Pricing Pharmaceuticals by Outcome

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This case study series was an input into the report *Payment by Outcome: A Commissioner’s Toolkit*. The case studies do not provide an explanation of how to design a payment-by-outcome system in the sectors studied. Rather, through the case studies, the authors sought to understand the challenges involved in using payment-by-outcome and the tools that have been employed to cope with them.
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Introduction

There has been a noticeable trend over the last 20 years in the negotiation of prices for novel and complex pharmaceutical products towards payment-by-outcome models as manufacturers have come under increasing pressure from purchasers to improve the cost-effectiveness of their treatments. Analysis of this development in the pharmaceutical industry can illuminate an important strand in contemporary thinking about public performance management, in particular, the application of similar payment-by-outcome frameworks to public service providers. Although essentially a product rather than a service, the purchase of drugs by large institutional insurers on behalf of users presents similar challenges to the large-scale commissioning of public services such as welfare to work, long-term condition management and offender management.

Traditionally, pharmaceutical prices have reflected manufacturers’ inputs into developing new treatments; however, purchasers – governments and insurers – have become increasingly concerned with patient value and actual health outcomes. Although pharmaceuticals have created huge health benefits, they have also caused demand to increase and driven up health spending. In order to contain runaway costs, governments have developed regulatory policies to cap profits and standardise prices using global reference points and internal tariffs. At the same time the rate of discovery for breakthrough drugs has begun to decrease and competition from similar brand-name products and generics has pushed prices down.¹

It is also increasingly common for the adoption of products to be contingent on the results of rigorous cost-effectiveness analyses quantifying the benefits of new therapies. Since its creation in 1999, the recommendations of the UK’s National
Institute for Health and Clinical Excellence (NICE) have not only influenced coverage under the National Health Service but have also become global reference points for pricing information. Furthermore, unfavourable NICE decisions have induced manufacturers to offer discounts and innovative pricing schemes.

A greater focus on prospectively calculating the cost-effectiveness of pharmaceutical products based on the results of clinical trials has also been mirrored by the tracking of outcomes in the community. Furthermore, purchasers have sought to share the risks of improving patients’ health through pricing schemes linking prices directly to their observable effects using validated measures to trigger rebates, discounts or price adjustments based on actual performance.

Development of Risk-Sharing Schemes
Risk-sharing schemes between insurers and manufacturers originated in the US in the 1990s. Early examples include ‘no cure, no pay’ strategies for male pattern baldness drugs, schizophrenia treatments and cholesterol-lowering statins. This approach, however, proved unsustainable since it benefited the insurer much more than the manufacturer, with the result that the agreements were either not renewed or the manufacturer attempted to break the agreements. In 2000, a similar strategy was pursued more successfully in England, in a local trial of a new branded statin based on a money-back guarantee.

Most outcome-based schemes in the UK have come about following an unfavourable recommendation by NICE based on lack of cost-effectiveness. The first national scheme agreed between the Department of Health and the manufacturers of a new generation of multiple sclerosis drugs arose in this way. The scheme pegged the price of the drugs to a threshold level of cost-effectiveness whilst the price would be reviewed on the basis of a study tracking patient disease progression. A similar scheme was initiated in 2004 in Australia to review the price of the drug bosentan for a rare degenerative lung disease based on tracking patients’ mortality rates.

In 2007, a simpler rebate scheme was introduced for a multiple myeloma (blood cancer) drug based on the reduction of abnormal proteins found in the blood. A similar rebate was introduced for a meta-static colorectal cancer drug, Erbitux, if scans revealed the tumour had not stabilised after six weeks of treatment. The company Novartis offered a dose-capping scheme to the NHS under which they
would bear the cost of eye treatment beyond 14 doses of Lucentis for patients with macular degeneration, if there was no improvement in visual acuity compared to standard care.

In the US, insurers have begun tentatively to re-adopt risk-sharing schemes. The manufacturers of an anti-osteoporosis drug have reached an agreement with a medium-sized insurer to reimburse costs associated with fractures for patients taking the treatment as prescribed. A slightly different approach has been taken by the manufacturer Merck, in agreeing with a major insurer, Cigna, to discount the cost of its anti-diabetic drugs following decreases in bloodsugar levels of patients taking any diabetes drug, with further discounts if patients are taking Merck drugs as prescribed. There is also some movement to extend value-based purchasing under a pay-for-performance model proposed by the Centers for Medicare & Medicaid Services to all branded drugs.4

Problems with risk-sharing schemes

Despite more than 20 years of development, these schemes are still judged (even by supportive commentators) to be in their infancy. In a recent review, the Stockholm Network argued strongly against seeing them as a ‘golden bullet’ for driving down costs as they are time-consuming to negotiate, costly to administer and difficult to assess. Instead they should be seen as one way of getting purchasers and manufacturers to work more closely together for the public good.5

Some schemes have also been criticised for ignoring the opportunity costs of using a new treatment, and the availability of such pricing models makes it more difficult to refuse to extend coverage outright to a drug based on low cost-effectiveness especially when physician and patient groups lobby for its use. The MS scheme, in particular, has suffered from problems in adequately measuring disability progression due to the complexity of the disease and therefore has not resulted in any completed price reviews despite evidence indicating little benefit to patients. Critics have suggested that the £50million per year spent on MS drugs could have been better spent on other patients or extending clinical trials.6
### Table 1: Outcome-Based Pricing Schemes

Some of the most-reported outcome-based pricing schemes are summarised in the table below. Further details can be found in the appendix.

