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It takes two to tango: when do conditional reimbursement risk-sharing schemes work for both parties?

SETTING OUT THE CONDITIONS IN WHICH RISK SHARING SCHEMES IMPROVE VALUE FOR MONEY

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RESEARCH REPORT
OCTOBER 2021

OHE

DECEMBER 2021

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Please cite this report as:
Towse, A. and Fenwick, E., 2021. It takes two to tango: when do conditional reimbursement risk-sharing schemes work for both parties? Setting out the conditions in which risk sharing schemes improve value for money. OHE Research Paper, London: Office of Health Economics. Available at: https://www.ohe.org/publications/ittakestwototango:whendoconditionsinwhichrisksharingschemes improve value formoney

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Funding and Acknowledgements

No funding was received for the writing of this paper. The authors are grateful to colleagues who provided feedback on earlier drafts and to the OHE reviewers.

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Abstract

There has been increasing emphasis by regulators on approving potentially important treatments rapidly, notably through accelerated access schemes.

As a consequence, there is a challenge to payers. Products are launched with less evidence, creating greater uncertainty as to: their relative effectiveness and value for money; the appropriate price to pay; and the best use to be made of the drug. If payers refuse to reimburse new treatments on the grounds of lack of good evidence of incremental effectiveness, there is likely to be challenge from patient groups and from the innovating pharmaceutical companies. Faster regulatory approval processes are, however, not necessarily achieving faster patient access.

This paper sets out a way forward using conditional reimbursement schemes with risk-sharing. These schemes have costs which, if allocated efficiently, will optimise incentives for appropriate uncertainty reduction. One important, but often overlooked, reason for introducing risk-sharing is to resolve differences of opinion between innovators and payers about the value of a technology to the health system. To date there has been no formal attempt to set out the circumstances in which risk sharing can increase the value of the options available to payers and innovators for mutual benefit. In this paper we explore how a value of information (VOI) framework can help to understand what a performance-based risk-sharing arrangement (PBRSA) can, in principle, add to a reimbursement scheme. We set out the conditions in which both parties should seek such an arrangement.

1 Introduction

The Impact Of Accelerated Regulatory Processes On Payer Uncertainty

There has been emphasis by regulators on processing potentially important treatments rapidly, notably through accelerated access schemes (e.g. the Breakthrough Therapy Designation (BTD and Accelerated Approval Pathway) in the US (McCaughan 2017) and Accelerated Assessment and PRIME in the EU). This includes the use of conditional licensing (such as EMA's Conditional Marketing Authorisation) and can be combined with the use of early scientific advice to help guide companies about study design and data collection. In Europe, regulators can impose requirements to undertake post-launch efficacy studies (post-authorisation efficacy studies, PAES) as well as post-launch safety studies (post-authorisation safety studies, PASS). The innovators of drugs given FDA Accelerated Approval are legally required to complete confirmatory trials. All of these measures allow regulators to approve drugs earlier but with the consequence that there is greater uncertainty about their benefits and risks at launch.

As a result, there is a challenge to payers in the US, Europe, and the many other countries which have adopted fast track regulatory pathways. Products are launched with less evidence, creating uncertainty as to their relative effectiveness. This in turn complicates assessments by payers, and their Health Technology Assessment (HTA) bodies or Drug and Therapeutic Committees, of the therapeutic added value or incremental cost-effectiveness they could expect to see delivered in their health systems through adoption of the drug. Payers face uncertainty as to the appropriate price to pay and the most appropriate use to make of the drug. Studies indicate that approval rates for reimbursement are lower for drugs going through accelerated processes (Vreman et al., 2019; Macaulay et al., 2018). Yet when payers decline to reimburse new treatments on the grounds of the uncertainty about evidence of incremental effectiveness and therefore of value for money, then there are likely to be challenges from patient groups and from the innovating pharmaceutical companies. The obvious challenge is "what is the point of the new faster regulatory approval processes if patients cannot get earlier access to the new medicines?"

The potential role for risk-sharing to address payer uncertainty within a VOI framework

We argue that the way forward is, in certain circumstances, for payers to use conditional reimbursement, with a performance based risk-sharing arrangement (PBRSA) as part of a Managed Entry Agreement (MEA)[1]. These are currently being used in some contexts, but we argue that their use is not currently optimal. Payers are often reluctant to use these schemes, identifying the practicality and cost associated with collecting data and administering the agreements, together with a concern that this is encouraging companies to collect less evidence in the first place.

How costs are allocated between the payer and the innovator, and the price and use set for a drug during a period of conditional approval, has implications for ensuring the efficient timing of evidence collection, as well as the resource impact for payers, both of which are major concerns.

[1] *A definition of the term Managed Entry Agreements is given in Klemp et al. (2011). "A Managed Entry Agreement is an arrangement between a manufacturer and payer/provider that enables access to (coverage/ reimbursement of) a health technology subject to specified conditions. These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of technologies in order to maximize their effective use or limit their budget impact." Most MEAs are about budget impact, see for example Dabbous et al. (2020). In the case of curative therapies, "a PBRSA has the de facto effect of phasing budget impact as well as formally addressing uncertainty."*

In this paper, we explore how a value of information (VOI) framework can help to understand what a conditional reimbursement together with a risk sharing scheme (which we call a performance based risk-sharing arrangement (PBRSA) following Garrison et al. (2013)) can, in principle, add to a MEA, setting out the specific circumstances where we believe there is potential value for a MEA with a risk-sharing scheme. To date, although PBRSAs have been discussed in the context of VOI, there has been no modelling using a VOI framework that explicitly seeks to illustrate and link the impact of risk sharing on the decision options faced by payers and innovators. Indeed, the literature does not explicitly separate the payer perspective from that of the innovator. We seek to fill this gap.

Structure of the Paper

The paper is structured as follows:

- Section 2 provides a recap of the VOI approach and the importance of looking at both the expected benefits of treatment and the opportunities to reduce the uncertainty associated with estimating those benefits;
- Section 3 reviews the existing literature on risk-sharing;
- Section 4 looks at where risk-sharing can add value for a payer;
- Section 5 explores situations where innovators and payers have different views about expected outcomes and on the cost of evidence collection;
- Section 6 discusses our findings and sets out some possible next steps for policy makers to take to implement them.

2 The theory of VOI and payer decision making

This section briefly sets out the VOI approach of looking at both the expected benefits of treatment and the opportunities to reduce the uncertainty associated with estimating those benefits.

For simplicity, we begin by assuming that the payer:

- is risk neutral. We follow the Value of Information (VOI) literature in assuming that the rational payer is indifferent to uncertainty unless it can be addressed by cost-effective research.
- is a price taker[2]. The innovator sets the price.
- decides whether or not it is willing to use the drug at this price and, if so, for which groups of patients (within the licensed indication) but there is no negotiation. If price changes, then decisions about use of the drug in particular groups of patients will change. Use can vary between zero and 100% of the populations covered by the licensed indication. We recognise that there is some form of price negotiation in most countries, and return to this point later.
- uses cost-effectiveness as the sole criterion for determining reimbursement and use, operating a threshold (k) for (yes/ no) acceptance. If the ICER > k, the technology is not adopted. An alternative way of expressing this is that the Incremental Net Benefit (INB) has to be zero or positive (INB ≥ 0) for acceptance, using k as the rate of exchange between monetary and health benefits.

Later we, briefly, consider the implications for our analysis of relaxing each of these assumptions.

Uncertainty about the effectiveness and/or cost-effectiveness of a medical technology "means that there is inevitably some risk that decisions based on the available information will be incorrect" (Fenwick et al. 2020). It could be that a decision not to adopt was made when the drug was cost-effective or, the reverse, a decision to adopt was made, and the drug turned out not to be value for money[3]. Uncertainty can be reduced by collecting more evidence. VOI analysis provides a formal framework to assess the costs and benefits of collecting more evidence (Fenwick et al., 2020, Rothery et al., 2020) and provides "a formal assessment of the value of research, based on the extent to which the information improves the expected payoffs associated with a decision. This value is compared with the cost of acquiring the information to determine whether it [the information] is worthwhile." Fenwick et al. (2020) defines this difference as the "net payoff or expected net benefit of sampling (ENBS) associated with a specific research study" proposed. If the payer is of the view that ENBS > 0, then it is worth them seeking additional evidence.

