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The Use of Pay-for-Performance for Drugs: Can It Improve Incentives for Innovation?

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1. Introduction

Interest is growing in schemes that involve "paying for pills by results" (Pollock, 2007), i.e. "paying for performance" rather than merely "paying for pills". Hard-pressed health care payers want to know that they are getting what they are paying for health interventions and other benefits for patients. Pharmaceutical companies are not prepared to accept prices that they believe do not reflect the innovative value that their expensive R&D investments are bringing to patients, the health care system and the broader economy. Paying for the outcomes delivered is a way of "squaring the circle." Payers know they are getting value; companies receive a return that incentivises future innovation.

Yet this approach is highly controversial and is disliked by many health care providers, policy makers, and pharmaceutical companies. One scheme in particular – the UK National Health Service (NHS) Multiple Sclerosis (MS) Risk Sharing Scheme (RSS) – has attracted fierce criticism (McCabe et al., 2010; Raftery, 2010).

This paper accomplishes the following.

- Defines pay-for-performance and the related terms used in discussions about these schemes
- Sets out a framework for understanding and interpreting these schemes
- Explores existing schemes, providing examples
- Discusses the benefits and weaknesses of the schemes
- Considers the value of such schemes as an incentive for innovation

We draw upon papers one or more of us has co-authored (Towse and Garrison, 2010; Carlson et al., 2010; Puig-Peiro et al. 2011).

2. What do we mean by pay-for-performance?

We use the term pay-for-performance to refer to an agreement between a payer and a pharmaceutical manufacturer where the price level and/or revenue received is related to the *future* performance of the product in either a research or real-world environment. This is broadly comparable to de Pouvourville's (2006) definition of "risk-sharing" as "a contract between two parties who agree to engage in a transaction in which . . . one party has sufficient confidence in its claims . . . that it is ready to accept a reward or a penalty depending on the observed performance." We therefore regard the terms as interchangeable and in this paper we use the term "pay-for-performance".

Other terms used in this context include "conditional reimbursement", "coverage with evidence development" (CED) and "access with evidence development". We regard these terms as interchangeable and use "CED". The implication is that some information is going to be collected and a review of reimbursement status will be held at some later point. However, these arrangements may not specify either (1) what type of evidence is to be collected or (2) how price/revenue and/or use is to be changed depending on what the

evidence says about the product. There may only be an agreement, understanding, or requirement that some sort of review takes place after a certain period of time. We can therefore see a pay-for-performance agreement as a subset of CED arrangements where (1) and (2) above *are* specified in advance. The others can perhaps best be summarized as "CED with renegotiation".

The term "only in research" (OIR) also is sometimes used, usually to indicate that there is not enough evidence to approve based on CED. This contrasts with CED that can best be thought of as "only *with* research". The difference is that in the first case all patients must be part of the research to be eligible for treatment. In the other case, it is only necessary that the research be conducted; not all patients must be part of it. "Only in research" is therefore best thought of as a "no". It typically involves restricting access to a small subgroup of the eligible population through recruitment to a randomised controlled trial (RCT). Of course it could in theory involve full access to the technology for all patients subject to some data being collected on them (e.g. via inclusion in a patient registry). In this case it is, effectively, a form of CED. An example of this was the US Center for Medicare and Medicaid Services coverage of implantable cardioverter defibrillators[1] where all patients were required to enrol in a registry[2].

We also use the terms "risk" and "uncertainty" interchangeably. A distinction is sometimes made between them according to whether or not the *probabilities* of outcomes are known or not. This is not helpful in this context. Decision makers must make assumptions. The role of evidence and analysis is to make them better informed. We therefore use the term "uncertainty" to refer to the extent to which decision makers are unclear whether or not they are making the right decisions, i.e. the one they would make with perfect information about all aspects of the incremental impact of the drug.

Some jurisdictions use terms that are specific to their systems. For example, the UK has "Flexible Pricing" (FP) and "Patient Access Schemes" (PASs). Both are defined by the Pharmaceutical Price Regulation Scheme (PPRS) of 2009. Under FP, companies can apply to increase their price if the evidence supports it. NICE agrees to use its normal evidence standards and the cost-effectiveness threshold it used earlier when initially agreeing to use the drug (Towse, 2010). However, no more detailed arrangements are outlined and resubmission is not required. By contrast, PASs are agreement specific. However, most are "financial" arrangements intended to provide the UK NHS with effective discounts from list price rather than being linked to "outcomes". The UK PASs therefore include pay-for-performance agreements, but are mainly types of discount agreements[3].

