

THE VALUE OF INNOVATION

REPORT BY THE DECISION SUPPORT UNIT

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22 May 2009

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1. Introduction

1.1 Aims of the review

The aim of this review is to provide an overview of how innovation is currently valued in the UK health system and the potential initiatives that can be adopted in order to promote innovation in the NHS. The report includes a review of the scientific, policy and economic literature relevant to the following questions:

- What key research has already been undertaken into valuing innovation in the health care and other sectors both in the UK and internationally?
- How may innovation be defined, a) in the context of health technology assessment and b) wider areas of economic activity?
- What approaches have been used, or are in development for assessing the value of the innovative nature of a) health technologies, and b) interventions used in other areas of economic activity?
- Where and how do the existing arrangements for healthcare technologies take the value of innovation into account, both at the macro level and for specific technologies? Are there any deficiencies in the current approaches including the implications of the timing of evaluations including those for licensing? What approaches have other health technology assessment agencies implemented?
- Are there any additional ways for taking the value of innovation account that could be integrated into NICE's decision-making processes? What might be the implications of these for NICE?

This report is structured as follows. This section provides a brief background to the current policy debate including relevant UK policy initiatives, the general approach taken to the appraisal of innovative health technologies in the UK and elsewhere and a summary of the core issues raised in submissions to the Kennedy review. Section 2 describes the how the value of an innovation can be defined and measured, with specific reference to how innovation is currently rewarded in the NHS. It examines how the current approach to appraisal rewards valuable innovations and provides incentives for long run efficiency. In doing so it makes comparisons with how innovation is valued and rewarded in other markets where intellectual property is

protected by patents. Section 3 describes the general principles of patent protection relevant to innovation across different markets, discusses whether the current incentives to innovate in the NHS are adequate, and outlines the potential policy initiatives that could be employed to address any shortfall. Section 4 considers whether the current methods employed by NICE adequately reflect the full value of innovative new technologies, including whether the measures and values used adequately capture all the health benefits of innovative technologies and a consideration of whether non-health benefits are appropriately taken into account. Some tentative conclusions are drawn in section 5.

1.2 Policy background

The question of how to value innovation and how to ensure that there are sufficient incentives for private investment in the development of socially valuable innovations requires a clear view of the social value of a health technology, its relationship to price, and the incentives this provides for private sector investment decisions. These important issues were central to the recent policy debate about value based pricing in the UK and a wider international debate. The Pharmaceutical Price Regulatory Scheme (PPRS), launched over 50 years ago, was designed to secure safe and effective drugs for the UK National Health Service (NHS) at reasonable prices, as well as to promote a strong and profitable pharmaceutical industry able to develop new and improved drugs. In 2007, the Office of Fair Trading (OFT) recommended to the UK Government that the PPRS should be radically reformed to deliver better value for money from the NHS drug budget and to focus business investment on drugs that have the greatest benefits for patients.¹ The proposed reform replaces profit and price controls with a value based approach to pricing. This approach relates the spending for drugs to their incremental clinical and therapeutic value to patients and the broader NHS. Such a policy has the advantage of reducing the arbitrariness of profit and price controls. Whilst it will reduce incentives for me-too drugs, it will increase incentives for more fundamental innovations in areas of unmet medical need, reducing the uncertainty of the ability to appropriate returns.

The OFT recommendations have been extensively debated leading to a wide range of responses, with positions for and against the OFT proposals.²⁻⁴ Nonetheless, the

knowledge that other countries have successfully introduced value based pricing and reimbursement schemes (ie, Sweden, Australia, Canada) is reassuring for the UK. The OFT studied pharmaceutical pricing in ten countries during two years of research. Australia, Sweden and Canada are pointed out as role models on assessment of value based on cost-effectiveness. Australia has the longest experience of applying cost effectiveness. It also has some of the lowest drug prices in the developed world. The cost-effectiveness studies are carried out by the Pharmaceutical Benefits Advisory Committee. Similarly in Sweden, where the system is based on health technology assessments, The Swedish system was argued to be better than many other systems, in particular because of its transparency, and because decisions were made to objective criteria, says the OFT. In Canada, cost-effectiveness assessments form the basis of reimbursement decisions and price negotiations. Pharmaceutical manufacturers submit clinical information and pharmacoeconomic evaluations of new drugs to the Common Drug Review, part of the Canadian Agency for Drugs and Technologies in Health. Health services in many countries base their prices on those in the UK, so implementing this reform might well have wider international consequences.

HTA agencies

We have briefly reviewed documents issued by national authorities worldwide responsible for deciding what medication and treatments should be available to the population. The countries scrutinised were Australia, Canada, New Zealand, United Kingdom, Ireland, France, Germany, Austria, Netherlands, Switzerland, and Belgium. All of the countries have formal Health Technology Assessment arrangements. In fact it is possible to identify in every case one or more entities that are in charge of the HTA agenda-setting and topic-selection as well as the assessment process in itself.

From the review it emerges that economic evaluation, in particular cost-effectiveness evaluation, is part of any HTA in any country. In all of the cases, though, decision making is not solely based on cost-effectiveness considerations. The technology is assessed based on the threshold range together with other criteria and in presence of high ICERs those other criteria become more important. Nevertheless, among the countries scrutinised only a few clearly state that one of the important “other” criteria is the value of innovation.

This is the case of England and Wales, for example.⁵ For interventions with an ICER between £20 000/QALY gained and £30 000/QALY gained, NICE takes account of the innovative nature of the technology, “specifically where the innovation adds benefits of a substantial nature compared with available alternatives which may not have been captured in the QALY measure”. We find another example in Scotland.⁶ The Scottish Medicine Consortium follows NICE guidance in making its decision, thus the innovative nature of the technology is an important criteria also for the Scottish HTA authority. Again in Belgium the decision making process for HTA explicitly refers to “true innovation”, against “adaptation” or “alternative” of already available products, as additional criteria on the assessment of medical necessity.⁷ Finally in France, the Haute Autorité de Santé (HAS) in its Annual Report (2007) states to set up a gateway to identify and promptly assess technological innovation likely to provide benefits to patients.⁸ New and emerging technologies can be identified by regular review of selected information sources (scientific and medical journals) and by establishing direct contact with manufacturers, practitioners, and researchers. The aim is a prompt assessment, i.e. as soon as the necessary scientific data are available. The innovations are reviewed using the two criteria HAS employs to assess all health technologies: the “expected benefit”, which measures clinical utility, and the “improvement in expected benefit”, which measures the added value provided by a technology in comparison with another, on a scale from I to V (level V is for no improvement).

The documents reviewed revealed that most of the countries do not formally account for the particular value of innovation over and above the benefits of the technology in their appraisal. Belgium, does refer to a value of innovation but does not set out formal and explicit methods and procedures. France claims to formally take account of the value of innovation in a structured way firstly by giving a definition of innovation (see e.g. Annual Report 2005) secondly by clearly stating the main criterion used by the Committees in charge in their assessment of innovation, i.e. the improvement in expected benefit.⁸ It is not clear how any additional weight is placed on innovation over and above the claimed benefits of the technology in question.

1.3 Core themes in submissions

The submissions made to the Kennedy review have been examined and common core themes have been identified which inform the structure of this report and content of the following sections.

The submissions almost universally acknowledge the key roles that the Institute has played in developing the methods and process health technology assessment, and setting standards in the NHS. Nevertheless, NICE's current technology appraisal programme performed by NICE is considered incapable of capturing all dimensions of the value of innovative technologies.

The primary concern in the industry submissions is focussed upon with the instrument used to calculate QALYs in the Appraisal Programme; i.e. the EQ-5D. The submissions argue that the descriptive system is too simplistic to capture the full range of benefits important to the patients, thus scoring very bad in capturing value of innovation.

The submissions propose 3 broad areas in which the current methods for capturing value is inadequate: value of health gain; value of convenience; and value of other economic gains.

Value of health gains

- Health gains from treatments that address a previously unmet need are valued in the same way as health gains in areas where there is already a number of treatments available. This can lead to denial of access to new treatments in conditions where there is currently no alternative treatment. This is particularly an issue for treatments of severe and rare conditions.
- The ICER approach, it is argued does not take account of the nature of health gain, whereby incremental short term benefits can drive much larger benefits in the long term. This relationship operates in a number of ways. The effectiveness of technologies may be dependent upon the stage of the disease process. A decision not to make such a technology available is irreversible; the health gain cannot be obtained later, even if the technology becomes cheaper

and thus cost effective for new patients. In addition, technologies that maintain the current health status may enable patients to benefit from future technologies, where the combination of the two technologies is cost effective, but the failure to make the first technology available means the patients cannot benefit from the second technology. Thirdly, the refusal to pay for the current new technology sends a signal to the innovator companies discouraging investment in future incremental innovations, even though the health gain from the future incremental innovation, compared to current practice, would be sufficient to make the technology cost effective.

Value of convenience of new treatments

- Health technologies can have process value which the standard EQ-5D framework will not capture. These may relate to the convenience of administration for the patient and/or the reduced burden of the patients' condition and treatment on their families and carers.