We thus have two separate but related decisions: i) the adoption decision, based on cost-effectiveness, looking at the expected value for money of the treatment (with the decision rule INB ≥ 0) and ii) the research decision based on the VOI i.e. whether uncertainty has been reduced to the point where the costs of further research prior to adoption exceed the benefits (ENBS ≤ 0). They

[2] In practice, different payers have different powers in relation to price. For a discussion see Walker et al. 2012b

[3] We can think of the analogy with a Type 1 error (where an intervention is thought to be a good value addition, but it turns out not to be) or a Type 2 error (where a new intervention is not adopted which turns out to be a good value addition.) Note that VOI uses a Bayesian framework, so we are not using p values to reject a null hypothesis, at least not in relation to cost-effectiveness. The assessment of clinical effect may well involve the use of p values.

come together in terms of a possible conditional reimbursement. Where the INB ≥ 0, the decision should be to adopt the treatment. Where the ENBS > 0, then more research is required. The question then becomes how do we achieve the research and how much time will it take to undertake? Can evidence collection be combined efficiently with adoption of the technology followed by a review of the adoption decision when the new evidence is available? It may not be possible to undertake the required research if the technology is adopted. In which case, should adoption be delayed, or limited, while the additional evidence is collected? If the current view of the expected value is positive, this may involve patients we expect to benefit not getting access for some time.

Decision maker options for reimbursement within a VOI framework for handling uncertainty have been categorized by Walker et al. 2012a, 2012b (WSCP) and by Eckermann and Willan (EW), (2007, 2009). We use the WSCP categorization. This is as follows:

- **Accept** the treatment, on the basis of the evidence offered, or, as EW would term it, AN: to Adopt the new treatment with No additional evidence collection. Applies when the payer expects INB ≥ 0 and ENBS ≤ 0.

- **Reject** the treatment as not cost-effective and seek no further evidence. Clearly, if INB < 0, and all available study designs have an ENBS ≤ 0, then it is not worth collecting further evidence about this technology.

- **Only In Research (OIR),** which is to propose further research, i.e. use the technology only as part of a study to generate new evidence, or as EW would term it, DT: to Decline to adopt and seek further evidence, for example from a Trial. For the payer INB < 0 but, crucially, ENBS > 0. However, there may be cases when evidence can only be collected through adoption of the technology[4]. In which case, in effect, the OIR option becomes a de facto OWR option (see below).

- **Only With Research (OWR)**, which is to approve for use, conditional on the collection of additional evidence, or as EW would term it AT: to Adopt but seek /require further evidence (for example via a Trial), e.g., coverage with evidence collection. For the payer INB ≥ 0 and ENBS > 0. This has the advantage of achieving use of a product expected to be good value for money, whilst increasing the evidence base. However, issues may arise if the research suggests that the technology is not, after all, cost-effective at the adopted price.

We can summarise the options below in Table 1

TABLE 1: REIMBURSEMENT OPTIONS FOR A NEW DRUG:

	ENBS > 0	**ENBS ≤ 0**
INB ≥ 0	OWR	Accept
INB < 0	OIR	Reject

This is, however, an oversimplification, as several other factors need to be considered

- We have two cases (OIR and OWR) where ENBS > 0. As noted above, the issue is whether evidence collection can be combined efficiently with adoption of the technology and a review of the adoption decision when the new evidence is available, or whether adoption should be delayed

[4] For example, where a trial would not be possible due to low patient numbers available to randomise e.g. a rare disease or where a large proportion of the population are already exposed to treatment, or where significant investment is required either in capital or skills and, as such, irreversibilities are considerable.

or restricted in some way? The payer should choose an adoption strategy which yields the greatest ENBS[5].

- Which option has the greatest ENBS will depend on feasible study designs (which may favour OIR as RCTs in a jurisdiction are more difficult when a technology has been adopted in that jurisdiction) but also on the potential loss of health gain. This arises if adoption of a technology that is expected to be cost-effective is delayed. If the lost patient benefit is high then it makes sense to use OWR, with evidence collected whilst patients are treated. A complicating factor is if "reversing the adoption decision is difficult or costly" (Fenwick et al. 2020) for example due to sunk costs or other irreversibility[6]. The existence of such costs will favour OIR;

- On the assumption that OWR is the preferred option, the payer has to agree to, or impose a requirement on the innovator to, undertake the study required. The innovator may or may not wish to collect this evidence, depending on its view of the likely outcomes. One further option has been discussed in the literature – that of approval with a lower price without the innovator having to do the research. In effect, the payer's uncertainty is "bought out" by the innovator with a price cut that produces the same expected outcome (in terms of reduced uncertainty) as undertaking the research would be expected to achieve. We return to this point in Figure 1 below. However, if the company believes that its product *will* perform as the evidence to date suggests, then it is likely to resist a permanent reduction in price in order to get early reimbursement. This option does, however, suggest the amount by which the price of the product should be reduced (and sums potentially rebated) if the company does not undertake the research required by the OWR decision.

- The VOI calculations will change, both in terms of the uncertainty but also the expected outcomes, whenever new evidence is analysed. Decision uncertainty may, in principle, increase rather than reduce, as a consequence. If the evidence does reduce uncertainty around a revised INB, we may still have ENBS > 0 for one or both parties, i.e. the value of further research continues to exceed the cost of undertaking it, taking account of any impact on patient access. As such, the dynamic aspect of evidence generation and price agreement should be taken into account.

[5] Strictly the ENBS for OIR (versus Accept) and the ENBS for OWR (versus Accept) should be compared using their respective optimal study sizes (EW, 2013).

[6] EW (2007) identify these as the public information costs of changing the health message, and any sunk costs such as specific equipment or training. Arguably there is also a reputational issue. Although citizens should in principle welcome a decision maker that changes decisions when new evidence is available, there is always an issue of credibility if this happens repeatedly.

3 Discussion of risk-sharing in the VOI literature

The literature to date on risk-sharing can be categorised as follows:

- there are some important strands that look at context, empirical use, typologies and non-VOI theoretical approaches;
- papers using a VOI framework that seek to cover Accept, Reject, OWR and OIR options comprehensively, but only include passing references to risk-sharing and do not integrate it into their framework;
- the ISPOR PBRSA TF (Garrison et al. 2013) which references VOI and sets out a clear definition of risk-sharing, but is mainly focussed on typology and application;
- Towse (2009), and EW (2013), who place risk-sharing theoretically firmly in the context of VOI but do not develop the concept in a way that can be practically used by payers and innovators.

We set out the main findings for each of these categories and then set out the gap in this literature.

Context, empirical use, typologies and non-VOI theoretical approaches.

Much of the literature about risk-sharing, outcomes-based agreements, and MEAs is about categorising schemes and exploring the use of different types of schemes used in practice by HTA bodies and payers (for example Kanavos et al., 2017; Wenzl and Chapman, 2019; Gamba et al., 2020). Another group of papers seeks to model the impact of risk-sharing on outcomes (Mahjoub et al., 2017; Pita Barros, 2011). There is also discussion of risk-sharing in the contract literature (for example Evans, 2012; Segal and Whinston, 2003). None of this literature puts risk-sharing in the context of a VOI approach.

Papers using a VOI framework that seek to cover Accept, Reject, OWR and OIR options comprehensively, but include only passing references to RS and do not integrate it into their framework.

WSCP discuss risk-sharing in the context of "outcome-based coverage decisions" in both Walker et al. 2012a, and Walker et al. 2012b. They make a distinction between those operating at the individual patient level (money-back guarantees, conditional treatment continuation, and price linked to a specific outcome for each patient), and those operating at the population level. However, there is no discussion of risk-sharing in the context of their discussion of coverage with evidence development (CED) schemes. They argue that prices in a CED scheme will have to be lower if there are irreversible costs, but not that this price might change following evidence collection. There is reference in their taxonomy of coverage options to a "conditional flexible pricing agreement" but no discussion as to what this means.

Claxton et al. (2012, 2016) set out an algorithm for approval in OIR and OWR settings, discussing the role of "changes in the effective price of a technology" in altering decisions between OIR, OWR, Accept and Reject, but do not consider risk-sharing.