[1] This scheme was controversial both because key data were not collected and no funding was available to analyse the data in order to revisit the coverage decision with more evidence.

[2] Strictly, one could think of pay-for-performance agreements where each patient is required to be tracked, for example in a responder scheme, as a form of "only in research", but this would be unhelpful. Responder-type pay-for-performance schemes are best understood as a form of CED in which it is clear (1) what type of evidence is to be collected and (2) how price/revenue is to be changed depending on what the evidence says.

[3] An effective price discount, of course, also has an impact on uncertainty. It does not increase the payers' knowledge of the expected outcome, but, for any given expected outcome and willingness to pay threshold, it does reduce the likelihood that the decision to adopt will subsequently turn out to have been wrong.

Italy has a scheme known as “managed entry agreements” that require review after two years. In some cases these are financially oriented, taking the form of a maximum volume agreement or a budget cap. In other cases, they are intended to target treatments to responders. The Italian Medicines Agency (AIFA) uses the terms “cost sharing” (where there is a price reduction for initial treatment cycles until it is clear whether a patient is responding), “payment by results” (where the manufacturer reimburses the payer for non-responders) and “risk sharing” (where only 50% of the costs of the non-responders are reimbursed by the manufacturer). All are pay-for-performance agreements under our criteria.

Thus, we can see pay-for-performance as an arrangement that is of increasing interest to payers. We now consider whether it is an efficiency way to reward and incentivize innovation.

3. A framework for understanding and interpreting these schemes

Towse and Garrison (2010) argue that “value of information” and “real option” theory offer the best framework for understanding and interpreting pay-for-performance schemes. Following Eckermann and Willan (2007) they state that payers have three decision choices in regard to a new drug: agree to list it for some or all of its licensed indications on the basis of current evidence without requiring additional research; refuse to list (leaving manufacturers with the option of coming back with more evidence and/or a lower price); or list subject to additional evidence (in essence a “yes, but.”)

Pay-for-performance can be seen as analogous to a form of “money back guarantee” for a consumer product. In the event of the product failing to perform, the buyer can get some or all of the money back. Indeed, Cook at al. (2008) have likened risk sharing agreements for drugs to a warrantee. The payer has the right to sell the product back to the manufacturer. This is called a “put option”. It is termed a “real option” because it relates to a physical product rather than a “financial option”. Offering a “put option” alongside the product makes it more likely that the payer will say “yes, but” than “no.” The value of the option to the payer depends on the information that will be generated during the period it can be exercised. If no more information is generated the value may be zero – the payer has no better idea as to whether, on balance, the drug is likely to be value for money than when they adopted it.

Which of the three decision choices the payer should make depends on the expected outcome (on the basis of current evidence) and the costs and benefits of additional evidence collection that will reduce the uncertainty about underlying cost-effectiveness. “Value of information” calculations can be used to inform judgements about expected outcomes, the extent of uncertainty around these outcomes, and the likely benefits of collecting extra evidence. If substantial uncertainty exists as to the likely cost-effectiveness of a new drug in practice, it may make sense not to begin using the drug, but instead to collect additional information to reduce that uncertainty. Uncertainty has a cost for payers because it means there is a chance the drug does not represent value and so they will be wasting money and failing to spend the money on other health interventions that provide

benefit to patients. Where costs also are associated with reversing a decision to use a drug (it may even be impossible to change prescriber behaviour unless, in the extreme, the drug is found to be unsafe and withdrawn from the market), then getting the initial decision becomes more important for payers. However, another possibility is that the payer says "no", but additional evidence shows that the drug *is* good value and many patients have lost out from not having access to the treatment during the period the payer refused to list the drug. The company will have lost revenues and the return on an innovation of value to the health care system will have been reduced, harming future incentives for innovation.

Payers therefore need to judge the likely costs and benefits of delaying use of a product while additional evidence is collected. The costs of collecting that evidence include both the out-of-pocket costs and the loss of patient benefits from use of the product while further evidence is being collected. The benefits are a reduction in uncertainty about the underlying cost-effectiveness of the drug and hence the ability to make a more informed decision (which is less likely to be wrong). Payers also may seek to reduce uncertainty by pushing for a lower price, which increases confidence that this expenditure represents good use of their scarce resources. However, companies may well resist this if they believe evidence will support their view of the medicine's net benefit to the health care system. In the absence of a compromise, patients will not get access to the medicine until the company provides the additional evidence to support the price it is seeking.