Value of broader gains to the economy

- The Technology Appraisal Process focuses upon the health gains from innovative technology and does not consider the value to the UK economy of improved labour force participation and improved productivity from individuals in work. The failure to take account of these substantial benefits means that the value of innovative treatments to society is likely to be understated in the evidence considered by the Institute's Appraisal Committees.
- The introduction of new treatments can lead to improved practice in the patient management, creating so-called 'spill-over' health benefits from a new technology. The focus on direct health gain from treatments, based upon estimates of effect from clinical trials does not take account of these benefits. Further spill-over benefits may accrue due to the development of new treatments and technologies as a direct response to the new treatment. The value of these potential benefits is completely ignored by the Technology Appraisal process and thus innovative technologies that society values may be inappropriately excluded from the NHS.

To address these concerns we have tried to distinguish those issues which are specific to innovative technologies from those that are relevant to all health technologies (new or old) and indeed to the appraisal of all NHS and other public health activities. Therefore, section 2 and 3 addresses the questions that are specific to innovations, e.g., should the NHS take account of the potential value of an innovation during appraisal? Section 4 addresses the wider questions, relevant to all technologies and interventions, of whether current measures of health gain sufficiently capture all socially valuable aspects of health and wider impacts on carers, family and the wider economy.

2. The Value of Innovation

There appears to be no universally agreed definition of innovation evident in the submissions to the Kennedy review or in relevant documents from HTA agencies around the world. In fact, innovation often seems to be defined by the particular view of what ought to be given additional value or consideration. The Oxford definition of innovation is, “noun. 1 the action or process of innovating. 2 a new method, idea, product, etc”. Although this is not particularly insightful, it does make clear that the essential characteristic of an innovation is its newness. It also seems clear that it is used to refer to new methods, ideas or products which are claimed to offer benefits over existing ones. Therefore, we have generally restricted our consideration of innovations to new products which are claimed to offer benefits. These will generally be patented products (pharmaceuticals and devices) with marketing authorisations which can be used in the NHS. However, it should be noted that there are other sources of innovation relevant to the NHS including new ways to deliver services as well as new surgical, diagnostic and other procedures.

The question of how to value innovation and how to ensure that there are sufficient incentives for private investment in the development of socially desirable innovations requires a clear view of the social value of a health technology, its relationship to price, and the incentives this provides for private sector investment decisions. These

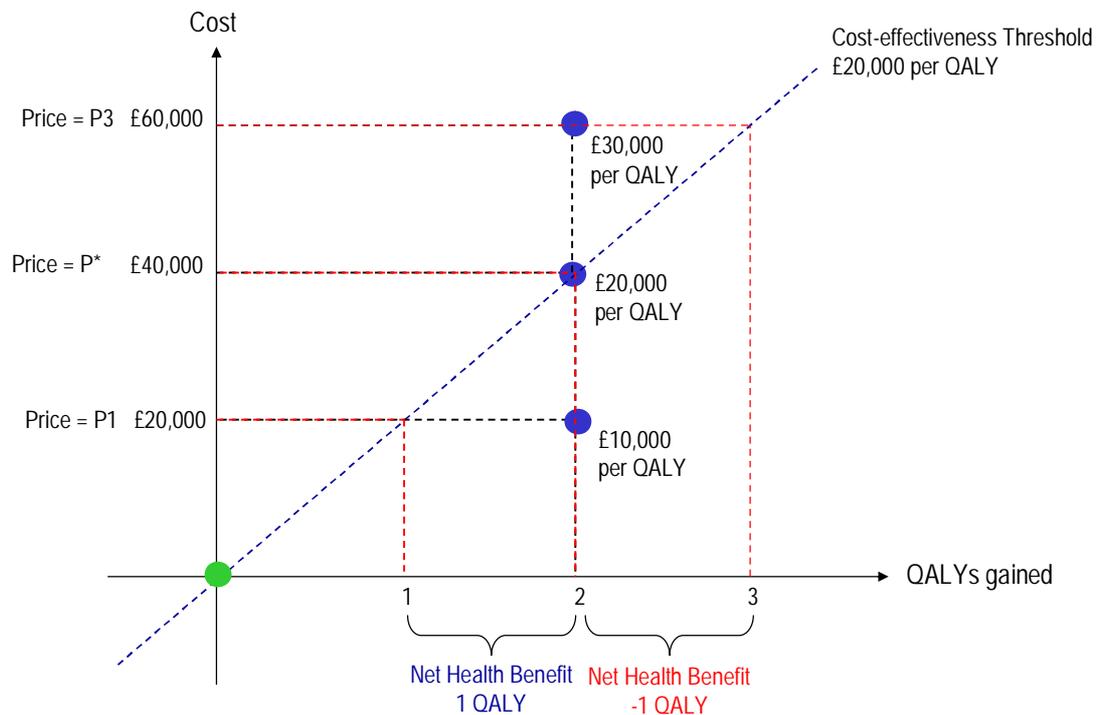
important issues are central to the role of NICE in providing clear and predictable signals to the private sector, the recent policy debate about value based pricing in the UK^{3:4} and the subsequent reform of the pharmaceutical price regulation scheme (PPRS)⁹ as well as a wider international debate.

2.1 How can value be defined and measured?

The value of an innovative technology to the NHS requires a clear definition of the social objectives of collectively funded health care and a means of measuring whether the technology at the price charged meets these social objectives. If the primary purpose of the NHS and the core remit of NICE is to improve health across the NHS then a technology can be said to be of value if the health expected to be gained from its use exceeds the health forgone as other NHS activities are displaced by its additional cost, i.e., if it is expected to improve overall health outcomes across the NHS. These assessments of health gained and forgone can be informed by estimates of cost-effectiveness, often summarised as an incremental cost-effectiveness ratio (ICER): the ratio of the additional health expected to be gained to the additional costs relative to another way of treating the same patients. These principles are central to the approach NICE takes in the appraisal of health technologies and the methods of analysis that are recommended.⁵

The concept of value and its relationship to price and cost-effectiveness is illustrated in Figure 1.

Figure 1. Value, price and cost-effectiveness



At price P1 a new technology offers a gain of two units of health outcome, here expressed as quality adjusted life years (QALYs) at an additional total cost to the NHS of £20,000 - an incremental cost-effectiveness ratio of £10,000 per QALY gained. The key question is whether the expected gain of 2 QALYs from this innovation is greater than the health outcomes (in QALYs) forgone elsewhere due to other NHS treatments being displaced by the additional cost. i.e., some threshold for cost-effectiveness. In Figure 1 this is represented by a threshold set at £20,000 per QALY - every £20,000 found from existing resources displaces one QALY elsewhere in the NHS. At price P1 the technology is thus expected to improve health by two QALYs and displace only one QALY elsewhere. There is a net health benefit of one QALY to the NHS as a whole and the technology is cost effective (the ICER is less than the cost-effectiveness threshold) and is a valuable innovation.

If the price of the technology were higher at P* then the NHS would anticipate the same health gains of two QALYs but at a higher additional cost of £40,000 - an ICER of £20,000 per QALY (which is the same as the threshold). These higher additional

costs will now be expected to displace two QALYs. The gains in health (two QALYs) are just offset by the health forgone elsewhere (also two QALYs) and overall net health benefits to the NHS are zero. In terms of the effect on health across the NHS, one is indifferent between introducing and not introducing the technology, i.e., price P* is the maximum the NHS can afford to pay for this technology. It represents the value of the innovation to the NHS given the resources currently allocated to health care.

At a higher price such as P3 the costs increase to £60,000 – an ICER of £30,000 per QALY (which is higher than the threshold). Now the health forgone due to the additional costs (three QALYs) exceeds the health gained from the technology (two QALYs) and overall net health benefits are negative (minus one QALY), i.e., this technology is not cost-effective at price P3 and does more harm than good in terms of the overall health of the nation. Price P3 is greater than the value of the innovation to the NHS. Therefore, an innovative technology (one that is novel and effective) may or may not be valuable to the NHS depending on the costs which fall on the NHS budget.

What is the threshold?

An assessment of the cost-effectiveness threshold is a key determinant of value. However, neither NICE nor any other decision making entity, including a practising physician, can know precisely which NHS activities will be displaced by their decisions nor exactly who will forgo which specific health benefits. The NICE threshold range of £20,000 to £30,000 per QALY represents an informed estimate of the health forgone, based on such evidence as is available about the productivity of other NHS activities.¹⁰⁻¹² More formal estimates are possible and recent empirical work indicates that the upper end of the current range used by NICE may well be too high.^{13;14} The critical point is that the threshold should represent the value of displaced NHS activities and is essentially a transparent and explicit empirical question subject to scientific analysis. NICE is currently reviewing the threshold range and the current evidence, some of which suggests that even the lower range maybe too high, particularly if activities are displaced in areas other than cancer and diabetes. A briefing note on the threshold which was circulated prior to the recent NICE workshop on the threshold is appended to this report.

