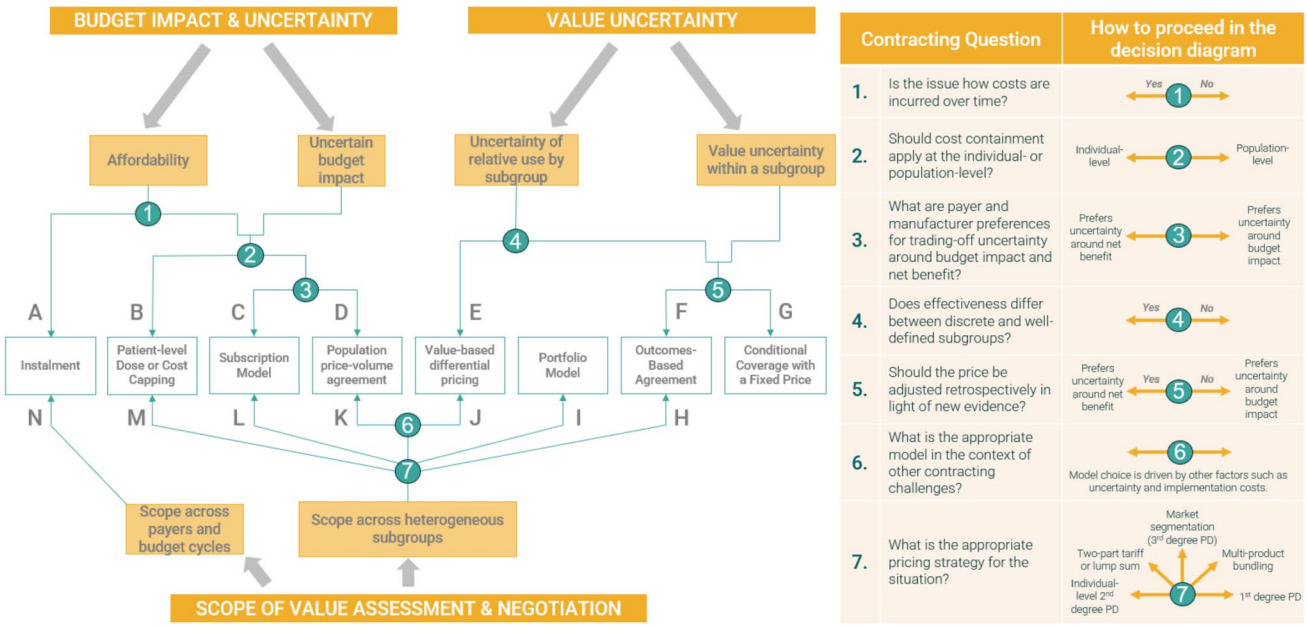

Fig. 1 Mapping of contracting problems to alternative payment model (APM) solutions. Decision guide to aid mapping of the contracting problem with the identification of the appropriate APM solution(s). The letters (A–N) next to the arrows denote specific pairs of contracting problems and APM solutions. These are further elaborated in Table 3

Table 2 Description of payment models

Model category	Description
CC	The product is covered for a period of time "Only with Research/Only in Research" with a fixed price, with the condition that further evidence is collected about the drug's effectiveness or use. Coverage and/or pricing after this period may be re-evaluated in light of new evidence. The evidence that is generated can be used by payers to inform future coverage decisions and/or by manufacturers to support future commercialisation efforts
OBA	An agreement that ties payment for a medicine to the clinical outcomes or effectiveness of that medicine in real-world practice. This re-allocates risk between the payer and manufacturer
PM	A payer purchases a bundle (i.e. a 'portfolio') of medications from a manufacturer at an agreed-upon price, rather than contracting for individual medications
VBDP	The price of a drug varies based on the subgroup in which it is used. This model reflects the principles of value-based pricing as it ties price to the expected value provided in each type of usage. One such case is when a drug's price varies between indications, in which case the model is often referred to as 'Indication-Based Pricing' or 'Multi-Indication Pricing'
PVA	The unit price of the pharmaceutical product depends on the volume purchased at the population-level
Patient-level dose/cost capping	The cost or reimbursable doses per patient is limited on the patient-level
SM	The purchaser of a medicine pays a fixed fee for unlimited access to a particular drug over a specified period of time

