ONLY IN RESEARCH WORKSHOP

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BRIEFING DOCUMENTS

Informing a decision framework for when NICE should recommend the use of health technologies only in the context of an appropriately designed programme of evidence development.

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1 Introduction and overview

NICE is increasingly making decisions about health technologies close to licence through the single technology assessment (STA) process. Inevitably these decisions are being made when the evidence base to support these technologies is least mature and when there may be substantial uncertainty surrounding their cost-effectiveness, including their effectiveness and potential for harms. In these circumstances further evidence maybe particularly valuable as it would lead to better decisions which improve patient outcome and/or reduce resource costs. However, a decision to approve a technology will often have an impact on the prospects of acquiring further evidence to support its use. This is because the incentives on sponsors (manufacturers) to conduct research, once positive guidance has been issued, are limited. Also the clinical community is unlikely to regard further randomised controlled trials (RCTs) to be ethical once positive guidance provides mandatory access. Therefore, the decision to approve a technology should account for both the potential benefits of access to a cost-effective technology, and the potential costs to future NHS patients in terms of the value of evidence that maybe forgone by early adoption. The general issue of balancing the value of evidence about the performance of a technology and the value of access to a technology can be seen as central to a number of policy questions. Establishing the key principles of what assessments are needed for 'only in research' (OIR) or 'approval with research' (AWR) recommendations, as well as how these assessments should be made, will enable them to be addressed in an explicit and transparent manner by the Institute.

The MRC methodology programme recently funded the Universities of York and Brunel to undertake research to help inform when NICE should recommend the use of health technologies only in the context of an appropriately designed programme of evidence development. The aims of this research are to:

i) Establish the key principles of what assessments are needed to inform an OIR or AWR recommendation.

ii) Evaluate previous NICE guidance where OIR or AWR recommendations were either made or considered, and examine the extent to which the key principles from i) are evident.

iii) Establish what impact OIR and AWR decisions may have had on publically funded and sponsored research.

iv) Evaluate a range of alternative options to establish the criteria, additional information and/or analyses which could be made available to help the assessments needed to inform an OIR or AWR recommendation.

v) Provide a series of final recommendations, with the involvement of key stakeholders, establishing both the key principles and associated criteria that might guide OIR and AWR recommendations, identifying what, if any, additional information or analyses might be included

in the TA process and how such recommendations might be more likely to be implemented through publically funded and sponsored research.

The relevance of this work to NICE has been evaluated through a series of two workshops involving key stakeholders. Establishing the key principles of what assessments are needed to inform OIR or AWR recommendation requires: a critical review of a diverse literature on principles and policy and previous NICE guidance; the development of a coherent conceptual framework; and consideration of whether such principles conflict with established ethical principles and the social value judgments adopted by NICE.

The first workshop took place in September 2010 and considered four main topics:

i) The relevance to NICE of existing literature.
ii) Whether the key principles and assessment that have been identified provide useful guidance on when OIR and AWR might be considered.
iii) The insights from a detailed review of previous NICE guidance.
iv) Whether the proposed methods to inform assessment and criteria to select case studies are suitable.

Relevant summaries and key issues were provided in the form of briefing documents which covered these four topics. These documents formed the basis for the workshop presentations, related group discussions and a summary of feedback from participants (see: http://www.york.ac.uk/che/research/teams/teehta/workshops/only-in-research-workshop/)
The primary output of this workshop was a set of principles and explicit criteria (a sequence of assessments and decisions) to support OIR and AWR recommendations which have subsequently been applied to a series of case studies. Each case study examines how the assessments might be made based on the type of evidence and analysis currently provided in NICE technology appraisals and how these assessments might be better informed with a range of additional information and/or analyses.

This second workshop in June 2011 will consider:

i) Whether the revised algorithm of assessments and the associated check list has identified the key judgements that need to be made when considering OIR and AWR guidance.
ii) Based on the application of this check list to the series of case studies, can such assessments be made based on existing information and analysis provided to NICE and in what circumstances could additional information and/or analysis be useful?
iii) What implications this more explicit assessment of OIR and AWR might have for policy (e.g. NICE guidance and drug pricing), the process of appraisal (e.g. greater involvement of

research commissioners) and methods of appraisal (e.g. should additional information, evidence and analysis be required).

The output of this workshop will be a list of possibilities that NICE might choose to take forward in the next revision of the Guide to the Methods of Technology Appraisal and how this might inform the formulation of guidance in the other NICE programmes. It might also suggest how a consideration of uncertainty and the need for evidence might influence value based pricing and the impact of patient access schemes on OIR and AWR guidance.

2 What assessments are needed?

Since an important objective of the NHS is to improve health outcomes across the population is serves, a technology can be regarded as valuable if its approval is expected to increase overall population health. The resources available to the NHS must be regarded as fixed (certainly by NICE), so it is not sufficient to establish that a technology is more effective (the health benefits compensate for any potential harms) than the alternative interventions available, because approving a more costly technology will displace other health care activities that would have otherwise generated improvements in health for other patients. Therefore, even if a technology is expected to be more effective, the health gained must be compared to the health expected to be forgone elsewhere as a consequence of additional NHS costs, i.e. a cost-effective technology will offer positive *net health effects*. A social objective of health improvement and an ethical principle that all health impacts are of equal significance, whether they accrue to those who might benefit from the technology or other NHS patients, is an established starting point for the NICE appraisal process (see Section 2.3).