2.2 How much should the NHS pay for innovation?

A new and innovative technology priced such that the ICER is just equal to the threshold (i.e., P^* in Figure 1) ensures that the health benefits offered by the drug are just offset by the health displaced elsewhere in the NHS and thus all the benefits of the innovation go to the manufacturer in the form of revenue, i.e., price P^* is the maximum the NHS can afford to pay without damaging overall public health. In these circumstances the NHS does not benefit overall from the innovation during patent protection and there is no incentive to increase early uptake of the drug within the NHS – the net health benefits are zero. Of course, in the longer run if cheaper generics become available following patent expiry then the NHS may ultimately benefit under certain conditions – most importantly that:

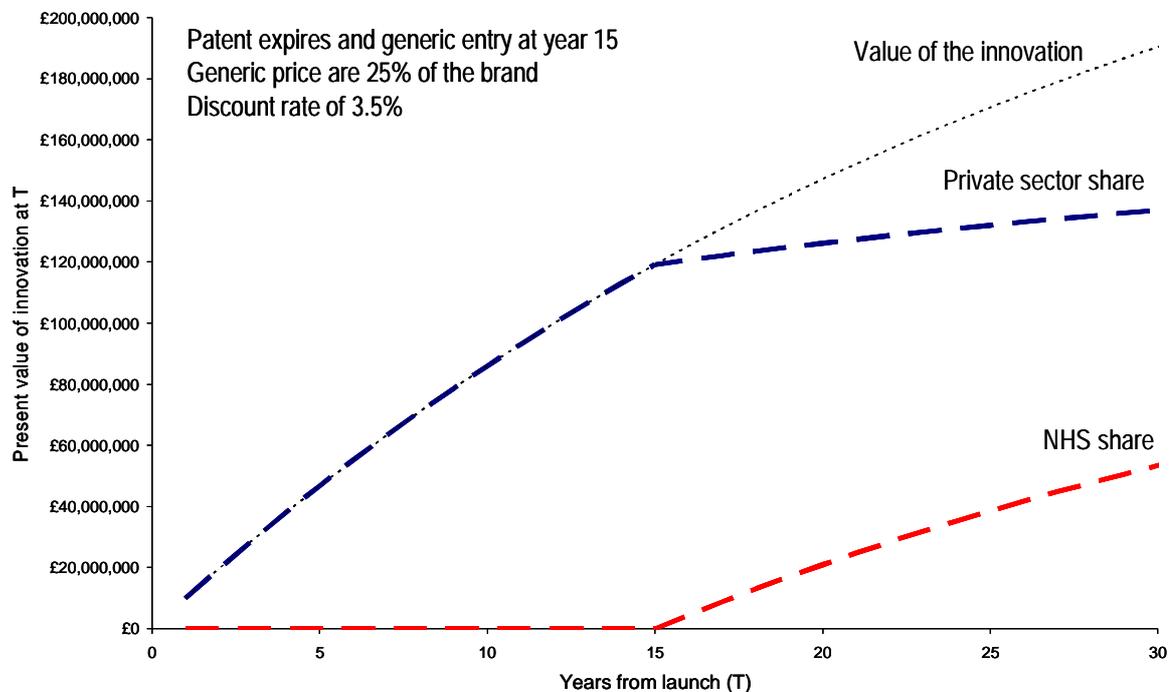
- The generic market remains competitive.
- The prices of future newly patented drugs reflect their value when compared to the cheaper generic versions of the previous innovation when they become available.

If either of these conditions is not met the NHS, as a whole, may never benefit from innovation. Without competitive generic entry all the benefits will be appropriated as the market share of premium priced brand will be maintained. Even if there is competitive generic entry, unless new patented technologies which replace the old are compared to the cheaper generic versions of the old brand then all the benefits will continue to be captured in the revenue received by the private sector. However, even when these conditions are met the private sector still retains a significant proportion of value in the long run.

For example, Figure 2 illustrates the cumulating value of an innovation over time (discounted at current NICE rate of 3.5%) and how this total value is shared between the private sector and the NHS. Initially, during patent protection price P^* means that all value is appropriated by the private sector. At 15 years from launch the patent expires and assuming that competitive generics enter then market prices will then fall. On average generic prices are approximately 25% of the patented brand, so assuming that either all prescribing is switched to generics or the price of the brand is cut to

generic levels and also assuming that any new patented drugs are priced relative to the generic version of the old then the NHS will begin to benefit from the innovation and start to share some of the value of the innovation with the private sector. However, the private sector will still retain most of the value even in the long run. In this example at 30 years the private sector appropriates 72% of the value and even at an unbounded time horizon (the innovation is forever relevant) it still retains 57%. Of course, this share will be higher if some prescribing of premium priced brands continues even when an equivalent generic is available.

Figure 2. Sharing of value of innovation



It is important that manufacturers should be able to appropriate the benefits of innovation through the temporary monopoly profits afforded by patent protection in order to incentivise future investment in research and development. The type of decisions based on cost-effectiveness illustrated in Figure 1 and representative of the current NICE approach to technology appraisal does precisely that – it offers full appropriation of all value to the temporary monopolist during patent protection. Where cost-effectiveness differs across identifiable subgroups within the indication

then manufactures in anticipation of NICE guidance are free to choose from the combinations of price and anticipated guidance.^{2;3} Just like in other markets which grant a temporary monopoly through patent protection, the manufacturer can choose any price they wish but mindful of the implications that very high prices will have for their sales (i.e. more restrictive guidance in the case of NICE), revenue and profit. The only difference here is that it is an assessment authority on behalf of the NHS rather than individual consumers that signal the demand based on an assessment of cost-effectiveness (arguably a more predictable situation than in other markets). In these circumstances the manufacturer and the NHS share the benefits during patent protection just like in other markets and will depend on where the manufacturer chooses to locate on the ‘NHS demand curve’ signalled by NICE.^{2;3}

2.3. How should the value of innovation be shared?

The current approach to the appraisal of health technologies by NICE effectively offers all of the value of innovation to the manufacture during patent protection. Nevertheless, some submissions and others imply that even this may not be enough.¹⁵ However, there are good reasons why the NHS should receive some share of the value at least in the longer run:

- The public sector subsidises research and development in a number of ways, through publicly funded research, tax incentives and infrastructure investment. Therefore, even if society was unconcerned about who benefits from innovation (NHS patients or the pharmaceutical industry) it would not be efficient to give all the benefits to the private sector – it would encourage over investment and the development of products which may not be worthwhile taking account of the social costs of the all the investment made.
- In other markets, where innovation is protected, society simply offers monopoly returns during patent protection but does not encourage full appropriation of the benefits even within patent protection and certainly not in the longer run. Indeed, society goes to some lengths to ensure any monopoly rights offered by patent protection are only temporary through bodies like the Office of Fair Trading and the Competition Commission.

- It is appropriate for society to be concerned about how the benefits are shared with manufacturers and it is reasonable that at least some of the benefits of innovation should accrue to NHS patients: not least because this provides some incentives for the NHS to increase the early uptake of new technologies - which should also be a concern for manufacturers.

Despite this some concerns have been expressed that an assessment of value based on cost-effectiveness will not recognise the potential value of an innovative technology, i.e., one that is likely to lead to the development of more valuable future technologies or use of the technology in other indications in the future.⁴ In other industries and markets private sector companies anticipate the benefits of innovation and the future market returns which flow from better products when making investment decisions. No one suggests that consumers should be compelled to buy products merely to provide an additional incentive for future innovation! Is the same not true in health care?

What is different in the health sector is that neither consumers (patients) nor their agents (doctors) are well-placed to identify and synthesise all relevant evidence and undertake the computation required fully to assess value. Even if such individual assessments were possible it is unlikely that they would lead to decisions that would be consistent with the NHS' collectively agreed objectives and resource constraints. Instead NICE has been given responsibility for assessing and signalling value on behalf of the whole NHS. This arrangement leaves patients free to communicate their history and preferences to their doctor and doctors free to establish relationships with their patients and, in response to the patients' need, select suitable interventions from those available in the NHS. So why should the NHS pay more than the value of the benefits from a new technology in the hope that a future technology of even more value will be developed? To do so would be to pay twice for the innovation and encourage inappropriate investments in innovations that are not worthwhile.

For example, if the NHS was to pay more than P^* in anticipation that the technology might be used in other more valuable indication in the future it would have paid once 'up front' for future benefits. If these benefits are realised and market authorisation granted for the new indication then the NHS would pay again for the benefits (pay the

P* for the new innovation) and would have paid twice, providing too much reward and distorting incentives. Therefore, the key questions are: i) who should anticipate the future benefits of an innovation (the NHS or manufacturer making investment decisions) and ii) when should the NHS pay for them (when they are realised or ‘up front’). If the NHS pays for benefits before they are realised there is clearly a danger of paying twice but even if this could be avoided it may well undermine incentives for realising the benefits that are anticipated.

Appropriating the future benefits of innovation?

It is commonly the case that some innovations today will provide the basis for subsequent innovations which may be even more valuable in the future. The concern is that an innovator may not be able to raise enough capital for the initial development if future anticipated benefits can not be appropriated but are expected to accrue to others offering incremental or radical innovations. This is a common circumstance in other markets. However, if investors have a sufficiently diversified portfolio they retain an incentive to offer capital to the innovator in the knowledge that the longer term rewards may accrue to other developers and innovators also within their portfolio of investment. As long as the initial patent protection is sufficient the innovator will be able to either raise enough capital for development or sell the patent on to other companies with sufficient capital and other resources for successful development.

