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Characterising uncertainty in the assessment of medical devices and determining future research needs

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ABSTRACT

Decisions about the adoption of medical interventions are informed by evidence on their costs and effects. For a range of reasons, evidence relating to medical devices may be limited. The decision to adopt a device early in its life cycle when the evidence base is least mature may impact on the prospects of acquiring further evidence to reduce uncertainties. Equally, rejecting a device will result in no uptake in practice and hence no chance to learn about performance. Decision options such as 'only in research' (OIR) or 'approval with research' (AWR) can overcome these issues by allowing patients early access to promising new technologies while limiting the risks associated with making incorrect decisions until more evidence or learning is established. In this paper we set out the issues relating to uncertainty and the value of research specific to devices: learning curve effects, incremental device innovation, investment and irrecoverable costs, and dynamic pricing. We show the circumstances under which an OIR or AWR scheme may be an appropriate policy choice. We also consider how the value of additional research might be shared between the manufacturer and health sector to help inform who might reasonably be expected to conduct the research needed.

1. INTRODUCTION

Establishing the clinical effectiveness and cost effectiveness of medical devices relies on evidence which is often less extensive and lower in quantity than evidence for many pharmaceutical products. This is largely because the evidence requirements for medical devices to achieve a CE mark is less demanding. Unlike pharmaceuticals, where evidence on efficacy and safety is legally required before marketing authorisation is obtained, devices usually only need to demonstrate performance and safety, with the CE mark acquired close to the point of market entry (Drummond et al., 2009, Sorenson et al., 2011). The availability of the device early may appear attractive as it can lead to rapid clinical uptake; however, decisions about the use of the device when the evidence base is least mature carries substantial risk. Uncertainty about the efficacy of the device and the learning or training required to achieve the desired efficacy can result in adverse consequences on patient outcomes and lead to an ineffective use of health care resources. Rapid approval of new entrants can also result in disincentive effects for manufacturers to invest in further research which would reduce these uncertainties (Claxton et al., 2012).

Balancing the value of early access to a technology and the value of additional evidence to resolve uncertainty has led to the development of novel approaches for reimbursement and coverage decisions under conditions of uncertainty (Claxton et al., 2012, McCabe et al., 2010, Stafinski et al., 2010, Walker et al., 2012). For example, Claxton et al (2012) developed a comprehensive algorithm to inform the sequence of assessments and judgements which lead to conditional coverage decisions of 'Only in Research (OIR)' and 'Approval with Research (AWR)' for health technologies (Claxton et al., 2012). These conditional coverage options allow patients early access to promising new technologies and permit manufacturers to make a return on investment, while limiting the risks associated with making decisions until additional evidence and/or further learning establishes value. Even in health systems where there is an absence of

firm budget constraints or where economic analysis is not explicitly incorporated into a decision making process, the same principles can be usefully applied to establish the value of additional research. For example, an assessment of uncertainty and the expected health benefits of additional evidence can be obtained directly from the results of standard meta-analysis or evidence on clinical effectiveness alone (Claxton et al., 2015). Therefore, regardless of the policy context, some consideration should be given to the characterisation of uncertainty in the assessment of medical devices and determining future research needs.

The unique characteristics associated with medical devices such as rapid incremental innovation, learning effects, and upfront irrecoverable costs, all present a challenge for the timing of reimbursement decisions and the value of waiting until additional evidence is conducted to support the technology. This means that conditional coverage decisions and possible risk sharing schemes (between the manufacturer and health sector) become even more important. One of the complexities associated with the evaluation of medical devices is the fact that any decision about the adoption of the device will also interact with the ability to gather more evidence and may affect future commercial developments of the technology. There is also a close link between the value of the device, the value of further research to reduce uncertainty and the price of the device. These links can offer incentives for manufacturers to price accordingly and decide whether there is sufficient value from further evaluative research. It also helps to establish how the value of the device and the value of future research might be shared between the manufacturer and the health sector in order to inform who might reasonably be expected to pay for (conduct) the research. Manufacturers also need an approach to make rapid decisions at the start of product development and to revisit the decision to continue development and research at different points in the development cycle. One example is the 'Headroom Approach' which has been discussed in the context of medical devices (Girling et al., 2015).

The purpose of this paper is to set out a framework for characterising uncertainty and informing coverage decisions in the assessment of medical devices. The framework is based on a number of common principles that are required for all technologies and a number of additional considerations or challenges specific to devices. The common principles are outlined first. We then present a more detailed description of the additional challenges (or ones which are more accentuated) for an assessment of uncertainty and the value of further research for devices. For some of the specific challenges, we use results from a case study of enhanced external counterpulsation (EECP), which is a device used to provide symptomatic relief from chronic refractory angina. EECP as an adjunct to standard therapy has previously been compared with standard therapy alone to estimate its expected cost-effectiveness and uncertainty associated with reimbursement decisions from a UK perspective (McKenna et al., 2010). Full details have been described elsewhere (McKenna and Claxton, 2011, McKenna et al., 2015). We use EECP to show the implications of significant irrecoverable costs and price changes on coverage decisions.

2. FRAMEWORK FOR CHARACTERISING UNCERTAINTY

A framework for characterising uncertainty is presented in Figure 1. This framework is based on a number of common principles that are required for all technologies: an assessment of the value of a technology, the value of additional evidence, the significance of investment and irrecoverable costs, future changes and the likelihood of research being conducted. Each of these elements are discussed briefly below and more detail is provided elsewhere (Claxton et al., 2012).