It might appear to be ideal for the manufacturer to have the evidence available at launch to demonstrate cost effectiveness to the payer. This may not be possible if it relates, for example, to the underlying validity of a surrogate marker for a clinical end point or if understanding longer term effects are key to a judgement about cost-effectiveness. The temptation for the payer in this situation is to say "no" until longer term evidence is provided. The temptation for the manufacturer is to lobby for approval without having to collect the longer term evidence. In these circumstances, the option of CED (a "yes, but") is potentially attractive to payers and companies. It enables patients to get access to new drugs that offer a positive incremental benefit over existing treatments while additional evidence is being collected.

As well as being a feasible compromise, CED can be seen as likely to produce a socially optimal outcome where the additional evidence is likely to be of value and the current best estimate is that the drug will represent value for money. However, some challenges need to be overcome in order for this to be the case. The most important are the following.

- It must be feasible to collect the evidence required while the drug is listed by the payer. It may not be possible, for example, to enrol patients in a clinical trial when they can have access to the drug outside the trial. Evidence can be collected in these circumstances from an observational study or from a trial conducted in another health care system. However, both may raise issues about the quality of the evidence generated: in one case around confounding, in the other, around the generalizability of data from one setting to another.

- Who bears the risk of the initial assessment of value being wrong? This is in part linked to whether an agreement is in place. In the absence of an agreement, each side may act

opportunistically. The company may not collect the data if it expects that that the payer will not be able to reverse its decision (patients will protest and/or prescribers will ignore the decision). The payer may refuse to award a higher price or broader use even if the evidence supports the company's claims.

- An agreement to collect data and adjust price will have costs attached to it. In part, these will reflect evidence collection costs, but also may include additional costs -- for example, administrative costs.

Another source of uncertainty for the payer is "utilisation uncertainty": even if agreement is reached around the price and use of the drug, it still may not be used in the agreed target patient group. This can be dealt with via ex ante testing of likely response or ex post testing of actual response. "Conditional treatment continuation" is a term used by Carlson et al. (2010) to indicate one form of pay-for-performance scheme targeting responders, and, as we noted above, Italian pay-for-performance schemes are targeted to responders. We need to differentiate here, however, between situations in which:

- Considerably uncertainty exits as to which patients will respond (i.e. achieve some threshold level of improvement) and, therefore, as to what proportion of the patient population *will be* responders. In other words, uncertainty remains about the cost-effectiveness of the treatment

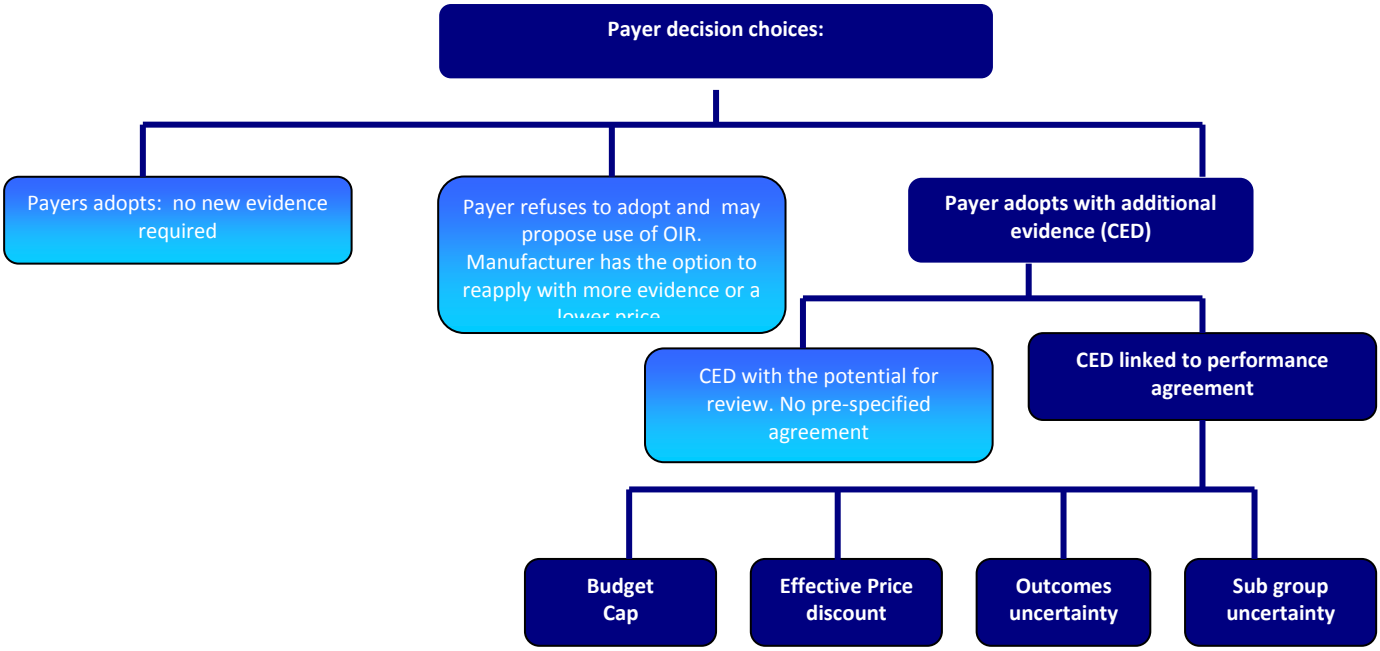
- The payer is aware to a high degree of the expected size or proportion of the population for which the treatment is cost-effective, and which patients therefore should receive it. The issue here is utilisation uncertainty, i.e. making sure these and only these patients receive treatment.