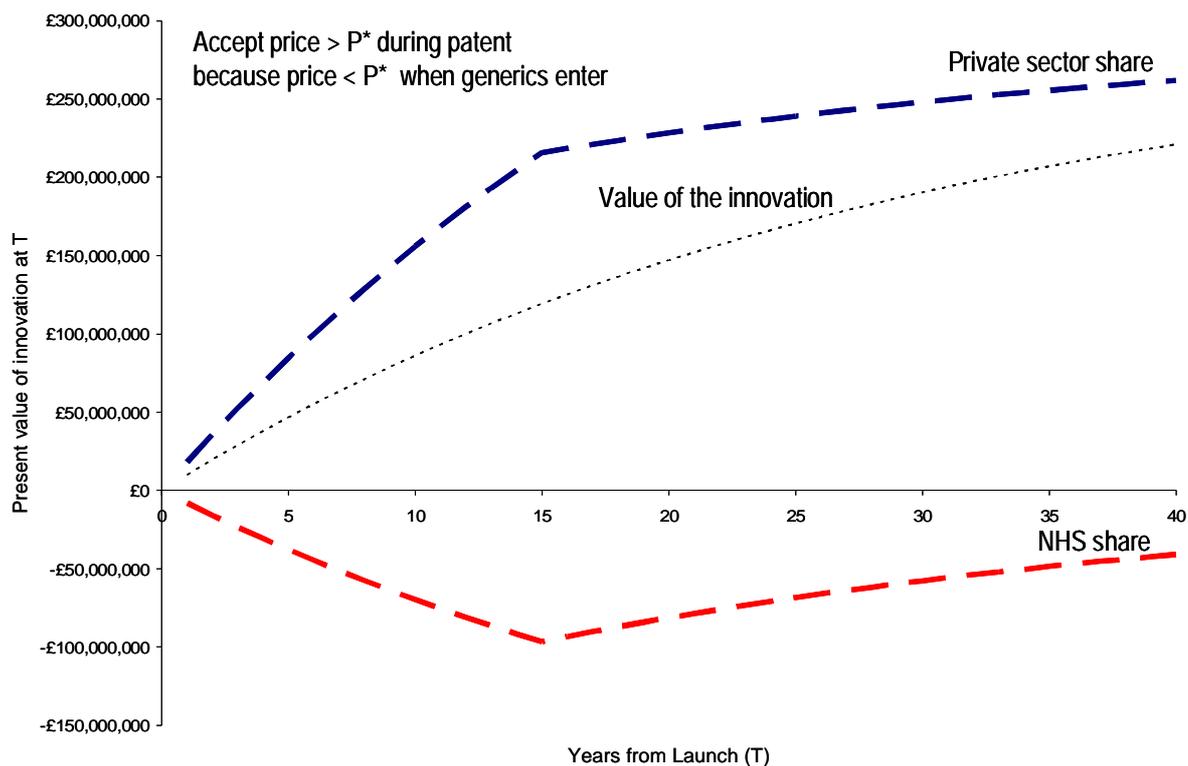
Therefore, it is important to distinguish between the returns to innovation as a whole and the way these returns are shared between the actors (originator, initial developer, and future innovator and developer). The former is ultimately determined by the NHS budget and the latter by the scale of patent protection and the relative efficiency of competing innovators and developers. Efficiency requires that enough value is retained to enable capital for initial development to be raised. It does not require that all the future potential benefits will be appropriated by the originator. That would be very inefficient because others may be better placed to exploit the initial innovation and it would also offer much more than actually required. As in other markets with patent protection those who are best able to exploit such future possibilities and develop better products more quickly and at lower cost will be rewarded with earlier patents, premium prices and a greater share of the total returns to innovation. So long

as the initial patent protection is sufficient, it is these incentives which ensure the entry of new and more efficient innovators in the future. Therefore, paying more than the value of a product now in the hope a valuable product in the future will be produced (for which a premium price P^* would also be paid) would not only lead to static (short run) inefficiency it would also reduce dynamic (long run) efficiency and damage incentives for future innovation.

Taking account of future prices

Similar arguments have been made based on the future benefits of an innovation to the NHS following patent expiry (see Figure 2). Some have argued that the reduction in price following patent expiry and generic entry should be taken into account when making decisions about branded drugs at launch, i.e., the NHS should be willing to accept a price greater than P^* at launch in anticipation that prices will be less than P^* once the patent expires and cheaper generics enter. In essence the NHS should accept negative health benefits (due to displaced NHS activities) in the short run as these will be just off set by positive net benefits in the longer run. This is illustrated in Figure 3. During patent protection (e.g., up to 15 years from launch) the NHS pays more than P^* and the innovation damages the NHS. The private sector gets more than the total value of the innovation during this period.

Figure 3. Accounting for future benefits



On patent expiry and the entry of cheaper generics the NHS starts to benefit, as long as the price of any new patented drugs which maybe launched are based on a comparison with these generic version of the old innovation. Over time these benefits start to off set the losses during the patent protection. Only in the very long run (an unbounded time horizon) will the net benefits to the NHS approach zero. In these circumstances the private sector appropriates all the future benefits of innovation as well as all the benefits during patient protection and there are no overall health gains from pharmaceutical innovation. At best and only in the very long run it is equivalent to extending patent protection indefinitely. At any finite time horizon it is worse - since more than the total value is appropriated by the manufacturer and the NHS overall is damaged by the innovation. Of course, it would be possible to agree some finite time horizon when the NHS would be expected to breakeven, e.g., 40 years.

However, this would be at best equivalent to simply extending patent protection to 40 years. In practice it would be worse because the NHS would face the risk that generic prices might not fall quite as much or that there would be some continued prescribing of the premium priced brand after generic entry.

Evidence and the potential value of an innovation

Concerns have been expressed that an assessment of value based on cost-effectiveness will not recognise the potential value of an innovative technology when the type of evidence available at launch may not yet be sufficiently well developed to demonstrate long term benefits. Of course, the methods adopted by NICE are intended to make best use of all evidence and are not restricted to assessments of cost-effectiveness within clinical trials, but more commonly use evidence synthesis and decision analytic modelling to extrapolate costs and benefits over more appropriate time horizons, compare different technologies and link surrogate endpoints to long term health outcomes. Nevertheless, at launch the evidence base for a new technology is inevitably least mature and there may be considerable uncertainty about its cost-effectiveness.

There are concerns that a technology which might prove to be valuable to the NHS may be rejected or its approval delayed. However, evidence about the performance of a technology is a valuable for the same reason that the development of a cost-effective technology is valuable - it improves health outcomes. Better evidence which reduces uncertainty allows better decisions to be made which improve net health benefits for future patients. Early approval of a technology will inevitably have an impact on the prospects of acquiring further evidence to support its use in the future, because the incentives on manufacturers to conduct evaluative research are removed and the clinical community may regard further experimental research to be unethical. Therefore, there is a trade-off to be made between value of early access technology and the value of the evidence that may be forgone for future NHS patients.

Some times the additional evidence needed may be provided alongside provisional approval of an apparently cost-effective drug. This type of 'coverage with evidence development' needs to establish when additional evidence is needed, the type of evidence required and whether this can be gathered while the technology is approved

for use in the NHS? For example, the type of observational registry data that are often envisaged will be unable to provide more precise estimates of relative treatment effect because a comparable control group will not be available. If the type of evidence required cannot be provided with provisional approval, then guidance can either be restricted to 'only in research' or the manufacturer can choose to reduce the price, i.e., the maximum the NHS can afford to pay for a technology given existing uncertainty is not P^* but a lower price which would make the cost-effectiveness of the technology less uncertain.

A link between price and the value of evidence is recognised in the recent reform of PPRS⁹ and the possibility of flexible pricing based on the results of evaluative research. Critically the link between evidence and price provides incentives for manufacturers to invest in the type of evidence needed by the NHS early in the development of their products. Other things being equal, those that do so invest and thereby reduce the uncertainty surrounding the cost-effectiveness of their product at launch, will be rewarded with higher prices than those that do not. The combination of the reformed PPRS and more clarity in the 2008 NICE Methods Guide⁵ about how an assessment of uncertainty informs guidance starts to avoid the danger that the evidence base for future NHS practice will be undermined by early approval and provides incentives for the development of type of evidence needed at launch.

2.4 Incentives for innovation?

The principles of NICE Technology Appraisal means that in the short run technologies will be approved for use in the NHS only at prices that ensure that their expected health benefits exceed the health predicted to be displaced elsewhere in the NHS (i.e. that they are cost effective). In the longer run these principles provide clear incentives for manufacturers to develop technologies which are more likely to demonstrate value and improve overall health across the NHS. The responsibility of the NHS, through assessment authorities like NICE, is to signal clearly and reliably what is of value. It is then for the manufacturers to choose to invest in the development of technologies which they believe will be valuable for the NHS and command prices and sales which will provide a satisfactory return on their investment.

The current role of NICE can be viewed as signalling the collective demand for health technologies on behalf of the NHS which is arguably a much more predictable situation than in other markets where innovators and investors must anticipate future market demand when investing in the development of new products. The transparent methods and processes adopted in NICE Technology Appraisal offers a greater degree of certainty about what types of innovation will be rewarded. Reducing the uncertainty about future rewards increases the value of patent protection and improves incentives for investment in those developments most likely to prove valuable to the NHS.