2.1 The value of a technology

A technology, whether it is a medical device or pharmaceutical, is considered to represent value if its additional health benefits are expected to exceed the health forgone from curtailing other

activities to accommodate the technology's additional costs, i.e. the technology is only considered cost-effective if it offers positive net health benefits. This holds true in both budget-constrained health care systems, where there is a threshold of cost-effectiveness representing the opportunity costs that fall on health expenditure, and systems where there is an absence of firm budget constraints but where opportunity costs manifest in terms of other forms of expenditure, e.g. through increased taxation or co-payments (Drummond et al., 2015). Therefore, the first assessment for any technology is its expected cost-effectiveness based on the evidence that is currently available. This relies on information about the technology's effectiveness, its impact on long-term health (including potential adverse consequences), additional costs and an assessment of the opportunity costs of the health that is likely to be forgone as a consequence of adoption.

2.2 Significance of investment and irrecoverable costs

Investment costs that are sunk costs cannot be recovered if a decision about the technology is changed in the future. These irrecoverable costs are most commonly thought of as investment costs associated with the capital expenditure on equipment, new facilities, or training and learning costs. Typically these costs are annuitized and allocated as per-patient costs by spreading the cost over the number of patients likely to be treated during the lifetime of the technology (or in the case of training and learning costs until performance has reached a steady state). If the adoption decision is unchanged throughout this period and there is no decision to take the device off the list of funded interventions, allocation of costs pro-rata has no influence. However, if a decision to end adoption changes before the end of the lifetime of the technology, these costs cannot be recovered. Therefore, any significant irrecoverable costs should be considered when assessing the value of a technology. There may also be costs associated with the removal of a technology from clinical practice if a decision about the technology changes in the future.

2.3 The value of additional evidence

The value of a technology in terms of its expected cost-effectiveness is based on the balance of evidence currently available. However, uncertainty in the existing evidence is unavoidable. This uncertainty arises from a number of sources including the evaluation of a technology early in its life cycle when the evidence base is least mature, establishing a treatment effect which often depends on the ability to approximate the counterfactual in the studied population, disentangling the interaction between effectiveness and user experience, establishing causal relationships between outcomes, combining multiple sources of evidence on the same outcome, missing information, and assessing the transferability of study findings to a population or setting of interest. This evidential uncertainty ultimately leads to uncertainty in the decision to adopt the technology. Additional evidence can reduce this uncertainty and therefore reduce the risk of making an incorrect decision about the use of the technology. An assessment of uncertainty, its consequences in terms of health lost from an incorrect decision, and the need for further research is required. The value of further research can be informed through methods of value of information analysis, which can also be used to inform the type and design of proposed research (Briggs et al., 2006). Some assessment of the likelihood that research is conducted, the length of time for research to report and the costs of conducting research are also required.

2.4 Incentivising research

An assessment of the value of additional evidence provides an incentive to the health care system to ensure that the type of research required is conducted without incurring significant irrecoverable costs. However, manufacturers may only retain an incentive to conduct research if a technology is rejected for use but for which they believe there are additional benefits which have not been evidenced. Some consideration of how the value of the technology and the value of additional research might be shared between the manufacturer and the health care system might inform whether manufacturers could reasonably be expected to conduct the research (or

make a contribution to the costs of publically funded research which might benefit their technology). Appropriate incentives or risk sharing agreements between the manufacturer and the health care sector should encourage and reward investment in the technology if it represents value to both sectors. Identifying situations when social and commercial values do not match and how costs and benefits might be shared between sectors is an important consideration. The payer may also influence the type, quantity and likelihood that the research is conducted.

2.5 Future changes

Further research is unlikely to be able to resolve all uncertainty. Some sources of uncertainty that cannot be reduced by further research may resolve by other changes occurring over time. For example, the effective price of the technology and/or its comparators may change in the future. The price clearly plays a key role in determining the value of the technology but it also affects the level of uncertainty by changing the likelihood of making an incorrect decision and the value of further research. The information generated by research will not be valuable indefinitely as new and more effective interventions may become available and make the information no longer relevant to future clinical practice. Therefore, new or incremental innovation will also change the value of a technology and the future value of research.

2.6 The value of early access

Early access to a technology is considered to represent value if the expected health benefits of approval are greater than the opportunity costs that may be forgone to future patients. These opportunity costs include the potential value of research forgone as a consequence of early access (e.g. if the research needed to resolve uncertainty is not conducted once patients have access to the technology) and the irrecoverable costs associated with reversing decisions. If the expected benefits are judged to be less than the opportunity costs then the commitment of irrecoverable opportunity costs (negative net health benefit) should be avoided, whereas if they

are judged to be greater, then early access would be considered appropriate. This assessment is informed by the above considerations of the long-term value of research, the significance of investment and irrecoverable costs, and the impact of future changes on both the value of the technology and the future value of research and/or learning.