Price-volume agreements are simple, albeit crude, mechanisms to tackle utilisation uncertainty. The numbers of eligible patients can be estimated and the revenues for the company restricted to price times eligible volume. Such an agreement also can allow for lower prices for other subgroups of patients for which the product is less effective. However, the downside is that there is no guarantee that the product is used on the right patients.

Some new drugs may add substantially to the drug budget and cause payers to worry about exceeding their budget (i.e. affordability) over and above any concerns about value for money (Sendi and Briggs, 2001). In this situation payers may be looking for a revenue cap arrangement.

We summarise the decision choices for the payer in relation to CED and pay-for-performance schemes in Figure 1 below.

Figure 1. Categorising Payer Choices at Launch. Adapted from Towse and Garrison (2010)



4. Numbers and types of schemes

In an earlier review, Carlson et al. (2010) collected evidence on pay-for-performance schemes over the period 1998–2009. Like us, they make a distinction within the category we have termed CED between coverage with the potential for review, for which they found 34 schemes, and pay-for-performance (including conditional treatment continuation schemes) for which they found 24 schemes. Stafinski et al. (2010) found 32 schemes of coverage with the potential for review and 26 examples of pay-for-performance schemes. Both studies pre-date the introduction of the UK PASs in the 2009 PPRS. Towse (2010) found ten PASs approved by NICE for use in the UK NHS, but these were mostly discount related. Only one was outcome related, the bortezomib (Velcade®) responder scheme, which pre-dated the 2009 PPRS and was included in the reviews by both Carlson et al. (2010) and Stafinski et al. (2010). It therefore appears that in the decade 2000-2009, up to 60 CED schemes were in operation, of which roughly 55% were CED with the potential for review and 45% were pay-for-performance schemes.

Towse and Garrison (2010) set out examples of the types of schemes observable, using the typology set out in Figure 1.

- Budget management. Agreements in France, Australia and New Zealand have capped expenditure.

- Achieving effective discounts from list price. The dose-capping agreement that NICE entered into for ranibizumab (Lucentis®) for macular degeneration could be seen as an effective price discount. Cost-effectiveness to NICE was only acceptable if the NHS

paid for up to 14 injections per eye of eligible patients. Novartis will bear the costs of treatment beyond this (NICE, 2008). NICE recommended ustekinumab (Stelara®) for severe plaque psoriasis on condition that Janssen-Cilag ensures that the costs of treating patients weighing more than 100 kilograms will be no more than patients weighing less than 100 kilograms (SCRIP, 2009). This equates roughly to purchasing two vials of ustekinumab (Stelara®) for the price of one.