An assessment of expected cost-effectiveness or net health effects relies on evidence about effectiveness, impact on long-term overall health and potential harms, as well as the costs which fall on the NHS budget together with some assessment of what health is likely to be forgone as a consequence (the cost-effectiveness threshold). Such assessments are inevitably uncertain and without sufficient and good quality evidence, subsequent decisions about the use of technologies will also be uncertain and there will be a chance that the resources committed by the approval of a new technology may be wasted if the expected positive net health effects are not realised. Equally, rejecting a new technology will risk failing to provide access to a valuable intervention if the net health effects prove to be greater than expected. Therefore, if the social objective is to improve overall health for *both* current and future patients then the need for and value of additional evidence is an important consideration when making decisions about the use of technologies.

This is even more critical once it is recognised that the approval of a technology for widespread use might reduce the prospects of conducting the type of research that would provide the evidence needed. In these circumstances there will be a trade-off between the net health effects for current patients from early access to a cost-effective technology and the health benefits for future patients from withholding approval until valuable research has been conducted. A key ethical question arising from this trade-off is whether the health impacts for future patients should be considered and regarded as of similar significance to impacts on current patients (see Section 2.3).

Since publically funded research also consumes valuable resources which could have been devoted to patient care, or other more valuable research priorities, there are a number of trade-offs which must be made. In making these trade-offs consideration also needs to be given to uncertain events in the near

or distant future, which may change the value of the technology and the need for evidence. In addition, implementing a decision to approve a new technology is, in general, not a costless activity and may commit resources which cannot subsequently be recovered if the guidance changes in the future. For example, there may be costs associated with implementing guidance, training health care professionals, or other investment costs associated with equipment and facilities. The irrecoverable nature of these costs can have particular influence on a decision to approve a technology if new research is likely to report or other events may occur in the future (e.g. launch of new technologies or change in the prices of existing technologies).

The primary purpose of this briefing document is to provide a non-technical exposition of the conceptual framework developed more formally in the technical Appendix to the main report, which identifies the key principles and assessments which are needed when considering both approval and research decisions. Within the remainder of this section, Section 2.1 outlines the key principles and the different types of assessment needed and how each sequence might lead to different categories of guidance. Section 2.2 examines how guidance might change if there are changes in the effective price of the technology or evidence. Section 2.3 highlights the social values and ethical principles associated with OIR and AWR. Importantly, within this section we do not presuppose how the assessments ought to be made since there are a range of different types of additional information, evidence and methods of analysis which might be useful. These alternatives are outlined in Section 3 of this briefing document where they are more fully explored and evaluated through four case studies.

2.1 Key principles and assessments needed

The key principles and assessments fall into four broad areas:

i) Expected cost-effectiveness and population net health effects (including benefits, harms and NHS costs).

ii) The need for evidence.

iii) Whether there are sources of uncertainty which cannot be resolved by research but only over time.

iv) Whether there are significant costs which once committed cannot be recovered once the technology is approved.

Guidance will depend on the combined effect of all these assessments because they influence whether the benefits of research are likely to exceed the costs and whether any benefits of early approval are greater than withholding approval until additional research is conducted or other sources of uncertainties are resolved.

This can be complex since these different considerations interact. For example, the effect of irrecoverable costs will depend on the need for additional research and will also influence whether

research is worthwhile. The sequence of assessments, decisions and resulting guidance can be represented by a flow chart or algorithm. Although such a representation is an inevitable simplification of the necessary trade-offs it helps to: i) identify how different guidance might be arrived at; ii) indicate the order in which assessments might be made; iii) identify how similar guidance might be arrived at through different combinations of considerations; and iv) identify how guidance might change (e.g., following a reduction in price), and when it might be reviewed and decisions reconsidered. The complete algorithm is complex (reported in Appendix A, Parts I to III for completeness), representing the sequences of assessments and associated decisions, each leading to a particular category and type of guidance. However, the key decision points in the algorithm, reflecting the main assessments and judgments required during appraisal, can be represented as a simple 7 point check list (see Section 3.1).

Four broad categories of guidance are represented within the algorithm and include 'Approve', 'AWR', 'OIR' and 'Reject'. Each of the categories is further subdivided and numbered to indicate the different types of apparently similar guidance that could arise from different considerations. 'Delay' is not considered a particularly useful category since NICE always has the opportunity to revise its guidance, i.e., a decision to 'Reject' can always be revised but it is only with hindsight that 'Reject' might appear to be delayed 'Approval'. The distinction made between assessment and decision reflects the NICE appraisal process; first critically evaluate the information, evidence and analysis (an assessment), which can then assist the judgements (decisions) which are required in appraisal when formulating guidance.