2.7 Coverage decisions

The above considerations lead to one of four decision options for a technology:

i. *Approve*: The technology is approved for widespread use on the basis that the evidence currently available suggests that it represents value to the health care system.

ii. *Reject*: The technology is rejected for widespread use on the grounds that the evidence currently available suggests that it does not represent value to the health care system.

iii. *Only in research (OIR)*: The technology is only available to patients involved in research, i.e. it is rejected for widespread use until further evidence establishes value.

iv. *Approval with research (AWR)*: The technology is approved for widespread use but conditioned upon the collection of additional evidence to support its use. This option means that the decision to approve the technology may be revised once the results of the research are established.[1]

Each decision option is based on the balance of evidence supporting the value of the technology, the value of additional evidence, future changes and the likelihood of research being conducted. Trade-offs, which can be expressed in terms of net health benefits, occur under each decision option: approval may mean that the type of research needed is not possible (ethical concerns, recruitment difficulties, limited incentives for manufacturers); rejection restricts access to a promising new technology if the actual health benefits are greater than expected; OIR restricts access until further research establishes value; and AWR may result in subsequent withdrawal of the technology when further research is completed.

[1] In many cases, however, there is often a 'dragging effect' where it is often hard to dismiss the use of a technology altogether once it has already been in use (approved). This has implications on costs in general and particularly on sunk or irrecoverable costs.

3. MEDICAL DEVICE CHARACTERISTICS AND UNCERTAINTY

The evaluation of medical devices raises a number of challenges over and above those for other technologies (Drummond et al., 2009, Sorenson et al., 2011). Devices also cover a wide range of products for which quite different issues may arise for the different class of device. The challenges which are often more accentuated for the assessment of uncertainty in the evaluation of devices are: learning curve effects; incremental device innovation; investment and irrecoverable costs; dynamic pricing; and incentivising further research. Each of these challenges and the implications for coverage decisions are discussed below.

3.1 Learning curve

When medical devices are diffused into clinical practice there is often a learning curve relating to user skills and training with the technology. This learning curve can have an important impact on the efficacy and performance of the device. The challenge for the evaluation of devices is the difficulty of disentangling the 'true' efficacy of the technology from the efficacy derived from the interaction between effectiveness and clinical experience using the technology. An early assessment of the technology is likely to be biased against the new technology as the performance of repeated tasks by the user is expected to change with experience over time (Ramsay et al., 2001). The learning curve effect plays a significant role in any type of device that requires a new advanced skill set. An excellent example of the effects of learning comes from the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) where the results from stenting appeared worse than endarterectomy in the early years of the trial because clinicians had only limited experience at that stage (Mantese et al., 2010). The learning curve effect can depend on a number of underlying mechanisms, e.g. user experience, community experience/system learning, and case-mix of patients in a given centre. These mechanisms will

not only change the estimate of effectiveness but will also affect the scale of the uncertainty over time, with greater uncertainty anticipated during the early stages of learning.

Methods for the statistical assessment of the learning curve are reported in Ramsay et al (2001) (Ramsay et al., 2001), while estimates of the learning curve profile could be obtained through formal elicitation of the judgements of clinical experts. For example, Cook et al (2012) showed that information on current practice, prior experience and beliefs regarding acquiring proficiency and the learning curve for two surgical procedures (open and arthroscopic rotator cuff repair) could be elicited in order to assess the likelihood of expertise impacting upon trial results (Cook et al., 2012).

The profile of investment risk associated with learning is important for coverage decisions as approval of the technology or AWR may commit opportunity costs of negative net benefit which are irrecoverable. For example, if the technology is approved for widespread use in the early stages of learning (with the anticipation that users will become more experienced) and this decision is later revised, either due to more user experience revealing that the technology is not as effective as initially expected or additional research and/or other changes reporting this, then these initial losses will have been incurred and cannot be compensated by later gains. In order to judge the most appropriate coverage decision at a particular point on the learning curve, the net benefit for the new technology relative to its comparator(s) is estimated based on the evidence available at that point. An estimate of the expected net benefit from further research (taking account of the number of patients who can benefit from research, the likelihood that research will be conducted and the time for research to report) is also required to inform the benefits associated with an AWR or OIR decision. Figure 2 illustrates the net benefit for coverage decisions at different points on the learning curve. In this example, OIR offers the best return at points early in the learning curve where there is most uncertainty (e.g. T_1 with less user experience). This is because OIR avoids the consequences of committing negative net benefit

until a more informed decision can be made with further experience and/or research reporting. A decision made at a later point on the learning curve (e.g. T_2) suggests that AWR offers the best return, while at a point even later (e.g. T_3) the net benefit from AWR is insufficient to outweigh the opportunity cost of not approving the technology. In reality, however, removing a technology once it has been approved for use is often difficult in practice. For example, when drug-eluting stents (DES) were first introduced, evidence was scarce but very positive. In some jurisdictions, DES were approved with research and clinicians were obliged to gather additional data on costs and effectiveness. When this new evidence was assessed, DES turned out to be much less effective than suggested at uptake compared with bare-metal stents. However, in many cases, DES still continued to be used with some jurisdictions trying to limit their use to particular subgroups of patients only.

Coverage decisions when there is a learning curve are further complicated by the fact that the rate of learning through user experience is also affected by the rate of uptake of the technology in practice. For example, if the technology is rejected there will be no uptake and hence no chance to learn further about the technology. If the technology is accepted only in the context of suitable research (OIR) then there will be slow uptake and slow learning. If the technology is approved, either conditionally or unconditionally on research being completed (i.e. Approve or AWR), the uptake of the technology will be greater and learning should reach a steady state at a faster rate. It is expected that Approve might have a greater uptake than AWR as the decision to approve conditional on research suggests significant levels of uncertainty and perhaps more caution in the use of the technology. This creates a situation where the learning curve not only affects the coverage decision but the coverage decision also affects the rate of uptake and learning. Given these concerns, 'Approval but in a limited number of centres' may be an appropriate policy option when there is a learning curve. This could potentially maximise the speed of learning whilst minimising initial investment costs in capital support and/or training.