CC conditional coverage with a fixed price, *OBA* outcome-based agreement, *PM* portfolio model, *PVA* population price volume agreement, *SM* subscription model, *VBDP* value-based differential pricing

Another issue is around the contractual complexity and cost of implementation (e.g., administrative burden, staff time, and set-up costs) [5, 8, 30, 63, 76]. Outcome targets, together with stakeholder roles and financial responsibilities for data collection and administration, should be clearly specified [77]. Simple design choices can minimise these challenges, as evidenced by the examples below.

Government price reporting and reference pricing (e.g., the Medicaid 'Best Price Rule' in the USA) is cited as another potential implementation barrier [30, 78, 79], but the extent to which APMs alleviate or exacerbate this challenge is scheme- and country-specific [43]. Finally, a critical enabler is a shared understanding among health system stakeholders of the problem and APM solutions [63].

Table 3 Explanations of problem-solution mappings in the decision guide

	Problem-solution pair[a]	Explanation	Stylised example scenario that provides rationale for APM	Stylised example of APM design and effects on payer	Real-world example or reference[b]
Budget Impact and Uncertainty	A	An instalment system spreads payment over several budget cycles, improving affordability and relieving budget constraints	A new medicine is cost effective but unaffordable as the budget impact would be $1 billion in the first year	Payment is spread into five $200 m instalments paid annually, which improves affordability	There was an instalment component of APMs agreed between payers and manufacturers of zolgensma and luxturna[c] [37–39]
	B	The cost per patient is capped, which reduces population-level budget impact and uncertainty around this budget impact [23]	The length of treatment ranges from one to 20 administrations, and the price of the medicine is fixed per administration. The estimated average number of administrations in the population is uncertain	At the patient level, the medicine is provided for free from the 15th administration onwards. This reduces budget impact and budget risk	Chassang et al (2018) conducted a financial simulation model of APMs in which total reimbursement was a nonlinear function of the number of doses provided per-patient [23] NICE recommended lenalidomide for multiple myeloma on the basis of a manufacturer-proposed patient access scheme in which the manufacturer paid for doses administered beyond 2 years [40, 41]
	C	Subscription models fix the population-level budget impact (at the expense of increasing uncertainty of net health benefit) [23, 25, 42]	The projected budget impact of a medicine is $1 billion plus/minus $200 m	A subscription payment for unlimited access to a drug is set at a fixed $900 m, reducing expected budget impact and uncertainty	Australian payers have implemented subscription models for direct acting antivirals (DAAs) that reduced uncertainty around budget impact[c] [43]
	D	PVAs can reduce population-level budget impact and reduce the uncertainty around budget impact [44]	A medicine is deemed cost effective but unaffordable at a proposed price of $100 k. Forecasts of the volume of drug consumed in the relevant patient population are highly uncertain, which generates uncertainty around budget impact	The first 1000 units are priced at $150 k and all subsequent units at $50 k. Under this agreement, if volumes exceed expectations, the effect on expenditure would be lower since the extra volume is sold at the reduced price, reducing budget risk	PVAs have been implemented for reimbursement of novel medicines in several countries including Italy and South Korea [45, 46]. In France and Lithuania, PVAs have been implemented to mitigate budget impact and budget risk [47]

Table 3 (continued)