2.1.1 Technologies without significant irrecoverable costs

Some element of cost which once committed by approval cannot be subsequently recovered is almost always present. However, the significance of these types of costs depends on their scale relative to expected population net health effects associated with the technology (see Section 2.1.2 and 3.3.2). In this section we consider the relatively simple sequence of assessments and decisions which lead to guidance for those technologies that are not judged to have 'significant' irrecoverable costs.

i) Technologies expected to be cost-effective

The sequence of assessments and decisions, which ultimately leads to guidance, starts with cost-effectiveness and the expected impact on population net health effects (see Figure 2.1). This is an assessment of expected cost-effectiveness (i.e. 'on average') based on the balance of the evidence and analyses currently available which includes an assessment of effectiveness, potential for harms as well as NHS costs (see the NICE Guide to Methods of Technology Assessment). Any assessment may be very uncertain with the scale and consequences of uncertainty assessed subsequently in the need for additional evidence. The sequence of assessments and decisions (judgements required) is illustrated in Figure 2.1. This figure demonstrates that an assessment of cost-effectiveness is only a first step and does not itself, inevitably lead to particular category of guidance. For example, a technology which

might on balance be expected to be cost-effective might nevertheless receive OIR guidance if the additional evidence that is needed cannot be acquired if the technology is approved.