This may also overcome the difficulties associated with removing a technology from widespread use at a later point in time when a more informed decision can be made. It is also worth noting that the rate of uptake may not only vary by the type of approval but also the social system in which the device is implemented. For example, the different coverage decisions may support varying adoption behaviours, particularly in relation to the diffusion of the medical device in practice (Rogers, 2003).

3.2 Incremental device innovation

Devices frequently undergo product modifications with new methods, upgrades and capabilities. This is partly linked to the desire to get devices to the market as quickly as possible and then follow with improved modifications. It is also linked to the interaction between clinical experience using the device and the device itself. For example, a substantial proportion of incremental innovation comes from end-users suggesting small improvements to manufacturers. An excellent example of this is transcatheter aortic valve implantation (TAVI). Implantable devices are often associated with newer generations with improved batter capacity and lower likelihood of implant failure, e.g. implantable cardioverter-defibrillator (ICD). As a consequence of incremental innovation, clinical efficacy and outcomes are unlikely to have reached a steady state when first evaluated. Therefore, the level of evidence depends critically on the position of the technology in the pathway of its life cycle. This suggests that an evaluation cannot be a one-off activity and an iterative approach may be required with revisions being made to the estimates as more evidence emerges over time (Drummond et al., 2009, Murphy, 2013, Vallejo-Torres et al., 2011). This will have implications for coverage decisions as it may be better to withhold approval until a later point is reached in the technology's life cycle. However, any decision that is made will also interact with the ability to gather additional evidence due to the close link between incremental developments and user experience.

Bayesian approaches to the synthesis of evidence which is evolving over time are particularly flexible for this purpose since they facilitate combining prior information from early evaluations of the technology with more updated evidence as it becomes available (Mantese et al., 2010). An iterative Bayesian approach could be used to address the question of the 'optimal' timing of adoption or reimbursement decisions. The value of continued development will require estimates of expected costs and benefits, an assessment of uncertainty and the need for further evidence at each developmental milestone. These estimates may provide a way of establishing the 'optimum point' to adopt the technology in its life cycle. This is even more important once it is recognised that a decision about the adoption of the technology for widespread use will also interact with the ability to gather more evidence on effectiveness and may affect future commercial developments of the technology. In this case consideration should also be given to how to maximise and speed up the rate of learning since most incremental innovation comes through end-user experience.

Incremental innovation is of benefit to both the healthcare system and the manufacturer. The manufacturer can learn from early use of the technology and to incrementally adapt it according to experience learned. The healthcare system benefits from improvements in net benefit over time. The value of incremental innovation to both sectors at different points in the technology's life cycle may be assessed in a similar manner to that described in Section 3.5.

3.3 Investment and irrecoverable costs

Compared to other technologies, costs associated with medical devices are more likely to become sunk costs if a decision is changed in the future. This is particularly the case for devices that have a large upfront investment cost associated with the capital purchase of equipment, e.g. magnetic resonance imaging (MRI) machine. These upfront costs are usually annuitized and allocated as per-patient costs.

If future changes lead to subsequent withdrawal of coverage of the technology before the end of the lifetime of the equipment, these costs represent irrecoverable costs. The irreversible nature of implantable devices also represents an irrecoverable cost. For example, if the implantable device turns out not to be as effective as initially thought, reversing the decision is less straightforward compared to drugs which can be stopped, often immediately, without incurring any additional costs. There may also be wider organisational implications from introducing a device into clinical practice. This may include training and learning costs and/or infrastructure adjustments such as the requirement for a specialised room (e.g. to limit radiation exposure from a new X-ray machine).

An assessment of the significance of these irrecoverable costs is required before commitment to the costs is made through approval of the technology or AWR. The potential significance depends on i) whether the estimate of cost-effectiveness would alter if a decision were to be revised earlier than anticipated; ii) the likelihood that the decision might be altered; and iii) the size of the irrecoverable costs as a proportion of the total costs of the technology. Figure 3 shows the net health benefit[2] for EECP compared with control (no EECP treatment) for a UK population of current and future patients whose treatment choice is to be informed by the decision. The initial costs of treatment with EECP are high and far in excess of the immediate health benefits resulting in negative net benefit in the early years of treatment. This negative net benefit is offset by positive net benefit in later periods but it is not until 17 years that the health care system recoups the investment. If research reports (or other changes occur) before this breakeven point of 17 years there is a chance that the results of the research will indicate that the technology is not cost-effective and approval is withdrawn. In this case the initial losses are sunk

[2] Net health benefit of an intervention is the health gain expected from the intervention relative to its comparator (incremental effectiveness) minus the health gain forgone elsewhere in other programmes by diverting resources (incremental costs) to the intervention under consideration (incremental costs/threshold of cost-effectiveness). If the net health benefit of the intervention exceeds that of the comparator (i.e. incremental net health benefit is greater than zero), the intervention is considered to represent value compared with the comparator given the threshold of cost-effectiveness.

costs since the additional health gains are not accumulated in a sufficient number of patients to outweigh the upfront investment costs. Even in the absence of capital costs, EECP exhibits irrecoverable costs, as shown in Figure 3 for non-capital expenditure, but the profile of investment is less risky, i.e. breaks even earlier at 6 years. The time horizon for the technology is also an important consideration. If approval is withdrawn before the end of the lifetime of the technology, the potential loss in net benefit is large since the capital costs allocated pro-rata to treating future patients cannot be recovered. In circumstances where there are significant irrecoverable investment costs, OIR avoids the commitment of these costs and preserves the option to approve the technology at a later date when the profile of investment is less risky. In reality, this is more likely to be the case for a single product such as EECP but may be less significant for a family of devices such as stents (e.g. the sunk costs associated with the first introduction of drug-eluting stents in the market were not a major issue since the investment costs associated with training, catheterisation labs, were borne when percutaneous coronary intervention with stents were introduced).