Grimm et al. in two papers (Grimm et al., 2016, 2017) seek to address how MEAs can be used to reduce the uncertainty associated with new medicines approved under EMA "adaptive pathways". An "HTA Risk Analysis Framework" is developed (Grimm et al., 2017), using VOI calculations to "quantify the risk associated with current decision uncertainty and how that risk would change under any MEA." MEAs are defined to "use a variety of mechanisms to address uncertainty …". Two types of MEA are considered, "financial", i.e. "price reductions", and "data-collection" or "research-based", by which they mean coverage with evidence development. The stated purpose of the "HTA Risk Analysis Framework" is to allow simultaneous consideration of financial and research-based schemes. Much of both papers is taken up by the introduction of the concept of "strategy-specific risk burden". This is additional to "decision uncertainty" which, as we use it, relates to uncertainty around the payer strategy that yields the highest INB, and involves the assessment of ENBS from further research. The new concept, "strategy-specific risk burden" or "payer strategy burden", is a risk that a decision maker "deviates from risk neutrality…. to consider recommending strategies expected to be cost-ineffective, under condition that further research is undertaken."[7] The proposed method to deal with "payer strategy burden" is a price cut. Further research is recognised as a tool to deal with normal decision uncertainty. Such research can include schemes where "price is contingent on health outcomes" such as a money-back guarantees. There is, however, no definition of, or discussion of, "risk-sharing" and in research-based MEAs, the emphasis is on evidence collection under an OWR decision option. Price reductions and evidence collection are considered as separate effects and not joined together in a risk-sharing scheme.

The ISPOR Task Force (Garrison et al. 2013), referencing VOI, setting out a clear definition of risk-sharing, but mainly focussed on typology and application.

The ISPOR Task Force report on PBRSA (Garrison et al. 2013) contributes a clear framework for distinguishing between types of MEAs, many of which are financial in motivation, i.e. designed to reduce uncertainty around budget impact. Those that address outcomes are divided into "performance linked reimbursement", which are termed "responder schemes", (i.e. payment for treatment for a particular patient is conditioned on the outcome for that patient) and coverage with evidence development schemes, whereby the average price is adjusted to reflect the average effect identified in the studied population. We have previously modelled an illustrative responder outcome-based scheme in our paper on Uncertainty and Cures (Towse and Fenwick, 2019). Here we focus on coverage with evidence development type schemes[8].

The ISPOR Task Force (Garrison et al. 2013) also set out five distinguishing characteristics of a PBRSA: (i) there is a program of data collection; (ii) this data collection is typically initiated during the time period following regulatory approval; (iii) the price, reimbursement, and/or revenue for the product are linked to the outcome of this program of data collection either explicitly, by a pre-agreed rule, or implicitly, through an option to renegotiate coverage, price, or revenue at a later date; (iv) the data collection is intended to address uncertainty; and (v) these arrangements provide a different

[7] The implication is that the payer is risk-loving, i.e. is using a technology that has a chance of being cost-effective but on current estimates the INB is negative.

[8] The responder scheme can best be viewed as another form of evidence generation which can be used to reduce the uncertainty over time. In other words, once the scheme has been running for a while it should be possible to estimate an average responder rate or responder effect and adjust price, eliminating the need to continue to collect patient specific responder data. Of course, patient specific data may be needed for aspects of clinical care, but it would not be needed to determine price or reimbursement status. Thus, for example, the Velcade responder scheme was replaced by an agreed uniform discount. Arguably responder type schemes are another form of coverage with evidence development scheme. However, given the starting point – linking payment to specific performance of the drug in each patient – it is useful to separate the two types. And in the event of long term uncertainties which impact value for money – for example in the case of one off curative therapies - then long term evidence generation may be required, in which case the responder scheme doubles as both a coverage with evidence development scheme and a risk-sharing agreement underpinning the scheme.

distribution of risk between the payer and the manufacturer than does the historical manufacturer-payer relationship.

We use the Task Force definition of PBRSA. We can therefore take as our working definition of risk-sharing that it is a variant of OWR in which an agreement to collect further evidence is supported by a contract or understanding that payments will be adjusted depending on the estimated INB that results from the evidence generation.

Towse (2009), and EW (2013) placing risk-sharing theoretically firmly in the context of VOI but not developing the concept in a way that can be practically used by payers and innovators.

Eckermann and Willan consider risk sharing within a VOI setting in one of their papers (EW 2013) in the context of their, understandable, preference for optimally designed global trials to maximise the early adoption of new drugs. This work builds on Towse, 2009. Towse sets out risk sharing as a variant of OWR whereby evidence collection is linked by a pre-agreed contract to adjust payments prospectively. Risk sharing depends on continuing collection of information on INB from routine practice and/or trial settings. From a payer perspective, risk sharing can offer full insurance: prospective price adjustment to maintain constant INB with available evidence, and even provide for costs of reversal where INB cannot be maintained by price cuts and the payer stops using the technology[9]. Towse identifies the potential attractions of overcoming the challenges of OWR with a local RCT by suggesting combining a global RCT with local observational data on events, effects, and resource use in practice. Using an example based on data from the CADET-Hp trial in Canada, Towse illustrates the benefits of risk sharing when added to OWR. In the example, the innovator is not willing to accept the CAN$105 price which is the payers view of the price at which INB > 0. The treatment is rejected. The innovator undertakes further research which it expects to support its value of CAN$140. Had OWR+ risk sharing been possible, then a CAN$105 price could have been used whilst the further research was conducted, providing access to Canadian patients during this period. Hence with translatable evidence and risk sharing the incentives of manufacturers and payers generally align for an optimal global trial over a locally optimal solution.

EW 2013 also define risk sharing as a variant of OWR "whereby evidence is linked by a pre-agreed contract to adjust payments". They identify two potential benefits of risk-sharing. The first is reducing or avoiding costs of reversal. In other words, the value of research (the ENBS) is reduced if there are costs associated with acting on the research to reverse the decision to use the product. These reversal costs can be eliminated for the payer if the risk-sharing agreement includes provisions that "prices are conditional on the evidence of INB to avoid the need for reversal and / or insurance provisions to compensate decision makers when costs of reversal arise"(EW, 2013). Secondly, it avoids the "opportunity costs of delay" by making adoption feasible whilst RCT evidence is collected elsewhere, thus increasing the ENBS of OWR as compared to OIR. Adoption is usually not compatible with conducting a clinical trial in the same health system.[10] However, the trial can be conducted in other jurisdictions.[11] In this case, the evidence collected locally is typically observational and

[9] Of course, negotiation over the terms of any scheme may mean that it addresses only prospective pricing, or partially recompenses the payer for losses. Alternatively, the payer may get full compensation with the innovator getting only partial gain from any value upside when the research reports.

[10] This is because the health system expects patients to benefit from the treatment, and so it is hard to justify ethically a trial in which a proportion of patients (usually 50%) will not get the treatment. It may also be difficult to recruit when this involves patients moving from the certainty of receiving a drug to a non-zero % chance of not getting a drug that is expected to benefit them. EW point out that there may be exceptions of (i) poor implementation (ii) the drugs are equivalent in benefit, the uncertainty is around costs or (iii) patients are paying out-of-pocket and many simply cannot afford the drug. In a pluralistic or decentralised health system there may be different payers making different decisions, perhaps reflecting different willingness to pay for health gain, as well as, or instead of, a different interpretation of the evidence. In this situation, a trial may be quite feasible in parts of the health system.

[11] A smart manufacturer will optimise VOI trial designs across jurisdictions taking account of the expected decisions and revenues. Trial centres will tend to be in smaller markets or those that are expected to Reject or insist on OIR. Markets

intended to be synthesised with continuing global RCT evidence. They also use numbers for INB taken from the CADET-Hp trial in their illustrative example, showing it is possible for the innovator to accept a lower price during the OWR period in the expectation that, if the innovator is correct, they can expect the price to increase towards their original price target.

