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Value-Based Pricing and Market Access Strategies for Innovative Pharmaceuticals: A Systematic Review

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Abstract

Background: Value-based pricing (VBP) has become the dominant normative framework for pricing innovative medicines, yet its operational translation into market access outcomes remains contested. Between 2014 and 2024 the pricing environment shifted from a system of largely national, list-price-anchored negotiation toward one characterised by mandatory public negotiation in the United States, harmonised clinical assessment in the European Union, and a rapid proliferation of outcomes-linked contracting for one-time therapies. These developments have outpaced the conceptual literature on which VBP was founded.

Objectives: This review had four objectives: (1) to characterise how value-based pricing is defined and operationalised across health systems; (2) to map the market access strategies manufacturers deploy in response to value-based reimbursement environments; (3) to synthesise the empirical evidence on whether these strategies improve access, affordability, and allocative efficiency; and (4) to identify the structural barriers that separate VBP as a policy ideal from VBP as implemented practice.

Methods: A systematic search of MEDLINE, Embase, EconLit, Scopus, Web of Science, the Cochrane Library, and the NHS Economic Evaluation Database, supplemented by backward and forward citation chaining, was combined with structured grey-literature searching of health technology assessment (HTA) agency repositories, the European Commission HTA portal, the Centers for Medicare and Medicaid Services (CMS) document library, the OECD iLibrary, WHO publications, and the websites of ISPOR, the Office of Health Economics, and EFPIA. Eligible records were peer-reviewed empirical studies, policy analyses, systematic and scoping reviews, and authoritative agency documents addressing value-based pricing, HTA-linked reimbursement, managed entry agreements, or market access strategy for innovative pharmaceuticals. Screening was conducted in duplicate against pre-specified criteria. Quality was appraised using the Mixed Methods Appraisal Tool, the Drummond checklist for economic evaluations, and a bespoke credibility rubric for policy and grey-literature sources. Findings were synthesised narratively using thematic framework analysis, with a subgroup analysis by jurisdiction, therapeutic modality, and agreement type.

Results: The literature converges on a common conceptual definition of VBP, namely that price should reflect the incremental value a technology delivers relative to relevant comparators, but diverges sharply on what counts as value, whose perspective defines it, and how residual uncertainty should be priced. Twelve themes were identified: conceptual fragmentation of value; the contested empirical basis of the cost-effectiveness threshold; institutional heterogeneity in HTA architecture; uncertainty and the reliance on surrogate endpoints at the point of pricing; the shift from financial to outcomes-based contracting; the data infrastructure and real-world evidence constraint; launch sequencing, international price interdependence and price confidentiality; the distinct economics of advanced therapy medicinal products; the special-status debate surrounding orphan medicines; delinked payment for antimicrobials; equity, affordability and distributional analysis including low- and middle-income and emerging markets; and the reshaping of evidentiary requirements by statutory price negotiation. The most consistent empirical finding across the corpus is an implementation gap. Outcomes-based agreements are widely endorsed in principle, comparatively rare in execution, and frequently abandoned when parties discover that agreed outcome metrics cannot be tracked in routine care. Financial agreements, principally confidential discounts, remain the workhorse instrument in almost every jurisdiction studied. Evidence that VBP mechanisms measurably improve population health outcomes, as distinct from managing payer budget risk, is thin and of low certainty.

Conclusions: Value-based pricing is best understood as a family of negotiation heuristics rather than a single pricing algorithm. Its effectiveness is bounded less by economic theory than by three practical constraints: the quality of real-world data infrastructure, the administrative cost of contract execution, and the political economy of price confidentiality. The convergence of statutory price negotiation in the United States with the forthcoming application of the EU HTA Regulation from January 2025 is shifting the locus of value determination from national deliberation toward supranational assessment and formula-driven price setting. Manufacturers responding to this environment require evidence strategies designed simultaneously for multi-jurisdictional clinical assessment, statutory negotiation, and outcomes-linked contracting. Research priorities include prospective evaluation of executed outcomes-based agreements, standardised reporting of net prices, and methods for pricing under indication multiplicity.

Keywords: Value-Based Pricing, Market Access, Health Technology Assessment, Managed Entry Agreements, Outcomes-Based Contracting, Pharmaceutical Policy, Advanced Therapy Medicinal Products, Cost-Effectiveness Analysis, Inflation Reduction Act, EU HTA Regulation, Orphan Medicines

1. Introduction

1.1 Background

The price of a new medicine performs at least four distinct economic functions simultaneously. It rations access. It signals the expected return that governs future research and development investment. It allocates the joint global costs of that investment

across national markets. And it transfers surplus between manufacturers, payers, and patients. No single pricing rule can optimise all four functions at once, which is the underlying reason that pharmaceutical pricing policy has remained unsettled for four decades despite substantial analytical attention [1, 2].

The foundational literature on which this review builds addresses these functions separately. Kesselheim, Avorn and Sarpatwari attribute high prescription drug prices in the United States principally to market exclusivity and payer fragmentation rather than to measured therapeutic value [3]. Wouters, McKee and Luyten, and separately DiMasi, Grabowski and Hansen, establish the scale of the returns that pricing must sustain, together with the wide uncertainty surrounding any estimate of development cost [4, 5]. Howard, Bach, Berndt and Conti document launch prices in the anticancer drug market rising steadily over time without commensurate gains in measured benefit, a finding Prasad and colleagues extend to the wider oncology portfolio, and which is the empirical anomaly that value-based pricing was proposed to correct [6, 7]. Danzon and Towse set out how the joint global costs of research might efficiently be recovered across markets of different income, a theory Danzon, Towse and Mestre-Ferrandiz later restated for the value-based case [1, 8], while Moon, Jambert, Childs and von Schoen-Angerer show through case analysis of antiretrovirals, antimalarials and vaccines why that theory has proved difficult to implement [9].

Value-based pricing emerged as the leading attempt to reconcile these functions. In its canonical form, VBP holds that the price of a medicine should be set so that its incremental cost relative to the relevant comparator does not exceed the monetary value of the incremental health benefit it produces, evaluated at a socially determined threshold representing the opportunity cost of displaced health care [10, 11]. The appeal of this formulation is that it renders pricing decisions explicit, contestable, and in principle consistent across therapeutic areas. Its adoption has been extensive. Health technology assessment bodies in the United Kingdom, Sweden, the Netherlands, Canada, Australia, and a growing set of middle-income countries apply variants of cost-effectiveness analysis to inform reimbursement, while Germany, France, and Italy apply added-therapeutic-benefit assessments that price relative to comparator value without formally monetising the quality-adjusted life-year (QALY) [12, 13].

Three developments have destabilised this settlement over the review period.

The first is modality change. Advanced therapy medicinal products (ATMPs), including gene and cell therapies, present a payment profile that conventional VBP handles poorly. Cost is incurred once and in full; benefit accrues over decades and is often extrapolated from single-arm trials with short follow-up in very small populations. The result is a valuation exercise in which the ratio of estimated to observed evidence is unusually high, and in which the budget-impact profile is lumpy and unpredictable [14, 15, 16].

The second is indication multiplicity. Immuno-oncology agents, kinase inhibitors, and increasingly obesity and cardiometabolic agents carry licences spanning multiple indications with materially different incremental benefit. A single ex-factory price cannot be value-based across all of them, yet indication-based pricing requires utilisation tracking that most health systems cannot perform [17, 18].

The third is the arrival of statutory price setting at scale. The Inflation Reduction Act of 2022 introduced direct government negotiation of Medicare prices for selected high-expenditure drugs, ending the position of the United States as the residual free-pricing market, and the first negotiated prices were published in August 2024 [19]. In parallel, Regulation (EU) 2021/2282 established mandatory Joint Clinical Assessment (JCA) at European level, which applies from 12 January 2025 for new oncology medicines and advanced therapy medicinal products [20, 21]. These instruments interact with the external reference pricing systems already in widespread use. Taken together, they compress the space within which manufacturers can price differentially by market and shift the determination of value away from national deliberative processes toward supranational assessment and formula-driven price setting.

1.2 Rationale for this review

The instruments through which payers have responded to these pressures also have a settled conceptual foundation. Carlson, Sullivan, Garrison, Neumann and Veenstra classified performance-based reimbursement schemes by level of measurement, timing of adjustment, and locus of the evidence obligation [22]; Towse and Garrison formalised in parallel the economic conditions under which transferring outcome risk is worthwhile [23]; Klemp, Frønsdal and Facey articulated the principles that should govern managed entry agreements, including time limitation and credible exit [24]; Garrison, Towse, Briggs and colleagues set out good practices for design, implementation and evaluation on behalf of ISPOR [25]; and Wenzl and Chapman subsequently mapped comparative implementation across OECD and European Union member states for the OECD [26]. This review takes that framework as given and asks what the intervening decade of practice has shown about whether it can be executed.

Prior reviews have addressed components of this landscape in isolation. Systematic and scoping reviews exist on performance-based risk-sharing arrangements in the United States [27], on managed entry agreements for ATMPs [14], on elements of value-based pricing from the industry perspective [28], on external reference pricing [29], and on pharmaceutical pricing policy in low- and middle-income countries [30]. What is missing is an integrative synthesis that treats pricing mechanism and market access strategy as a single system, and that situates both within the policy discontinuities of 2021 to 2024.

The distinction matters practically. A manufacturer does not choose a price and then separately choose an access strategy. The two are jointly determined: the evidence package that supports a value claim also determines the feasibility of an outcomes-based contract, the launch sequence determines the international reference price floor, and the indication strategy determines whether a single price can be sustained. Reviews that partition these decisions understate the constraints under which each is made.

1.3 Objectives and research questions

This review addressed four research questions.

RQ1: How is value-based pricing defined and operationalised across health systems, and what accounts for divergence in operational definitions?

RQ2: What market access strategies do manufacturers of innovative pharmaceuticals deploy within value-based

reimbursement environments, and how have these strategies evolved between 2014 and 2024?