3.4 Dynamic pricing

For medical devices, prices are much more likely to change over time compared with pharmaceuticals. This is largely due to the market entry of new products, iterative incremental developments over time and more flexible procurement for devices (Drummond et al., 2009, Sorenson et al., 2011). The price of the device and/or comparators clearly plays a key role in determining whether the device is expected to be cost-effective. However, the price will also have important implications for uncertainty and the value of additional evidence. In its simplest form, if the price of the technology is reduced there will be greater benefits of early access to the technology and, if the technology is already expected to be of value at the original price, the value of additional evidence will tend to fall. The outcome of a decision about the technology can also directly influence pricing. For example, the price for the comparator technology (i.e. the

one that is not considered to be cost-effective) may be rapidly driven down and it might fall faster than the price of the new technology, changing the implied estimate of cost-effectiveness and level of uncertainty (Drummond et al., 2009).

The price at which a technology would just be expected to be cost-effective is commonly referred to as the value-based price for the technology. It describes the threshold price at the point of indifference between accepting and rejecting the technology (assuming that there is no uncertainty in cost-effectiveness). At this price, the incremental net benefit for the technology is zero; therefore, it represents the maximum price that the health care system can afford to pay for the technology without imposing negative net benefit (Claxton et al., 2008). However, in most circumstances there is uncertainty and a number of other value-based prices exist, each of which represent the threshold price at which the decision option changes. For example, OIR for a technology, which is expected to be cost-effective but with uncertainty (or significant irrecoverable costs), might be revised to Approve with a sufficient price reduction. Similarly, AWR might be revised to Approve if the benefits of early approval now exceed the value of additional evidence.

Figure 4 shows the price thresholds at which the decision changes for EECP based on the maximum net health benefit of the different decision options when research takes 3 years to report. The decision option on the outer envelope of the curves is the one which offers the highest net benefit at each price. Although EECP, on the balance of evidence, is expected to be cost-effective at its current price of £4,347 per patient in the UK, OIR offers greater expected net health benefit at this price. This is because it avoids the commitment of significant irrecoverable costs which cannot be recovered if the results of research indicate that its initial approval should be withdrawn (McKenna and Claxton, 2011). The price to ensure unrestricted access to EECP, i.e. not restricting to OIR, needs to be considerably lower due to the significant irrecoverable opportunity costs. For example, the price threshold for AWR|OIR, i.e. the price

below which AWR offers the highest net benefit and above which OIR offers the best return, is 18% below the effective price of EECP. A price reduction of just over 60% would be required for approval of EECP without conditional access (i.e. price threshold for Approve|AWR).

3.5 Incentives for further research

The threshold price for the different decision options represents the maximum price that the health care system can afford to pay at the time that the medical device is being evaluated and when the results of any subsequent research has not yet been undertaken. Manufacturers may only retain an incentive to conduct the research that is needed if they believe that there are additional benefits which have not been evidenced at the time of the evaluation (Claxton et al., 2012). Consideration of how the value of the technology and the value of additional research might be shared between the manufacturer and the health sector can help to inform who might reasonably be expected to pay for (conduct) the research specified under AWR or OIR.

Table 1a illustrates an example of a technology that is expected to be effective based on the evidence available at the time of the evaluation (i.e. without research the expected change in quality-adjusted life years, ΔQALYs, relative to its comparator technology is positive) but it is not certain to be effective (i.e. under some realisations of uncertainty the technology has a negative impact on health, corresponding to a negative change in quality-adjusted life years, e.g. realisation 3). The price of the technology is fixed at the value-based price so that, on average, the change in net benefit for the technology, ΔNB, is equal to zero. In other words, without further research to resolve the uncertainty in effectiveness, the health system is expected to gain (or lose) nothing from the use of the technology, while the manufacturer is expected to gain a revenue equivalent to 3 QALYs. Here the additional costs of the technology, ΔCosts, are assumed to represent acquisition costs and are expressed in terms of health benefits, i.e. the additional costs are expressed as the health that will be forgone elsewhere in other programmes

by diverting resources to this technology (e.g. additional costs of £60,000 are divided by the threshold of cost-effectiveness of £20,000 per QALY to give 3 QALYs). There is a chance that a decision to approve the technology could result in a loss of 6 QALYs, with a probability of loss equal to one third (see realisation 3 in Table 1a). The health system can avoid this loss by ensuring that further research is conducted under an AWR or OIR decision. The results of research indicate whether the technology would be accepted or rejected for a particular realisation of uncertainty (see Table 1b). The expectation over the possible realisations in Table 1b indicates that both the health system and the manufacturer could gain an additional 2 QALYs from further research.