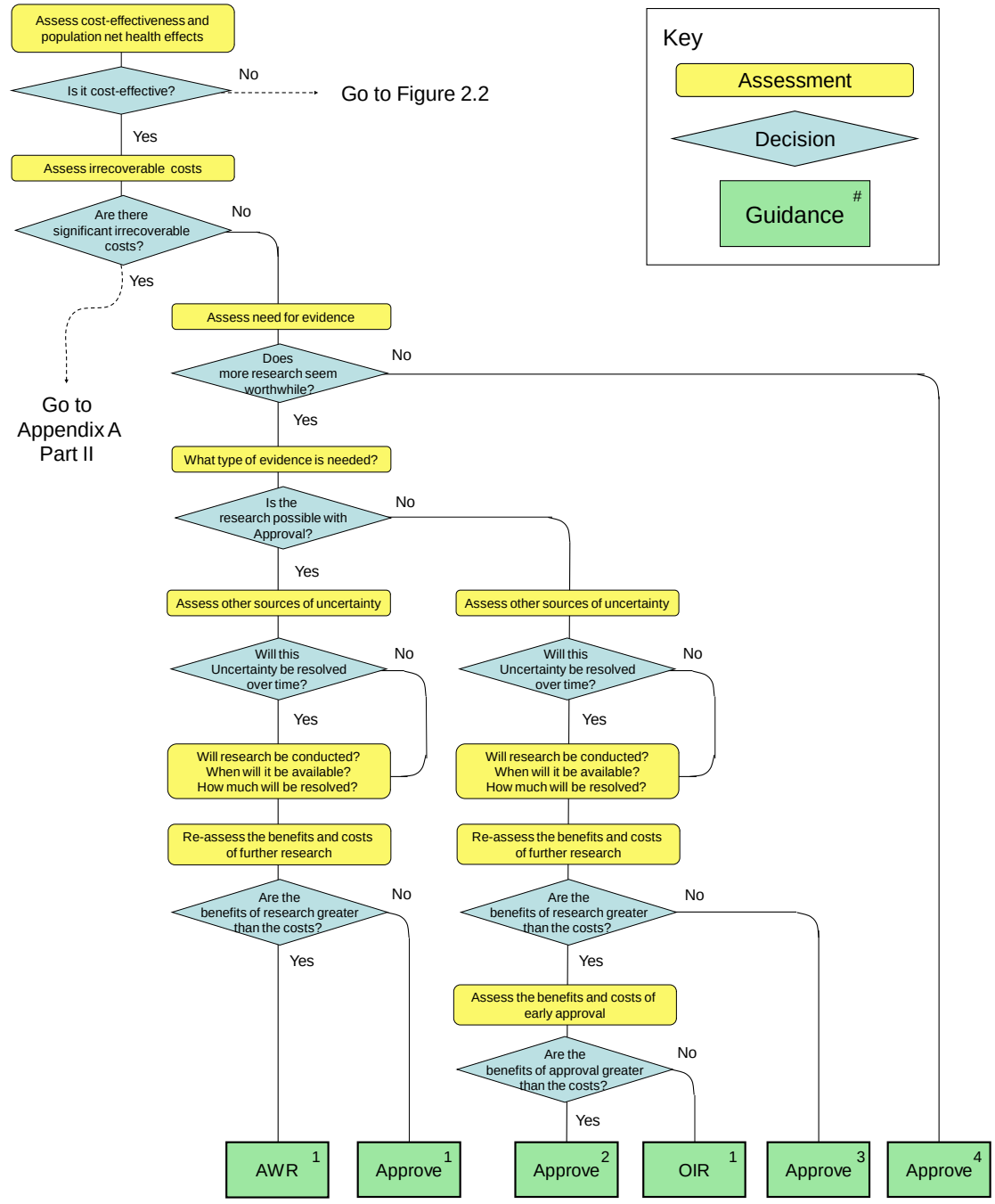
Need for evidence

Some initial assessment of the need for further evidence and a decision about whether further research might be potentially worthwhile is important because a 'No' at this point can avoid further and complex assessments, e.g. a technology offering substantial and well-evidenced health benefits at modest additional cost is likely to exhibit little uncertainty about whether the expected population net health effects are positive. In these circumstances, further research may not even be potentially worthwhile (i.e. the opportunity costs of conducting this research exceed its potential value) so guidance to approve could be issued on the basis of existing evidence and at the current price of the technology (e.g. Approve [4] in Figure 2.1). If additional evidence is needed and further research might be worthwhile, then further assessments and decisions are required before guidance can be issued. Critically, some assessment is required of the type of evidence that is needed and whether or not the type of research required to provide it can be conducted if approval is granted.

Research is possible with approval

If research is possible with approval, some further assessment of the long term benefits of research is required, including: i) the likelihood that the type of research needed will be commissioned by research funders or conducted by manufacturers; ii) how long until such research will recruit and report and iii) how much of the uncertainty might be resolved by the type of research which is likely to be undertaken. An assessment of other sources of uncertainty which will only resolve over time is also needed (e.g. changes in prices or the launch of new technologies). These sources of uncertainty will influence the future benefits of research that could be undertaken as part of AWR. For example, even if the current benefits of research, which might be very likely to be undertaken are considerable, if the price of the technology is likely to fall significantly before or shortly after the research reports (or if future innovation makes the current technology obsolete) then the future benefits, once the research reports, might be very limited. In these circumstances it might be better to approve (rather than AWR) and reconsider whether and what type of research is needed at a later date once these uncertainties have resolved. The judgement of whether the long term benefits of research are likely to exceed its expected costs determines guidance, with AWR [1] and Approve [1] in Figure 2.1 dependent on 'Yes' and 'No' respectively.

Figure 2.1 Technologies expected to be cost-effective



Research is not possible with approval

The type of research needed may not be possible once a technology is approved for widespread NHS use, e.g. randomised clinical trials (RCTs) may not be possible once the technology is approved (due to ethical concerns, recruitment problems and limited incentives for manufacturers). In these circumstances the expected benefits of approval for current patients must be balanced against the benefits to future patients of withholding approval to allow the research to be conducted. Initially, the same assessment of the long term value of the type of research that might be conducted if approval is

withheld is still required. Similarly, the impact of other sources of uncertainty on the longer term benefits of research is also needed. If the benefits of research are judged to be less than the costs (i.e. research is not worthwhile anyway), the technology can be approved based on current evidence and prices (Approve [3] in Figure 2.1). However, judging that research is worthwhile at this point is not sufficient for OIR guidance. In addition, an assessment of whether the benefits of early approval (expected population net benefits for current patients) are greater than the opportunity costs (the net benefit of the evidence likely to be forgone for future patients as a consequence of approval) is required. If the expected benefits of early approval are judged to be less than the opportunity costs (the expected net benefits of research forgone by approval) then OIR guidance would be appropriate (OIR [1] in Figure 2.1). Alternatively, if the expected benefits of early access for current patients are judged to be greater than the opportunity costs for future patients, then approval would be appropriate (Approve [2] in Figure 2.1). All these assessments, including the benefits of early approval and the value of evidence will change if the effective price of the technology is reduced (see section 2.2.1).

ii) Technologies not expected to be cost-effective

A technology which is not expected to be cost-effective will, on balance, impose negative population net health effects if it is approved. These negative net health effects can arise because the technology may not be effective, the potential for harm exceeds any benefits and/or the additional NHS costs do not justify the magnitude of the expected health benefits offered. In these circumstances Approval can be ruled out, but which of the other categories of Guidance might be appropriate will depend on subsequent assessments and decisions (see Figure 2.2).

Need for evidence

Any assessment will be uncertain, so it remains possible that a technology which is not expected to be cost-effective on the balance of existing evidence might offer positive net health effects. Therefore, the scale and consequences of this uncertainty must be considered to make an initial assessment of the need for additional evidence and whether additional research might, in principle, be worthwhile. If it is not, then the technology can be rejected based on existing evidence and its current price (Reject [4] in Figure 2.2). Alternatively, if further research might be worthwhile then an additional assessment is required of whether the type of evidence and research that is needed can be conducted without approval.