- Tackling outcomes uncertainty. The UK MS drugs scheme addresses outcome uncertainty with an observational study of patient health status with price linked to a cost-per-QALY threshold. In Australia, the agreement for bosentan (Tracleer®) links price to patient survival following an observational study (Wlodarczyk et al., 2006). Money-back guarantees have been offered by a number of companies, including Merck if simvastatin (Zocor®) did not help lower low-density lipoprotein (LDL) and cholesterol levels in combination dietary modifications; Parke-Davis (now Pfizer) in a 2003 UK "outcomes guarantee" for atorvastatin (Lipitor®) reducing LDL levels to a target; and by Novartis with a "no-cure-no-pay" initiative for valsartan (Diovan®) and a money back guarantee for nicotine chewing gum (Moldrup, 2005).

- Tackling subgroup uncertainty, conditional on expected outcomes

    - via selection or response uncertainty. The UK bortezomib (Velcade®) example tackles subgroup uncertainty, ensuring identification of responders. Payer reimbursement is retrospective for non-responders. Responders receive further doses of the product. The Italian AIFA, as we noted, has established several responder-related pay-for-performance agreements with discounts for trial periods, and rebates for non-responders. For responding patients, the treatments are reimbursed at full price.

    - via utilisation uncertainty. In Australia, expenditure caps also can be viewed as risk-sharing agreements, having implicitly tied revenue to outcomes, under the assumption that high volumes mean cost-ineffective care at the prevailing price.

We discuss below the costs and benefits associated with the schemes, combining our theoretical framework with the findings in recent literature.

5. Benefits and weaknesses of pay-for-performance schemes

Pueg-Peiro et al. (2011) conducted a systematic literature review to identify existing knowledge about the costs and benefits, qualitative and quantitative, of: risk sharing schemes; performance based reimbursement; PASs arrangements; and FP schemes for pharmaceuticals. A total of 24 publications including original research papers, reviews, letters and editorials were examined. The research found that:

- More than 40% of the publications referred to the MS RSS implemented in the UK since 2002

- No studies were able to evaluate the overall economic impact of a scheme. All studies included qualitative discussions of costs and benefits, with the exception of the MS RSS where some costs were reported.

The costs most commonly cited in qualitative terms in the reviewed publications were:
- Transactional/implementation costs (costs of negotiation, contracting, monitoring and data collection and analysis)
- Also specifically mentioned often were:
    - specific administrative burdens for the payers' health system
    - the potential for more methodologically complex ways of generating the evidence to push up cost and lengthen the time of the schemes.

Cited benefits included:
- Greater access to new treatments
- Paying a price closer to the value of the drug (a "value-based" pricing approach)
- The potential to improve the efficiency of the pharmaceutical market by rewarding innovation
- Reducing uncertainty in the payer's decision making process

With respect to the MS RSS, many challenges were identified. The UK's MS RSS was negotiated in 2002 between the UK Department of Health and four pharmaceutical companies supplying MS drugs after NICE rejected any use of these drugs under the NHS. A ten-year observational study with a historic cohort as a control was performed. It took three years rather than the expected 18 months to recruit 5,000 patients at 73 centres. The results of the two-year assessment of accumulated disability of the 5,000 patients recruited were not reported until 2009, seven years after the agreement to the scheme. In reporting the results Boggild et al. (2009) said that "the outcomes so far obtained in the pre-specified primary analysis suggest a lack of delay in disease progression". However, prices were not adjusted downwards on the grounds that the evidence was not conclusive. This raised issues as to: the design of the study and the time delays in generating the evidence; the enforceability of the contract in relation to the link between prices and outcomes; problems of governance of the scheme including the independence of the scientific advisory group (which was vigorously defended by its chair[4] (Lilford, 2010); the usefulness of the Expanded Disability Status Scale as the outcome measure; and the impact on the choice of comparator when evaluating subsequent new drugs for the same indications.

Critics also argued that a longer RCT in the UK NHS would have been preferable (McCabe et al., 2010). This seems not only politically unrealistic, but also ignores the costs associated with evidence collection. This problem is not unusual. New therapy in an untreated disease area often shows great promise in short term RCTs using a combination of surrogate markers and some intermediate clinical end points and obtains a license on that basis. The unanswered question is how much long term health benefit for patients is likely to actually accrue. Waiting for the results of a ten-year post-launch trial is not realistic. It also is likely

[4] Lilford blamed the design of the study for the failure to draw safe conclusions about effectiveness after two years.

to be bad economics if a viable option is pay-for-performance with an effective form of evidence collection and appropriate governance and contract enforceability.