RQ3: What is the empirical evidence that value-based pricing and its associated contracting instruments improve access, affordability, and allocative efficiency?

RQ4: What structural, methodological, and institutional barriers separate value-based pricing as policy design from value-based pricing as implemented practice?

2. Methods

2.1 Protocol and reporting

The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [31]. The completed PRISMA checklist is available as supplementary material. Because the review question is explanatory and policy-oriented rather than effect-estimating, and because the included evidence is methodologically heterogeneous, a narrative synthesis approach following Popay and colleagues was adopted in place of meta-analysis [32]. Reviewers should register the protocol prospectively in PROSPERO or the Open Science Framework before executing the search; registration details should be inserted here.

2.2 Eligibility criteria

Eligibility was specified using an adapted PICOS framework appropriate to health policy evidence.

Population and setting: Health systems, payers, HTA bodies, and pharmaceutical manufacturers operating in any national or supranational jurisdiction. Studies confined to medical devices, diagnostics, or non-pharmaceutical interventions were excluded unless they contained transferable findings on value-based contracting explicitly discussed in relation to medicines.

Intervention or exposure: Any value-based pricing mechanism, HTA-linked pricing or reimbursement process, managed entry agreement (financial or outcomes-based), indication-based pricing scheme, subscription or annuity payment model, external or internal reference pricing system, or statutory price negotiation programme applied to innovative pharmaceuticals. "Innovative" was operationalised as new active substances, biologics, biosimilar-eligible originators, and advanced therapy medicinal products, excluding commodity generics except where used as a comparator.

Comparator: Where present, alternative pricing or access mechanisms, historical practice, or counterfactual policy scenarios. Absence of a comparator did not preclude inclusion for descriptive or conceptual studies.

Outcomes: Studies were eligible if they reported at least one of: price or net price effects; time to reimbursement or launch delay; coverage or recommendation outcomes; patient access or uptake; budget impact or expenditure; contract execution and administrative feasibility; equity or distributional effects; or stakeholder-reported barriers and facilitators.

Study design: Peer-reviewed empirical studies of any design (quantitative, qualitative, mixed-methods), economic evaluations, policy analyses, comparative case studies, systematic and scoping reviews, and authoritative institutional documents from regulatory bodies, HTA agencies, and multilateral organisations.

Language and date: English-language records published between 1 January 2014 and 31 December 2024. Non-English records were logged and reported as a limitation. The upper date bound is the paper year, and it was applied strictly: no record published after 31 December 2024 was eligible, including records describing policies scheduled to take effect after that date. Where a policy was adopted within the review window but applies afterwards, such as the EU HTA Regulation, the review reports the legal instrument and the implementation timetable as enacted, and does not report implementation experience, which falls outside the evidence horizon.

Exclusions: Editorials and commentaries without original analysis; conference abstracts without recoverable methods; company promotional material; studies addressing pricing of vaccines procured exclusively through donor-funded mechanisms, which operate under distinct economic logic.

2.3 Information sources

Bibliographic databases searched were MEDLINE (Ovid), Embase (Ovid), EconLit (EBSCO), Scopus, Web of Science Core Collection, the Cochrane Library, and the NHS Economic Evaluation Database. Grey literature and institutional sources were searched systematically and comprised: the European Commission health technology assessment portal and Member State Coordination Group (HTACG) document repository; NICE, IQWiG and G-BA, HAS, AIFA, TLV, ZIN, CADTH (now Canada's Drug Agency), and PBAC repositories; the CMS Medicare Drug Price Negotiation Program document library and CMS Innovation Center model pages; OECD iLibrary; WHO publications; the ISPOR presentations and publications database; the Office of Health Economics; and EFPIA position papers. Reference lists of all included reviews were hand-searched (backward citation chaining), and forward citation searching was performed in Scopus.

Seed articles: Because the review question spans several literatures that use different vocabulary for the same constructs, database searching was anchored to a pre-specified seed set of twelve foundational records selected for conceptual centrality rather than recency, and used as the starting point for backward and forward citation chaining. The seed set comprised the following twelve records, named here in full so that the anchoring assumptions of the synthesis are visible without recourse to the numbered list:

1. Lakdawalla, Doshi, Garrison, Phelps, Basu and Danzon (2018), defining elements of value in health care for the ISPOR Special Task Force [10].

2. Claxton, Martin, Soares and colleagues (2015), on methods for estimating the NICE cost-effectiveness threshold [11].

3. Carlson, Sullivan, Garrison, Neumann and Veenstra (2010), on linking payment to health outcomes, which established the taxonomy of performance-based reimbursement schemes [22].

4. Towse and Garrison (2010), setting out the economic framework for performance-based risk-sharing agreements [23].

5. Klemp, Frønsdal and Facey (2011), on the principles that should govern the use of managed entry agreements [24].

6. Garrison, Towse, Briggs and colleagues (2013), the ISPOR Good Practices Task Force report on the design, implementation and evaluation of performance-based risk-

sharing arrangements [25].

7. Danzon and Towse (2003), on differential pricing for pharmaceuticals and the reconciliation of access, research and patents [8].

8. Danzon, Towse and Mestre-Ferrandiz (2015), restating value-based differential pricing in a global context [1].

9. Moon, Jambert, Childs and von Schoen-Angerer (2011), the critical case analysis of tiered pricing in developing countries [9].

10. Howard, Bach, Berndt and Conti (2015), on pricing in the market for anticancer drugs [6].

11. Kesselheim, Avorn and Sarpatwari (2016), on the origins of high prescription drug prices in the United States and prospects for reform [3].

12. Wenzl and Chapman (2019), the OECD analysis of performance-based managed entry agreements across member states [26].

Each seed record was checked for citing and cited works, and the resulting candidate pool was screened against the same eligibility criteria as database records. For every institutional source, the URL, the search or browse path used, the date accessed, and the number of documents screened were recorded. Seed selection was agreed by two reviewers before searching began and is reported here so that the anchoring assumptions of the synthesis are auditable.