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Disease</th>
<th>Year Started</th>
<th>Manufacturer</th>
<th>Purchaser</th>
<th>Outcomes</th>
<th>Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin Outcome Guarantee Pilot</td>
<td>Coronary Heart Disease</td>
<td>1999</td>
<td>Pfizer</td>
<td>North Staffordshire Health Authority, NHS (England)</td>
<td>Reduction in LDL cholesterol blood concentration to National Service Framework standard for 80% of patients at high risk of CHD</td>
<td>Refund total cost of treatment during pilot.</td>
</tr>
<tr>
<td>Beta Interferons and Glatiramer Acetate risk-sharing scheme</td>
<td>Multiple Sclerosis</td>
<td>2002</td>
<td>Various</td>
<td>NHS (England)</td>
<td>Maintain cost-effectiveness at or below £36,000 per QALY based on disability progression and number of relapses.</td>
<td>Reduction in prices to meet cost-effectiveness criteria.</td>
</tr>
<tr>
<td>Bosentan Patient Registry</td>
<td>Pulmonary Arterial Hypertension</td>
<td>2004</td>
<td>Actelion Pharmaceuticals</td>
<td>Medicare (Australia)</td>
<td>Lower actual annual mortality rate for patients compared to predicted rate.</td>
<td>Price reduction based on actual mortality rates.</td>
</tr>
<tr>
<td>Cetuximab (Erbitux) Cost Share Programme</td>
<td>Metastatic Colo-Rectal Cancer</td>
<td>2007</td>
<td>Merck</td>
<td>NHS (England)</td>
<td>Improvement or stabilisation in tumour response after six weeks based on patient scans.</td>
<td>Refund in cost of treatment for non-responders.</td>
</tr>
<tr>
<td>Lucentis dose-capping scheme</td>
<td>Wet Age-related Macular Degeneration</td>
<td>2008</td>
<td>Novartis</td>
<td>NHS (England)</td>
<td>Improvement in visual acuity compared to standard care.</td>
<td>Manufacturer bears cost of scheme beyond 14 doses if there has not been sufficient improvement.</td>
</tr>
<tr>
<td>Januvia &amp; Janumet -Oral drug scheme</td>
<td>Diabetes Type II</td>
<td>2009</td>
<td>Merck</td>
<td>Cigna (US)</td>
<td>1) Improvement in blood sugar levels of all patients. 2) Improvement in blood sugar levels of all those taking Merck drugs as prescribed.</td>
<td>1) Discount on drug price to insurer. 2) Further discount to insurer.</td>
</tr>
<tr>
<td>Actonel Fracture Protection pilot programme</td>
<td>Osteoporosis</td>
<td>2009</td>
<td>Sanofi-Aventis</td>
<td>Health Alliance (US)</td>
<td>Reduction in non-spinal osteoporotic fractures.</td>
<td>Reduce insurer’s cost of purchasing drug by average medical expenses for treating fractures.</td>
</tr>
</tbody>
</table>
2 Pricing Models

The aim of outcome-based pricing schemes is to link manufacturers’ total remuneration more closely to the actual performance of their pharmaceutical products. Benchmark prices are initially set following a rigorous cost-effectiveness analysis of available data, usually from clinical trials. Based on a survey of a range of schemes (see Table 1), there are three identifiable models:

1. rebate based on the price of the drug;
2. rebate based on the costs of harm; and
3. price adjustment (up or down) based on observed outcomes.

In practice, prices tend to start high and gradually decrease over time and thus far price-adjustment schemes have only allowed for downward corrections. Manufacturers can try to mitigate their revenue risk by seeking to justify as high an entry price as possible to cover input costs.

Price rebates
Rebate schemes can be high-stakes agreements since they effectively offer an all-or-nothing penalty based on a binary evaluation of patient response. In 2000 the manufacturer Pfizer offered a money-back guarantee for a limited pilot period to North Staffordshire Health Authority for all sales of its atorvastatin treatment for coronary heart disease if it failed to lower a sufficient proportion of patients’ LDL cholesterol levels. Offering such a broad rebate is not typical and a principal driver behind this approach was to prove the drug’s effectiveness compared to other similar products which were due to go off-patent and therefore reduce sharply in price.
Most price rebates are triggered by individual patient responses. The Velcade Response Scheme for multiple myeloma (blood cancer) offered a refund if levels of the abnormal M-protein in patients' blood failed to decrease by a pre-agreed percentage. However, this created a great deal of tension around the optimal level of threshold response, requiring detailed scrutiny of evidence. Whilst NICE managed to negotiate higher expected standards of performance, raising the minimum reduction from 25% to 50%, patients whose response fell below this mark could lose out on further treatment despite showing evidence of some benefit. To mitigate this risk an extra cycle of treatment was allowed. However, given each cycle of treatment costs around £3,000 this also increased the manufacturer’s potential exposure if a refund was triggered.7