Identifying the gap

Thus to date, although PBRSAs have been discussed in the context of OIR and OWR, there has been no modelling that explicitly seeks to illustrate and link the impact of risk sharing on the decision options faced by payers and innovators. Indeed, the literature does not explicitly separate the payer perspective from that of the innovator. We now seek to fill this gap.

that are expected to Accept, or approve subject to OWR, will be excluded, or only included in an early trial. EW (2009) model globally optimal trial design, on the assumption that evidence is freely transferable across jurisdictions. They refer to "global societal decision maker trials" (EW 2013). However, in order for jurisdictions to move from locally optimal trial design to a trial design that is globally optimal, that for some involves more patients and cost, "financial arrangements need to be made", i.e. some jurisdictions will need to compensate others. No indication is given as to how this trading might be facilitated. It is more plausible to see the innovator as the agent of global trial optimisation. Providing payers are clear what evidence they want in order to be willing to accept a particular price, then the company has a profit maximising incentive to be the "global societal decision maker" in delivering the globally optimal trial programme. This is discussed in Willan and Eckermann (2012). An earlier paper setting out such an approach was Backhouse (1998).

4 When in principle might risk-sharing be helpful?

As noted above, we take as our working definition of risk-sharing that it is a variant of OWR in which an agreement to collect further evidence is supported by a contract or understanding that payments will be adjusted depending on the estimated INB that comes from the evidence generation[12].

Risk-sharing allows payers to overcome two important concerns they may have about conditional approval, coverage with evidence development type schemes:

- First, it allows prospective (and retrospective) price adjustment which could have the aim of maintaining a constant INB based on available evidence. For example, the early UK Multiple Sclerosis Risk-sharing Scheme (MSRSS) was designed to lock in the £36,000 per QALY the government was willing to pay for health gain for MS patients;

- Second, it reduces the likelihood of any need for early reversal of a decision to adopt. This is because, in principle, price adjustments should be able to maintain a positive INB. Of course, the technology may be found to have such poor effectiveness that even a price of zero cannot deliver a positive INB. In which case a comparator treatment is better for patients. In these circumstances it should be possible for payers to stop using the technology and explain to patients that this is on the grounds of poor effectiveness. There may be irreversibilities arising in this situation, for example because of sunk investments associated with implementation of the technology. In this situation, the payer may need the guarantee of some compensation – effectively an insurance policy from the company that irrecoverable costs will be reimbursed[13]. The combined impact of price flexibility and an insurance policy is to provide assurance to payers that risk-sharing contracts can make irreversibilities irrelevant to adoption decisions in most situations[14].

From the perspective of the payer we can readily see therefore that risk-sharing can, in principle, create three opportunities:

- **Move payers from a position of OIR to OWR**, which will enable them to give patients access to treatment whilst additional evidence is collected, shift the expectation of achieving the expected INB, and reduce or even eliminate any cost of irreversibility that may arise from adoption without risk-sharing. Thus, whilst uncertainty remains about likely effectiveness, the expectation that the product will provide value for money improves.

[12] Thus, we would argue that as well as schemes labelled risk-sharing such as the Italian registry system, the NICE CDF regime is a type of risk sharing, as is the French scheme which allows for specification of post-launch evidence collection and reassessment criteria.

[13] The patient has to suffer the consequences of receiving a less effective product without financial or other compensation. In extreme the product may be inferior to standard of care or even cause harm. Arguably the clinical benefit risk assessment is one that is initially for the drug licensing body, although the payer may also have a view on acceptable clinical risk to patients arising from the uncertainty about the performance of the product.

[14] Of course, over time technologies will be displaced by new superior products, as happened in the case of the technologies included in the UK MSRSS. However, in most cases this will be well beyond the initial period in which evidence of cost-effectiveness was uncertain.

- **Move payers from Reject to OWR** in some circumstances, if the innovator is willing to offer a lower price in the context of a risk-sharing scheme, there is now a high enough expectation for the payer about likely value for money that they move from Reject (INB < 0, ENBS ≤ 0) to OWR (INB ≥ 0, ENBS > 0). The price reduction offered in a risk-sharing scheme has two effects: it makes INB positive and alters the decision uncertainty.

- **Make OWR more attractive to payers.** As we have shown, there are strong theoretical and pragmatic arguments for the use of conditional approvals (OWR) in certain circumstances. The addition of risk-sharing can help to make OWR attractive to payers in more situations, by increasing the likelihood that an OWR decision will provide health gain to patients and value for money to the health system.

From the perspective of the innovator, risk-sharing can, in principle, achieve three possibilities:

1. **Move payers from a position of OIR to OWR,** which will provide innovators with greater access to the market while undertaking research, albeit at a reduced price, but with the possibility of renegotiating price once the research is complete.

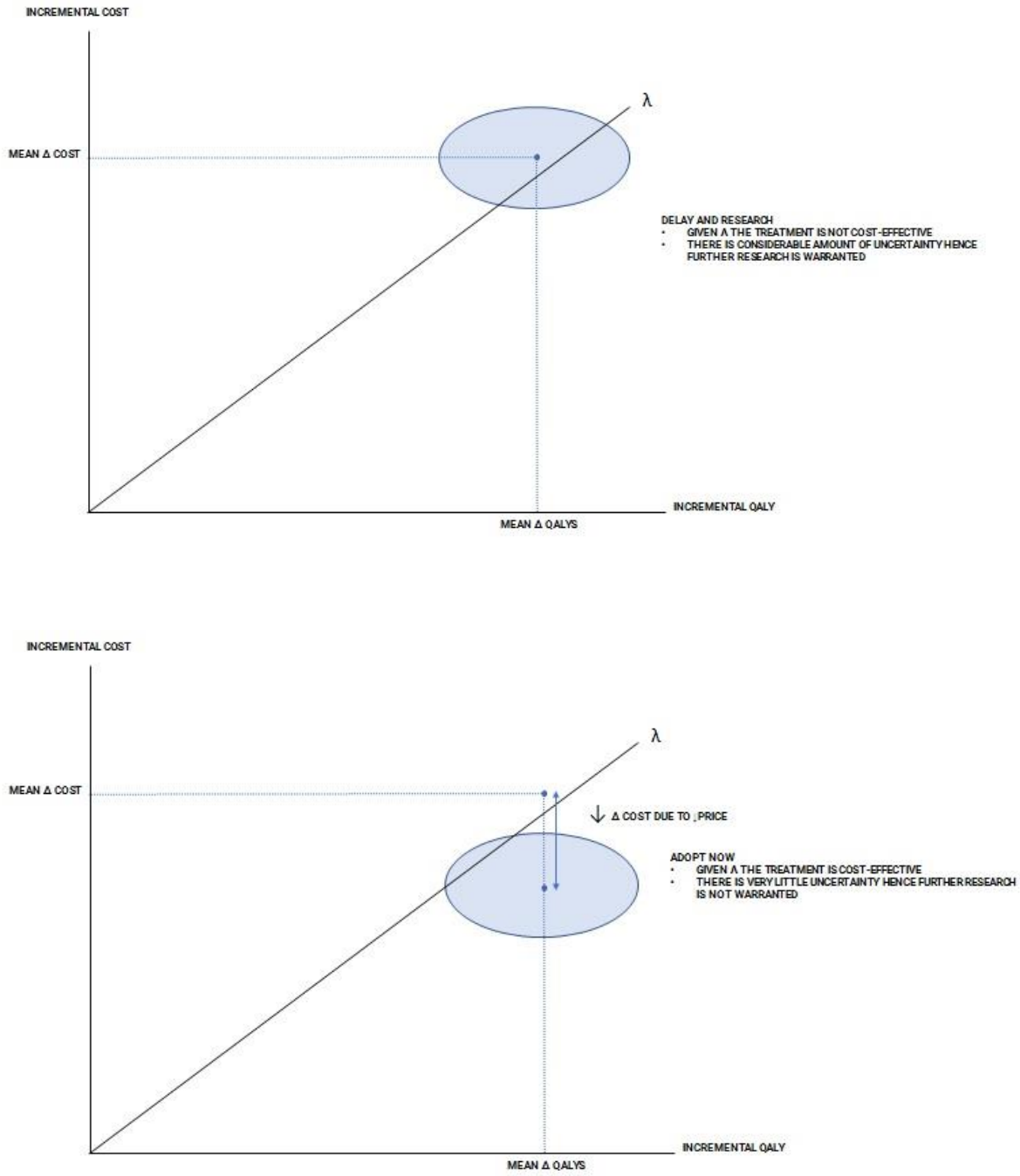
2. **Move payers from Reject to OWR** which will provide innovators with access to the market while undertaking research, albeit at a reduced price, but with the possibility of renegotiating price once the research is complete.