Evidence on the costs and effects of other schemes is limited. Although the UK PASs are largely discount arrangements rather than pay-for-performance, the experience is relevant. Williamson (2010) reports on a survey of oncology pharmacists in 31 NHS hospitals. Transaction costs for the NHS were the biggest concern. Variation across the administrative requirements of different schemes added to the problem. Some concern was expressed that money due back may not have been claimed in some cases. In other cases, the money came back to the provider hospital, but the purchaser (commissioner) was not aware of this. The "two schemes linked to a measurement of clinical response, cetuximab [Erbitux®] and bortezomib [Velcade®], showed a trend towards being the worst. Response-based schemes pose challenges for tracking patients and ensuring claims are made to refund non-responders" (Williamson 2010). This is of concern as these are, in effect, pay-for-performance schemes. The Italian pay-for-performance schemes, however, appear to have been well received. This in part may be because of a national electronic patient registration system.

The review by Puig-Peiró et al. (2011) thus found a lack of consensus on the welfare consequences of the schemes and their social desirability, partly explained by the scarce evidence available. Some authors recommend outcome-based agreements only in exceptional cases given their complexity and high costs. For example, writing about the MS RSS, Raftery (2010) concludes "Outcome based schemes should probably be avoided if at all possible". However, such evidence as we have on the other outcome based scheme – e.g. that for the bosentan (Tracleer®) scheme -- suggests it works. Raftery suggests this may be because of use of a smaller patient group (528 patients), a well-defined outcome measure (death), and a health system more used to negotiating agreements.

In the literature, identified benefits are countered by significant costs and challenges and therefore the overall balance remains unclear, despite strong opinions regarding one specific scheme (the MS RSS). A strong sentiment against outcomes based schemes is clear. Yet rewarding those products that can be shown to deliver performance (in the form of health gain and other benefits) is likely to be highly effective in stimulating innovation.

There appear to be two related problems. The first is a tendency to focus on the negatives of experience to date. Collecting evidence is expensive (in terms both of elapsed time and out-of-pocket cost) and administering a scheme also can be expensive. Yet, so far, the literature provides little evidence on the overall costs and benefits of schemes undertaken to date. Estimates of the cost of the MS RSS focus on the drug costs at list price. The literature does suggest concern on the part of health care providers of the costs of administering schemes and it is clear that the evidence generated as part of the MS RSS has so far not reduced uncertainty around outcomes and that the contract arrangements have been unsatisfactory. The question is whether use of the schemes could have been expected to produce a better outcome than alternative decision choices on the part of the payer. It is also clear from the literature that there is a great emphasis on CED schemes where outcomes for individual patients are tracked through prospective observational studies of

one form or another. This seems to be at the expense of alternatives that may provide a more cost-effective use of resources, namely:

- The collection of evidence in another jurisdiction in parallel to the use of the product (Eckermann and Willan, 2009)

- The use of sample studies, rather than including all patients in evidence assessment

The second problem is that there seems to be a rather naïve view about the alternatives to risk-sharing or pay-for-performance arrangements. The alternatives are as follows:

1. More information collected pre-launch, reducing uncertainty, enabling "adopt now" decisions "at launch". Early payer-company dialogue (in the form of a scientific review) has begun about evidence requirements for at-launch health technology assessment. The ability to generate information to reduce uncertainty at launch may be limited, however, by the feasibility of and time delays associated with pre-launch data collection. The assumption seems to be that in this case prices should just be lower, at least until better evidence is generated. Yet prices cannot go up in most markets[5]. Manufacturers are unlikely to be willing to accept permanently lower prices to handle outcome uncertainties at launch.

2. More delays and sequential resubmission and negotiation with new information and prices. This is unlikely to be efficient, leading to substantial delays in patient access while a cost-effective price is found.

In short, there are no easy options for identifying and rewarding the value of new innovation. Pay-for-performance offers an important way forward to handle uncertainty around expected value in routine clinical practice. It does not require every treated patient to be followed, and performance can be taken from an RCT or other study elsewhere in the world if needed. Costs may come down as payers and manufacturers gain experience with operating these agreements.

[5] An exception in principle is the UK Flexible Pricing arrangement introduced in the 2009 PPRS. However, to date this has not been used.

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