The burden of making claims tends to fall on the purchaser (in this case, hospital pharmacy departments) and evidence from NHS patient access schemes for oncology drugs (such as Velcade and Erbitux) suggests that administrative costs are high as a result. Outcome-based schemes are reported to take (on average) at least twice as long to administer than simple price-volume discounts. Strict deadlines on claims coupled with the administrative burden may have resulted in lost refunds. The Erbitux scheme was criticised heavily in a survey of NHS pharmacists for its very tight deadlines as reimbursement forms had to be faxed within five days, and some respondents suggested they did not participate for this reason. In the case of Velcade only around half of respondents reported that all refunds had been received.8

A lower-stakes approach is used under the Lucentis dose-capping scheme whereby the manufacturer provides the treatment at no further cost after the first 14 rounds if an adequate response has not been achieved. This reduces the manufacturer’s potential exposure through a guaranteed revenue stream but caps the profit per patient. Moreover, it alleviates the purchaser’s duty to scrutinise performance, since, in contrast to the all-or-nothing nature of the rebate schemes above, a claim only has to be made where further treatment is thought to be worthwhile and therefore provides an incentive to pursue the free doses.

Cost-of-harm rebates
The willingness of manufacturers to assume greater risk is evident through rebate schemes that are related to the cost of harm which sharply increases potential exposure from claims. To date, the concept has been applied only to one US
scheme for anti-osteoporosis tablets whereby the average medical expenses associated with a non-spinal osteoporotic fracture are reimbursed to the insurer. Depending on the type of fracture, this can cost the manufacturer up to $30,000 per patient which is very high compared to the cost of the drugs, around $1,000 per year. Claims are restricted, however, to those patients taking the drug as prescribed for at least six months and downside risks are further mitigated through a cap on the total number of reimbursable fractures per year. Data from the first nine months of the scheme showed that the reimbursement rate was well below the maximum for the year.9

Price adjustments
An alternative discount model has been used for adjusting the price of oral diabetes drugs whereby improvements in patients’ blood sugar levels trigger reductions. The agreement between the US insurer Cigna and Merck for Januvia and Janumet drives both greater adherence and greater volume sales by providing one set of discounts if blood sugar levels of all patients decrease, regardless of the medication, and a second set if patients have been taking Januvia or Janumet as prescribed. Merck benefits from increased sales volumes and the ability to pass discounts onto policyholders in the form of lower co-payments and premiums.10

More complex price-adjustment schemes have pegged the price of pharmaceutical products to a maximum incremental cost-effectiveness ratio of cost per quality-adjusted life-year. This model was used to regulate the price of beta-interferons for MS sufferers. A ten-year study was conducted to compare the actual disease progression in all patients taking these drugs with the results predicted by historical and clinical trial data. The difference between actual and predicted performance is then used to calculate a new cost per QALY ratio and thus a new price. However, to date this scheme has struggled to provide a reliable evidence base for altering price hence no adjustments have taken place.

Nevertheless, a similar scheme in Australia has proved more robust. Patients prescribed bosentan were enrolled in a registry that tracked their annual mortality rates. The study model in this scheme was much shorter than for MS, lasting only three years instead of ten, the patient cohort was smaller and the outcome objectively measurable.
Monitoring

High-trust models have been employed to monitor schemes, leaving much of the data collection and verification to the purchaser. Cigna was responsible for reviewing blood sugar levels and claims data of patients taking oral diabetes drugs to see if they were taking the drugs as prescribed. Under the Velcade response scheme the manufacturer was only interested in auditing claims if they rose above a predicted rate of 15%.

Manufacturers have also been willing to sponsor the independent studies to monitor outcomes, lasting up to ten years in the case of beta-interferons for MS. However, the complexity of some of the price-adjustment schemes, particularly for beta-interferons and bosentan, makes them much less responsive to patients and much more sensitive to data interpretation. Despite an interim finding in the MS study that the drugs were not cost-effective (in fact, less effective than no treatment), no action was taken to lower prices due to uncertainty around the evidence base and application of the predictive model. However, reported benefits of the scheme have been that the manufacturers lowered their prices in advance so as to qualify, whilst the scheme also facilitated an expansion in specialist MS centres and nurses around the UK which improved the overall quality of treatment.
Choosing Measures

In order to link remuneration to performance and ultimately improved health outcomes, there must be an adequate basis for measurement. The process of research and development itself is rooted in an iterative scientific process of discovery and measurement, which examines the nature of connections between processes and outcomes. Broadly speaking, medical outcomes can be understood along three dimensions:

- Economic: direct, indirect and intangible costs compared with the consequences of medical treatment alternatives;
- Clinical: medical events that occur as a result of disease or treatment; and
- Humanistic: consequences of disease or treatment of patient functional status or quality of life.11

This model, often referred to as the ECHO model, is useful for categorising outcomes and presents a balanced assessment framework for appraising overall health benefits of different treatments. All three elements are also present in the calculation of cost-effectiveness such as cost per quality-adjusted life-year (see below). However, collecting and interpreting data to analyse outcomes across all dimensions is laborious and time-consuming and it is preferable for pricing schemes, wherever possible, to use fewer measures to evaluate performance.