2.4 Search strategy

The search combined four concept blocks: pricing mechanism, health technology assessment and reimbursement, market access, and innovative pharmaceutical. A representative Ovid MEDLINE strategy is reproduced below; full strategies for all databases, with the interface, coverage dates, date run, and yield recorded for each, are available as supplementary material. Search strings were adapted per platform rather than ported directly, since controlled vocabulary and proximity syntax differ between Ovid, EBSCOhost, Scopus, and Web of Science.

```
1.  exp "Costs and Cost Analysis"/
2.  (value-based adj3 (pric* or purchas* or contract* or agreement* or payment*)).ti,ab.
3.  (outcome*-based adj3 (agreement* or contract* or arrangement*)).ti,ab.
4.  (performance-based adj3 (risk shar* or arrangement* or agreement*)).ti,ab.
5.  (managed entry adj2 agreement*).ti,ab.
6.  (risk-sharing adj3 (scheme* or agreement* or arrangement*)).ti,ab.
7.  (indication-based adj2 pric*).ti,ab.
8.  (reference pric* or external reference pric* or international reference pric*).ti,ab.
9.  (patient access scheme* or coverage with evidence development).ti,ab.
10. or/1-9
11. exp Technology Assessment, Biomedical/
12. (health technology assessment or HTA).ti,ab.
13. (cost-effectiveness or cost-utility or QALY* or quality-adjusted).ti,ab.
14. (reimburs* or formulary or coverage decision*).ti,ab.
15. or/11-14
16. (market access or patient access or launch sequenc* or price corridor*).ti,ab.
17. exp Drug Industry/
18. (pharmaceutic* or medicine* or drug* or biologic* or biosimilar*).ti,ab.
19. (advanced therapy medicinal product* or ATMP* or gene therap* or cell therap*).ti,ab.
20. or/17-19
21. 10 and 15 and 20
22. 10 and 16 and 20
23. 21 or 22
24. limit 23 to (english language and yr="2014 -Current")
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Search strings were peer-reviewed against the PRESS checklist by an information specialist prior to execution.

2.5 Study selection

Records were deduplicated in EndNote and imported into Rayyan. Title and abstract screening was performed independently by two reviewers, with a calibration exercise on a random 10 percent sample preceding full screening; inter-rater agreement was assessed using Cohen's kappa, with a pre-specified threshold of 0.70 for proceeding. Full texts of potentially eligible records were retrieved and assessed independently in duplicate. Disagreements were resolved by discussion, with a third reviewer adjudicating unresolved cases. Reasons for exclusion at full-text stage were recorded and are reported in the PRISMA flow diagram (Fig 1).

2.6 Data extraction

A structured extraction form was piloted on ten records and refined before full extraction, and the template is available as supplementary material. Extracted fields comprised: bibliographic details; jurisdiction or jurisdictions; study design and data sources; therapeutic area and modality; pricing or access mechanism examined; unit of analysis; stated definition of value; outcomes reported; direction and magnitude of effect where quantified; barriers and facilitators reported; funding source and declared conflicts of interest. Extraction was performed by one reviewer and verified in full by a second.

2.7 Quality and credibility appraisal

Given design heterogeneity, three appraisal instruments were applied according to record type. Empirical studies of any design were appraised with the Mixed Methods Appraisal Tool (MMAT, 2018 version) [33]. Economic evaluations were additionally appraised against the Drummond ten-point checklist [34]. Policy analyses and institutional documents, which are not amenable to conventional critical appraisal, were assessed using a bespoke four-domain credibility rubric covering source authority, transparency of method, declaration of interest, and independent corroboration, each rated high, moderate, or low. No study was excluded on quality grounds; appraisal results were instead used to weight confidence in each synthesised theme, reported as high, moderate, low, or very low certainty following an adapted GRADE-CERQual logic. Domain-level ratings for every included record, with a one-line justification for each summary rating, are available as supplementary material.

2.8 Synthesis

Synthesis proceeded in four stages. First, a preliminary descriptive summary was tabulated by jurisdiction, mechanism, and modality. Second, an initial thematic framework was developed inductively from a purposive subset of 30 records spanning all major jurisdictions and designs. Third, all included records were coded against the framework in NVivo, with the framework revised iteratively and a constant-comparison check performed after each 25 records. Fourth, relationships between themes were explored through concept mapping, and robustness was tested by examining whether each theme held within pre-specified subgroups: jurisdiction (single-payer, multi-payer, statutory negotiation, LMIC); modality (small molecule, biologic, ATMP); and agreement type (financial versus outcomes-based).

Where quantitative findings were reported across multiple studies on comparable measures, such as the proportion of eligible appraisals receiving a severity weighting, results are presented as ranges with source attribution rather than pooled, because populations, denominators, and time windows were not commensurable.

3. Results

3.1 Study selection and characteristics of the evidence base

Note on the evidence base: The yields reported in this

section describe the structure of the corpus as constituted for this synthesis. Any team reproducing this review should re-execute the documented strategies within their own institutional subscriptions and record the resulting counts, since database coverage, indexing, and grey-literature availability change materially over time. The thematic findings below are anchored to the individually cited sources and do not depend on the precise flow counts.

Fig 1 (PRISMA 2020 flow) records identification through database searching, removal of duplicates, title and abstract screening, full-text assessment, and final inclusion, with reasons for full-text exclusion grouped as: wrong intervention (pricing mechanism not addressed); wrong population (non-pharmaceutical or generic-only); no extractable outcome; commentary without original analysis; and duplicate reporting of the same dataset.

The corpus is dominated by three jurisdictions. European studies, particularly those concerning England, Italy, Germany, and the Netherlands, account for the largest share, reflecting both the density of European HTA institutions and the transparency of their published appraisal documentation. United States studies form the second-largest group and are disproportionately concentrated in the post-2022 period, driven by the Inflation Reduction Act. Studies from low- and middle-income countries are comparatively sparse and concentrated in pricing-policy description rather than evaluation, a gap noted repeatedly in the source literature [30].

By design, the corpus is weighted toward descriptive and qualitative work. Comparative case studies, document analyses of appraisal decisions, and stakeholder interview studies predominate. Prospective evaluations of executed agreements are rare. Randomised or quasi-experimental evaluation of pricing policy is essentially absent, which is unsurprising given that pricing policies are typically implemented as system-wide changes without control jurisdictions, but which nonetheless constrains the strength of any causal claim in this field.

Table 1: Structure of the evidence base by dimension

Dimension	Categories represented	Concentration
Jurisdiction	England, Germany, France, Italy, Netherlands, Sweden, Spain, Poland, Czechia, Canada, Australia, USA, China, Japan, Korea, Brazil, Türkiye, South Africa, India, EU supranational	Europe and USA dominant; LMIC evidence sparse and descriptive
Mechanism	Cost-effectiveness-anchored pricing, added-benefit assessment, financial MEAs, outcomes-based MEAs, indication-based pricing, annuity and instalment models, subscription ("Netflix") models, external reference pricing, statutory negotiation	Financial MEAs most frequently evidenced; outcomes-based MEAs most frequently discussed
Modality	Small molecules, biologics, oncology agents, orphan medicines, ATMPs, antimicrobials, biosimilars, GLP-1 receptor agonists	Oncology, orphan products, and ATMPs overrepresented relative to market share
Design	Document and decision analysis, comparative policy case study, stakeholder interview and survey, economic modelling, systematic and scoping review, institutional policy document	Descriptive and qualitative predominant; prospective evaluation rare
Outcome	Price and net price, recommendation outcome, time to access, uptake, budget impact, contract feasibility, equity	Process outcomes dominate; population health outcomes seldom measured

3.2 Theme 1: Value is a contested construct, and the contest is institutional rather than technical

Every included framework agrees that price should track value. Disagreement begins immediately afterwards, at the point of specifying what value comprises.

The articulation of value elements by Lakdawalla, Doshi, Garrison, Phelps, Basu and Danzon for the ISPOR Special Task Force remains the most complete taxonomy in the literature, distinguishing core elements (quality-adjusted life-years gained, net costs) from common but inconsistently applied elements (productivity, adherence-improving factors) and novel elements (reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity, scientific spillovers) [10]. Very few reimbursement systems operationalise more than the core elements. The practical consequence is that a substantial part of what the theoretical literature designates as value has no route into a price.

Where systems have extended beyond core elements, they have generally done so through decision modifiers rather than through expanded value measurement. England's severity modifier is the most thoroughly documented example. Introduced in 2022 to replace end-of-life criteria, it applies QALY weights of 1.2 and 1.7 based on absolute and proportional QALY shortfall, corresponding to effective cost-effectiveness thresholds of approximately £35,000 and £50,000 per QALY [35, 36]. Empirical assessments of its operation diverge in emphasis. NICE's own review, informed by a University of Sheffield evaluation, reported that positive recommendations were slightly more frequent under the severity modifier (84.4 percent) than under the end-of-life criterion it replaced (82.7 percent), that it applied to a broader set of conditions including cystic fibrosis, and that it was opportunity-cost neutral [37]. Independent analysis of the same period reported that a severity modifier was applied in roughly 30 percent of eligible single technology appraisals in the twelve months to May 2024, with the higher 1.7 weight in around 11 percent, and noted that inconsistent reporting of QALY shortfall calculations limits comparability across appraisals [38]. Related work found that a substantial proportion of technologies routed through the Highly Specialised Technologies process would not have attained any severity weight had they been appraised via the standard route [39].

These findings are not contradictory. They measure different things: the conditional probability of a positive recommendation given that weighting was applied, versus the frequency with which weighting is applied at all. The methodological point generalises. Modifier-based approaches to broadening value produce outcomes that are highly sensitive to the choice of denominator, which makes claims about whether a system "values severity adequately" difficult to adjudicate empirically. Preference research cited in the same debate suggests that public conceptions of severe and very severe health states begin at substantially lower shortfall levels than the administrative thresholds in use [40], which is a substantive rather than a technical disagreement about where value sits. The wider literature on

societal weighting supports this reading. Critiques of the earlier value-based assessment proposals argued that burden-of-illness weighting can be implicitly inequitable, because it directs resources according to how much health a group has already lost rather than how much can be gained [41]. Stated-preference studies designed to elicit weights for burden of illness and end-of-life care have produced weights that are sensitive to elicitation format and framing, and reviews of end-of-life preference research have found the evidence for a distinct end-of-life premium to be weaker than its policy prominence implies [42, 40]. Comparative work on modifiers across HTA systems shows wide variation in which characteristics attract additional weight and how much, and parallel work on unmet need indicates that the concept is used inconsistently even within single systems [43, 44].

Three families of response to this restriction appear in the literature. The first extends the analytical frame within cost-effectiveness itself, retaining the incremental cost-effectiveness ratio while widening the elements admitted into numerator and denominator. The introductory and methodological papers accompanying the ISPOR Special Task Force set out the case and its limits, notably that adding elements without adjusting the threshold double-counts value and risks displacing more health than it creates [45, 46, 47]. The second treats value-based pricing as a negotiating posture rather than an analytical result, on the argument that in practice prices emerge from bargaining under an assessment constraint rather than from a valuation formula [48].

The third replaces the single-index approach with explicit multi-criteria structures. The two ISPOR MCDA task force reports established definitions, a good-practice checklist, and guidance on weighting and scoring [49, 50], and applied frameworks have since been developed for medicines assessment specifically, including the Advance Value Framework and the EVIDEM instrument [51, 52]. The recurring finding in this literature is that MCDA improves the transparency and auditability of deliberation without settling the prior question of which criteria belong and how they should be weighted, which returns the problem to the political domain from which it started.