3. **Make OWR more attractive to innovators** through provision of a process by which prices can be renegotiated once the research is complete. In other words, rather than accept a price that the innovator believes is too low, it provides a route to achieving a higher price after collecting more evidence.

However, even when there could be agreement about the potential value of a risk-sharing scheme, there may be differences of view as between the payer and the innovator. We set out below three such circumstances.

First, the usual response of payers to uncertainty is to seek a lower price to make adoption (Accept) more attractive. We illustrate this in Figure 1 (below) where, at the innovators target price, the treatment is not cost-effective and the uncertainty leads to a recommendation of OIR, (i.e. INB < 0 and ENBS > 0). We show this in the top part of the Figure. The payer pushes for a price reduction to get to the lower part of Figure 1, such that INB ≥ 0 and ENBS ≤ 0. As we noted earlier, in effect, the payer is wanting its uncertainty to be "bought out" by the innovator. However, the price reduction may not be acceptable to the innovator if they are of the view that INB ≥ 0 and ENBS > 0. They will be prepared to undertake further research, but not to accept a permanently lower price. We would end up with OIR and no patient access.

FIGURE 1: AN ILLUSTRATION OF THE CHALLENGES OF DECISION UNCERTAINTY*



** In each panel of Figure 1 the uncertainty in the cost-effectiveness is represented by the oval shape.*

Where the payer believes that OWR is appropriate (i.e. INB ≥ 0 and ENBS > 0), then we may expect resistance from innovators to a risk-sharing scheme, if they are of the view that the payer should be using an OWR without the need for a contractual commitment to price change or a discount for the duration of the scheme. The company may take the view that further research is not necessary or that a commitment to collect data to enable a payer reappraisal based on the evidence is sufficient, without an agreement to reduce price during the period of data collection. This is because the expected value (INB) for the payer is positive at the current price.

There may also be circumstances in which a risk-sharing scheme is not acceptable to the innovator even if offered by the payer. If the innovator is of the view that INB < 0 and ENBS ≤ 0 at the price it is seeking, any risk-sharing scheme becomes, from the innovator's point of view, a potentially complex and costly way of offering a price cut, given that it expects the price reduction to be permanent once the results of the research are known. In this circumstance, it may simply choose to accept a reject decision or to offer a larger price cut that moves the payer to Accept (i.e. buys out the payers uncertainty) as illustrated in Figure 1.

These three possibilities take us to one important, overlooked, reason for introducing risk-sharing – that of resolving differences of opinion between innovators and payers on the value of a new technology to the health system. Of course, innovators may submit estimates of INB that the payer may regard as optimistic (i.e greater than the mean expected outcome from the payers'perspective). This can be seen as part of a bargaining process to arrive at the mean estimate of INB used by the payer. But consideration of risk-sharing in the context of VOI has, hitherto, made the assumption that the payer's estimates of both INB and ENBS are unbiased and that any differences of view from the innovator are part of a bargaining process and do not reflect different information, assumptions or analysis.

However, bargaining posturing aside, the innovator may believe that its estimate is correct, and may prefer to walk away (take a Reject or an OIR) rather than accept a permanent reduction in price that will achieve Accept[15]. In this situation, risk-sharing becomes a mechanism to enable the two sides to reconcile their positions. In the absence of such a scheme, payers will not adopt, where for them INB < 0. However, if the innovator is correct, then non adoption would lead to lost health gain.

We summarise the implications for the payer and the innovator of the three possibilities that risk-sharing can, in principle, achieve in Table 2 on the next page. We note that one absent "benefit" from Table 2 is making OWR more attractive to payers than Accept. This may be a concern of innovators, as it offers payers an additional backstop. However, OWR with a PBRSA has costs associated with it for the payer, even if the costs of research and of transacting the agreement are met by the innovator.

[15] This is particularly likely to be the case if reimbursement prices, once set, cannot be increased but can be reduced. If there is a re-review after a period in which prices could go up, then companies may be more likely to accept a reduction in price that will achieve Accept in the hope that it will be temporary whilst they collect more evidence of the underlying performance of the drug.

TABLE 2: SUMMARY OF RISK-SHARING BENEFITS FOR PAYERS AND FOR INNOVATORS

Potential effects of a risk-sharing scheme	Move payers from a position of OIR to OWR	Move payers from Reject to OWR	Make OWR more attractive to payers
Implications for the payer	Access achieved through a lower price whilst research is done to address uncertainty. Enables payer to provide access to patients. Payer will be compensated if research shows technology is not cost-effective.	Access achieved through lower price whilst research is done to address uncertainty. Enables payer to provide access to patients. Payer will be compensated if research shows technology is not cost-effective.	Additional benefit of compensation if research shows technology is not cost-effective.
Implications for the innovator	Technology is reimbursed whilst evidence is collected – allowing greater market access. Option for a price increase / renegotiation if research shows technology is cost-effective.	Technology is reimbursed whilst evidence is collected allowing market access. Option for a price increase / renegotiation if research shows technology is cost-effective. But innovator may not be convinced that the research is worthwhile, in which case risk-sharing not appealing.	Option for a price increase / renegotiation if research shows technology is cost-effective. Innovator would expect a "high" price during the scheme, and may be resistant to adding a risk share to OWR.

5 Understanding the role of Risk-sharing in the context of Payer and Innovator views on INB and ENBS

A complete overview of when a risk-sharing scheme (a PBRSA) may be helpful for achieving an optimal reduction in decision uncertainty from both payer and patient perspective requires us to take account of the views of both the innovator and the payer. We need, therefore, to take explicit account of the gain to each when they have similar/dissimilar perspectives.

In the literature to date, the innovator perspective has often been ignored. Yet, the societal welfare gain from the introduction of a new technology is the sum of the surplus enjoyed by the payer (the INB) and that enjoyed by the innovator. Here we focus on the benefits to the payer, recognising however, that the role of the innovator is key to determining the outcomes achieved by the payer. As we are assuming that the innovator will undertake the research or fund the costs of evidence collection in a PBRSA scheme, the innovator's commercial calculations, around the price and volume consequences of investment in evidence collection, matter. Its decisions, if it is a global profit maximizer, will take into account the impact of local data collection on the generation of evidence and on consequential pricing on a global basis. If the innovator expects to receive a value-based price that reflects the value of the health gain to the payer, then its evidence generation incentives will be aligned with the global requirements of payers.[16]

Note that both parties are estimating the INB for the payer, and the overall ENBS, i.e. the benefits of research in terms of reduced uncertainty for the payer and the costs of collecting the evidence. Whilst the innovator will look at the implications for its global business of any research or of any price agreement that is in the public domain, we are focussing on each parties view of the payers INB and the benefits and costs of reducing uncertainty for the payer, i.e. the ENBS.

Payers and innovators may agree, or differ, over one or both of whether INB ≥ 0 and ENBS > 0 for the payer. We set out the options for INB and ENBS above in Table 1. There are 2 decisions for each player:

1. Adoption decision based on cost-effectiveness – i.e. cost-effective if INB ≥ 0, Not cost-effective if INB < 0
2. Research decision based on expected value of research – Research (is worthwhile) if ENBS > 0, No research (is worthwhile) if ENBS ≤ 0

To reiterate, we are looking at INB and ENBS for the payer, and comparing the assessments being made separately by the payer and by the innovator as to whether or not, on the basis of current evidence, INB ≥ 0 and ENBS > 0 for the payer.

[16] We have previously noted that the EW global trial paper argues for payers to co-ordinate globally optimal trial / launch patterns and proposes payment mechanisms that allow this to happen. However, it is likely to be much more efficient to align incentives such that the company has an incentive to generate optimal amounts of evidence as part of its research and development strategy for the product.