Research is possible without approval

Generally, most types of research (including RCTs) will be possible without approval. Further assessment of the longer term benefits of the type of research which is likely to be conducted, and when it might report is required, including the impact of other sources of uncertainty which will resolve over time. If, following this re-assessment, the expected benefits of research are judged to exceed the associated costs then OIR would be appropriate (OIR [2] in Figure 2.2). Alternatively, if the costs of

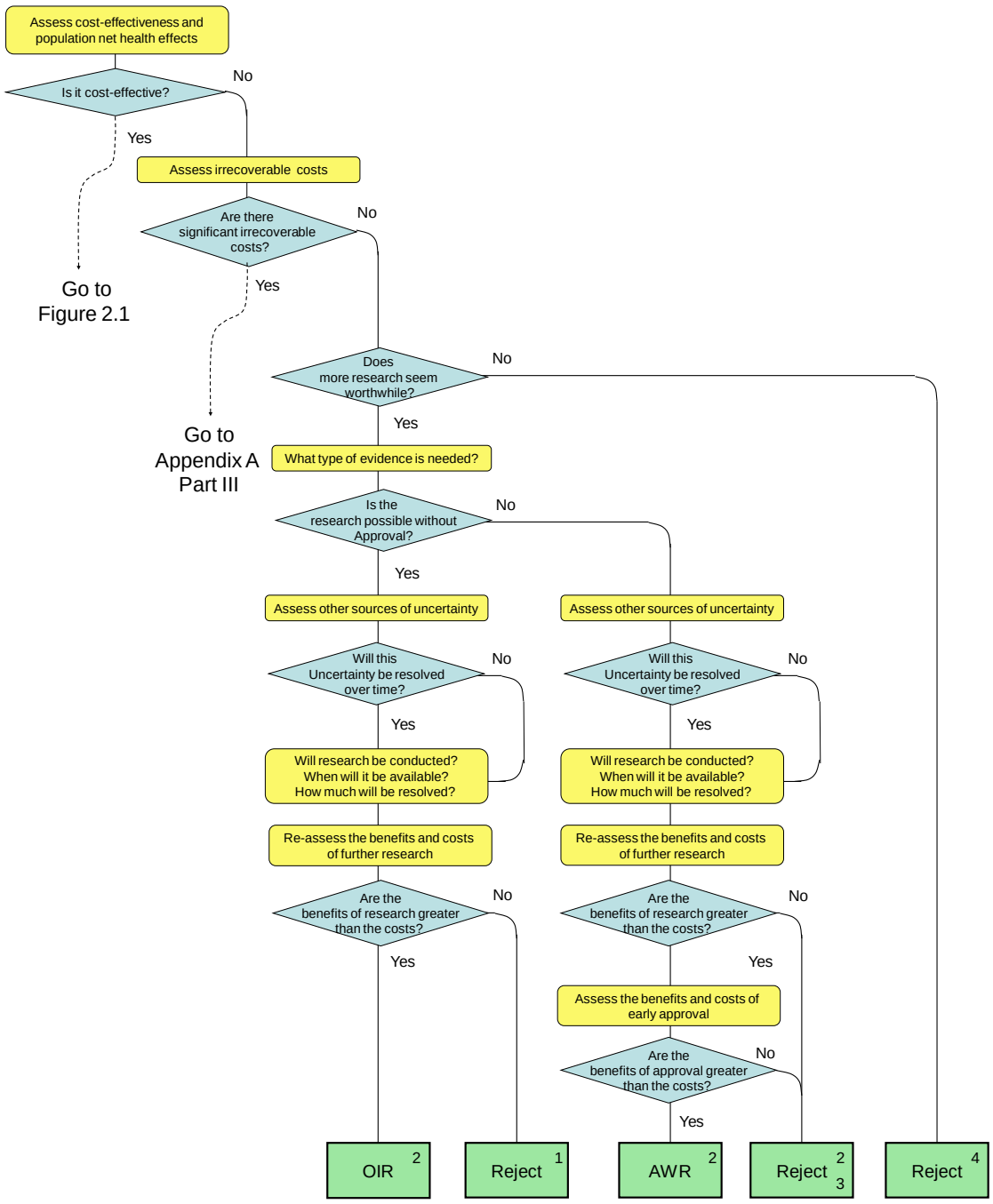
research are likely to exceed the longer term expected benefits then the technology should be rejected at this point (Reject [1] in Figure 2.2).

Research is not possible without approval

In some circumstances it is possible that certain types of evidence might only be acquired, or be more easily acquired (more quickly and at lower cost), once a technology is in widespread use, e.g., linking surrogates (specific to the technology) to longer term health outcomes, longer term and/or rare adverse events, or greater understanding of learning and incremental improvements in the use of a technology. In this less common situation, where the type of research needed is not possible (or is significantly more costly) without approval, the same assessment of the longer term benefits of research is required. If further research is judged not to be worthwhile following this re-assessment, the technology can be rejected (Reject [2] in Figure 2.2). Alternatively, if research is judged worthwhile an additional assessment of whether the benefits of approval exceed the costs is required. In this case, approval, which would make the research possible, will impose opportunity costs (negative expected population net health effects of widespread use of a cost-ineffective technology). The key question is whether the net benefits of the research exceed these opportunity costs. If they don't, then the technology should be rejected even though research, had it been possible without approval, would have been worthwhile (Reject [3] in Figure 2.2). Alternatively, if the net benefits of research more than offset the opportunity costs then AWR would be appropriate even though the technology is expected to be cost-ineffective (AWR [2] in Figure 2.2).