It should be recognised that not all innovation is worthwhile. Appropriate incentives should discourage investment in the development of products that are unlikely to be sufficiently valuable to the NHS to justify the investment required. If the anticipated benefits of the development of an innovative technology means that the price and sales it might command is unlikely to provide an adequate return on the investment needed to bring it to market then these resources would be better invested in other more valuable developments whether in health or elsewhere in the wider economy.

This has a number of implications. The size of the potential market (the total health gains on offer to the NHS) matters. Those technologies which improve health for more NHS patients, i.e., areas of greater unmet need, will tend to be rewarded with greater revenue. Whether society should be willing to sacrifice health outcomes of those who happen to have a more common disease to support those with a rare condition has been debated elsewhere and previously reviewed by NICE.^{12;16-18} In a competitive environment, innovators and developers compete to be first to launch a new product in a class. Inevitably this means that some will be second or subsequent to market and be at a disadvantaged because they will necessarily have a shorter period to generate revenue before generics become available. However, these are wholly appropriate incentives in a number of respects: i) it rewards those who are able to develop valuable products more quickly and at lower cost; ii) early followers will receive greater rewards than truly 'me too' products which enter much later without offering additional benefits and iii) it provides incentives to seek innovation

and development in areas of unmet need or develop products which demonstrated valuable benefits over existing products.

Appropriate incentives should encourage and reward investment in those products that are valuable to the NHS. Existing manufacturers and future innovators will naturally invest in the development of products that they expect to reward them best – which will also be those that are most valuable to the NHS. Those incumbents and future entrants who are able to develop valuable products more quickly and at lower cost will tend to succeed but those unable to do so will tend to fail, i.e., the appropriate incentives for long run efficiency. In any competitive environment there must be winners and losers. The losers are inevitably among the existing incumbents.

However, some of the winners will be new entrants or new management structures and business models for existing companies, i.e., future innovators who do not yet exist. Even those incumbents who are more likely to be winners have little short term interest in championing a more rigorous ‘demand side’ for health technologies.

Therefore, the primary responsibility for a body like NICE is to ensure that the NHS continues to meet its social objectives (protect the known and unknown patient equally) in a way that does not undermine the development and entrance of future innovators who will be better able to respond to health care needs, i.e., protect the unknown innovator. Therefore, technology appraisal informed by cost effectiveness analysis can provide commercial incentives which lead to the achievement of social goals in the short and long run without direct political or regulatory influence on research and development decisions.

In essence the role of NICE can be regarded as signalling a collective demand for health technology on behalf of the NHS. By ‘fixing the demand side’ in this way it will appropriately encourage and reward those innovations that are socially valuable, align incentives for future innovation with value to the NHS and provide an environment which will encourage the development of new and more efficient innovators. Some of the objections to the type of approach NICE has taken to technology appraisal seem not to be about cost-effectiveness analysis itself but either objections to the notion of collectively funded health care (that it should be individuals rather than the NHS that should signal demand for health technologies) or that the NHS budget does not reflect some alternate social valuation of health and

should be dramatically increased – a question clearly beyond the remit of NICE or even the Department of Health and given current social arrangements more appropriately one for parliament and the checks and balances of social democracy.

If problems with incentives remain (e.g., due to the high costs imposed by regulation or insufficient protection of intellectual property) then the appropriate response, if the case can be made, is not to change the ‘demand side’ but to address the supply side by reforming patient protection, reducing the costs of development and/or offering other direct or indirect subsidies (discussed in section 3 below). Therefore, the primary responsibility for NICE is to ensure the NHS continues to meet its social objectives (protect the unknown as well as the known patient) in a way that does not undermine the development and entrance of future innovators who will be better able to respond to health care needs (protect the unknown innovator). It is for other areas of government policy to consider whether there are sufficient incentives for innovation and adopt policies which encourage future innovators rather than protect incumbents who might not necessarily be best placed to respond to the needs of the NHS expressed by a more rigorous demand side for health technologies.

3. Are there Sufficient Incentives?

3.1 Principles of Optimal Patent Protection

The theoretical framework for identifying the appropriate degree of patent protection is founded on the observation that new knowledge (invention) is a public good – i.e. First, they are non-rival in consumption, meaning that a person’s use of that good does not affect the amount of it available to others. Second, they are non-excludable, meaning that anyone can enjoy it once it becomes available.

Non-excludability is a problem for innovation in a competitive market setting because of the free rider problem; i.e. that companies who have not invested in the development of the invention will reap the rewards of that invention, and this removes the incentive for companies to invest. Schumpeter (1943) demonstrated that if

governments wish companies to invest in research and development they will have to accept the creation of monopolies in order to remove the free rider problem; i.e. governments must create a legal framework giving exclusive ownership of the inventions produced to the companies that invested in their development.¹⁹ This is what patents do.

The dilemma of the patent system is that, by creating a monopoly situation, it adversely affects the efficient use of innovation. Therefore, key questions for governments are how broad the exclusivity should be, how long it should last for and how 'high' it should be. The length of the patent determines the duration of monopoly power. The breadth of the patent defines the range of products encompassed by the claims of the patent and therefore protects innovators from potential imitators. . The height of the patent, on the other hand, confers protection against improvements or applications that are trivial. These features need to be carefully calibrated to ensure that they provide sufficient incentives for research and development whilst avoiding providing excessive monopoly power to the patent holder.

The benefit to the patent holder, and therefore the incentive to invest in research and development, increases with patent length; however the value of the investment to society decreases.²⁰ This is because during the patent period the full value of the invention accrues to the company e.g. when new treatments are priced such that the incremental cost effectiveness ratio is just equal to the cost effectiveness threshold, the health of the population is unchanged. It is only after the patent lapses that society benefits, in the case of drugs in the NHS, through the entry of less expensive generics.

A broad patent will inhibit the development of product variants; e.g. the introduction of me-too drugs in the NHS. Gilbert and Shapiro (1990), demonstrate that there is a constant trade-off between the length and breadth of a patent.²¹ They argue that narrow patents of long duration are more likely to be optimal as they protect the patent holder's ability to exploit the invention whilst minimising barriers to the availability of alternative products. Klemperer (1990) argues that broad patents of short duration or narrow patents of long duration may be optimal based upon the structure of demand.²² In health care, we may wish to see a reasonable number of product variants. In which case, governments should avoid broad patent protection.

However, public transport vehicles such as trains where the total demand is small, we may not wish to see a substantial number of product variants and therefore allow for broad but short patents.

Similarly, patents of significant height will impede product development. In areas where there is a perception of substantial development potential, perhaps because of advances in basic science, society may wish to avoid high patents in order to encourage the translation of the basic science knowledge into new products. Thus, high patents in health care are unlikely to be consistent with government policy focussed on promoting the rapid translation of advances in genomic, proteomics etc... into new health care interventions. La Manna (1992), demonstrates that patent height can be traded off against patent length in order to identify the optimal patent protection.²³

In summary, if society wishes to see both rapid translation of advances in basic science into health care interventions, and a substantial number of product variants; the literature indicates it will need to provide narrow, low but long patent protection.

3.2 Is there evidence of barriers to investment in R&D?

Establishing the sufficiency or otherwise of incentives for investment in R&D in the pharmaceutical sector is complex. Whilst we have observed a steady reduction in the number of new products launched, the absence of effective demand for these products – as evidenced by the increasing difficulty in achieving market access – may indicate that this reduction in new products is in line with society's objectives and that the current incentive structure is approximately correct.

The development of new treatments is extremely expensive. Di Masi et al. (2003) estimate that it could be as much as \$800 million per new chemical entities (NCE).²⁴ The study also analyses the probability that a drug will eventually be brought to the market: about 78% of NCE are never marketed. Critics of the industry claim that most of the new drugs developed and approved are not fundamentally different but only minor diversifications to existing compounds. Criticisms are based on figures from the FDA that in 2001 approved 98 new drug applications (NDA), among these, 27

were new molecular entities, what remaining was new formulations and methods of delivering existing drugs.

Risk of failure stems from both “exogenous” factors such as unanticipated safety problems, but also from business decisions or “portfolio considerations”.²⁵ The study’s figures show that among a group of 28 pharmaceutical manufacturers, estimating that clinical safety issues accounted for 20.2% of terminations in 2000. In addition, 19.4% of terminations involved toxicology concerns, 22.5% were due to disappointing clinical efficacy results, 16.2% were due to various other factors and 21.7% were based on “portfolio considerations”. This means that changes on the revenue side would lead to different decisions about which drugs to carry forward in the development process, and would thus change the average cost picture.

This suggest that a more rigorous demand side giving clear predictable and reliable signals is likely to reduce the average costs of development. By signalling what is of value based on cost-effectiveness, NICE allows the manufacturers to more clearly identify worthwhile investments as well as to abandon projects that are unlikely to be rewarded, thus cutting the costs of failure in R&D.

There is evidence in the literature that the return on the investment in this sector is slightly above the average in the capital markets.²⁶⁻²⁸ This would suggest that the barriers to investing in R&D in this sector were not excessive, and that the returns on such investment were not excessive either. Further, the increasing concentration of the industry and maintenance of profit levels indicates that there is, or has been, substantial scope for increasing efficiency in the industry and it would seem appropriate to require efficient utilisation of the current rewards to investment in R&D before looking to systematically increase them. In fact, it would be difficult to specify the evidence that would be required to support a definitive conclusion of excessive barriers to investment in R&D in the pharmaceutical sector. However, consideration of the characteristics of the pharmaceutical market – both demand and supply structures, does not appear to support even a tentative conclusion that society’s demand for new health care technologies is being failed due to insufficient incentives for investment in R&D.