This gives us 4 options per player:

a) INB ≥ 0, ENBS ≤ 0 – Adopt & no research = Accept

b) INB ≥ 0, ENBS > 0 – Adopt & research = OWR

c) INB < 0, ENBS > 0 – Do not adopt & research = OIR

d) INB < 0, ENBS ≤ 0 – Do not adopt & no research = Reject

Mapping this out for the 2 players gives us the 16 combinations illustrated in Table 3.

TABLE 3: 16 PAYER/INNOVATOR DECISION COMBINATIONS

	Payer view	**Innovator view**
1.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)
2.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)
3.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i > 0$ (OIR)
4.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)
5.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)
6.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)
7.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)
8.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)
9.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)
10.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)
11.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)
12.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENB_i \leq 0$ (Reject)
13.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)
14.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)
15.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i > 0$ (OIR)
16.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)

We use INB_P, $ENBS_P$ to show the views of the payer and INB_I, $ENBS_I$ to show the views of the innovator.

We assume that the company is the first mover in making a submission: they submit with the aim of receiving Approve, i.e. reimbursement without the need to collect additional evidence, irrespective of their unbiased view of the underlying cost-effectiveness of the technology and the potential value of additional research. The payer then responds in the light of its assessment of the price, the evidence, the degree of uncertainty and the value of further research. We assume that the payer responds by revealing its unbiased assessment of the technology. Either party could be first to propose a risk-sharing agreement. It could be proposed by the payer in its response to the submission, or through further interaction between the parties.

We analyse these options in relation to the potential value of risk-sharing as follows:

Rule 1. Where the payer wishes to adopt with no further research (Accept), the innovator should accept irrespective of their own view on cost-effectiveness or uncertainty. As such, scenarios 1,2,3 and 4 → Accept. Agreement is reached between the payer and the innovator and the product is reimbursed. There is no need for further research and no need for any form of risk-sharing agreement.

TABLE 4: APPLICATION OF RULE 1

	Payer view	Innovator view	Decision
1.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Accept
2.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Accept
3.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Accept
4.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Accept
5.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	
6.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	
7.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	
8.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	
9.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	
10.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	
11.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	
12.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENB_i \leq 0$ (Reject)	
13.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	
14.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	
15.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	
16.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	

Rule 2. Where the unbiased assessment of the payer is to reject ($INB_p < 0$ and $ENBS_p \leq 0$), they should not offer the innovator a risk-sharing agreement. In these circumstances, the innovator can take one of several options. The innovators choice at this point will depend on their own view of the cost-effectiveness and value of further research as follows.

Rule 2a. Where the unbiased estimate of the innovator is also to reject ($INB_i < 0$ and $ENBS_i \leq 0$), as in scenario 16, then they should also not propose a risk-sharing agreement. The innovator will not want to undertake further research to support the existing price as it does not believe it will bring a return, i.e. have a good enough chance of showing that the current price is a cost-effective one for the payer. In practice, the innovator is likely to either propose a price reduction or will have to accept that the product will not be reimbursed in this jurisdiction. If the innovator proposes a price reduction, this will change both the cost-effectiveness and the value of future research. Thus, both parties will have a different assessment of the cost-effectiveness and the value of research and the process will begin again.

TABLE 5: APPLICATION OF RULE 2A

	Payer view	Innovator view	Decision
1.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Accept
2.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Accept
3.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Accept
4.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Accept
5.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	
6.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	
7.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	
8.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	
9.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	
10.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	
11.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	
12.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENB_i \leq 0$ (Reject)	
13.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	
14.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	
15.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	
16.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Reject

Rule 2b. Where the innovator believes that either the treatment is cost-effective ($INB_i \geq 0$) and/or that there is sufficient uncertainty surrounding the cost-effectiveness ($ENBS_i > 0$), then the innovator should offer to enter into a risk-sharing scheme with the payer as this would provide a mechanism to get the technology, which the innovator believes either is, or has the potential to be, cost-effective (either with or without research), funded.

Specifically, where the innovator believes that there is sufficient uncertainty surrounding whether the treatment is cost-effective that further research is potentially worthwhile ($ENBS_i > 0$), irrespective of whether their expectation is that the product will be cost-effective at the current price or not, then an risk-sharing agreement can be made to work. The innovator sees that more information would be beneficial to address the uncertainties around the performance of the product. It may even be that the new research supports the current price, even though this may not be the expectation. The innovator's best option is to suggest that the payer undertakes a risk-sharing agreement as this provides a mechanism to get the treatment funded while the research is undertaken and may allow for a price rise once research is complete if the research shows the product performs better than the payer expects. As such scenarios 14 and 15 → Risk share. Although the innovator's view of whether the product is cost-effective differs between the two scenarios, in both cases it sees value in further research, and so avoiding rejection. It should be willing to accept a price during the PBRSA that reflected the payer's view of what was cost-effective, subject to agreement that the price could return to that proposed by the innovator if the research supported that price.

Where the innovator believes that the treatment is cost-effective ($INB_i \geq 0$) and there is no further requirement for research ($ENBS_i \leq 0$), offering to enter into a risk-sharing agreement with the payer would still be in the innovator's best interest as this will provide a mechanism to get the treatment funded and, again, will offer an opportunity for a price rise once the research is complete if the research results support the innovators original price. The obvious question is why would the innovator fund and undertake research that it thinks is of no value ($ENBS_i \leq 0$)? Firstly, the reason the innovator believes that further research is not worthwhile is because it believes that there is already enough evidence to show that the technology is cost-effective at the price that is proposed. Therefore it expects the research to confirm this. Secondly, it is, in effect, the entry fee to the market. Without it, the innovator will not sell in this market at this price. As such scenario 13 → Risk share. The innovator should be willing to accept a price during the PBRSA that reflected the payer's view of

what was cost-effective, subject to agreement that the price could return to that proposed by the innovator if the research supported that price.

TABLE 6: APPLICATION OF RULE 2B

	Payer view	Innovator view	Decision
1.	**$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)**	**$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)**	**Accept**
2.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Accept
3.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Accept
4.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Accept
5.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	
6.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	
7.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	
8.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	
9.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	
10.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	
11.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	
12.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENB_i \leq 0$ (Reject)	
13.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Risk share
14.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Risk share
15.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Risk share
16.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Reject

Rule 3. Where the payer does not expect the product to be cost-effective ($INB_p < 0$), but believes that the level of uncertainty means that further research is needed ($ENBS_p > 0$), i.e. OIR is appropriate, then they should offer the innovator a risk-sharing agreement. In these circumstances, a PBRSA would provide patient access, but the payer is likely to demand either (i) that the price during the PBRSA is set at a level that it believes would achieve cost-effectiveness, or (ii) that the price adjustment mechanism built into the agreement once the additional evidence is available is applicable retrospectively, i.e. the payer is reimbursed for its "loss" of value during the PBRSA. At this point, the innovator should either accept or reject this offer based on their own view of the cost-effectiveness and uncertainty associated with the treatment as follows.

Rule 3a. Where the innovator believes that the product is cost-effective ($INB_i \geq 0$), then the innovator would expect the results of the research to show that the product is beneficial. In this case, risk-sharing provides a useful mechanism, from the innovator's point of view, to get the treatment funded while research is undertaken. Depending on the nature of the risk-sharing agreement, it may allow for the original price to remain in place while the research is undertaken or to be put back in place once the research is complete, if the results of the research reflect the expectations of the innovator. As such scenario 10 → Risk Share. For scenario 9, as in scenario 13, the innovator is confident that the existing evidence base supports its proposed price ($ENBS_i \leq 0$). However, as in scenario 13, the payer believes $INB_p < 0$, and without undertaking the research the product will not be made available. Using risk-sharing within a PBRSA means that the innovator can market the product whilst keeping open its options to get the price it believes the evidence supports. As such scenario 9 → Risk share.