	Problem-solution pair[a]	Explanation	Stylised example scenario that provides rationale for APM	Stylised example of APM design and effects on payer	Real-world example or reference[b]
Value Uncertainty	E	VBDP reduces uncertainty in net benefits ('value') when there is uncertain use by subgroup	A medicine has multiple indications with differing clinical benefits. The relative use between these indications is uncertain	VBDP is used to implement indication-specific prices such that each indication provides the same net benefit. Keeping constant total product volume, population-level net benefits would remain unchanged even as the relative use by indication changes	Indication-based pricing and blended pricing has been implemented in Italy for products with multiple indications [48]
	F	OBAs reduce uncertainty of net benefits (at the expense of increasing uncertainty of budget impact)	A medicine was only tested in a clinical trial with a small sample, increasing uncertainty around clinical benefits. If reimbursed at a predetermined fixed price, this results in significant uncertainty around net benefits	An OBA partially or fully aligns reimbursement for the drug with realised net benefits. However, because total expenditure depends not just on volume but also on net benefits, both of which are uncertain, uncertainty of budget impact also increases	Clopes and colleagues analysed payer motivations behind an OBA for an oncology product between payers in Catalonia and AstraZeneca [49][c]. OBAs between NICE and the manufacturer of interferon-beta and glatiramer acetate ensured that net benefits were positive over the long term [40, 50]
	G	Conditional coverage with a fixed price can reduce long-term value uncertainty [51]	The net benefit of the medicine—and thus its value-based price—is highly uncertain Additional evidence generation can reduce this uncertainty but will take time to develop	The payer agrees to reimburse the medicine at a fixed price for two years; thereafter, reimbursement is conditioned on the generation of additional evidence of the medicine's clinical benefits. Under the arrangement, the payer bears short-term value uncertainty, but long-term value uncertainty is reduced	CED and 'approved with research' schemes have been implemented in the USA and UK, respectively [52, 53]. Sweden's pharmacy benefits board (TLV) has implemented CED schemes to share risk around the product's cost effectiveness until a pre-specified point at which the manufacturer must submit additional supporting evidence and adjustments may be made to price/reimbursement [54, 55]
Scope of Value Assessment and Negotiation	H	An OBA can be used to align net benefits with costs at an individual- or subgroup-level [44, 56]	A medicine provides health benefits for a patient population but, under a uniform price, patient access is restricted only to the highest expected responders due to a stratified CEA	An OBA is designed to ensure positive net benefit regardless of expected treatment response. Even under a stratified CEA, the medicine will be cost effective in all individuals/subgroups with positive expected clinical benefits	An OBA between the Australian Department of Health and the manufacturer of bosentan, a medicine indicated to treat pulmonary arterial hypertension, ensured that the effective price (net of rebates) would maintain the original ICER if the product's observed real-world effectiveness (as measured by the mortality rate) was lower than expected [57]
	I	A portfolio model allows the payer and manufacturer to negotiate over a product bundle [58–60]	A payer is considering several drugs manufactured by the same company	The sponsor and payer negotiate over prices and coverage for some or all of the drugs manufactured by the company	Portfolio agreements or 'product bundles' have been used in paediatric vaccines in the USA [60]

Table 3 (continued)