3.3 Potential policy responses

If there were convincing evidence of significant barriers to investment in research and development; there are a number of potential policy responses. These include reducing the cost burden of current regulation; amending one or more domains of the patent protection framework and the provision of both direct and indirect investment in research and development through tax breaks, subsidies and direct funding.

The burden of regulation

Much of the costs of regulation in the development of new health technologies are driven by international regulatory authorities such as the EMEA and the FDA. The ability of the UK alone to change these costs is obviously constrained. However, it is notable that through its support of the centralisation of licensing processes at a European level, the UK has already contributed to a reduction in the regulatory burden associated with the development of new treatments. The scope for further cost reductions has been identified in the areas of pharmacovigilance and early phase safety testing. However, experiences such as those at Northwick Park Hospital and with Vioxx in the US and Europe, could be taken as an indication that the safety hurdle is not obviously too high.

Further, whilst the creation of NICE is often portrayed as the imposition of an additional and costly hurdle, the mandatory nature of technology appraisal guidance has substantially reduced the need for large pharmaceutical sales teams marketing new technologies to individual clinicians. It is perfectly possible that the combined impact of NICE is a net cost reduction for the manufacturers.

Amending the patent protection framework

As discussed above, the patent protection framework has three domains; length, breadth and height. Increasing the protection in any of these domains has implications for the value of innovation to the NHS and society. Longer patents delay the point at which monopoly power ends and the new technology contributes to improved population health; broader patent protection reduces the development of product variants thus constraining the ability of clinicians to match treatment to patients needs and preferences; and raising patent height impedes the development of future

innovations, thereby slowing the rate of translation of advances in basic science into health care interventions.

The optimum patent protection framework is dependent upon what society values and the structure of demand for the products. Long narrow patents may be more attractive to investors developing interventions to treat chronic diseases; but are less likely to be attractive for investors developing interventions for acute conditions, where broader patents will keep products variants out of the market and thus protect monopoly power more effectively. Investors wishing to operate in markets characterised by early adopters of new technologies are likely to prefer patents with a strong height domain.

Subsidising research and development.

Public policy could also address a perceived shortfall in investment in R&D by direct public expenditure. This could take the form of direct funding for research infrastructure within the NHS; direct funding of research including clinical trials; or tax allowances for companies' research and development expenditures.

The study by Di Masi et al (2003) reports estimates of the average costs of trials in the order of \$400 million per NCE, a large fraction of total development costs.²⁴ Jayadev and Stiglitz (2009) suggest the public funding of phase III clinical trials as an effective policy to increase efficiency in drug innovation.²⁹ Jayadev and Stiglitz report an array of arguments in favour of public funding for clinical trials. These include reducing the costs of development and lowering the barriers to entry of new innovators. In addition the public good characteristics of the evidence generated by clinical research could be fully exploited with wide access to data and evidence by the health care system and other manufacturers. There are different ways of implementing a range of public subsidies depending on the policy context, but overall drug prices should be lower in consequence of the major savings that the industry is granted by such policies.

Interestingly, all of the policies listed above currently operate in the UK. The National Institute for Health Research represents a substantial investment in both research infrastructure within the NHS – creating the comprehensive clinical research networks; and in research including both early stage trials through the EME and later

stage trials through the HTA trials and the Programme Grant programmes. Tax incentives for investment in research and development have been long established. Whether any of these policies are operating at the correct level to address any perceived shortfall in R&D investment depends upon the target level and focus of the investment and an understanding of the factors that cause the perceived shortfall.

4. Do the Measures of Health Capture All Social Value?

It has been argued that the current NICE Appraisal processes and decision making criteria do not adequately reflect the full value of innovative new technologies. The arguments advanced can be gathered into three broad groups: (1) that the descriptions of health used by the NICE Appraisal Programme are inadequate to capture the health effects of new technologies; (2) that the values attached to the health do not adequately capture the society's value; and (3) that there are other non-health benefits from the technologies that NICE should, but does not consider. In section 4.1.1. we consider the arguments that the descriptions of health used by NICE do not capture all the health benefits of innovative technologies. Section 4.1.2 considers the arguments that the values that NICE attaches to the health benefits of innovative technologies do not fully capture the value society attaches to them. Section 4.2 considers the arguments for NICE taking account of the non-health benefits of innovative technologies.

4.1 Adequacy of the descriptions of health used by NICE

The NICE Guide to the Methods of Technology Appraisal specifies the EQ-5D as the preferred measure of health for use in the economic evaluation of technologies for use in the NICE Technology Appraisal Programme.⁵ The EQ-5D describes health using 5 dimensions (mobility, self-care, usual activity, anxiety & depression and pain), and each level has three dimensions (No problems, some problems, unable). This generates a relatively small descriptive system of 243 distinct health states. There is a prima facie case that the EQ-5D is not an adequate description of health for many conditions. However, there is a substantial empirical literature reporting its reasonable

performance as a measure of health related quality of life across a wide range of conditions.

It is important to note that whilst the EQ-5D is the recommended outcome measure, it is not the only measure of health that NICE will accept. Indeed, the methods guide makes explicit that organisations may make non-reference case submissions to the Technology Appraisal Programme. Further, within the NICE process, there is a difference between the evidence that is submitted to the process and the factors that the Appraisal Committee can consider in arriving at a recommendation. The section of the Methods Guide describing how Appraisal Committees arrive at their decisions states that one of the reasons for approving a technology within an ICER in excess of £20,000 per QALY is when, “there are strong reasons to indicate that the assessment of the change in HRQL has been inadequately captured, and may therefore misrepresent the health utility gained.”⁵ Reviewing the Considerations section of published Final Appraisal Determination, it is clear that Appraisal Committees have used this facility in practice.

Issues of safety and adverse events are most commonly captured in appraisal by assigning disutilities to the possible events (using the EQ5D descriptive system or other non reference case methods) and using these estimates within a decision analytic model which included evidence on the frequency of particular event to estimate an overall expected quality of life. Similarly convenience and improved administration is commonly included in appraisals by modelling the impact of administration on NHS resource use and modelling the impact of convenience through adherence to health outcomes and costs.

4.2 Reflecting the social value of health benefits

The NICE reference case states that the default position is to value health gains equally irrespective of the characteristics of the recipient of the health gain⁵, where recipients can include carers as well as patients. However, there is an extensive literature that shows that often the value attached to a health gain is not independent of other factors. Four broad categories of factors that modify the value attached to health gain; characteristics of the individual who receive the health gain (e.g. age, sex, dependents, employment status); characteristics of the condition that is treated (e.g.

prognosis, prevalence, severity, risk of imminent death); characteristics of the technology (e.g. primarily a mortality or quality of life effect); and social policy objectives (e.g. solidarity, equity). Submissions to the Kennedy review made specific mention of the inadequacy of the current approaches for capturing the value of treatments for severe and rare conditions and treatments for which there is currently no treatment.

Whilst the reference case specifies analyses that do not take account of these value modifying factors, the Methods Guide welcomes alternative analyses submitted, alongside the reference case (see para 5.9.7). More importantly however, the Methods Guide draws a clear distinction between the factors that should be incorporated into the reference case analysis and the factors that the Appraisal Committees are directed to consider in arriving at their recommendations.

The critical question for the NHS and the deliberations of the appraisal committee is, how much of some one else's life expectancy ought to be given up to provide access other aspects of benefit, e.g., greater convenience not already accounted for in estimates of health benefit or earlier return to work. Therefore, consideration of benefits not already captured in measures of health benefit must address the trade-off that is necessary when additional benefits come at additional NHS costs, i.e., based on measures (like EQ5D) which ask individuals to make these trade-offs with their own health.

Chapter 6 of the Methods Guide describes in some detail the criteria that the Appraisal Committees consider in arriving at a recommendation. The Committees consider issues of distributive justice, taking into account factors including "age; sex/gender or sexual orientation; people's income, social class or position in life; race or ethnicity; disability; and conditions that are or may be, in whole or in part, self-inflicted or are associated with social stigma." (See Para 6.2.20). Further, the Committees explicitly consider; "Whether there are strong reasons to indicate that the assessment of the change in HRQL has been inadequately captured, and may therefore misrepresent the health utility gained." and "if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure." (See Para 6.2.23). To the extent that

there is evidence of additional social value for health gain from treatments for severe or rare diseases, or for treatments where current practice is best supportive care, the technology appraisal process will not ignore it.

The Methods Guide clearly directs the Appraisal Committees to consider adequacy of the measures of health gain, and the values attached to health gains when arriving at a recommendation. Despite this there remains a distinct concern that inadequate consideration is given by the Committees to these issues. Two possible sources for this concern present themselves. The first is that those expressing this concern have failed to understand the role of the reference case analysis in the technology appraisal process; believing that the recommendations are made on the basis of reference case analyses. The function of the reference case is to facilitate comparability between appraisals by creating a common analytical framework. It also facilitates assessment of alternative analyses by specifying a reference point from which departures are allowed and even encouraged, but must be justified. The reference case is focussed upon the organisation, quality assessment and synthesis of the evidence base which informs the decision. However, there is always a gap between the available evidence and the decision that must be made. It is the responsibility of the Appraisal Committee to bridge that gap and it is clear that the process by which they do so, includes consideration of whether the impact of a technology on health has been adequately captured in the evidence base; whether the social value of that impact has been adequately captured in the utilities used in the cost effectiveness analysis, and whether there are additional socially valuable benefits from the technology that the QALY model has not captured.