The question that now remains is who might reasonably be expected to pay for this research? The value of research to the manufacturer is 2 QALYs only if the original decision was either Reject or OIR (see Table 1c). If the original decision was Approve (or AWR) the manufacturer would have no incentive to conduct the research as it could result in a potential loss of 1 QALY (since revenue before research was equivalent to 3 QALYs). Therefore, research only runs a risk to manufacturers that approval is withdrawn under some realisations of uncertainty. In these circumstances, it might only be reasonable to expect the health sector to pay for or conduct the research. It is unlikely that a possible trade could be negotiated between the manufacturer and health sector whereby the manufacturer compensates the health system for not doing the research; because in this case, the manufacturer would only be willing to pay up to 1 QALY in such a trade but the health system would need a minimum of 2 QALYs to forgo the research. If the original decision was OIR, both sectors could potentially share the costs of the research. However, the costs of the research must also fall below 2 QALYs for the research to be of potential value to either the health sector or manufacturer. Determining how the costs and benefits might be shared between sectors and identifying situations when the social and

commercial values do not always match is an important consideration for incentivising further research and innovation in medical devices.

Another important factor relating to incentivising research in medical devices is that other manufacturers can sometimes claim near-equivalence to a device that is already on the market, thereby avoiding the need to collect data on their own device.[3] This also raises the important issue of transferability of evidence and learning across devices. The extent to which evidence from one technology is applicable to another is likely to depend on the class of the device. Here we have only outlined the most straight-forward application of the approach when there is only one device available to treat a given condition. If other devices are available (or likely to become available in the near future) and/or evidence and learning can be inferred from one device to another, then other policies will be required. For example, if the first device to treat the condition is undergoing OIR or AWR and another device is deemed to be near equivalent, it would make sense to include that device in the existing OIR/AWR scheme. This would both speed up the accumulation of data and also provide further information on whether the near-equivalence assumption is justified. Furthermore, in situations whether the manufacturers were being asked to contribute financially to the OIR/AWR scheme, it would enable some cost-sharing between the two manufacturers.

Assessing the value of the technology and the future value of research for medical devices is further complicated by the immediacy of competitive products and the speed of partial obsolescence as technologies evolve over time. This makes it difficult to assess the timescale over which additional information generated by research is likely to be valuable for. Some assessment may be possible based on historical evidence and expert judgments about future

[3] This is the basis of the US Food and Drug Administration (FDA) 510(k) notification scheme, discussed in the paper by Ciani et al in this journal supplement.

innovations in the area and other evaluative research that may be planned or underway (e.g. through registries, expert elicitation and historic evidence of diffusion).

4. DISCUSSION

This paper has set out the conceptual issues that require consideration when dealing with uncertainty and the value of further research in relation to medical devices. The paper has focussed on the principles and assessments that are required rather than the methods of analysis. This distinction between the assessments required and the methods of analysis recognises that how the assessments might be informed is likely to differ across different types of health care systems and jurisdictions. The methods of analysis are likely to be more straightforward to implement than the principles themselves (e.g. using standard cost-effectiveness analysis, probabilistic sensitivity analysis, value of information analysis and statistical assessment of learning curve data). Even if these concepts are not implemented through formal methods of analysis, some consideration should be given to them as part of the deliberation process when making decisions about a technology. For example, even in health systems where there is an absence of firm budget constraints or where economic analysis is not explicitly incorporated into the decision making process, the same principles can be applied (Claxton et al., 2015). The key considerations are outlined in this work but we do not presuppose how different aspects of health gained and forgone might be measured and valued as this is going to differ across different health care systems.

The development of the framework is intended to improve transparency in communicating the considerations that play an important role in the adoption of innovative clinically and cost-effective medical technologies and to identify when research might reasonably be expected to be provided by sponsors. This is important given the growing interest among both payers and producers of medical products for agreements that involve some form of 'risk-sharing' (Garrison

et al., 2013). An example is the recent NHS England Commissioning through Evaluation programme, which is for devices and procedures which have typically less evidence available to support the development of a full commissioning policy. These programmes allow patients early access to promising new treatments whilst new data is collected. Such programmes should consider the issues raised in this paper, in particular, those relating to irrecoverable costs. Many health care systems are now adopting 'coverage with evidence development (CED)' schemes of a similar nature to the one proposed here. For example, the French have introduced a CED scheme under Article L. 165-1-1 of the French Social Security Code, Germany has introduced a CED scheme under Section 137e SGB V run by the Federal Joint Committee, while the US has more than 20 documented performance-based risk-sharing arrangements (PBRSA) including CED (Garrison et al., 2013, Martelli and van den Brink, 2014). All of these schemes are aimed at narrowing the gap between getting innovative medical devices into practice and funding studies for the collection of valuable evidence. CED schemes are intended to contribute to improved collaboration between health care systems and manufacturers to ensure value to all stakeholders. If these schemes are to work effectively then improved collaboration at all stages of the process is required. One of the challenges for many countries is the separation between decision making bodies responsible for making reimbursement decisions from research funding bodies responsible for making research decisions. This makes it all the more important that manufacturers retain an incentive to fund research. In this work we have highlighted the circumstances when manufacturers have an incentive to either price accordingly to achieve approval, conduct research at an earlier stage so that the need for additional evidence is eliminated, or accept restricted access until the results of research become known. It seems important that some consideration should be given to the likely prospects that research will be conducted and who should reasonably be expected to pay for it, i.e. whether it is a priority for public funding or for manufacturers to undertake.