	Problem-solution pair[a]	Explanation	Stylised example scenario that provides rationale for APM	Stylised example of APM design and effects on payer	Real-world example or reference[b]
	J	VBDP is used to segment the market by subgroup, which improves efficiency and access compared to a uniform price. Rather than setting a uniform price which applies to all uses of the product, a distinct price is set corresponding to use in each subgroup—when the subgroups correspond with clinical indications, the practice is commonly referred to as 'indication-based pricing' or 'multi-indication pricing' [61–63]	The payer makes a stratified reimbursement decision based on subgroup-specific health benefits and a uniform price. Relatively low value subgroups are not cost effective at the uniform price even though they provide clinical benefit	VBDP sets subgroup-specific prices that ensure positive expected net benefits in each subgroup	Various forms of indication-based pricing have been applied in countries worldwide [64]. NICE recommended ustekinumab for treatment of adults with psoriasis condition on a patient access scheme in which the per-vial charge is adjusted to ensure cost effectiveness in two subgroups (patients with a body weight exceeding 100 kg and patients with a body weight not exceeding 100 kg) [65]
	K	PVA is used to segment the market and assign different prices to different quantities according to expected sales in each market segment [44]	The payer makes a stratified reimbursement decision based on indication-specific health benefits and a uniform price Relatively low value indications are not cost effective at the uniform price even though they provide clinical benefit	PVA sets a price schedule corresponding to expected volume by indication	In Australia, for instance, payers have used PVAs to allay concerns about low-value or 'excess' use [29]
	L	Subscription model is used to implement a two-part tariff or lump-sum 'Netflix-style' pricing model [42, 58, 66]	The payer makes a stratified reimbursement decision based on indication-specific health benefits and a uniform price. Relatively low value indications are not cost effective at the uniform price even though they provide clinical benefit	A subscription model is designed that generates positive expected net benefit at the population level using the total expected payment (lump-sum and expected per-unit costs) as well as positive net benefits at the individual/subgroup level using per-unit costs	Australian payers have implemented subscription models for DAAs that expanded access a wide range of patients, including those with relatively low (but still positive) expected clinical benefit from treatment[c] [43]
	M	Patient-level dose or cost capping [40]	The length of treatment ranges from one to 20 administrations, and the price of the medicine is fixed per administration. The marginal clinical benefits decline, but remain positive, as the number of previous administrations increases	At the patient level, the medicine is provided for free from the 15th administration onwards	On the individual-level, dose capping can be used to implement second-degree price discrimination at the individual level to ensure that treatment remains cost effective for poor responders, as has been applied in the UK in NICE appraisals of ranibizumab and pegaptanib [67] and sunitinib for first-line treatment of advanced and/or metastatic renal cell carcinoma [40, 68]

Table 3 (continued)

Problem-solution pair[a]	Explanation	Stylised example scenario that provides rationale for APM	Stylised example of APM design and effects on payer	Real-world example or reference[b]
N	Instalment model to align benefits and costs and address payer agency problem	Due to insuree churn, insurers on average only internalise future cost savings up to three years into the future. A curative one-off new technology is cost effective over a time horizon of five years but not of three years	The technology is paid for in instalment payments over five years such that each instalment payment is proportional to the share of net benefits which accrue in that year. If the patient changes insurer, liability for remaining instalments is held by the patient's new insurer	By spreading payments over time, an instalment model can better align the timing of payments when benefits accrue to patients [18]. In some variations of the model designed to address insure churn, payer liability can follow patients if they change insurers [69–71]

APM alternative payment model, *CEA* cost-effectiveness analysis, *CED* coverage with evidence development, *DAA* direct-acting antivirals, *ICER* incremental cost-effectiveness ratio, *NICE* National Institute for Health and Care Excellence, *OBA* outcome-based agreement, *PVA* population price volume agreement, *VBDP* value-based differential pricing

[a]The letters (A–N) denote specific pairs of contracting problems and APM solutions, which are represented visually in Fig. 1

[b]Stylised or real-world examples are not exhaustive of all APMs which have been implemented for this problem-solution pair

[c]Real-world example selected as a case study for APM implementation in the main text based on the availability of detail of the APM and the rationale for its implementation

Engagement and collaboration between payers, manufacturers, and providers is key [80], and early experiences should be leveraged to foster a shared understanding of the benefits of entering into an APM.

These barriers understandably lead to concerns from payers and manufacturers about the feasibility of implementing APMs in practice [8, 30]. However, recent experiences demonstrate that these barriers can be effectively navigated across multiple APM and product types, providing a practical framework for APM execution.

3.3.1 Example 1: OBAs for Oncology Treatments Bevacizumab and Gefitinib

A pilot OBA between Priority Health, a US payer, and Genentech, a biotechnology company, for oncology treatment *bevacizumab* for non-small cell lung cancer (NSCLC) addressed uncertainty and successfully navigated issues around data requirements, privacy, and government price reporting [81]. Notably, in an article detailing lessons learned from the scheme, the parties identified all four of the key challenges described above and describe how they were mitigated or overcome [81]. A pragmatic approach was taken to establish the rebate threshold using the endpoint of progression-free survival. Patient eligibility was determined through agreed-upon practical assumptions, and reasons for treatment discontinuation—a part of the rebate criteria—were ascertained using electronic health record data. When these data were unavailable, treatment records were obtained from providers by the payer with support from the manufacturer. Potential effects on government price reporting were manageable given the scale and duration of the scheme. The parties emphasised the importance of pragmatism and collaboration in the implementation of OBAs.