The second possible source for the concern is a failure to understand the nature of the decisions that the NICE Technology Appraisal Programme makes. Some of the submissions suggest that a higher cost effectiveness threshold is required to reflect the social value of innovative technologies. This implies that the cost effectiveness threshold reflects a social willingness to pay for health gain. When the value of the health gain from a technology is increased, the willingness to pay applied to that technology should be increased. However, as Culyer and colleagues have described, in the presence of a fixed budget, which cannot be changed by the decision maker, the cost effectiveness threshold is not a measure of the willingness to pay for health.³⁰ It

is an estimate of the opportunity cost (health foregone by others) of substituting a new technology into the portfolio of technologies provided. Thus the cost effectiveness threshold is not determined by the characteristics of the patient, technology or disease under consideration in any specific appraisal.

Once this is understood it becomes clear that in any NICE decision there at least two groups of patients being considered – the *identified* patients who will benefit from a positive recommendation and the *unidentified* patients who will bear the opportunity cost of a recommendation. Widening the scope of the value assessment applied in technology appraisals changes the assessment of the value of the health gained by one group and the value of the health foregone by the other. Whether changing the scope of the value assessment increases or decreases the proportion of new technologies that are recommended for introduction to the NHS, depends upon the relative prevalence of value modifying characteristics amongst those who would gain and those who would bear the opportunity cost.

It is worth noting that whilst the discussion above has presumed that the primary objective of the NHS is to maximise the health gain generated from the consumption of its budget, similar arguments would apply if the objective of the NHS was changed. Given any objective, the current portfolio of NHS technologies will have a certain level of effectiveness and efficiency. Reallocation of NHS resources to innovative technologies will depend upon demonstrating that these innovative technologies are more efficient in meeting that objective than the current technologies that would have to be displaced to pay for them. In the presence of a fixed budget, demonstrating that new technologies have effects that are valued by society is a necessary but not a sufficient condition for their reimbursement. The sufficient condition is that they produce more value than the technologies which their reimbursement would necessarily displace.

4.3 Other non health social value (perspective)?

Decisions based on cost-effectiveness analysis complete and reasonable if the objective of collectively funded health care is to improve health across the health care system; that the measure of health gained and forgone captures enough aspects of

health and other aspects of social value to be useful; and that the budget for health care ought to be regarded as fixed by the decision making body. However, it also relies on the assumption that there are no effects outside the health care sector or any effects are small or not socially valuable compared to the effects within the health sector. These effects fall into two broad types: i) direct costs of care that do not fall on the health care budget and ii) the indirect external effects on the rest of the economy.

Some of the direct costs of care are borne by patients such as out of pocket costs as well as their time in accessing care. It may also include the direct financial consequences of ill health (and earlier recovery) for patients and families if these are not fully captured in measures of health related quality of life. It will also include the time and resources devoted to caring for patients outside the health care system. Although, direct costs may fall on marketed and non marketed activities (e.g., time and informal care) they can in principle be valued in terms of the equivalent consumption forgone and expressed as a consumption cost for the wider economy. An effective health technology may reduce these costs (e.g., a quicker recovery) or increase them (e.g., prolong survival in a chronic state).

The indirect external effect on the wider economy are effects external to the patients, their family or informal carers but are valued by the rest of society. For example, returning a patient to active participation in the labour market will in many circumstances add to production in the economy. This will be a net benefit to society if the value of the additional production exceeds the individual's additional consumption over their remaining life expectancy. Therefore, an effective health technology may provide external benefits by reducing mortality in economically active groups whose production is likely to exceed their consumption. However, it may also impose external costs on the economy if it reduces mortality in populations where remaining life cycle consumption exceeds the value of production, i.e., older populations.³¹ All these direct and indirect external effects can be expressed as a net consumption cost, which if positive indicates net consumption losses to the wider economy and if negative indicates net consumption benefits.

The problem for policy is that in the face of budgets set by a socially legitimate higher authority (government) it is not clear how or whether a broader social perspective which would include all these effects on all sectors should be implemented – particularly if transfers between sectors are not possible. There is also the fundamental difficulty of specifying how the trade offs between health, consumption and other social arguments, as well as the valuation of market and non market activities, ought to be done. This is particularly acute when there is no consensus on how to prescribe social choice, each alternate view generating potential conflicts with other agreed social objectives.

Even if some consensus could be reached, the effect of repeated application of feasible decision rules to a series of decisions will ultimately lead to non marginal changes, i.e. a sufficient number of ‘marginal’ changes tending in the same direction will have non marginal effects. This poses a number of problems: i) a failure to account for non marginal effects will lead to a biased assessment of cost-effectiveness and an unambiguous increase in the possibility of false positive decisions; ii) even when non marginal effects are accounted for and bias is avoided, unless transfers are made to compensate for the non marginal effects, then the implied reallocation of resource between sectors may not be socially desirable, particularly if an explicit welfare function cannot be completely specified; and iii) the informational requirements to fully account for non marginal effects are generally not available so can not represent a realistic or feasible policy option. There are also longer run dynamic effects of policies which attempt to account for these external effects which in the absence of transfers may not be socially desirable and will tend to undermine other social objectives of public policy. Therefore, the UK Department of Health has commissioned a review of the current NICE perspective and the implications of alternative policies which will be completed in summer 2009.

5. Conclusions

The following conclusions seem to be supported by the examination of the submissions to the Kennedy review, the principles of how innovation is valued in other markets and within the NICE appraisal process:

- The NICE approach to appraisal offers the opportunity and incentive for manufacturers to appropriate the full value of innovation during patent protection. This aligns incentives for investment in research and development with the needs of the NHS and the budget constraint it faces.
- Although there are potential future benefits of innovation, the case that NICE should anticipate these future benefits and reward them before they have been realised is not well supported and could lead to the NHS paying twice for innovation and distorting incentives for future innovations.
- If the case can be made that current patent protection is insufficient (which would require comparisons with other sectors) there are a number of more appropriate and effective policy responses, all of which would require consideration by other government departments.
- There is a case that the existing measures of health benefit used by NICE may not capture all aspects of outcome that might be regarded and socially valuable. This is already recognised in the appraisal process and in the considerations of the appraisal committee.
- These other aspects of health benefit and its social value are not specific to innovations (new technologies) but are also relevant to all NHS and other public health interventions. Any amendment to the measurement of health benefit is part of a debate which is wider than the specific question of valuing innovation. It also suggests that:
 - Demonstrating other benefits outside measures of quality of life is not sufficient. There would also need to be a demonstration that they exceed the other benefits that may be forgone elsewhere in the NHS
 - Any formal measure of these other aspects of benefit would also need to reflect how much life expectancy (of other patients) ought to be given up to achieve these additional benefits – since this is the

question posed if the additional benefits come at additional costs to the NHS.

- It is well established that health technologies can have an impact on non NHS costs of care bourn by patients, carers and families and have effects on the wider economy. However, this is not specific to innovation but to all health technologies and other NHS activities. Therefore, it is not enough to identify non NHS cost savings or wider benefits. The case that the benefits offered are greater than those forgone elsewhere would need to be made. It should also be noted that an effective technology may increase as well as reduce non NHS cost and impose net costs as well as benefits on the wider economy.
- This question of perspective has much wider implications including other public sectors. Some of the difficulties include non marginal effects when the NHS budget is fixed and the dynamic consequences (e.g., prices) which could lead to socially undesirable reallocations of resources between sectors. For this reason the Department of Health has commissioned a review of perspective which is due to report in summer 2009.

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A briefing note on the threshold

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What is the threshold?

The threshold represents an estimate of health forgone as other NHS activities are displaced to accommodate the additional costs of those technologies recommended in NICE guidance.

No one can ever know for sure what will be displaced or who will actually forgo health but we do know for sure that on average across the NHS some activities will have to be displaced and some health will be forgone.

What is likely to be forgone?

We need an estimate of what is likely to be forgone in the NHS as we find it. Of course some things that the NHS spends a lot of money on can not be displaced (GP and consultant contracts as well as previous mandatory NICE guidance) and other things are more difficult to displaced, e.g., investment in buildings, waiting list initiative and other national mandated policies etc.

What could be displaced?

Arguably there are inefficient activities in the NHS which could be cut without much impact on health, so in an ideal world if we could reorganise the NHS and reallocate all the money then we could have a different threshold. In this idealised world the threshold would initially be much lower (the NHS would be much more productive of health) but once all the savings had been spent on other effective activities then the threshold will be some what higher (although not necessarily as high as the original threshold).

However, this notion of the threshold (what could be forgone in an idealised NHS) is not what is relevant to NICE. NICE must take the NHS as it is - not how it might be in some idealised world. An estimate of what is likely to be forgone on average across the NHS as a result of NICE guidance is needed – call it k for short hand and imagine $k = £20,000$ per QALY.