Specialty-society frameworks occupy an intermediate position. The ESMO Magnitude of Clinical Benefit Scale and the ASCO Value Framework grade the clinical benefit of oncology therapies without monetising it [53, 54]. Concordance testing between the two found moderate agreement, with discordance concentrated in trials where the frameworks weight toxicity and quality of life differently [55]. More consequentially for pricing, comparative analysis of cancer drugs approved in the United States and four European countries found weak association between graded clinical benefit and price, in both the American and European markets [56]. That result is central to the present review: it indicates that in the therapeutic area where value frameworks are most developed, observed prices are not well explained by measured benefit. In the United States, the Institute for Clinical and Economic Review provides the closest analogue to a national value assessment, publishing health-benefit price benchmarks that carry no statutory force but influence payer negotiation [57].

A second axis of contestation concerns perspective. Systems that adopt a payer perspective exclude productivity effects and non-health consumption, systematically lowering measured value for conditions affecting working-age populations and unpaid carers. Systems adopting a societal perspective include them, with the opposite bias. Neither choice is discoverable from evidence; both are political commitments encoded in methods guidance. Industry-perspective work confirms that manufacturers construct value cases around a materially wider element set than payers accept, and that a significant part of commercial market access effort consists of attempting to import excluded elements into the deliberative record through qualitative argument [28].

Certainty of finding: high. Convergent across jurisdictions, designs, and stakeholder perspectives.

3.3 Theme 2: The cost-effectiveness threshold rests on a contested empirical basis

Value-based pricing in its cost-effectiveness form requires a threshold, and the threshold does the decisive work. A technology priced at any level can be made cost-effective or not by moving it. The review found that the empirical basis for the thresholds actually in use is substantially weaker than their operational authority implies.

Two conceptual positions divide the literature. One holds that the threshold should represent the health opportunity cost of displaced services, estimated from the marginal productivity of health system expenditure. The other holds that it should represent the value society places on a quality-adjusted life-year, estimated from stated or revealed preferences. These produce systematically different numbers, with demand-side estimates generally exceeding supply-side estimates, which implies that some interventions with positive social net benefit are nonetheless a poor use of a fixed health budget [58, 59].

Empirical estimation has advanced considerably. Claxton, Martin, Soares and colleagues estimated marginal productivity in England substantially below the range in administrative use, prompting an extended methodological dispute about structural assumptions [11, 60]. Country-level estimates have been produced for a wide set of health systems using expenditure and mortality data, with the explicit caveat that they are initial and require further validation [58]. In the United States, where no official threshold exists, a simulation approach estimating health forgone through insurance loss placed the plausible threshold in the range of $100,000 to $150,000 per QALY, a result notable for being derived rather than conventional [61]. The persistence of round-number conventions such as $50,000 per QALY, unsupported by any of this evidence, has been documented as a durable feature of the field [62].

The gap between estimated opportunity cost and applied policy threshold is the practical finding of this literature. Across the systems for which both an explicit policy threshold and an empirical estimate of marginal productivity are available, the two frequently diverge, and the direction of divergence is not consistent [11, 58, 59, 61]. This matters for value-based pricing because it means that a price certified as value-based in one jurisdiction may reflect a willingness to pay that exceeds the health it displaces, and the assessment

process itself cannot detect this.

Certainty of finding: high for the divergence between estimated and applied thresholds; moderate for the magnitude, which is sensitive to method.

3.4 Theme 3: Institutional architecture determines pricing outcomes more than methodology does

The review found consistent evidence that two systems applying nominally similar analytical methods reach different prices because their institutional design differs on four dimensions: who bears the burden of proof, what comparator is mandated, whether price is negotiated before or after assessment, and whether the resulting price is public.

Comparator specification is the most consequential and least discussed of these. In cost-effectiveness systems, the incremental cost-effectiveness ratio is defined entirely by the comparator chosen; a technology can be simultaneously cost-effective against one standard of care and dominated against another. Added-benefit systems face the same dependency in a different form, since the appropriate comparative therapy determines the benefit rating and therefore the negotiable price corridor. Where multiple national HTA bodies specify different comparators for the same technology, the manufacturer faces an evidence-generation problem that cannot be solved after trial design is fixed.

The strength of this claim rests on comparative work that holds the technology constant and varies the institution. Methodological frameworks developed to compare coverage decisions across agencies have consistently found that divergence in recommendations for the same product traces to differences in comparator choice, evidence admissibility, and the treatment of uncertainty rather than to differences in the underlying clinical data [63]. Germany's AMNOG process provides the clearest quantitative illustration, because the added-benefit rating is public while the negotiated rebate is not. Analyses of the full assessment record have shown that the granted benefit rating is the dominant predictor of the negotiated discount, that discounts are significantly larger where no additional benefit is proven, and that orphan status, target population size, adherence to the specified appropriate comparative therapy, and the inclusion of health-related quality of life data are all associated with negotiation outcomes [64, 65]. Further work has demonstrated that a design decision made years earlier, specifically whether the pivotal trial is additive or substitutive relative to the backbone therapy, systematically shapes the achievable price premium [66]. Ten-year retrospectives confirm that products without proven additional benefit face strict price capping, effectively converting an evidentiary judgement into a pricing rule [67]. Comparable institutional determinism has been documented across Asia-Pacific systems, where the same technology encounters materially different pricing architecture depending on whether the jurisdiction operates external referencing, formal economic evaluation, volume-based procurement, or negotiated listing [68].

This is precisely the problem that the EU HTA Regulation is designed to address. Regulation (EU) 2021/2282 establishes a permanent EU framework in which health technology developers make a single submission for Joint Clinical Assessment, with the scope defined through a PICO scoping process that consolidates input from Member State HTA bodies [20, 21]. The framework applies from 12 January 2025 for new oncology medicines and ATMPs, extends to orphan medicines in 2028, and covers all new medicinal products from 2030 [20, 21]. Because JCA timelines are anchored to validation of the marketing authorisation application, the assessment will run in parallel with regulatory review rather than after it, compressing the window in which evidence gaps can be addressed [69].

The principal risk identified in the preparatory literature is PICO proliferation. Because member states retain divergent standards of care and divergent views on relevant subpopulations, the consolidated PICO set for a single product may encompass a large number of distinct research questions, each notionally requiring its own comparative analysis, and the published scoping guidance does not constrain how many may be specified [70]. Preparatory analysis conducted before application found industry readiness low and identified the compressed timeline as the dominant operational concern [69]. The Regulation therefore harmonises the procedure of clinical assessment without harmonising its substance, and it does not touch pricing or reimbursement, which remain national competences. Whether methodological coherence is achievable across member states with different assessment traditions is, at the close of the review window, an open question that implementation has yet to test.

The implication for market access strategy is direct. A JCA dossier must be constructed to serve many national PICOs simultaneously, which increases the value of pre-specified subgroup analyses, indirect treatment comparison capability across multiple comparators, and early engagement through Joint Scientific Consultation. It also raises the cost of failing to anticipate a member state's preferred comparator at the point of pivotal trial design, since that failure now propagates across the entire European market rather than one country.

Certainty of finding: high.

3.5 Theme 4: Prices are set on evidence that is provisional, and the provisionality is rarely priced

Value-based pricing assumes a measured benefit to price against. In a growing share of launches, that benefit is estimated rather than observed, and the review found this to be a structural rather than a marginal feature of the current environment.

Expedited regulatory pathways have expanded the proportion of products reaching the market on incomplete evidence. Analyses of European approvals have documented a substantial group of products authorised with uncertain benefit-risk profiles, frequently on the basis of single-arm studies or unvalidated surrogate endpoints [71]. In the United States, studies of the accelerated approval pathway have shown that preapproval and postapproval evidence frequently rests on the same surrogate measures, that confirmatory trials often do not test overall survival, and that a substantial proportion of accelerated approvals in oncology have not demonstrated benefit on patient-relevant outcomes at the point of assessment [72, 73]. The regulator's own transparency initiative now tracks the status of oncology accelerated approvals explicitly, including indications subsequently withdrawn [74]. Methodological reviews of surrogate endpoints in oncology set out why response rate and progression-free survival are weak predictors of survival benefit in many settings and why single-arm designs inflate apparent effect [75].

The pricing consequence is direct. Payers are asked to set a price today for a benefit that may not exist, and expenditure incurred on indications later shown not to deliver benefit is not generally recovered [76]. Two methodological responses appear in the corpus. The first concerns extrapolation: because most economic models depend on projecting trial-period effects across a lifetime horizon, the choice of survival model can dominate the resulting incremental cost-effectiveness ratio, and formal guidance on selecting and justifying extrapolation approaches is now standard practice in several systems [77]. The second concerns making the value of resolving uncertainty explicit, so that the decision to reimburse now under uncertainty is separated from the decision about price, and the expected cost of being wrong is quantified rather than absorbed [78].

Neither response fully resolves the problem, because both operate on the payer side of a transaction whose price has already been anchored by the manufacturer's launch decision. This is the analytical link to Theme 5: outcomes-based contracting exists precisely because value-based pricing cannot price provisional evidence, and reimbursement decisions must nonetheless be made.

Certainty of finding: high. Convergent across regulatory, HTA, and methodological literatures.

3.6 Theme 5: The migration from financial to outcomes-based contracting is incomplete and slower than advocacy suggests

Managed entry agreements are the principal instrument through which value-based pricing is operationalised under uncertainty. The literature distinguishes financial-based agreements (FBAs), which manage budget risk through confidential discounts, price-volume arrangements, expenditure caps, and dose-capping, from performance- or outcomes-based agreements (OBAs), which link payment to observed clinical results at the individual patient or population level [79, 26].

The taxonomy has been stable for over a decade. Carlson and colleagues distinguished performance-based schemes by whether the outcome is measured at individual or population level, whether payment is adjusted prospectively or retrospectively, and whether the evidence obligation sits with the manufacturer or the payer [22]. Towse and Garrison set out the conditions under which risk transfer is worthwhile, principally that the payer is more risk-averse than the manufacturer, that the outcome is observable at acceptable cost, and that the arrangement does not simply relabel a discount [23]. Klemp, Frønsdal and Facey articulated governing principles for the use of managed entry agreements in parallel, emphasising that agreements should be time-limited, that the evidence generated should be capable of changing the decision, and that exit provisions must be credible [24].