TABLE 7: APPLICATION OF RULE 3A

	Payer view	Innovator view	Decision
1.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Accept
2.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Accept
3.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Accept
4.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Accept
5.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	
6.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	
7.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	
8.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	
9.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Risk share
10.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Risk share
11.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	
12.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENB_i \leq 0$ (Reject)	
13.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Risk share
14.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Risk share
15.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Risk share
16.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Reject

Rule 3b. Where the innovator believes that further research is potentially worthwhile ($ENBS_i > 0$) even though its expectation is that the product will not be cost-effective at the current price ($INB_i < 0$) then a risk-sharing agreement can still be made to work. The innovator sees that more information would be beneficial to address the uncertainties around the performance of the product. It may even be that the new research supports the current price, even though this is not the expectation. The innovator's best option is to accept the payer's offer of a risk-sharing agreement, perhaps at a reduced price, as this provides a mechanism to get the treatment funded while research is undertaken and may allow for price maintenance/rise once research is complete if it shows the product performs better than both the innovator and the payer expects. As such scenario 11 → Risk share.

TABLE 8: APPLICATION OF RULE 3B

	Payer view	Innovator view	Decision
1.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Accept
2.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Accept
3.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Accept
4.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Accept
5.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	
6.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	
7.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	
8.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	
9.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Risk share
10.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Risk share
11.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Risk share
12.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENB_i \leq 0$ (Reject)	
13.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Risk share
14.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Risk share
15.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Risk share
16.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Reject

Rule 3c. Where the innovator believes that the product is not cost-effective ($INB_i < 0$) and also believes that further research is not worthwhile ($ENBS_i \leq 0$), the innovator has no expectation that

more information would be beneficial. In this case, the innovator would be best placed to reject the proffered risk-sharing agreement. Instead, the innovator is likely to propose a price reduction or to simply accept that the product will not be reimbursed in this jurisdiction. The innovator would not undertake further research to support the existing price as it does not believe it will bring a return, i.e. have a good enough chance of showing that the current price is a cost-effective one for the payer. As such in scenario 12 there is no role for a risk-sharing agreement → Price reduction.

When the innovator proposes a price reduction, in addition to changing the cost-effectiveness of the product it may also impact the value of future research i.e. the price drop may or may not be significant enough to buy out the payer's uncertainty. Thus, both parties will have a different assessment of the cost-effectiveness as well as the value of research and the process will begin again. Each time the price changes and/or some research is undertaken, all of the VOI calculations need to be updated, to take account of the value and cost of reducing uncertainty in the new environment.

TABLE 9: APPLICATION OF RULE 3C

	Payer view	**Innovator view**	**Decision**
1.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Accept
2.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Accept
3.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Accept
4.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Accept
5.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	
6.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	
7.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	
8.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	
9.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Risk share
10.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Risk share
11.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Risk share
12.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENB_i \leq 0$ (Reject)	Price reduction
13.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Risk share
14.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Risk share
15.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Risk share
16.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Reject

Rule 4. Where the payer expects the product to be cost-effective ($INB_p \geq 0$), but also believes that the level of uncertainty means that further research is needed ($ENBS_p > 0$), i.e. OWR is appropriate, then they should offer the innovator a risk-sharing agreement. In these circumstances, logically, given the payer view that OWR is appropriate, then the price agreed during the risk-sharing scheme should be the innovator's. There would not need to be any rebate agreement, but a review of price when the research was completed, with an adjustment mechanism agreed. At this point the innovator should either accept or reject this offer based on their own view of the cost-effectiveness and uncertainty associated with the treatment.

Rule 4a. Where the innovator believes that the product is cost-effective ($INB_i \geq 0$), then the innovator would expect the results of the research to show that the product is beneficial. In this case, risk-sharing provides the innovator with access to the market while undertaking research and a mechanism for price maintenance/rise once the research is completed.For scenario 5, as in scenarios 9 and 13, the innovator is confident the existing evidence base supports its proposed price ($ENBS_i \leq 0$). However, despite the payer view that $INB_p \geq 0$, it will not accept the current price without further research. Using risk-sharing risk-sharing within a PBRSA means the innovator can market the product whilst keeping open its options to get the price it believes the evidence supports. As such scenarios 5, 6 → Risk share.

TABLE 10: APPLICATION OF RULE 4A

	Payer view	Innovator view	Decision
1.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Accept
2.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Accept
3.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Accept
4.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Accept
5.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Risk share
6.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Risk share
7.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	
8.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	
9.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Risk share
10.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Risk share
11.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Risk share
12.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENB_i \leq 0$ (Reject)	Price reduction
13.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Risk share
14.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Risk share
15.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Risk share
16.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Reject

Rule 4b. Where the innovator believes that further research is potentially worthwhile ($ENBS_i > 0$) even though its expectation is that the product will not be cost-effective at the current price ($INB_i < 0$) then a risk-sharing agreement could be made to work. The innovator sees that more information would be beneficial to address the uncertainties around the performance of the product. It may even be that the new research supports the current price, even though this is not the expectation. The innovator's best option is to accept the payers offer of a risk-sharing agreement as this provides a mechanism to get the treatment funded while research is undertaken and may allow for price maintenance once research is complete if it shows the product performs better than the innovator expects. As such scenario 7 → Risk share.

TABLE 11: APPLICATION OF RULE 4B

	Payer view	Innovator view	Decision
1.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Accept
2.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Accept
3.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Accept
4.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Accept
5.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Risk share
6.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Risk share
7.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Risk share
8.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	
9.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Risk share
10.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Risk share
11.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Risk share
12.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENB_i \leq 0$ (Reject)	Price reduction
13.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Risk share
14.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Risk share
15.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Risk share
16.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Reject

Rule 4c. Where the innovator believes that the product is not cost-effective ($INB_i < 0$) and also believes that further research is not worthwhile ($ENBS_i \leq 0$), the innovator has no expectation that more information would be beneficial. It could be argued that in this scenario, when the payer will be offering OWR, that use of the product at the innovator's price during research would be commercially valuable. However, any revenues would have to be offset against the cost of doing the research that

the innovator does not expect will support its price. And we note that accepting OWR is not the same as accepting a PBRSA where the innovator is potentially locked in to accepting a lower price if the research shows the results the innovator expects. It may make more sense for the innovator to reject the proffered risk-sharing agreement and instead propose that price now, and potentially avoid undertaking the research. As such in scenario 8 there is no role for a risk-sharing agreement → Price reduction.

If the innovator proposes a price reduction, in addition to changing the cost-effectiveness of the product it may also impact the value of future research i.e. the price drop may or may not be significant enough to buy out the payer's uncertainty. Thus, both parties will have a different assessment of the cost-effectiveness as well as the value of research and the process will begin again.

TABLE 12: SUMMARY TABLE OF ALL OPTIONS

	Payer view	**Innovator view**	**Decision**
1.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Accept
2.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Accept
3.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Accept
4.	$INB_p \geq 0$, $ENBS_p \leq 0$ (Accept)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Accept
5.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Risk share
6.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Risk share
7.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Risk share
8.	$INB_p \geq 0$, $ENBS_p > 0$ (OWR)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Price reduction
9.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Risk share
10.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Risk share
11.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Risk share
12.	$INB_p < 0$, $ENBS_p > 0$ (OIR)	$INB_i < 0$, $ENB_i \leq 0$ (Reject)	Price reduction
13.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i \leq 0$ (Accept)	Risk share
14.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i \geq 0$, $ENBS_i > 0$ (OWR)	Risk share
15.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i > 0$ (OIR)	Risk share
16.	$INB_p < 0$, $ENBS_p \leq 0$ (Reject)	$INB_i < 0$, $ENBS_i \leq 0$ (Reject)	Reject

Revisiting Transaction costs

We are assuming that the innovator pays for the costs of additional research, either by funding it directly, or by reimbursing the payer for its costs relating to the collection of evidence. Typically, if a clinical trial is extended or newly commissioned by the innovator, then the innovator would pay. However, if observational data is collected in the health system, or if a responder scheme is put in place, then these costs would be directly incurred by the health care system. Pitta Barros (2011) explores a model of risk-sharing in which the payer must incur a cost *c* to verify the outcome of the treatment. The optimal outcome occurs when *c* is zero, and when price reflects benefit to responders. This would occur if the innovator reimburses the payer for the costs of running the scheme, or it is reflected in a lower price, i.e. any evidence collection and verification costs incurred by the payer are included in the calculation to arrive at a value-based price. Initially, when NICE introduced risk-sharing arrangements, following revisions to the government - industry pricing agreement in 2009, the template made clear that the costs to the NHS of administering the scheme were to be included along with the cost of the technology[17]. However, there may be other negotiation

[17] *We can note that the providers were not reimbursed by the payer for monitoring costs incurred, and so objected to the arrangements. Most were replaced with "simple" confidential price discounts and "complex" schemes were discouraged, until revisions to the Cancer Drugs Fund were introduced in 2016.*

and monitoring costs to the payer, which also need to be taken into account when agreeing price or that need to be reimbursed by the innovator to the payer as part of the scheme[18].