Clinical trials carried out during the development of new products provide the necessary groundwork to enable the measurement of performance but they provide insufficient information to purchasers about how pharmaceuticals perform under real-world conditions. Trials only address a drug’s efficacy, i.e. its capacity to produce an effect under controlled conditions, rather than its effectiveness when used in populations and doses that have not been studied.
Primary and surrogate outcomes

In clinical trials, outcomes are normally set as primary or surrogate endpoints. A primary endpoint is the occurrence of the disease, symptom, sign or abnormality that constitutes the outcome itself such as death, recurrence or prevalence of disease. Primary endpoints can form the basis for pricing schemes, as in the case of the Bosentan Patient Registry, which used annual mortality rates for patients with pulmonary arterial hypertension as the basis for re-calibrating prices, or the Actonel Fracture Protection Programme, where rebates were triggered by fractures in osteoporosis patients. However, using primary endpoints as a basis for such schemes is rare.

A surrogate is an intermediate measure or biomarker which is an objectively measurable biochemical feature that has a strong correlation with the target outcome. Surrogate events are more numerous and can produce more data for analysis than a clinical endpoint and their use in risk-sharing schemes may provide early warning of undesired outcomes such as death or heart attack. In the case of bosentan, above, there was firstly no clear biomarker available although the working of the disease was quite well understood. Secondly, the average time between diagnosis and death was around three years which made it amenable to study over the medium-term and finally, some supplementary measures could be employed to assess intermediate progress.

One of the best examples of a biomarker being used in a risk-sharing scheme is the Velcade Response Scheme for patients with multiple myeloma, where response was measured by a reduction of abnormal M-protein cells in the blood. Nevertheless, there is always some uncertainty around interpreting biomarkers. There are concerns that M-protein is not a good surrogate for life expectancy, whilst 10-15% of patients do not have measurable M-protein levels. Doubts also linger about the link between LDL-cholesterol and coronary heart disease since patients with elevated levels may not develop the disease yet those with normal levels may still be at risk. In these cases the purchaser has clearly taken on the risk of that link’s effectiveness whilst the manufacturer provides a guarantee of their product’s performance in altering the biomarker. Progress towards the discovery of more molecular biomarkers such as LDL-cholesterol, in contrast to physiological markers such as blood pressure, may also suggest that through the use of surrogates drug prescribers and purchasers can build up a more granular picture of performance and patient response.
Functional measures
Where endpoints cannot be measured or evidence-based surrogates do not exist, functional measures based on cruder assessments of progress have been used. The Lucentis scheme for patients with macular degeneration passes on the costs of treatment to the manufacturer if there has been no improvement in eyesight compared to standard care based on visual acuity scores. The more complex bosentan scheme also used more detailed functional measures collected every six months based on six-minute walking distances and results of echocardiograms to track the progress of patients and decide whether to continue treatment.

In the case of multiple sclerosis there is a dearth of measures that can be used to approximate hard outcomes, such as the need to use a stick or a wheelchair, since the disease unfolds over decades with only about half of those affected becoming moderately disabled within a decade. A scale from zero (perfect health) to 10 (death), known as the Expanded Disability Status Scale, is widely accepted as the principal assessment of disease progression and is being used in the current UK risk-sharing scheme to measure the impact of beta-interferons. However, the scale has been criticised for concentrating too much on external signs of disability rather than patient-reported fatigue and other debilitating symptoms. The number and severity of relapses and the number and size of lesions as revealed by MRI scans are also measured, and whilst these demonstrate very broad static relationships with present symptoms they are, like EDSS, poor predictors of how the disease will progress.\textsuperscript{12}

Cost-effectiveness
The efficiency of products can be captured through incremental cost-effectiveness ratios (ICER). These are usually based on quality-adjusted life-years (QALY) which are a measure of how many extra months or years of reasonable quality life a patient might gain as a result of treatment, based on average life expectancy. Life expectancy is usually extrapolated from the results of clinical trials whilst the quality adjustment is based on patients’ experiential response to the level of pain, mobility and general mood which are usually expressed as a weighted utility value of between 0 and 1. The final calculation of the ratio is based on the difference in the cost to QALY ratio between the new drug and the standard available treatment.