Empirical mapping has followed. Reviews of oncology agreements in Europe found extensive use of confidential financial arrangements with comparatively few executed outcome-linked schemes, and identified administrative burden as the principal reported constraint [80]. Systematic reviews of risk-sharing arrangements across European Union member states documented a steady growth in the number of agreements alongside persistent opacity about their terms and effects [81, 82]. Work on agreements in the context of adaptive pathways examined whether managed entry can bear the evidentiary weight that conditional and staged approval places on it, and concluded that it can do so only where post-launch data collection is genuinely enforceable [83]. Detailed case work on outcomes-based agreements for rare disease treatments, including nusinersen and tisagenlecleucel, has produced the most granular account of what execution actually requires: agreed response definitions, a data custodian, an adjudication process, and a payment reconciliation mechanism, each of which must be built rather than assumed [84]. Stakeholder research spanning United States and European contracting parties reported broadly consistent perceptions of value alongside consistent reports of implementation difficulty [85], and dedicated analysis of spread and instalment payment for one-shot curative therapies identified accounting treatment, patient mobility between payers, and budget-rule incompatibility as distinct barriers from the measurement problem [86, 87].

The normative literature strongly favours OBAs. The ISPOR good practices report by Garrison, Towse, Briggs and colleagues set out design principles for performance-based risk-sharing arrangements more than a decade ago [25]; industry position papers recommend OBAs specifically as the instrument for managing residual uncertainty about real-world outcomes [88, 89]; and value-based negotiation frameworks have been proposed to structure their design [90]. Survey evidence among European payers and experts found broad expectation that both outcome-based and financial agreements would become more widespread [91].

Empirical findings on execution tell a different story. Across the corpus, FBAs remain dominant in practice in essentially every jurisdiction examined. The systematic review of performance-based risk-sharing arrangements in the United States found a comparatively small number of publicly documented arrangements relative to the volume of policy discussion, with limited published evaluation of their effects [27]. The systematic review of MEAs for ATMPs, which screened 787 records and included 42, clustered barriers into evidence generation and data management, financial and reimbursement issues, administration and resources, negotiation, and governance, law and regulation, and found that challenges were not specific to cell versus gene therapy but were amplified for ATMPs generally [14]. Stakeholder research in Central and Eastern Europe reached compatible conclusions, identifying trust, technical infrastructure, and data availability as prerequisites that legislation alone does not supply [92, 93].

The most instructive failure mode reported in the literature is quiet abandonment. Agreements are negotiated, and then not executed, because the parties discover after signature that the agreed outcome metric cannot be reliably ascertained in the relevant patient population using available systems. Where OBAs have succeeded, they have typically depended on a pre-existing linked registry or claims infrastructure capable of following individual patients across care settings [14, 84]. This is a capability constraint rather than a contracting-design constraint, and it explains the geographic pattern of OBA adoption better than differences in payer willingness.

Three further practical constraints recur. First, attribution: outcome measures must be sensitive to the drug's effect and not confounded by concomitant care, which restricts the usable metric set to a small number of objective, proximate endpoints. Second, time horizon: for chronic and one-time therapies, the outcomes of interest occur long after the payment decision, and payer or plan turnover means the

entity that pays is often not the entity that benefits. Third, transaction cost: the administrative burden of adjudication, reconciliation, and dispute resolution can exceed the expected value of the risk transfer, particularly for products with modest budget impact.

Certainty of finding: high for the dominance of financial agreements; moderate for the specific mechanisms of OBA failure, which rest largely on qualitative and case-study evidence.

Table 2: Taxonomy of value-linked pricing and access instruments identified in the corpus

Instrument	Mechanism	Primary risk transferred	Principal execution constraint	Observed frequency
Confidential discount / rebate	Net price reduced below list	Price level	Undermines reference pricing integrity; obscures net-price transparency	Very high
Price-volume agreement	Unit price falls above volume thresholds	Utilisation	Requires reliable volume data only	High
Expenditure cap / payback	Manufacturer refunds spend above ceiling	Budget	Attribution across indications	High
Dose or duration cap	Payer pays for defined maximum exposure	Utilisation intensity	Clinical acceptability	Moderate
Coverage with evidence development	Reimbursement conditional on data collection	Clinical uncertainty	Study completion and re-decision credibility	Moderate
Patient-level outcomes agreement	Refund or non-payment for non-responders	Individual effectiveness	Response definition, ascertainment, follow-up	Low
Population-level outcomes agreement	Price adjusted on aggregate real-world results	Population effectiveness	Registry quality, comparator absence	Low
Indication-based pricing	Distinct price per licensed indication	Value heterogeneity	Indication-level utilisation tracking	Very low
Annuity / instalment payment	Payment spread over years, often outcome-contingent	Timing and durability	Accounting treatment, patient mobility, budget rules	Very low but growing
Subscription ("Netflix") model	Fixed periodic fee for unlimited access	Volume and stewardship	Suits antimicrobials and public health targets specifically	Very low
Statutory negotiated price	Government sets price by formula and negotiation	Price level, systemwide	Political durability; spillover to other payers	Rising sharply

3.7 Theme 6: Data infrastructure and real-world evidence capability are the binding constraint

The single most consistent finding across the entire corpus is that the feasibility of value-based payment is determined by the quality of the underlying data infrastructure, and that this constraint is systematically underestimated at the point of contract design.

The requirements are demanding. An executable outcomes-based agreement requires unique patient identification persisting across providers and payers; capture of the specific clinical outcome in structured, analysable form; linkage between the dispensing or administration record and the outcome record; a defined and auditable adjudication process; and governance permitting the necessary data flows under prevailing privacy law. Few health systems satisfy all five conditions for most therapeutic areas. Systems that have executed outcomes agreements at scale have generally done so in disease areas where a mandatory clinical registry already existed for other reasons, most commonly oncology and rare disease.

The real-world evidence literature converges on the same conclusion from a different direction. A comprehensive review of real-world data in health technology assessment identifies a consistent barrier set: limited access to local data, non-randomised design complexity, data quality and completeness, privacy and governance constraints, and fragmentation across custodians [94]. It also reports strong stated interest among decision-makers in using real-world evidence to resolve uncertainty in funding decisions alongside limited established policy infrastructure to do so, and finds the contribution of real-world evidence to be greatest for advanced therapies and rare diseases, precisely where randomised evidence is thinnest [94]. Work on patient-reported outcomes in real-world evidence generation documents an additional layer of difficulty, since the outcomes payers increasingly say they value, including functioning and tolerability, are the least likely to be captured in routine records without deliberate instrumentation [95]. Multi-stakeholder consensus work has produced broadly compatible recommendations centred on prospective agreement about data standards before rather than after launch [96], and analyses of artificial intelligence applied to large claims and registry datasets identify capability and trust constraints that are most acute in exactly the jurisdictions with the least developed data infrastructure [97].

This finding explains several otherwise puzzling patterns. It explains why OBA adoption correlates with health system integration rather than with payer sophistication or stated policy enthusiasm. It explains why ATMPs, despite being the modality for which outcomes-linked payment is theoretically most compelling, have relatively few executed patient-level agreements. And it explains why fragmented multi-payer systems generate extensive OBA discussion and comparatively little OBA execution, since the entity holding the outcome data is frequently neither the payer nor the manufacturer.

The corollary for policy is that investment in registries, interoperability standards, and linkage permissions is a precondition of value-based payment rather than an accompaniment to it. Position papers from both industry and independent health economics bodies converge on this recommendation, calling for enhanced data collection infrastructure to permit iterative post-launch assessment of

value and for standardisation of value metrics to improve comparability [88, 89].
Certainty of finding: high.

3.8 Theme 7: Launch sequencing, price interdependence, and confidentiality constrain national value determination

External reference pricing (ERP), under which a national price is set by reference to prices in a defined basket of comparator countries, is used in some form by a majority of European countries and by a growing number of middle-income countries [29]. Its effect is to convert national pricing decisions into inputs for other countries' pricing decisions, which produces two well-documented manufacturer responses.

The first is launch sequencing. Manufacturers order market entry to protect the international price floor, launching first in high-price, low-reference-weight markets and deferring or withholding launch in markets whose low prices would propagate through referencing baskets. The welfare consequence falls on patients in lower-price countries, who experience launch delay or non-launch. This is a predictable equilibrium outcome, not a failure of manufacturer conduct, and it is the principal reason that theoretical work on differential pricing insists that sustainable price differentiation requires higher-income countries to forgo importing low prices through referencing and parallel trade [98, 8].

The empirical basis for this is well developed. Comparative price studies have repeatedly found United States branded prices substantially above those in comparable countries, with the most recent large-scale comparison estimating a multiple of roughly three for branded originator products, and a considerably smaller multiple once estimated rebates are applied [99, 100]. Econometric work on launch behaviour in interdependent markets has demonstrated that price regulation in one market measurably delays or prevents launch in others, and that the effect is strongest for markets that are small relative to the referencing damage they cause [101, 102]. Analysis of the referencing system itself has questioned whether it remains sustainable at all as net prices diverge further from list prices [103].

The access consequence is documented most systematically in the European availability data. Successive iterations of the industry-sponsored waiting-time indicator report large and persistent differences in the proportion of centrally approved medicines available across member states and in the interval between marketing authorisation and reimbursement, with the gap between fastest and slowest systems exceeding a factor of six and average delay increasing rather than decreasing over the review period [104]. The accompanying root-cause analysis attributes delay to a combination of late filing, duplicative evidence requirements, national pricing and reimbursement procedures, and regional or local decision layers, rather than to any single mechanism [105]. These sources originate with the industry and should be weighted accordingly, but their directional findings are not contested in the independent literature.

The second is confidentiality. Because list prices propagate through referencing while net prices do not, manufacturers and payers have a shared interest in confidential rebates. The result is a system in which published prices are widely known to be fictional and net prices are known only to the contracting parties. This produces a durable analytical problem for this literature: most published studies of pricing outcomes are conducted on list prices, and the direction and magnitude of the resulting bias cannot be estimated. Survey evidence indicates that stakeholders prefer transparency of the negotiation process over transparency of net prices, which suggests the confidentiality equilibrium is stable [91]. Cross-national survey work with public and statutory payers found that confidential discounts are near-universal, that payers regard them as necessary, and that payers simultaneously regard them as an obstacle to their own price benchmarking [106]. Survey work through the European price-information collaboration reached compatible conclusions on the interaction between confidentiality and managed entry agreements [107]. The World Health Assembly resolution on transparency of markets for medicines placed net-price disclosure on the international policy agenda, with limited subsequent implementation [108]. Experimental economics offers the only causal evidence located in this review: a laboratory replication of European price negotiation found that transparency regimes changed negotiated outcomes in ways that were not uniformly favourable to payers, which is consistent with the theoretical argument that transparency can eliminate differential pricing without lowering the average price [109]. Analysis of originator biologics facing biosimilar entry provides an instructive parallel, showing list prices holding or rising while net prices fell, so that the observable price series moved in the opposite direction to the transacted one [110].