Therefore, AWR guidance for technologies not expected to be cost-effective is certainly possible but only appropriate in certain circumstances, where: i) the type of research needed is not possible without approval; ii) the long term benefits of the research are likely to exceed the expected costs and iii) the additional net benefits of such research exceeds the opportunity costs of approving a cost-ineffective technology. More commonly, research might be possible but more costly without approval. In these circumstances, AWR guidance could only be considered if the additional costs of research without approval exceed the opportunity costs of approving a cost-ineffective technology.

Figure 2.2 Technologies not expected to be cost-effective



2.1.2 Technologies with significant irrecoverable costs

Irrecoverable costs are those which once committed cannot be recovered should guidance be revised at a later date. In most NICE appraisals these are included in the expected (per patient) cost of a technology. However, rarely is their potential additional impact explored when future events, such as research reporting or other sources of uncertainty resolving, might mean that guidance will be revised in the near or distant future. These types of cost are commonly thought of as capital expenditure on equipment or facilities which have a long life expectancy, but they might include the resources required

to implement guidance, to train staff to use a new health technology or a period of 'learning' where health outcomes are lower. Although these costs are incurred 'up-front', they tend to be included in NICE assessments as if they are paid per patient treated over the life time of the equipment or facility. This common assumption will have no effect, so long as guidance is certain not to change during this period. However, if it is possible that initial approval might be withdrawn at some point, then, although future patients will no longer use the technology, these upfront costs cannot be recovered (see Section 3.3.2). Therefore, the possibility that Approve or AWR might be reconsidered after research reports, for example, and the impact this would have on expected costs needs to be considered before committing these types of capital costs, i.e. it may be better to withhold approval and avoid commitment of resources until the uncertainty is resolved.

However, irrecoverable costs may be much more common. Even in the absence of capital investment in equipment and facilities, most new technologies offer a 'risky investment profile' for each patent treated. Generally they impose initial per patient treatment costs which exceed the immediate health benefits (see Section 3.3.1). These irrecoverable treatment costs are only offset by cost savings and health benefits in the longer run, i.e. initially negative net health effects (losses) are only gradually compensated by later positive ones (gains), so a cost-effective technology may only be expected to breakeven (when accumulated 'gains' compensate earlier 'losses') after some considerable time. If guidance is likely to change before it 'breaks even' the initial losses will not be compensated by later gains and the expected additional net health effects will not be realised. This type of 'investment profile' becomes significant if the decision to treat a presenting patient can be delayed until uncertainty is resolved (e.g. research reports or other events occur) because the commitment of irrecoverable opportunity costs (negative net health effects) can be avoided (see Section 3.3.2). In these circumstances, OIR or reject avoids this commitment and preserves the option to approve the technology at a later date when its purchase by the NHS represents a 'less risky investment'.

Although aspects of irrecoverable cost are almost always present, their potential significance also depends on their scale relative to expected population net health effects of the technology. Critically, their impact depends on the chance that guidance will be revised in the near or distant future due to new evidence becoming available or changes in prices and technologies. The full algorithm becomes more complex (see Parts II and III of the Algorithm in Appendix A), so here we focus on the key differences from section 2.1.1.

The presence of irrecoverable costs associated with a technology that is expected to be cost-effective will only influence guidance and be regarded as 'significant' if there are future events (research reporting or other sources of uncertainty resolving) which might change guidance. For example, if research is possible with approval and is expected to be worthwhile, AWR does not necessarily follow as previously (e.g. see AWR [1] in Figure 2.1) because the impact of irrecoverable cost must also be

considered. Now OIR may be more appropriate than AWR (e.g. the choice between OIR [4] or AWR [4] in Part II), even though the research would be possible with approval, because OIR avoids the commitment of irrecoverable costs until the results of research are known. This is especially so when there are also other sources of uncertainty which might resolve while the research is being conducted in so far as they increase the chance that guidance will be revised (e.g. OIR [3] or AWR [3] in Part II).

If research is not possible with approval, but is expected to be worthwhile, then OIR will be appropriate if the opportunity costs of early approval are judged to exceed the benefits (e.g. OIR [6] rather than Approve [9] in Part II). These opportunity costs will now also include the impact of irrecoverable costs when guidance might be changed as well as the value of evidence that will be forgone by early approval. Therefore, irrecoverable costs will tend to make OIR rather than approval more likely, particularly when there are other sources of uncertainty which might resolve while the research is being conducted (e.g. OIR [5] rather than Approve [7] in Part II).