However, to make sense of the ICERs it has been necessary to establish thresholds beyond which drugs are no longer deemed cost-effective. NICE has
established a notional upper limit of £20-30,000 per QALY above which a drug will generally not be recommended, although in exceptional circumstances this can be increased as was the case for beta-interferons, where it was raised to £36,000. Understandably applying this threshold can be highly emotive since it requires a maximum price to be put on patients’ health, so recommendations are subject to pressure from patient and practitioner groups. In the US, insurers have reported that state regulations and market pressures make it virtually impossible for them to refuse a drug.13

This type of cost-effectiveness calculation is usually carried out during a product appraisal by a purchaser prior to approval of an entry price for a new drug. A refund scheme, such as for Velcade, is priced into the calculation of the incremental cost-effectiveness ratio (ICER) so that the scheme proceeds on the assumption that the price is reflective of the product’s value. The more complex price-adjustment schemes establish a maximum cost-effectiveness threshold as the endpoint and vary the price according to the difference between actual and expected outcomes. The Bosentan Patient Registry links the price to the difference between the actual mortality rate and the predicted rate. In the MS scheme the cost per QALY is calculated based on a deviation score of the average observed utility-weighted disease progression for patients in the scheme compared to the expected loss calculated by the predictive model for patients on treatment.

Establishing cost-effectiveness is heavily dependent on the quality of data available regarding quality of life and life expectancy. Initial calculations of the cost-effectiveness of beta-interferons for MS based on randomised control trials prior to the risk-sharing scheme produced widely divergent results ranging from £20,000 to £1m per quality-adjusted life-year.14 Therefore it is perhaps unsurprising that interim results of the MS risk-sharing scheme’s ten-year monitoring study have also failed to provide any further clarity. The predictive model also employed a strict assumption that patients could not display any improvement in disability from one year to the next thus all such results were automatically censored. When this assumption was lifted and the data re-analysed, the observed group reported better outcomes than predicted.
Improving Outcomes

Governments and health insurers must strike a balance between asserting control over high pharmaceutical costs and continuing to foster innovation in new products so as to improve outcomes. Voluntary agreements with industry to regulate gross profits, such as the UK’s Pharmaceutical Price Regulation Scheme, and taxation aimed specifically at manufacturers, as used in the US, have also been used to dampen pricing incentives but are inevitably imprecise in their application.

There are three main areas which are considered to be related to the improved performance of drugs:

- discovery of new compounds that produce novel effects;
- increasing patients’ adherence to product indications; and
- targeting products more accurately at the patient population most likely to benefit.

Breakthrough innovation and R&D risk

Manufacturers assume a great deal of risk in researching and developing new drugs. Out of 5,000 to 10,000 compounds that may be considered at an initial screening, as few as five may make it through to clinical studies on human subjects and only one will be marketed, a process which can take up to ten years. In addition, manufacturers assume the risk of gaining final approval from regulators and insurers whilst competition from similar products can further erode potential revenues. Whilst patents provide 20-year protection for intellectual property rights, this period substantially overlaps with the R&D period and applications are themselves an additional cost.15
Most new drugs do not deliver a sufficient return to cover average R&D, production and marketing costs, and the pharmaceutical industry has traditionally relied on an upside surprise generated by super-profits from a minority of ‘blockbuster’ drugs. The huge risks involved in undertaking research and development also affect the design of remuneration schemes for manufacturers as it is unclear how much pressure can be applied by purchasers without stifling innovation.

Health Impact Fund
A theoretical alternative to the traditional model of patent pricing has been developed, based on paying for the benefits of new products retrospectively from the proceeds of a pooled prize fund. The fund would be composed of donations from developed countries in lieu of that portion of their foreign aid budget dedicated to health. Manufacturers registering with the fund would gain protection for intellectual property rights but also agree to sell their product at cost price. At the end of each year, manufacturers would be remunerated with payments out of the fund commensurate to the number of additional quality-adjusted life-years attributable to their products.

It is envisaged that the annual size of the fund would amount to at least US$6 billion with guaranteed funding for a minimum of ten years to maintain manufacturers’ interest in innovation and to lay the foundations for a future pipeline of opportunities. The scheme leaves it open to companies to decide which will be the most effective drugs for improving global health and therefore generally would provide greater incentives to develop products, such as anti-malarials, that would improve health standards in developing economies on a large scale.16

Although this remains a purely theoretical proposal it has some significant academic, medical and political weight behind it. Critics, however, regard the size of the fund as trivial compared to revenues from sales in the developed world, especially compared to the amount companies have risked on R&D. This may in practice restrict the fund’s coverage to drugs developed to fight infectious diseases and therefore limit its influence on manufacturers. On the other hand some economists have speculated that by participating in the fund, companies may find they can reduce overheads by avoiding some of the typical spending on market access specialists, anti-counterfeiting and litigation associated with monopoly pricing under patents which induces companies to pursue profit-maximising behaviour more aggressively.17
Medication adherence

During drug trials patients are given a great deal more information and attention than in a normal clinical setting so that adherence to medication is likely to be much higher. Under normal circumstances a significant proportion of patients forget to take their pills, take the wrong dose or abandon the course of treatment without consulting their doctor. Outcome-based schemes can furnish a similar level of care and attention as that provided by a trial so as to drive increased adherence. The Atorvastatin Outcome Guarantee employed a 20% margin of non-adherence to the expected outcomes which in the event seemed unnecessary given the very close correlation between the targets unadjusted for non-adherence and the actual results. The assignment of specialist nurses to groups of patients and the provision of further information are the likely causes of higher-than-average adherence rates.