What about the social value of a QALY?

Some have cited values for a social value of health (a QALY) much higher than the current threshold. These values represent how much money (consumption) people are willing to give up for one QALY – call it v for sort hand. Even if we accept such values (e.g., $v = £60,000$) they are largely irrelevant to NICE decisions for two reasons.

Is it Health?

If the primary purpose of the NHS is to improve health then all that is needed is an estimate of k because we need to ask whether the health expected to be gained from the use of a technology ($\Delta h = 2$) is greater than the health expected to be forgone due to the additional costs ($\Delta c = \text{£}60,000$). In this case the health expected to be forgone

$\left(\frac{\Delta c}{k} = \frac{\text{£}60,000}{\text{£}20,000} = 3 \right)$ exceeds the health expected to be gained by approving the technology. A social value of health (a value of v) is entirely irrelevant. If improving health given available NHS resources is the primary social objective then NICE should accept a technology if:

$$\Delta h - \frac{\Delta c_h}{k} > 0,$$

i.e., if the net health benefit is positive. Alternatively and equivalently, this can be expressed as a more familiar comparison of the ICER to the threshold. The technology should be accepted if:

$$\frac{\Delta c_h}{\Delta h} < k$$

In this example,

$$\Delta h - \frac{\Delta c_h}{k} = 2 - \frac{\text{£}60,000}{\text{£}20,000} = -1, \text{ or alternatively } \frac{\Delta c_h}{\Delta h} < k = \frac{\text{£}60,000}{\text{£}20,000} = \text{£}30,000 > k$$

The technology is not cost-effective and should be rejected because health outcomes across the NHS would be reduced if it was approved.

Is it the consumption value of health?

If the primary purpose of the NHS is not to improve health but consumption value then the health expected to be gained needs to be valued more highly using v . But the health that is expected to be forgone elsewhere in the NHS must also be valued more highly as well. If consumption value is the social objective a technology should be accepted if:

$$v \cdot \Delta h - v \cdot \frac{\Delta c_h}{k} > 0$$

i.e., if the net health benefit is positive. Since a higher social value of health simply scales up the value of the benefits and the value of the opportunity costs it makes no difference to the decision. In this example,

$$v \cdot \Delta h = \text{£}60,000 \times 2 = \text{£}120,000 \text{ and } v \cdot \frac{\Delta c}{k} = \text{£}60,000 \times \frac{\text{£}60,000}{\text{£}20,000} = \text{£}180,000$$

The net consumption benefit is -£60,000 and the technology should be rejected even though the $ICER = £30,000$ is much lower than the social value of health, $v = £30,000$.

There are some clear implications:

- Even if a social objective of consumption rather than health was acceptable for the NHS and the higher values of health or life used in other public sectors (e.g., transport) or derived from individual or social preferences (social value of a QALY or willingness to pay) where acceptable, NICE would still need the same estimate of the threshold to make decisions, i.e., even if a value for v is used an estimate of k is still required.
- If all the costs fall on the health budget any value of v will make no difference to the decision anyway. Although, if v is expected to grow over time it will have a relatively minor influence - reflected in lower discount rates for both health and costs.
- The question of whether and how NICE should take account of costs and benefits to the wider economy is under review by the Department of Health. If these are to be formally taken into account then a value of v is important but the same estimate of k is still required.
- The only circumstances in which using a value for v instead of an estimate of k could be justified is when there is no fixed budget for health care, i.e., when a body like NICE also had the remit to determine the total public expenditure on health care.

How does the threshold change over time?

Three things happen over time which will influence the threshold: i) the budget can change, the prices of NHS inputs can change and iii) the productivity of NHS activities can change

Budget changes over time

If the technology of the NHS is fixed (all the things that make up what the NHS does, not just drugs and devices but procedures and the delivery of care stay the same) and prices are also fixed then an increase in the budget will mean that the threshold will grow as the additional budget is spent less productive activities. However, even in these circumstances the threshold will only grow as long as the expanding budget is spent on things that could later be displaced by future NICE guidance.

However, there are three general problems with the naive view that an increase in budget necessarily means the threshold must grow:

The technology of the NHS is not fixed

Firstly, the technology is not fixed. Over time the NHS is be expected to be more productive – there is innovation in medicine so more effective technologies are introduced and more effective procedures are developed. If the growth in productivity is greater than the growth in the budget then the threshold will fall rather than grow with the budget.

In fact NICE itself contributes to this process and ensures that technologies are not fixed. As cost-effective technologies are approved for use and displace less cost-effective activities (if the threshold is not set too high) then the mix of existing activities becomes more cost-effective and the threshold will tend to fall. The implication is that even if the budget is constant and prices do not change the threshold will fall over time.

Things that can not be displaced

Secondly, if all the extra budget is spent on things that can not or can not easily be displaced then the additional costs of a new technology must displace other more effective activities and the threshold will remain constant (if the technology is fixed) or fall with any growth in productivity. This seems closer to the case of the NHS over the last 10 years. Much of the additional budget has been spent on things that are not easily displaced: the GP and consultant contracts; agenda for change, mandatory NICE guidance, waiting list initiative, IT initiatives, building and capital programmes etc. If there has been any growth in what remains it will be much more modest and more likely to be less than the growth in the productivity of displaceable activities (drugs, procedures, devices etc).

Prices are not fixed

Finally prices are not fixed over time. If the budget and the technology of the NHS was fixed but the prices of all NHS inputs grew by the same amount then the threshold would rise (the NHS would be less efficient in nominal terms).

However, it is not the general rise in prices that is important. Nor is it the NHS inflator (inflation rate for the overall mix of NHS expenditure), but the changes in prices of those things that can be or are likely to be displaced by NICE guidance. Much of the NHS inflation is driven by staff costs much of which can not easily be displaced (e.g. GP and consultant contracts and agenda for change etc) as well as other capital and overhead costs (e.g., fuel and capital charges) which also can not be displaced. What is relevant is the prices of inputs which could be displaced, one important element of which is drug prices. Of course, branded drug prices do tend to rise but at the same time previous branded drugs go generic on patent expiry and the prices fall dramatically (in general the generic prices are 25% of the brand). For example, statins were cost-effective when introduced and improved the productivity of the NHS (tending to reduce the threshold). They then became much cheaper on generic entry dramatically increasing productivity (also tending to reduce the threshold further).

In Summary

- The threshold will not necessarily rise with the budget and will fall if the budget is constant.
- Given that most of the additional budget has been spent on things that can not be displaced the threshold is more likely to have fallen
- Observing general inflation or NHS inflation does not necessarily mean that the threshold has grown.
- Given the importance of drugs and significant price falls with generic entry the productivity of that part of NHS activities which could be displaced could well have increased in nominal terms over the last ten years i.e., the threshold may have fallen.
- Simply increasing the threshold in line with budget growth and or inflation can not be justified

But what is the best estimate of threshold now?

In a sense the argument about whether the threshold has grown, stayed constant or fallen is not really the point. The point is what is the best estimate of the current threshold and what do we expect to happen to it in the future.

For example, even if one believes that threshold grew, if the £20,000 to £30,000 threshold used by NICE was originally set too high, as many have suggested, then even with growth this threshold may still be too high. Inflating the current threshold would compound the problem.

I would argue that the work by Martin et al 2008 is the best (UK and international) estimate of the actual thresholds on average across the NHS. It estimates the change in mortality due to a change in expenditure by ICD code (based on variation on expenditure across PCTs). It controls for both observable and unobservable covariates, using the best data we have and the best econometric methods available. It is published in the best international Journal in the field with rigorous peer review. These estimates suggest that even the lower range is probably too high, particularly if things get displaced in areas other than cancer and diabetes.

A few things to note about this analysis

- The estimates of budget elasticities (thresholds) are based on what all PCTs actually do (those that spent more and those that spent less) which is what is needed
- The estimates provide the threshold on average across the NHS which is what NICE needs as its task is to make national not local decisions
- The estimates of QALY gains for a change in expenditure only capture improvements in length of life (they simply QALY weight life expectancy). If any of the expenditure was used to improve quality of life rather than length of life (e.g., palliative care and treating conditions without a mortality risk) then this has not been accounted for. Since some, if not much, of health care is about quality rather than length of life this means the benefits are underestimated and the actual threshold will be lower in each area.

- The caveats to the analysis are all clear and well stated in the paper – most important is limited outcome data which should improve overtime
- It is difficult to compare the 05/06 with 07/08 unpublished estimates to infer changes in threshold as the same outcome data was used so they only reflect changes in expenditure.

What can expect over coming years?

It seems clear that budgets are likely to grow less fast or more likely fall over coming years. Productivity might be expected to grow more quickly as pressures to make better use of more limited resource will grow. Branded drugs will still go generic and prices will fall by at least as much in a more competitive international environment. Other prices will tend to grow less fast or even fall in a deflationary cycle. Unlike a period of growing budgets and rising prices all these effects work in the same direction – the threshold is more likely to fall.

Summary

- The best estimates of the current threshold come from Martin et al 2008.
- These over estimate the value of the threshold (it will be some what lower).
- All this suggest that if anything even the lower range might be too high.
- In the future the threshold is more likely to fall for the NHS.