If research is not judged worthwhile, approval does not necessarily follow as previously (e.g. Approve [1, 3, 4] in Part I). Now the technology should only be approved if there are no other sources of uncertainty. If there are other sources of uncertainty, then an assessment of the benefits and costs of early approval is needed which takes account of irrecoverable costs and the risk that guidance might change in the future. Therefore, reject rather than approval is possible, even though a technology is expected to be cost-effective, because the decision to commit the investment costs can be reconsidered once the other sources of uncertainty have resolved (e.g. Reject [5, 6] in Part II).

ii) Technologies not expected to be cost-effective

The presence of irrecoverable costs for technologies not expected to be cost-effective does not change the categories of guidance, or how they might be arrived at. However, it does mean that reject is more likely to be appropriate than AWR when research is not possible without approval (see AWR [5] in Part III). This is because a decision to reject, although it may be revised to approve, generally does not commit irrecoverable costs. Although there may be resources associated with making sure subsequent approval is properly implemented, these costs are properly considered as an investment cost associated with approval (rather than a reversal cost of reject). There may be circumstances when implementing guidance to reject a technology also requires resources if it has already diffused into clinical practice. If these are significant they should be taken into account in the same way as other investment costs, tending to make AWR more likely to be appropriate.

2.1.3 Different types of guidance

Each sequence of assessment and decision, leads to different categories and 'types' of guidance for technologies with differing characteristics, indications and target populations. The different 'types' of guidance illustrates how similar guidance might be arrived at in different ways, helping to identify the

particular combination of considerations which might underpin guidance, contributing to the transparency of the appraisal process. The possible categories and types of guidance are summarised in Table 2.1 where the numbers in the body of the table refer to the numbered guidance in Figures 2.1 and 2.2 and Appendix A.

The categories of guidance available to NICE have wider application than is reflected in previous guidance (see previous briefing document). For example, there are 5 different types of OIR which may be appropriate when a technology is expected to be cost-effective. Indeed, OIR maybe appropriate even when research is possible with approval if there are significant irrecoverable costs. AWR can only be considered when research is possible with approval but Reject remains a possibility even for a cost-effective technology if there are irrecoverable costs. Therefore, the full range of categories of guidance (OIR and Reject as well as AWR and Approve) ought to be considered for technologies, which on the balance of existing evidence and current prices, are expected to be cost-effective.

Table 2.1a **Different types of guidance** (technologies expected to be cost-effective)

	No significant irrecoverable costs					Significant irrecoverable costs				
Research	Not needed	Possible with approval		Not possible with approval		Not needed	Possible with approval		Not possible with approval	
		Benefits > costs	Benefits < costs	Benefits > costs	Benefits < costs		Benefits > costs	Benefits < costs	Benefits > costs	Benefits < costs
Approve (12)	4		1	2	3	11, 12		5,6	7, 9	8, 10
AWR (3)		1					3,4			
OIR (5)				1			3,4		5,6	
Reject (3)						7		5		6

Table 2.1b **Different types of guidance** (technologies not expected to be cost-effective)

	No significant irrecoverable costs					Significant irrecoverable costs				
Research	Not needed	Possible without approval		Not possible without approval		Not needed	Possible without approval		Not possible without approval	
		Benefits > costs	Benefits < costs	Benefits > costs	Benefits < costs		Benefits > costs	Benefits < costs	Benefits > costs	Benefits < costs
Approve (0)										
AWR (2)				2					5	
OIR (2)		2					7			
Reject (8)	4		1	2	3	11		8	9	10

It is only approval that can be ruled out if a technology is not expected to be cost-effective, i.e., cost-effectiveness is necessary but not sufficient for approval but lack of cost-effectiveness is neither necessary nor sufficient for rejection. Although likely to be uncommon, there are circumstances when AWR maybe appropriate even when a technology is not expected to be cost effective. More commonly the choice of appropriate guidance will be either Reject or OIR. Importantly, which category of guidance

will be appropriate only partly depends on an assessment of expected cost-effectiveness and hence this assessment should only be regarded as an initial step in formulating guidance. Guidance will depend on a number of other key assessments which include: i) the need for evidence; ii) whether the type of research required is possible with approval; iii) the expected longer term benefits and costs of the type of research likely to be conducted; iv) the impact of other sources of uncertainty which will resolve over time; and v) the significance of any irrecoverable costs.

2.2 Changes in prices and evidence

The type of guidance that might be appropriate will be influenced by changes in the effective price of the technology, the type of evidence available to support its use and whether further research is likely to be undertaken, either by manufacturers or research commissioners, as a result of OIR or AWR guidance.

2.2.1 Changes in effective prices

Any change in the effective price of the technology, either through patient access schemes (which offer some form of discount that reduces NHS costs), or direct price changes (possibly negotiated though a future value based pricing scheme) will affect key assessments and decisions, leading to different 'paths' through the algorithm, consequently changing the category of guidance that would be appropriate. For example, provisional OIR guidance for a technology, which is expected to be cost-effective, might be revised to Approve with a sufficient price reduction because the benefits of early approval will be greater and uncertainty about its cost-effectiveness and therefore the value of additional evidence will tend to be lower (e.g. from OIR [1] to Approve [2] in Figure 2.1).[1] Similarly, AWR might be revised to Approve if the benefits of early approval now exceed the value of additional evidence (e.g. from AWR [1] to Approve [2] in Figure 2.1). [2]

Equally, provisional guidance to reject a technology which is not expected to be cost effective, might be revised to OIR if the reduction in price was not sufficient to make it cost-effective, but made the costs associated with a reject decision more uncertain and hence made the value of research worthwhile (e.g. from Reject [1] to OIR [2], in Figure 2.2).[3] If the reduction in price was greater and was sufficient to make the technology cost-effective, then guidance might be revised to AWR, if research remains worthwhile and possible with approval (e.g. from Reject [1] or OIR [2] in Figure 2.2 to AWR [1] in Figure 2.1). Clearly, with an even greater reduction in price, it is possible that provisional guidance to reject could be altered to early approval (e.g., Approve[1] in Figure 2.1). Even if research is not possible with approval a

[1] If the primary source of uncertainty is whether the technology is effective (i.e., whether there any health benefits

[2] See footnote 1.