An OBA between the Catalan Health System and AstraZeneca for the oncology product *gefitinib* effectively addressed payer challenges around uncertainty and imposed little additional cost burden for implementation [49, 82]. The scheme was motivated by value uncertainty, particularly around the translatability of real-world evidence; in addition to the statistical uncertainty surrounding gefitinib from trial results, there were additional uncertainties linked to the effectiveness of the compound in the Spanish population, as the pivotal studies were conducted in Asian patients. Costs were quantified and noted as minimal, due to the existing enabling data infrastructure in place to administer the agreement. However, the report by Clopes and colleagues detailing the scheme recognises that the enabling infrastructure that was available in the Catalan Health Service (CalSalut) may not be available in other health systems, highlighting the reality that the best choice, design, and ultimate feasibility of APMs may be contingent on factors specific to the local context.

3.3.2 Example 2: Instalment and OBA Models for Gene Therapies Zolgensma and Luxturna

Outcome-based agreements and instalment models for high-cost gene therapies *zolgensma* and *luxturna* have been employed to address payer challenges around uncertainty and budget impact [37, 39, 83]. Both are gene therapies that treat rare diseases and bring potentially life-altering benefits to patients.

In the case of *luxturna*, the manufacturer, Spark Therapeutics, contracted with several US payers and commercial insurers [39]. The parties identified an instalment-style scheme to address problems related to the time horizon of cost-effectiveness assessment, as well as to mitigate payer concerns around budget impact. An OBA component was also proposed to address budget risk and value uncertainty issues. The proposals were designed to carefully navigate regulatory barriers that hinder instalment or OBA models, and both sides intend to collaborate with regulators in finding ways to overcome these barriers going forward [39].

AveXis has also offered payers an APM, which combines the instalment and OBA models for its spinal muscular atrophy product *zolgensma* [37, 38]. The wholesale acquisition cost of the product was $2.125 million in 2019, raising concerns about the budget impact of the product in the face of uncertain value. The initial clinical evidence available to demonstrate its value was limited to a single-arm, open-label study with a median follow-up of two years, generating uncertainty about the extent of its efficacy as well as its safety and durability [84]. Instalments served to "*ease possible short-term budget constraints*", and an outcomes-based component was offered to reduce the cost-effectiveness risk associated with uncertain outcomes [37]. This type of scheme was implemented in Italy, while other countries addressed uncertainty concerns with conditional coverage approaches [85, 86]. Registries have also been established or utilised to monitor appropriate prescribing in certain health systems [87].

3.3.3 Example 3: Subscription Model for Direct-Acting Antivirals (DAAs)

Subscription agreements between manufacturers of DAAs and Australian payers facilitated broader patient access by addressing concerns around budget impact and the scope of value assessment and negotiation [43]. The model addressed two core contracting problems: first, the scope of value assessment and negotiation across a patient population with heterogeneous expected net benefit. Payers could offer universal access to DAAs because the marginal cost was low, meaning that "*the payer need not unduly restrict patient access*" only to patients expected to have the highest clinical benefit from treatment [43]. The model has also addressed a second core contracting problem: budget risk. Fixing annual payments benefits payers by eliminating budget uncertainty as well as benefiting manufacturers by providing them with cash-flow stability.

Subscription models face fewer implementation barriers related to data requirements and contractual complexity. In this example, external reference pricing was not a concern as the two-part tariff pricing model complicates efforts of other countries to negotiate prices downwards based on the price of DAAs in Australia. Given that the scheme was voluntary, participation by the payer and manufacturers indicates that the scheme was mutually beneficial [43].