Some schemes also seek to drive greater adherence through the use of financial incentives that reward purchasers, as seen above with the osteoporosis drug, Actonel, and the oral diabetes drugs. This is especially relevant where taking the pills as prescribed is mainly the responsibility of the patient on a day-to-day basis. In these cases, savings can be passed onto patients by lowering their annual premiums and co-payments for drugs in order to motivate greater adherence. The manufacturer of the oral diabetes treatment, Merck, also chose the insurer, Cigna, largely on the basis that they already offered their own diet and life-style programmes to help manage the condition.18

Manufacturers themselves have been willing to invest heavily in technology to increase adherence by, for example, developing oral forms of medicines which are easier to take than administering injections or designing more concentrated doses to reduce frequency. Technological solutions are also being developed including a telephone reminder system by Pfizer, whilst Novartis has recently produced blood pressure pills with microchips that can trigger a text message that is sent via a receiver implanted on the patient’s shoulder when a dose is missed.19

Population selection

Manufacturers have an incentive to recruit narrowly for trials, selecting just enough participants for statistical purposes to determine whether a drug produces the main desired effect, but expanding coverage after the product has been licensed. Purchasers generally seek to narrow the patient population eligible to receive expensive treatments so as to contain costs and treat only those who have a high probability of responding.
Inclusion criteria

Clinical trial participants are often healthier than an average patient population as the frail and elderly will be excluded to minimise the risk of adverse consequences as much as possible. However, it is this group that is most likely to feature amongst eventual recipients. Raw figures for average annual mortality rates of the Bosentan Patient Registry had to be adjusted down from 11.8% to 8.8% as patients participating in the scheme were found to be significantly older and far less functional than those recruited to clinical trials which estimated mortality rates at 5.2%.²⁰

In order to restrict the number of eligible patients after launch to maintain cost-effectiveness, especially for very expensive cancer drugs, purchasers have employed highly contingent selection criteria. For example, in the Velcade scheme, NICE set guidelines that only those patients with a first relapse (but not a second) who had tried one prior therapy and when a bone marrow transplant was not an option were permitted to take part.

For more day-to-day products such as statins for heart disease, risks have traditionally vested in doctors’ best judgement on whether their patients will benefit, whilst pharmaceutical companies have employed direct sales techniques to influence prescribing patterns and boost sales. However, when companies’ revenues are put at risk they change strategy. The authors of a study examining the Atorvastatin Outcomes Guarantee found that by making the statin manufacturer accountable for LDL cholesterol levels in the patient population, it was more likely that the drug would be targeted at those who would benefit the most.²¹

Where there is less certainty about the mechanism and the impact of the drug, a more cautious approach may have to be taken. The UK risk-sharing scheme for beta-interferons was applied to a group of MS patients broadly defined by the Association of British Neurologists. Eligible patients were defined as those who retained a certain amount of independent mobility but had experienced recent relapses. The treatment, however, was not thought to be suitable for patients who suffered from very aggressive and progressive forms of the disease whilst those who were very lightly affected were less likely to experience any meaningful change and may have suffered more from side effects.

Advances in understanding the structure of the human genome have hastened the adoption of more personalised medicine, so that much more can be known about individuals’ susceptibility to disease and likely response to medication. This
will allow treatment to be tailored more effectively and preventive care to be applied more intelligently.

Many new oncology drugs are now marketed with an accompanying test to define the most likely responders. In 2007 UnitedHealthcare entered an 18-month risk-sharing trial with the maker of a genetic test (Oncotype DX), priced at around US$3,500, which determined whether a woman with early-stage breast cancer would benefit from chemotherapy. The insurer paid for the test during the trial in the expectation that a lower price would be negotiated if their costs of chemotherapy had not reduced in line with test results.\textsuperscript{22}

**Continuation criteria**

Some outcome based agreements also employ explicit continuation criteria which permit or require the exclusion of enrolled patients for whom the treatment is not effective. Whilst a randomised control trial cannot exclude participants based on sub-optimal performance, in real world conditions, physicians will use their judgement in line with professional guidelines when observing patients on a course of medication and decide whether to alter dosage, switch to different medication or stop treatment altogether. Targeting the most responsive patients can activate a virtuous circle of improvement since patients will be more likely to keep taking a drug as prescribed and display greater co-production where they feel greater benefit.