In conclusion, CED schemes for medical devices offer great potential for getting timely access to new innovative technologies and the collection of valuable evidence to reduce uncertainty.

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Table 1: An illustration of the value of further research to the manufacturer and health sector

a.

Without research			
Realisation of uncertainty	**ΔCosts**	**ΔQALYs**	**ΔNB**
1	3	9	6
2	3	3	0
3	3	-3	-6
Expectation	**3**	**3**	**0**

b.

With research		
Decision	**ΔNB**	**Revenue**
Accept	6	3
Accept	0	3
Reject	0	0
Expectation	**2**	**2**

c.

	Payoff	
Decision option	**Health sector**	**Manufacturer**
Approve	0	3
Reject	0	0
With research	2	2
Value of research	**2**	**– 1 (Approve/AWR) 2 (Reject/OIR)**

QALYs, quality-adjusted life years; NB, net benefit;
ΔCosts, additional costs for new technology relative to comparator, expressed in terms of equivalent QALYs (see footnote above on net health benefit);
ΔQALYs, incremental quality-adjusted life years for new technology relative to comparator;
ΔNB, incremental net benefit for new technology relative to comparator, expressed in terms of equivalent QALYs (i.e. difference between ΔQALYs and ΔCosts)

Figure 1: Framework for characterising uncertainty in medical devices.

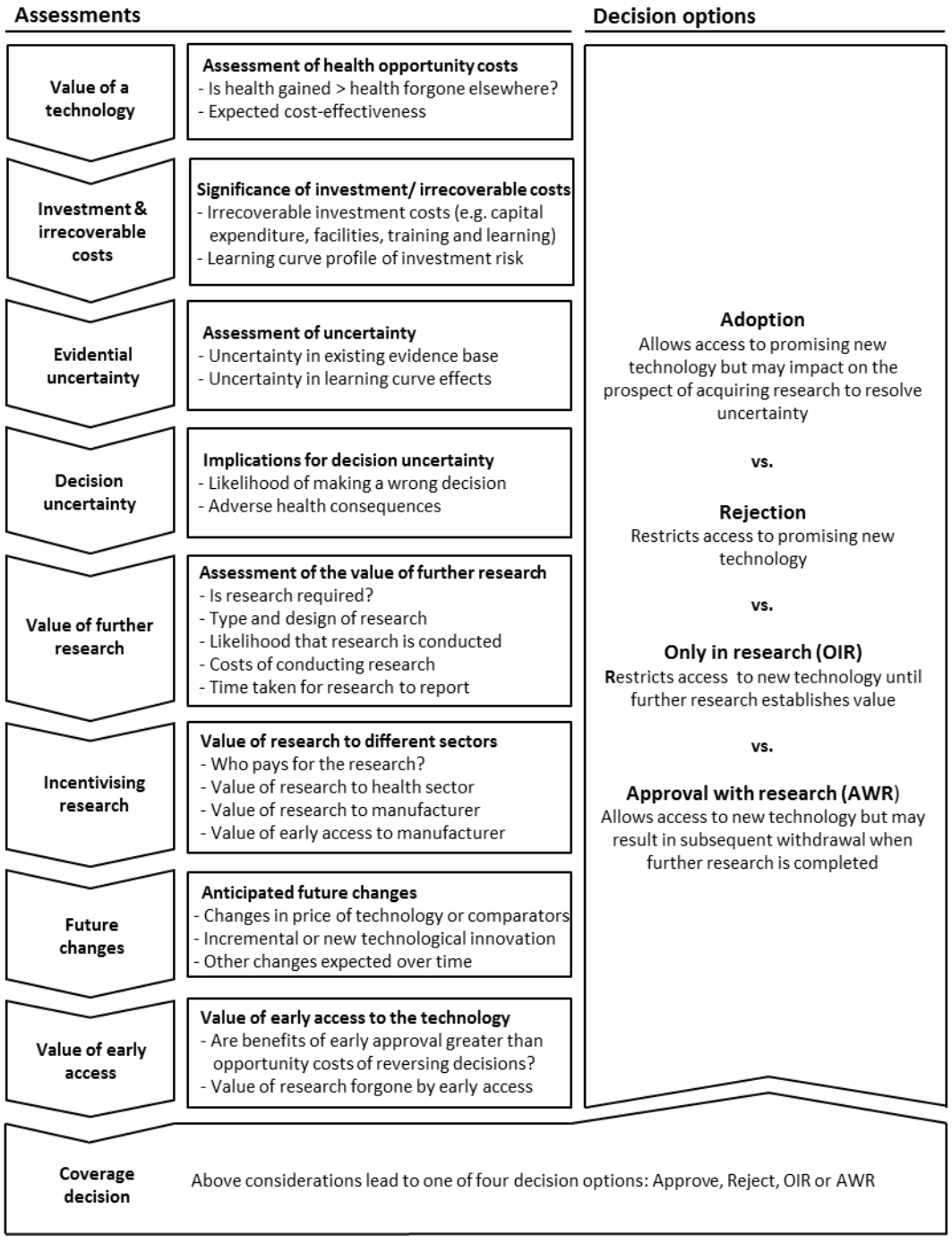

Figure 2: An illustration of coverage decisions at different points on the learning curve