The strategic significance of these two mechanisms is that they operate on each other. The larger the share of global revenue earned in markets that reference other markets, the greater the cost to a manufacturer of any single national concession, and the stronger the incentive to withhold supply rather than concede. The structural asymmetry that has historically sustained the system, in which one large market prices freely while others reference each other, is therefore the condition on which differential pricing depends. Any policy that links prices in that market to prices set elsewhere would invert the incentive, making European and middle-income price concessions globally costly and increasing the likelihood of launch delay or non-launch in lower-price markets. Proposals of this kind were under active discussion in the United States within the review window without being implemented, and this review therefore treats the question as a live risk to differential pricing rather than as an observed outcome.

Certainty of finding: high for ERP effects on launch sequencing and for the persistence of access delay; moderate for the transparency trade-off, where the evidence is largely survey-based with a single experimental study.

3.9 Theme 8: Advanced therapies expose the limits of conventional value-based pricing

ATMPs concentrate every difficulty identified above. Evidence at launch typically derives from small single-arm studies with surrogate endpoints and limited follow-up; the therapeutic claim is durability of effect over decades; the payment is immediate and large; and the eligible population is small enough that a handful of patients can dominate a payer's annual variance.

Dedicated methodological work on cell and gene therapies has questioned whether the standard economic evaluation reference case is fit for purpose in this setting, given the

combination of curative intent, extreme extrapolation, and single-arm evidence [16, 111]. Affordability is a distinct problem from cost-effectiveness here: a therapy can be cost-effective at its list price and still be unaffordable within an annual budget cycle, and payer-side analyses have examined whether payers are institutionally equipped to fund durable one-time therapies at all [112, 113]. Proposals for sustainable financing span reinsurance pools, dedicated national funds, amortisation across budget years, and outcome-linked instalments, each of which trades a different constraint [114].

Three responses appear in the literature. The first is methodological: extended extrapolation with structured sensitivity analysis, and explicit modelling of durability scenarios. This does not resolve the underlying uncertainty; it displays it. The second is contractual: outcomes-based agreements with staged payments contingent on continued response, sometimes combined with instalment structures that spread payment across years [115]. Documentation of executed arrangements for CAR-T therapies across major European markets provides the most detailed available account, and reports considerable variation in what was actually agreed under nominally similar headings [112]. The third is institutional: dedicated funds, separate budget silos, or specialised assessment routes that isolate ATMP expenditure from routine budget-holder decision-making.

The most substantial natural experiment initiated within the review window is the CMS Cell and Gene Therapy Access Model, announced in January 2024. Under the model, the federal government negotiates multi-state outcomes-based agreements with manufacturers on behalf of state Medicaid agencies, with an initial focus on gene therapies for sickle cell disease [116, 117]. Participating states are to receive guaranteed discounts and rebates where therapies do not deliver the agreed therapeutic benefits, with CMS responsible for establishing financial and clinical outcome measures, reconciling data, and evaluating results, and with optional federal funding available to support implementation, outreach, and data tracking [118]. State participation and model start dates fall after the close of the review window, so the model is assessed here on its design rather than on its uptake or its results.

Several design features of this model directly address the barriers identified in Theme 5 and Theme 6. Multi-state negotiation aggregates purchasing power and, more importantly, amortises the fixed cost of contract design across many payers, which is the dominant cost driver for small-population therapies. Centralising outcome measurement and reconciliation at CMS removes the requirement for each state Medicaid agency to build its own adjudication capability. The choice of sickle cell disease as the initial focus reflects a population in which Medicaid is the predominant payer, which mitigates the payer-turnover problem that undermines long-horizon outcomes agreements elsewhere [117].

The model has not yet been evaluated, and no conclusions about its effects on access, expenditure, or outcomes can be drawn from the current evidence. It is, however, the clearest example in the corpus of a policy response designed around the implementation constraints that the preceding literature identified, rather than around the theoretical attractions of outcomes-based payment.

Certainty of finding: moderate. The characterisation of ATMP valuation problems is well supported; the effectiveness of the responses is not yet evidenced.

3.10 Theme 9: Orphan medicines occupy a contested special status that value-based pricing cannot resolve internally

Orphan medicinal products account for a disproportionate share of new approvals and of pricing controversy, and the review found a distinct literature addressing whether they warrant assessment on different terms.

Descriptive comparative work shows that most jurisdictions have not created separate pricing processes for rare disease treatments, applying the same submission requirements, committees, and decision criteria used for common conditions, while introducing procedural modifications such as budget-impact-conditional exemptions from full assessment [119]. Where agencies have adapted, the adaptations concentrate on how uncertainty is handled and how social value judgements are made explicit, rather than on the valuation method itself [120, 121]. Scoping work mapping the criteria actually applied to orphan products across public healthcare systems found substantial heterogeneity in whether rarity, severity, unmet need, or absence of alternatives is treated as a distinct criterion or absorbed into general deliberation [122].

The normative literature is unresolved. A systematic review of moral arguments concerning orphan drug reimbursement identified more published reasons in favour of special status than against, while noting that the arguments in favour are heterogeneous and rest on incompatible ethical premises, including rule of rescue, equity of access, and incentive preservation [123]. The same review notes that the arguments against special status rest largely on opportunity cost and are comparatively few in number, which is itself informative about the composition of the debate rather than about its merits [123]. Analyses in Central and Eastern European settings show these debates resolving differently under tighter budget constraints, where the affordability question dominates the valuation question [124].

Two constructive contributions stand out. The first is analytical work deriving what a reasonable price for an orphan product would be from the economics of small populations, treating the fixed cost of development and the size of the eligible population explicitly rather than treating rarity as a justification for an unconstrained premium [125]. The second is multi-stakeholder process work on how regulatory and HTA evidence requirements for rare disease products might be better aligned, which identifies the divergent acceptability of real-world evidence between regulators and payers as the central operational gap [126].

Certainty of finding: moderate. Descriptive evidence is strong; normative and pricing-method evidence is contested.

3.11 Theme 10: Delinked payment for antimicrobials demonstrates that value-based pricing can be re-engineered when the value case demands it

Antimicrobials present the inverse of the ATMP problem. The clinical value of a new agent active against resistant organisms lies substantially in its being held in reserve, so volume-linked reimbursement rewards exactly the behaviour public health policy seeks to prevent. Conventional value-based pricing, which prices per unit dispensed, cannot express this.

England's response is the most fully documented instance in the corpus of a health system rebuilding the payment mechanism around a value case rather than fitting the value case to the mechanism. Following analytical work

commissioned to establish how the population-level value of an antimicrobial could be quantified, including the spectrum, transmission, enablement, diversity, and insurance components of value that fall outside individual patient benefit [127], NICE and NHS England piloted a fixed annual fee delinked from volume for two agents, informed by a health technology assessment of value to the health system rather than by units used [128]. The pilot was subsequently converted into a standing commissioning route with published eligibility criteria, a weighted evaluation covering activity against priority pathogens and other attributes, and value banding determining contract value [129].

Two cautions recur in the independent commentary. The first is that early declarations of success preceded any data capable of supporting them, since the relevant outcome, namely stimulation of antimicrobial research and development, cannot be observed within the timescale over which success was announced [130]. The second concerns implementation at the clinical interface: survey work with infection specialists in England found substantial uncertainty about how delinked funding should affect prescribing behaviour and stewardship practice, and identified the population-level value components as the least well understood part of the model among those expected to act on it [131].

The transferable finding is that the mechanism was redesigned because the value case could not be expressed within the existing one. This is the reverse of the pattern documented in Theme 5, where contracting instruments were fitted to value stories that the data environment could not support.

Certainty of finding: moderate for the design account, which is well documented; low for effectiveness, which is unevaluated.

3.12 Theme 11: Equity, affordability, and distributional analysis remain weakly integrated into pricing practice

Value-based pricing as conventionally implemented is efficiency-oriented. It asks whether a technology delivers health gain at acceptable opportunity cost, and it is largely silent on the distribution of that gain. Distributional concerns enter through modifiers, through separate orphan or highly specialised routes, and through political override, rather than through the valuation method itself.

The methodological gap is not the obstacle. Distributional cost-effectiveness analysis is a mature method with a standard reference text, published tutorials, and an aggregate variant designed specifically to be feasible without rebuilding the underlying economic model [132, 133, 134]. It quantifies who gains and who bears the opportunity cost, and expresses the trade-off between total health and its distribution using an explicit inequality aversion parameter, which converts an implicit political judgement into a stated one [135]. The obstacle is data and demand. Assessment of the data requirements for routine distributional analysis of health technologies found that the subgroup-level information required, covering baseline health by social group, differential uptake, differential effect, and the incidence of opportunity cost, is rarely available in the form appraisal timelines require [136]. The result is that equity analysis remains an occasional research exercise rather than a standing element of value assessment.

The equity question is sharpest internationally. Value-based differential pricing, in which each country pays a price reflecting local value and ability to pay, is the theoretically efficient means of recovering global joint research costs while permitting access at widely different income levels, as Danzon and Towse originally argued and Danzon later developed [1, 98, 8, 137]. Its implementation record is contested. Critical case-study analysis by Moon, Jambert, Childs and von Schoen-Angerer across antiretrovirals, artemisinin combination therapies, drug-resistant tuberculosis medicines, and vaccines found that tiered pricing was inferior to competition in achieving the lowest sustainable prices, that market divisions were often arbitrary and left middle-income countries facing high prices, and that it concentrated decision-making power with sellers [9]. Systematic review of pricing policy in developing countries has found tiered structures useful where accompanied by transparent regulatory practice, centralised price information, and consistent price review, and weak where those conditions are absent [30].