Table 4 maps each example to the framework. Despite the successful examples shown here, further practical steps can be made towards improving health system and country readiness to effectively consider, negotiate and implement APMs. These include: data tracking of utilisation and/or outcomes; appropriate contract/billing infrastructure that meets the requirements of the APM; an enabling legal framework for contracting and data capture; a regulatory environment that facilitates workable APM compliance with government price regulations and reporting; and, most importantly, buy-in across stakeholders that such arrangements are a beneficial tool that can support patient access to cost-effective therapies [5, 79, 82]. While the taxonomy can help stakeholders articulate core problems and map them to potential APM solutions, improved stakeholder (openness to) collaboration is needed for effective APM implementation to realise the full potential value that APMs can bring.

4 Discussion

We proposed a decision guide that can help payers and manufacturers identify potential solutions to contracting challenges and successfully implement the right payment model. When assessing the need to propose APMs during the negotiation process, stakeholders should start by articulating the core problem they face and identifying whether it is fundamentally a contracting issue—for which an APM may be useful—or a 'pure' price negotiation issue, for which a simple discount may suffice. The guide allows payers to make informed decisions by mapping the core contracting problem(s) to potential APM solutions.

Once potential APM solutions are identified, the payer and manufacturer should assess the implementation feasibility and choose the right model design in order to overcome implementation barriers. Who initiates APMs, and when, may vary between countries, but experiences with APMs demonstrate that payer-manufacturer collaboration is a key step to successfully identify and implement a feasible 'win-win' solution tailored to unique characteristics of the health system and products [2]. By addressing the

Table 4 Framework for effective APM implementation: evidence from case studies

Example of APM implementation	Articulate the core problem	Map problems to solutions	Assess feasibility of implementation	Payer-manufacturer collaboration
1. OBAs for oncology treatments bevacizumab and gefitinib	Value uncertainty within a subgroup	OBAs	Issues around data requirements, privacy, and government price reporting were successfully navigated	Partnerships were essential in overcoming data barriers and implementing rebates
2. Instalment and OBA models for gene therapies zolgensma and luxturna	Budget impact and uncertainty Value uncertainty within a subgroup Scope of value assessment and negotiation	OBAs Conditional coverage Instalments	APM choice and design were informed by regulatory constraints and context-specific data collection infrastructure	Collaboration between payers, manufacturers, and regulators recognised as key approaches to overcome implementation barriers
3. Subscription model for DAAs	Scope of value assessment and negotiation Budget impact and uncertainty	Subscription model	The subscription model faced fewer implementation barriers than many other APMs	Mutually beneficial scheme between the payer and four DAA manufacturers

APM alternative payment model, *DAA* direct-acting antivirals, *OBA* outcome-based agreement

key challenges that can arise in assessing or paying for drugs, APMs can benefit all system stakeholders, but successful implementation requires that these stakeholders work together to realise this.

Our findings contribute to ongoing discussions on drug pricing and reimbursement reforms by offering a broad taxonomy of APMs and the challenges they address, along with considerations and success factors for implementation. A limitation of our work is that it only considers contracting solutions, when other non-contracting alternatives—such as risk pools or reinsurance—may also be available to address specific payer challenges [88]. Recognising that APM contracting is incredibly product- and context-dependent, our work can serve as a useful guide to at least consider the main factors in APM negotiation and implementation. The guide could be made more effective if complemented by further research that assesses when and how different APM types can be combined. Users could also be well served by additional resources offering a more comprehensive understanding of how the most appropriate APM type and design in a particular situation will depend on product- and context-specific factors. The framework could be further strengthened through a multi-stakeholder consensus generating exercise to refine and validate it, which we propose would be a worthwhile next step.

The proposed step-by-step framework can aid payers and manufacturers in the process of effectively identifying, agreeing on, and implementing APMs where they can address challenges in the process of contracting for medical innovations. While several barriers to APM implementation remain, the shifting landscape of medical innovation means that payers and manufacturers should increasingly consider APMs as a way to advance patient access to cost-effective medicines and provide efficient incentives for future innovation. Appropriate usage of APMs can help health systems achieve objectives around improved patient access to innovation, better alignment of price and value, improved fiscal sustainability, and efficient incentives for bio-pharmaceutical R&D.

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