Whilst such criteria explicitly require the removal of certain patients from schemes, this should be based on clear evidence that patients have ceased to benefit compared to the cost. Patients enrolled in the bosentan registry were removed to maintain the scheme’s cost-effectiveness if results from their six-minute walking distance test and echocardiograms showed clear deterioration. In some cases the outcome itself defined the threshold for discontinuing treatment, such as the Velcade Response Scheme which set a minimum target of 50% reduction in M-proteins following the fourth cycle of treatment.
Conclusion

Outcome-based pricing schemes are part of an evolving dialogue in the development of a more sophisticated allocation of risk between purchasers and manufacturers. However, there has been little serious study of their effects and costs and there is a great deal more to be learnt from examining practical examples.

Since pharmaceutical companies hold a monopoly over the exploitation of their product and an information advantage over how it works, there seems to be a strong case for making them more accountable for realising the benefits. This also has the potential to embed more dynamic information sharing between the parties involved and greater incentives to engage users in order to better understand the nature of demand. Ultimately this could even feed back into the research and development of new products and help to reduce the upstream costs.

These schemes also hold valuable lessons about the tools that can be used to establish payment-by-outcome schemes outside the pharmaceutical sector. They demonstrate that providers are willing to accept greater financial exposure to the real-world effects of their interventions and take greater risks in delivering outcomes in return for the opportunity to increase sales. This evolution is marked by a countervailing consensus amongst purchasers that uncertainty about performance has become less acceptable whilst greater accountability for providers can unlock important benefits, especially greater collaboration and information sharing in achieving health outcomes.

One important area where a more streamlined approach to outcomes can help realise the benefits of new interventions is the identification of the target population. The use of intelligently defined inclusion and continuation criteria based on the iterative refinement of theoretical knowledge and practical experience can be a particularly effective tool to weed out non-responders and release savings for
other patients. The likelihood of response is also affected by users’ capacity to co-produce. Providers’ involvement in innovating in this area by providing additional support is highly desirable so as to extract maximum value-for-money.

However, experience also points to a number of caveats. Firstly, the adoption of high-level outcomes as performance measures can make reimbursement more complex and less responsive to changes in performance. Surrogate measures can provide better information on progress. Secondly, high-stakes incentives tend to cause more adversarial behaviour and therefore preclude the longer-term benefits of co-operation. Finally, difficult decisions may have to be taken in allocating resources and as delivery becomes more personalised, the benefits also become more exclusive.
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Appendix: Case Studies

1. Atorvastatin Outcomes Guarantee

In 1999, North Staffordshire Health Authority began a pilot collaboration with Pfizer. The drug company provided an outcomes guarantee for statins in lowering blood cholesterol concentrations amongst patients at high risk of coronary heart disease. Cardiovascular disease had been identified as a local priority and the link between statins, reduced cholesterol levels and decreased risk of coronary heart disease and cardiovascular events is broadly accepted and incorporated into prescribing guidelines.

Pfizer guaranteed to reduce the LDL cholesterol levels of the patient population prescribed atorvastatin to at or below national guideline levels or refund the costs of its statins. Guarantee targets were set at 80% of predicted targets to allow for patients not properly adhering to their medication. For example 89% of patients with mild elevation in LDL-C taking 10mg atorvastatin were predicted to reach the target level, therefore the guarantee for this group was set at 71%. A study of the pilot reported that all patients taking up to a maximum 80mg dose of atorvastatin reached target levels very close to the predicted rates and therefore well above the guarantee targets. However, the numbers involved were limited. Of 378 patients prescribed atorvastatin, only 162 were eventually included as part of the guarantee. The rest were either still having their dose adjusted or had to be excluded due to lack of baseline data.23

2. Multiple Sclerosis Risk-Sharing Scheme for Beta-Interferons and Glatiramer Acetate

Four different drugs were developed to slow the progression of MS and reduce the rate of relapses. Clinical trials showed that the drugs reduced the number of relapses by one-third and that some patients stopped relapsing completely and thus required less hospital treatment.
After NICE decided in August 2001 not to recommend the drugs on the basis that they were too expensive and money could be better spent on other treatments, the Department of Health entered into a risk-sharing scheme with the manufacturers. The drug companies agreed to lower their prices to achieve a cost-effectiveness ratio of £36,000 per quality-adjusted life-year and prescribed for a defined population subject to a ten-year monitoring study which would be used to alter product prices to maintain or decrease this ratio.

The main finding of an interim report on the scheme based on two-year data was that there was little evidence that the drugs had slowed disease progression and it was possible that they had worsened patients’ conditions. However, sensitivity analysis of the data revealed that a very wide variation in results was possible if certain assumptions were eliminated and an independent advisory board found that the data and methodology were not robust enough to support a revision in price. A further analysis based on four-year data is due to follow. The scheme continues until 2012.\textsuperscript{24}

3. Bosentan Patient Registry
In 2004 the Australian Pharmaceutical Benefits Scheme (APBS) listed bosentan as a subsidised treatment for pulmonary arterial hypertension. This is a rare progressive and severe disease with a relatively short life expectancy without treatment of around three years from diagnosis. In order to track mortality rates, a registry of all patients prescribed the drug was created. The manufacturer, Actelion Pharmaceuticals, agreed to lower their prices if mortality rates were observed to be above those predicted with treatment.