The most substantial evidence on affordability at scale within the review window comes from China's national reimbursement drug list negotiation, the largest centralised value-based price negotiation outside the United States, in which candidate products are assessed on safety, efficacy, reference price, comparative value, and clinical need before a negotiated payment standard and reimbursement restrictions are set together. Interrupted time series analysis of anticancer drugs following listing found substantial increases in utilisation and reductions in patient cost after negotiation, indicating that centralised negotiation can convert price concessions into realised access where the reimbursement decision is taken simultaneously [138]. The same literature notes persistent regional variation in implementation, since a negotiated national price does not by itself deliver uniform access where provincial procurement and hospital formulary decisions intervene [138]. The resulting prices sit well below those in high-income comparator markets, which raises the referencing problem examined in Theme 7 in acute form [99, 103].

The normative framework for this territory has been articulated most clearly through the concept of fair pricing, which asks that a price be affordable to the health system and sufficient to sustain supply and innovation, and which explicitly declines to reduce fairness to cost-effectiveness [139]. Institutional analyses of cancer medicine pricing, of the relationship between pharmaceutical innovation and access, and of access to medicines as a matter of international policy reach compatible conclusions about the limits of any purely national valuation exercise [140, 141, 142].

Two structural obstacles recur. External reference pricing and parallel trade transmit low prices upward into high-income markets, which destroys the manufacturer's incentive to offer deep discounts to lower-income markets. And the middle-income category, which now contains the majority of the world's poor, sits awkwardly between the tiers that donor-funded access mechanisms were designed to serve [137, 9]. Neither obstacle is amenable to a purely methodological solution.

The practical consequence for market access strategy is that equity-based tiered pricing, which industry position papers endorse [89], requires reference-pricing carve-outs and enforceable market segregation to be sustainable. Absent those, the commercially rational response is uniform high pricing with delayed launch in low-price markets, which is the pattern the empirical launch literature documents.

Certainty of finding: moderate. Consistent direction of findings, but the LMIC evidence base is thin and dominated by descriptive policy analysis.

3.13 Theme 12: Statutory negotiation is reshaping evidentiary requirements and innovation incentives

The Medicare Drug Price Negotiation Program introduced by the Inflation Reduction Act of 2022 represents the most consequential change in United States pharmaceutical pricing in two decades, and the review found that its effects extend well beyond the selected products.

The first negotiation cycle concluded in August 2024, when CMS published maximum fair prices (MFPs) for the ten selected Part D drugs, applicable from January 2026. The published prices represented reductions against list price across a wide range, and CMS estimated that they would have produced net Medicare savings of approximately $6 billion, around 22 percent of spending on the selected products, had they applied in 2023 [143, 19]. The selection criteria, the negotiation procedure, the factors CMS is required to consider, and the sequencing of subsequent cycles including the later addition of Part B drugs are set out in the programme guidance [144]. A second selection cohort was due to be announced by February 2025, after the close of the review window.

Three strategic implications emerge from the corpus.

First, the statutory factors CMS is directed to consider function as a de facto value framework. They require evidence on comparative effectiveness against therapeutic alternatives for the Medicare population specifically, which places weight on outcomes relevant to older adults and people with complex chronic conditions, and on patient-centred measures reflecting daily functioning, tolerability, and quality of life [144]. This is a materially different evidence specification from the one that supports regulatory approval or that satisfies European added-benefit assessment, and it applies at a point in the lifecycle, nine or thirteen years post-approval, long after pivotal trial design is fixed. Manufacturers must therefore anticipate negotiation-relevant evidence needs during development, or generate them through real-world evidence programmes in the intervening period.

Second, the programme changes lifecycle economics in ways that propagate backwards into portfolio decisions. The differential eligibility timeline for small molecules and biologics, commonly termed the pill penalty, creates an explicit incentive gradient between modalities, and the timing of price applicability interacts with indication sequencing and post-approval indication expansion.

At the close of the review window no empirical evaluation of these effects was available, and the claims in circulation were projections rather than observations. Official scoring estimated a small reduction in the number of new medicines over a thirty-year horizon [145], while industry-aligned analyses projected substantially larger effects. The two sets of estimates differ principally in their assumed elasticity of research investment to expected revenue, a parameter that is weakly identified in the underlying literature, and the review found no basis on which to adjudicate between them. The methodological point stands independently of the magnitude: because subsequent indications for high-expenditure small molecules are frequently approved several years after initial licensure and often rest on post-approval trials or real-world evidence, any policy that shortens the interval before price setting will bear disproportionately on post-approval evidence generation. Whether it in fact does so is an empirical question that the available evidence cannot yet answer.

These findings are early, contested, and largely observational, and the identification problem is severe: the enactment coincided with a broad contraction in biotechnology financing driven by interest rates. The review's judgement is that a directional effect on post-approval evidence generation is plausible and partially evidenced, while the magnitude and the counterfactual remain unestablished.

Third, statutory negotiation interacts with the external reference pricing systems already operating elsewhere. A price set by formula in the largest revenue market is, unlike a confidentially rebated price, observable, and observable prices propagate. The programme therefore has consequences beyond the jurisdiction that enacted it, reducing the flexibility available to manufacturers to price differentially and weakening the credibility of country-specific value claims. This is a prediction from the structure of the referencing literature rather than an observed effect, and it is offered as such [29, 101, 102, 103].

Certainty of finding: high for the descriptive account of the programme; low for its downstream effects on innovation, launch behaviour, and access, which remain unevaluated.

3.14 Quality of the included evidence

Appraisal produced a consistent picture. Qualitative and mixed-methods studies were generally adequate on the MMAT criteria for research question clarity and data collection but frequently weak on reflexivity and on justification of sampling, particularly in stakeholder interview studies with small purposive samples drawn from a single country. Economic evaluations were generally strong on modelling transparency and sensitivity analysis and generally weak on the two Drummond criteria most relevant here, namely the justification of comparator selection and the handling of price confidentiality, since most were necessarily conducted on list prices. Policy and institutional documents scored high on source authority and low on independent corroboration, and a substantial proportion of grey literature carried undisclosed or partially disclosed commercial interests.

Three cross-cutting limitations of the corpus deserve emphasis. Publication and reporting bias is likely severe with respect to managed entry agreements, since successful arrangements are more likely to be publicised than abandoned ones, and confidentiality clauses prevent systematic reporting of either. Outcome measurement is concentrated on process rather than health: the corpus contains many studies of time to reimbursement and very few of health outcomes attributable to a pricing mechanism. And causal identification is essentially absent, since pricing policies are implemented without control jurisdictions and the relevant counterfactuals are not observable.

4. Discussion

4.1 Principal findings

Four findings carry the synthesis.

The four findings below should be read against the wider literature on why pharmaceutical prices are what they are. That literature attributes prices principally to market structure, exclusivity, and payer fragmentation rather than to

measured value, and documents both the scale of development costs and the wide uncertainty around estimates of them [3, 4, 5]. Analyses of the anticancer drug market in particular have shown launch prices rising steadily over time without corresponding increases in measured benefit [6, 7]. Value-based pricing entered this environment as a corrective. Assessing whether it corrected anything is the purpose of this synthesis.

First, value-based pricing is not a pricing algorithm. It is a family of negotiation heuristics that share a common justificatory vocabulary and differ substantially in what they measure, whose interests they encode, and how much discretion they leave to decision-makers. The apparent convergence of international pricing policy on VBP language conceals persistent divergence in substance. This is why identical evidence packages produce different prices in different systems, and why manufacturers must maintain jurisdiction-specific value narratives rather than a single global one.

Second, the constraint on value-based payment is operational rather than conceptual. The theoretical case for linking payment to realised outcomes has been settled for over a decade [25]. What has not been solved is the measurement problem. Across every jurisdiction examined, the rate-limiting factor for outcomes-based contracting is the ability to observe the outcome in routine care, attribute it to the therapy, and adjudicate the resulting payment at acceptable cost. Where that capability exists, agreements are executed. Where it does not, agreements are announced and then quietly abandoned [14, 84].

Third, the evidence that value-based pricing improves health is weak, and this weakness is structural rather than incidental. The corpus measures process outcomes (recommendation rates, time to reimbursement, discount magnitude) because those are observable, and does not measure health outcomes because attribution to a pricing mechanism would require counterfactuals that pricing policy implementation does not generate. This is a genuine epistemic limit, and it should temper confident claims in either direction about whether VBP has succeeded. It is compatible with VBP having improved allocative efficiency substantially, and equally compatible with it having chiefly redistributed surplus between payers and manufacturers while leaving allocation broadly unchanged.

Fourth, the policy environment established between 2021 and 2024 is shifting the locus of value determination upward and outward, from national deliberation toward supranational assessment and formula-driven price setting. The EU HTA Regulation moves clinical assessment to European level while leaving pricing national [20, 21]. Statutory negotiation in the United States sets prices by procedure and bargaining rather than by value assessment [143, 19, 144]. External reference pricing already ties many national prices to prices set elsewhere [29, 102, 103]. Each of these individually is defensible. Collectively they produce a system in which the price a country pays is determined substantially by decisions taken in other countries, which is difficult to reconcile with the premise that value is context-specific and locally determined.

4.2 The implementation gap and why it persists

The gap between the volume of advocacy for outcomes-based payment and the volume of executed agreements is the most striking pattern in this literature. Three explanations are commonly offered, and the evidence supports a fourth.

The first explanation is payer conservatism. This is not well supported; survey evidence indicates payers expect and largely welcome expansion of outcomes-based arrangements [91]. The second is manufacturer reluctance to accept risk. This is partially supported but insufficient, since manufacturers have signed agreements in precisely the settings where infrastructure permits execution. The third is legal and regulatory obstruction, including anti-kickback provisions, best-price rules, and data protection constraints. This is a genuine and documented barrier, and it varies substantially by jurisdiction [14, 27].

The fourth explanation, which the evidence supports most strongly, is that outcomes-based contracting has fixed costs that are large relative to the expected value of risk transfer for most products. Designing an outcome definition, building an ascertainment pathway, negotiating an adjudication process, and running reconciliation are largely independent of the number of patients treated. For a small-population, high-cost therapy, these costs are trivial against contract value. For a mid-size product with moderate budget impact, they are not. This predicts, correctly, that outcomes-based contracting concentrates in ATMPs and rare disease [84, 86], that it is more common where a payer can amortise design costs across many products or many payers, and that centralised multi-payer contracting is the natural institutional response. The CMS Cell and Gene Therapy Access Model is the clearest instance of that response in the corpus, aggregating state Medicaid programmes and centralising outcome measurement and reconciliation at federal level [116, 117, 118].

4.3 Implications for manufacturers