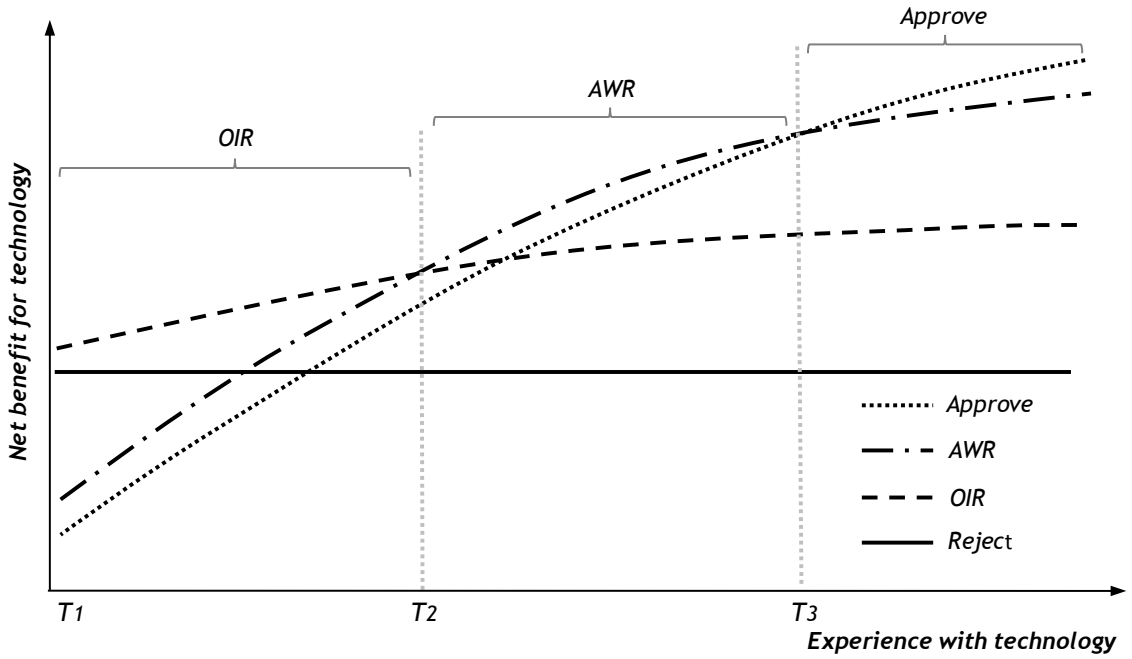

Figure 3: Cumulative incremental net benefit of EECP compared with control for the population of current and future patients whose treatment choice is to be informed by the decision

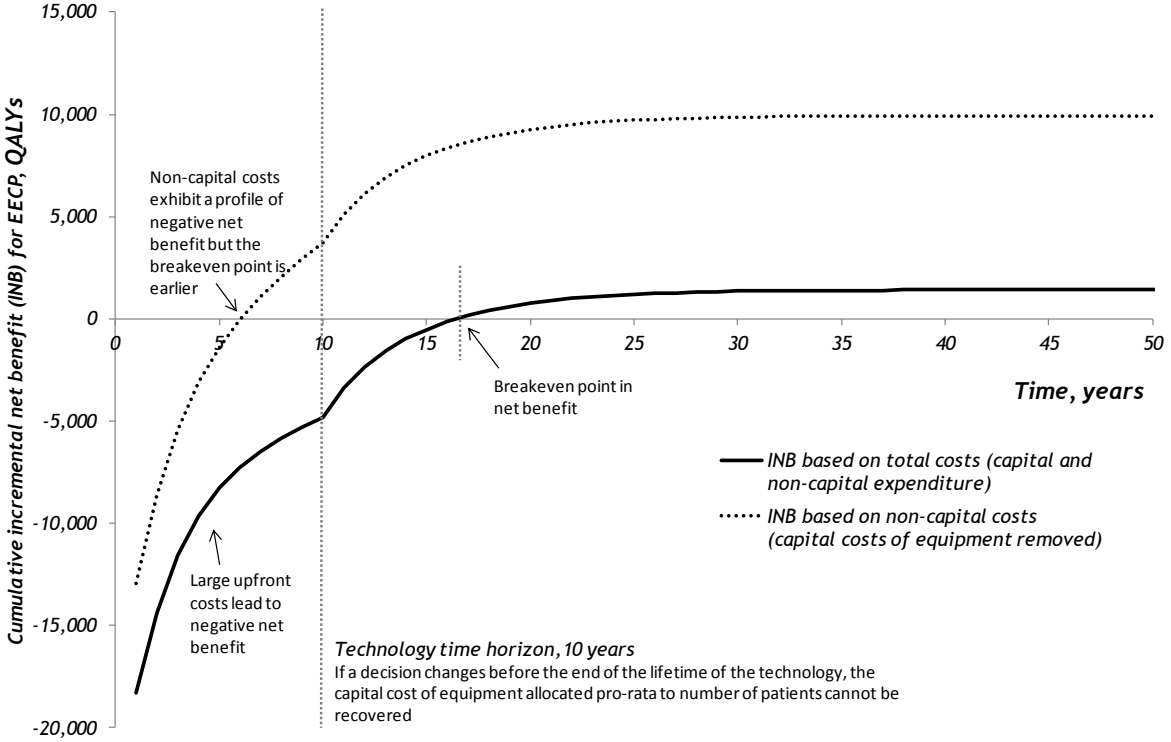

Figure 4: Price thresholds based on the maximum net health benefit of different decision options for EECP when research takes 3 years to report. Net health benefit is expressed at a population level for current and future patients whose treatment choice is to be informed by the decision