Relaxing assumptions

We made several important assumptions. We now briefly consider how our approach would need to be adapted if they were not to apply:

- We have assumed risk neutrality. Such an approach is underpinned by the Arrow-Lind theorem (Arrow and Lind, 1970) which assumes that govenments are able to spread risk across many investments in a way that makes them indifferent to the variance of returns and so focus only on the expected outcomes. Trowman et al. 2021, which summarises discussion by HTA bodies and industry at an HTAi Global Policy Forum meeting, assumes that HTA bodies are risk averse, but no evidence or references are given for this in the paper or in the supporting Background Paper (Trowman 2021). We are aware of unpublished work by Kirwin, presented at the CADTH Symposium 2021, which seeks to formalise a VOI approach in which payers adopt a risk averse approach. Whilst the value of research to payers would increase, the framework we have set out would still apply. If one or both of the payers / innovators were not risk neutral (risk averse or risk loving), then the VOI calculations for that party would change, because the starting point would be different. In the case of risk aversion, the value of a reduction in uncertainty would increase, increasing the ENBS for that party. Potentially, risk-sharing becomes more attractive to them as scenarios 5-12 are, arguably, more likely to occur.

- We have assumed that payers are price takers. We recognise that there is some form of price negotiation in most countries, but we do not see relaxing this as undermining the relevance of our approach. Arguably, the VOI framework offers the context in which a price would be negotiated, and risk-sharing enables the negotiated price to be provisional subject to the gathering of further information. Our thinking is that as long as innovators can discuss and influence the price, the qualitative results will remain valid. A related issue is whether payers have the power to commission or facilitate research being undertaken. We can accommodate this possibility also, because, as we set out below, we expect innovators to be responsible for undertaking the relevant research.

- We are using a cost-effectiveness / cost per QALY threshold framework. In a therapeutic added value system in which (i) QALYs may not be the outcome measure and (ii) prices are negotiated after the health outcome is assessed, we would argue that the same VOI framework applies, albeit QALYs are not the outcome metric, and *k* the threshold or currency converter for outcomes into money may vary by disease area or type of product, or be linked to another approach to price determination. The point is that both parties understand the relationship between expected outcome and price, and that the payer wants to see additional evidence generated to reduce uncertainty around the outcome, depending on the cost of collecting that evidence.

[18] These costs could be regarded, from the payers perspective, as irrecoverable if they were not reimbursed by the innovator. Value of information theory tells us that an irreversibility, i.e. a cost associated with a decision, which cannot be recovered, must be taken into account in calculating the value of an OWR decision. However, as we have set out in the paper, a PBRSA can eliminate such a cost by requiring the innovator to reimburse these costs. Anticipated costs associated with a PBRSA can be factored in the cost-effectiveness calculation. In theory, unanticipated costs could be reimbursed retrospectively by the innovator. However, some form of cost-sharing is likely to be optimal to ensure the payer has an incentive to run the PBRSA efficiently.

6 Policy Implications

Table 12 indicates that risk-sharing provides the optimal solution in 9 out of 16 combinations of payer and innovator expectation about the outcome of treatment and the value of further research. However, the literature shows very clearly that although risk sharing is feasible (Vreman et al. 2020a) transaction costs are a barrier to implementation and payer experience with outcome-based schemes has been mixed (Wenzl and Chapman 2019). Payers and HTA bodies do not like using risk-sharing schemes, because of the resources involved, in both negotiating and monitoring the schemes, and in the collection and analysis of the data (Cole et al. 2021). Innovators also dislike the cost and effort involved in evidence collection and in administering the agreement. However, the possible alternatives are also associated with issues. Payers see the alternatives as either lower prices or innovators providing additional evidence. Innovators see the alternatives as the payer adopting the technology, on the basis of the price and evidence offered by the company. Hence, we end up with the case for risk-sharing schemes, albeit with the proviso to take account of transaction costs not included in the assessment of the value of further research.

The key is to align incentives correctly. Implementing risk-sharing does impose costs. If the innovator is getting a value-based price, this price needs to be adjusted for the costs incurred by the payer in implementing a risk-sharing scheme. This was indeed the approach taken by NICE when risk-sharing was first implemented in the English NHS in the 2009 PPRS. A costing template required costs incurred by the NHS in managing the scheme to be included in the cost-per-QALY calculation. However, this did not mean that the parts of the health system collecting data and managing the scheme were reimbursed for their effort. Busy clinicians and pharmacists resisted taking on additional work designed to support a price agreement for which no resourcing was made available to them. An alternative, more practical approach, that tackles this problem is for the innovator to pay separately for the costs of the scheme. This money then needs to be distributed to those incurring the costs. The Italian risk-sharing registries were funded by payments from participating companies., although it is not clear that resources went to the hospitals completing the data inputs. Where there is separate payment, the value-based price needs to be set excluding these costs.

It will be important that the fees collected in this way are remitted to those incurring the costs of running the scheme. It will also be important, however, that the commitment for the innovator is not open-ended and that administration is not "gold-plated" at its expense. Preset formulas could be used which would retain the incentive for the system to undertake data collection efficiently, and/ or some form of cost sharing could be used if costs exceed a certain percentage above the sum specified by the formula.

By requiring the innovator to meet the costs of implementing a risk-sharing agreement, the incentives are then aligned for efficient decision making in the development programme. Innovators face the true costs and revenues associated with either (i) speeding up development and licensing and obtaining accelerated approval, in recognition that this is likely to lead to the costs associated with risk-sharing schemes if they are to access revenues more quickly, or (ii) taking more time to develop the evidence base so that the chances of getting an "Accept" from a payer increase.

It is always possible that innovators do not undertake the research they have agreed to do. This has been a major concern in regulatory fast track processes (see for example Kaltenboeck et al., 2021 and Eichler et al., 2012). In the case of payers, it is in principle more straightforward to ensure that the innovator faces appropriate financial penalties. This is the cost of buying out the uncertainty that

the research was expected to deliver. It would need to be applied retrospectively.[19] Of course, there may be good faith occasions on which the research takes longer to initiate or to complete. The agreement would need to reflect this. The value of the research would be reduced, and indeed the cost may have increased. At some point it may no longer be worth undertaking the research, in which case a reassessment would need to use the evidence available of the most likely INB, and proceed as if that were the outcome of the research.

We can also note the global trial perspective of EW, which we discussed earlier in the paper. The innovator can take a global perspective, taking the costs of risk-sharing into account in its sequencing of the location of launches and the timing and location of clinical and economic studies intended to support the evidence base for the product. If it faces the underlying societal costs and benefits of use in different countries, then both the development and launch programme should be globally efficient.

Finally, we should note although we refer to 9 out of 16 combinations, in practice the use of risk-sharing may be less frequent than this ratio implies, even within our framework, due to transaction costs and because innovators may choose to find ways to improve evidence generation prior to launch. Regulators, HTA bodies and payers can help with this, for example by seeking greater alignment between regulators and HTA bodies (Vreman et al. 2020b) or by building in opportunities for pre-launch dialogue around post-launch evidence generation (Moseley et al., 2020).

In conclusion, there are steps that can be undertaken to make risk-sharing more practical, both in terms of ensuring that HTA bodies and payers consider risk-sharing as an option and of ensuring that the costs to the health system of implementing risk-sharing fall upon the innovator in an efficient way. The end result should be earlier access to cost-effective treatments for patients, with the innovator getting revenues, and the payer having confidence that it is not wasting money.

[19] *Kaltenboeck et al. (2021) propose reimbursement penalties to incentivise completion including mandatory discounts (in effect assuming the research addressing the uncertainty is not going to be done, until it is competed) and outcome-based contracts, i.e. PBRSAs building on the evidence requirements of the regulatory regime.*

References

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