The synthesis supports five practical propositions for market access strategy. They are inferences from the reviewed evidence rather than findings, and should be read as such.

Design evidence for assessment, not only for approval: The evidence that satisfies a regulator is systematically insufficient for the assessments that now determine price. European Joint Clinical Assessment requires comparative evidence against multiple member-state-preferred comparators, which must be anticipated at protocol design because it cannot be retrofitted [20, 70]. Medicare negotiation requires evidence salient to an older, multimorbid population, including functioning, tolerability, and patient-reported quality of life [144]. Neither requirement is met by a standard registrational programme. The corollary is that HTA and payer input belongs in phase II design decisions, not in the pre-launch period.

Treat comparator strategy as the highest-leverage decision: Because incremental value is defined entirely by the comparator, comparator selection determines the achievable price more than any subsequent analytical choice. Under JCA, comparator divergence across member states becomes a single consolidated problem rather than a series of national ones, which raises both the risk and the return on getting it right [69, 70]. Investment in indirect treatment comparison capability, common-comparator anchoring, and pre-specified subgroup structures follows directly.

Match the contracting instrument to the data environment, not to the value story: The reviewed evidence indicates that agreements fail on ascertainment

rather than on design elegance. A simple financial arrangement that executes reliably delivers more access than a sophisticated outcomes agreement that cannot be adjudicated. Diligence on whether the required outcome can actually be observed, linked, and audited in the target system should precede rather than follow contract negotiation [14, 84].

Model the international price consequence of every national concession: With external reference pricing widespread and proposals under discussion to extend referencing logic to the largest revenue market, a discount granted in one market carries a quantifiable global cost [29, 101, 102]. Launch sequencing, confidential net-price structures, and market-specific presentation strategies are the available responses, each with access consequences that should be assessed explicitly rather than treated as an operational detail.

Build the post-launch evidence system before launch: Every mechanism examined here, from coverage with evidence development to outcomes agreements to statutory renegotiation, depends on evidence generated after approval. Real-world evidence capability is therefore infrastructure rather than a project, and its absence forecloses options that cannot be recovered later.

4.4 Implications for payers and policymakers

Three propositions follow for the payer side:

Investment in data infrastructure has higher expected return than refinement of valuation methodology. The methodological literature on value assessment is mature; the measurement infrastructure is not. Registries, unique identifiers, linkage permissions, and interoperable outcome capture are the binding constraint on almost every mechanism examined [14, 94].

Pricing and reimbursement policy should be evaluated as a package rather than instrument by instrument, since comparative policy analysis consistently finds that individual instruments interact and that outcomes depend on the combination in force rather than on any single measure [146].

Modifier-based approaches to broadening value should be monitored on application rates, not only on outcomes conditional on application. The English severity modifier illustrates the point: the same instrument can be described as working as intended on one denominator and as under-recognising severe disease on another [37, 38, 147]. Publishing the shortfall calculations underlying every eligible appraisal, and not only those where weighting was applied, would resolve much of this dispute empirically.

Price confidentiality has costs that are now large enough to warrant explicit assessment. Confidential net prices sustain differential pricing and therefore support access in lower-income markets [98, 8]. They also make external reference pricing meaningless, prevent evaluation of pricing policy, and render most published research in this field an analysis of prices nobody pays. Whether the access benefit still outweighs the analytical and accountability cost is an open empirical question that the field has largely declined to ask.

4.5 Relationship to previous reviews

This synthesis is consistent with prior reviews on their specific questions and extends them by integration. The industry-perspective scoping review documented a wider value element set than payers accept [28]; this review locates that divergence institutionally rather than treating it as a communication problem. The ATMP managed entry agreement review identified evidence generation and data management as the dominant barrier cluster [14]; this review finds that the same constraint operates across all modalities and is amplified rather than created by ATMPs. The United States performance-based risk-sharing review documented limited executed arrangements relative to discussion [27]; this review supplies a cost-based explanation for that pattern that also accounts for its geography. Work on the weighing of evidence by HTA bodies has shown that agencies handle equivalent uncertainty differently [148, 63]; this review argues that the EU HTA Regulation harmonises the procedure of assessment without harmonising that weighing, and that the distinction will determine whether it reduces or merely relocates evidentiary burden. Reviews of real-world evidence in assessment identified data access and governance as the principal barriers [94]; this review finds the same constraint operating on contracting, which suggests a single underlying infrastructure deficit rather than two separate problems. Threshold research has established that applied policy thresholds diverge from estimated health opportunity costs [58, 59, 61]; the implication drawn here, which that literature does not draw, is that a price certified as value-based cannot be assumed to be welfare-improving.

4.6 Strengths and limitations

Strengths include the breadth of the search across bibliographic and institutional sources, duplicate screening and verified extraction, appraisal instruments matched to record type, transparent separation of the peer-reviewed corpus from the recent policy update, and explicit certainty ratings for each theme.

Limitations are substantial and should constrain interpretation.

The restriction to English-language records excludes a body of national pricing-policy literature published in German, French, Italian, Spanish, Japanese, Korean, and Chinese, and this exclusion is likely to bias the corpus toward jurisdictions whose HTA processes publish in English.

Price confidentiality is a limitation of the field rather than of the method, but it bites here. Because net prices are unobservable, no included study can report the actual price effects of the mechanisms it evaluates, and the direction of bias in list-price analyses cannot be determined.

Publication bias with respect to managed entry agreements is likely severe and non-random. Executed and successful agreements are publicised; abandoned ones are not reported, and confidentiality clauses prevent systematic capture of either.

Narrative synthesis involves interpretive judgement. Framework development, theme boundaries, and certainty ratings reflect reviewer judgement even under duplicate coding and constant comparison, and a different team might reasonably partition the same evidence differently.

The date bound is strict and this has an analytical cost as well as a benefit. Several instruments central to the synthesis were enacted within the review window but apply after it, notably the EU HTA Regulation and the later cycles of Medicare negotiation. The review can therefore report their design but not their operation, and conclusions about how they will function are inferences from institutional structure rather than findings. Readers consulting this work after the implementation record becomes available should weight

those passages accordingly.

A related limitation concerns source type. A proportion of the corpus, particularly on access delay, innovation effects, and industry practice, is produced by parties with commercial or political interests in the conclusions. Provenance is flagged in the text wherever such sources carry an argument, but it cannot be fully corrected for.

Finally, the pace of policy change in this domain means that any review of it has a short half-life. The instruments described here were, at the close of the review window, either newly operative or not yet applied, and both their detail and their effects remain subject to legal, political, and administrative revision.

4.7 Research agenda

Six priorities follow from the gaps identified.

1. Prospective evaluation of executed outcomes-based agreements, reporting execution rates, adjudication costs, payment adjustments actually triggered, and reasons for abandonment. The absence of this evidence is the largest single gap in the field.

2. Empirical evaluation of the EU Joint Clinical Assessment, examining whether consolidated PICO scoping reduces or increases total evidence burden, whether JCA outputs are used consistently in national pricing decisions, and whether time to national access changes.

3. Causal evaluation of statutory negotiation effects, using the staggered selection of drugs across Medicare negotiation cycles as a source of quasi-experimental variation in price exposure, with pre-specified outcomes covering access, utilisation, and subsequent development activity.

4. Methods for pricing under indication multiplicity that are executable without indication-level utilisation tracking, including weighted-average approaches with periodic reconciliation.

5. Distributional analysis as standard practice, extending distributional cost-effectiveness analysis from methodological demonstration to routine appraisal, so that equity effects enter valuation rather than arriving as post hoc override.

6. Empirical study of the confidentiality trade-off, quantifying the access benefit of confidential differential pricing against its costs to accountability and evaluability, which is currently asserted on both sides without measurement. The single experimental study located in this review indicates that the question is tractable under laboratory conditions [109].

7. Empirical evaluation of innovation effects, since the current evidence on the effects of statutory negotiation on research investment consists of projections resting on weakly identified elasticity assumptions rather than observations, and since any subsequent observational work will need to separate policy effects from concurrent financing conditions [145].

8. Prospective evaluation of delinked payment, using the English antimicrobial subscription model as a natural experiment with pre-specified outcomes covering research investment, prescribing behaviour, and resistance patterns, which the current commentary explicitly notes has not yet been possible [130, 131].

5. Conclusion

Value-based pricing has succeeded as a language and only partly as a practice. It has given payers, manufacturers, and regulators a shared vocabulary for contesting price, and it has made the grounds of reimbursement decisions more explicit and more contestable than the administrative and cost-plus approaches it displaced. It has not delivered a reliable mapping from measured value to price, because value remains institutionally rather than technically defined, and because the payment instruments that would tie price to realised outcomes depend on measurement infrastructure that most health systems do not possess.

The strategic environment is now changing faster than the underlying methods. Clinical assessment is moving to supranational level in Europe while pricing remains national. The United States has adopted statutory negotiation, and proposals to tie its prices to those set in other countries were under active discussion at the close of the review window. One-time therapies continue to arrive with valuation profiles that conventional cost-effectiveness handles poorly. The combined effect is to compress the space for differential pricing at exactly the moment when modality diversity makes flexible pricing more necessary.

For manufacturers, the implication is that evidence strategy must serve several distinct assessment logics simultaneously, and must be designed years before the assessments occur. For payers, the implication is that the return on investment in data infrastructure now exceeds the return on further methodological refinement. For both, the central unresolved question is whether the value of a medicine can remain a locally determined judgement in a system where prices are increasingly set by international reference. The evidence reviewed here does not answer that question. It does establish that the answer will be determined by institutional design and measurement capability rather than by economic theory.

6. Declarations

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Ethics Approval: Not required. This review analysed published literature and publicly available institutional documents and involved no human participants.

Data Availability: All search strategies, screening decisions, extraction data, and appraisal ratings should be deposited in a public repository and the DOI cited here.

Author Contributions: To be completed using CRediT taxonomy: conceptualisation, methodology, investigation, formal analysis, writing (original draft), writing (review and editing), supervision.

Protocol Registration: Insert PROSPERO or Open Science Framework registration number and date.

Use of artificial intelligence: Disclose any use of generative AI tools in drafting, in accordance with the target journal's policy. Authors remain responsible for the accuracy of all content and for verification of every cited source.

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