In 2009, a report was published on the results of the registry data. Actual annual mortality rates were found to be 8.8% compared to a predicted rate of 5.2% whilst treatment with conventional therapy alone was predicted to incur a rate of 26.6%. APBS is now considering price adjustments.\textsuperscript{25}

4. Velcade Response Scheme
In 2007 the drug manufacturer Johnson & Johnson agreed to reimburse the NHS for the cost of treating patients who did not respond to their new drug Velcade for multiple myeloma (a cancer of the blood). Under their initial review, NICE had concluded that Velcade was not cost-effective.

The measure of patient response was based on a reduction of serum-M protein antibody in the patient’s blood after four cycles of therapy. If the protein was reduced
by at least 50%, the NHS continued to fund treatment. If not, therapy was stopped, and Johnson & Johnson refunded the cost of the drug already administered.26

The manufacturer reportedly expected to give rebates in 15% of cases but there has been no rigorous evaluation of this scheme. Although the Velcade scheme was the most popular with 100% uptake by Primary Care Trusts, some problems were identified that suggested it was complex and time-consuming to administer and only a proportion of available rebates had been received. Only half of survey respondents confirmed all refunds had been received.27

5. Cetuximab (Erbitux) Cost Share Programme for 2nd/3rd line metastatic colorectal cancer
The manufacturer Merck-Serono proposed this scheme for their metastatic colorectal cancer drug after it was not recommended by NICE in January 2007. They offered to refund the cost of any vials for patients that fell into a pre-agreed non-responder group at up to six weeks. If scans show that the tumour has not responded to the treatment, the company issues replacement stock or a credit note.

6. Lucentis Dose-Capping Scheme
Following a re-review by NICE in the UK in 2008, the NHS agreed to bear the cost of treatment for the first 14 injections of Lucentis, a drug for patients suffering from wet age-related macular degeneration. After this the manufacturer, Novartis, would assume the risk of further treatment if required. NICE also expanded the application of the scheme for patients suffering wet AMD in both eyes, so that they received treatment for both rather than just the better eye.

In evidence to NICE, Novartis estimated that 14-24 injections over a two-year period should be enough for most patients to benefit whilst also calculating that it could recoup costs with a widening of the patient population.28 In trials, patients treated with Lucentis had been found to have improved their performance on visual acuity tests. Those taking Lucentis gained 9.0 letters at day 98 compared to those receiving standard care who lost 4.9 letters based on the number of letters read on the early diabetic retinopathy study chart.

7. Actonel Fracture Protection Programme
In April 2009, Procter & Gamble and Sanofi-Aventis announced the launch of a Fracture Protection pilot programme with Health Alliance, a small US Midwestern
insurer. This covered the anti-osteoporosis drug Actonel for post-menopausal women at risk of osteoporosis, who had been taking Actonel correctly for at least six months. Under the arrangement the manufacturers promised to reimburse a maximum number of non-spinal osteoporotic bone fractures per 1000 patients over one year based on average treatment costs - $30,000 for hip and $6000 for wrist fractures. Reimbursement would be made by reducing Health Alliance’s cost of purchasing the drug in proportion to the number of fractures. This could in turn lower future premiums for subscribers.²⁹

Results announced by the insurer three-quarters of the way through the pilot were described as ‘promising’. The manufacturer’s reimbursement rate was 79% below the maximum and the incidence of non-spinal fractures consistent with clinical trial data.³⁰

8. Januvia/Janumet oral diabetes drug discount scheme
In April 2009, Merck and the insurance company Cigna announced an innovative deal for Merck’s oral diabetes drugs Januvia and Janumet for type II diabetes patients which offered two-fold discounts:

i. when patients’ blood sugar levels are found to fall, regardless of the drug prescribed, and

ii. when Januvia and Janumet are taken as prescribed.

Cigna is responsible for reviewing both blood sugar levels and claims data to assess adherence. The insurer can make cost savings by stalling the progression of diabetes and reducing the incidence of heart or kidney failure, amputations and blindness whilst the manufacturer can increase their brand loyalty and sell more of its products through the scheme. The insurer also offers a Prescription Drug Price Comparison tool which allows patients to calculate their out-of-pocket expenses and makes them more sensitive to bulk price reductions.³¹
Endnotes

8. Steve Williamson, A Report into the Uptake of Patient Access Schemes in the NHS, Cancer Network Pharmacist Forum, November 2009; accessed: http://www.nice.org.uk/nicemedia/pdf/TA129Guidance.pdf (In NICE’s guidance, see n.7 above, the committee noted that the Department of Health “considered that the scheme would not impose a disproportionate organisational burden on NHS organisations in England”.)
11. Margaret J Gunter, ‘The Role of the ECHO Model in Outcomes Research and Clinical Practice Improvement’, American Journal of Managed Care, Volume 5, No.4, Supplement pp217-224


28. NICE Technology Appraisal 155 – Ranibizumab and pegaptanib for the treatment of age-related macular degeneration, August 2008