[3] Any reduction in price will make a cost-ineffective technology less so (the net health effects, even if remaining negative will be greater, so a decision to reject will be more uncertain. However, there are limits to the effects of price reductions since even at a zero price the technology might not be cost-effective and/or further research still may be required, because there is no confidence that it is effective (harms may not be compensated by benefits) and/or it imposes other non acquisition costs on the NHS

sufficient reduction in price could also lead to early approval (e.g. from Reject [1] or OIR [2] in Figure 2.2 to Approve [2, 3, 4] in Figure 2.1).[4]

Therefore, consideration of the effect of price changes on OIR and AWR is needed when assessing the potential impact of patient access schemes and more direct price negotiation through value based pricing. It should be noted that, all other things equal, the presence of significant irrecoverable costs will require greater reductions in effective price to achieve the same revision to a more permissive category of guidance.

Threshold prices and VBP

The price at which the technology would just be expected to be cost-effective is commonly regarded as the value based price for the technology, i.e., the maximum price the NHS can afford to pay without imposing negative health effects. This single price describes the threshold for Approve/Reject decisions and would be the relevant threshold price or VBP where: i) OIR or AWR guidance is not available to the decision maker or there is no uncertainty in cost-effectiveness; or ii) the research, if needed, can be conducted with approval; and iii) there are no irrecoverable costs. In all other circumstances there are a number of other threshold (value based) prices. The number and value of these thresholds depends on the characteristics of the technology (the path through the algorithm), however, the threshold prices for Approval will always be lower than the single Approve/Reject price based on expected cost-effectiveness.

For example, for a technology (without significant irrecoverable cost) where research could be conducted without approval but not with it, there are two threshold prices: the threshold which would move guidance from Reject to OIR and then from OIR to Approve. The latter will always be lower than the price which would move the same technology from Reject to Approve if OIR was excluded from consideration. If a technology also imposes significant irrecoverable costs then there may be more threshold prices. For example, when research can be conducted with or without approval there are three thresholds: Reject to OIR; OIR to AWR and AWR to Approve. Again the latter will be lower than the Approve/Reject threshold for the same technology if AWR was excluded from consideration. All other things equal the presence of irrecoverable costs will tend to reduce the threshold price for Approval.

Even in circumstances where price negotiation becomes possible alongside NICE appraisal, it will be important to retain the OIR and AWR as available categories of guidance for two reasons. Firstly, there is no guarantee that manufacturers will always agree to the lower price threshold which would lead to

[4] The price reduction required for these different types of approval will generally be greater if research is not possible with approval. However, these also differ. Approve [2] would require the greatest reduction in price and Approve [4] would require the lowest. However, any price reduction (price greater than zero) may not make approval appropriate in these circumstances.

Approval rather than OIR or AWR. Secondly, and possibly more importantly there may be many circumstances when there is no effective price reduction which would make Approval appropriate.[5] For example, Reject or OIR Guidance may still be appropriate even if the effective price of a technology was zero if there is substantial uncertainty about its effectiveness and/or potential for harms.

2.2.2 Incentives for evaluative research

These threshold prices represent the maximum effective price at launch to achieve a particular category of guidance when the results of any subsequent research, which might be undertaken, are not yet known. This is different to the type of flexible pricing agreements, described in the current PPRS, where price is revised once the research reports and the results are known; increasing prices if the evidence suggests that benefits were originally underestimated, or reducing it if they where overestimated. This means that manufacturers retain an incentive to conduct further evaluative research if they believe that there are additional benefits which could not be evidenced at launch. Publically funded evaluative research, however, will still be required where these incentives are insufficient and especially in those cases where the original evidence is likely to have overestimated the benefits or underestimated the potential for harm. However, it should be noted that linking effective prices to the results of publically funded research means that the NHS will only benefit if the results lead to a lower price or more restrictive Guidance if the technology is found not be cost-effective (thus avoiding the losses associated with negative net health effects). Manufactures will, however, be able to appropriate the value of evidence when it suggests that net health effects were originally underestimated through higher prices within the flexible pricing scheme (or a VBP scheme that might replace it). Even under current arrangements this value can be appropriated when the technology is reappraised by NICE (e.g. any PAS could be withdrawn or less restrictive positive Guidance issued). Consideration of how the NHS and manufacturers are likely to share the value of evidence might inform whether manufacturers should be expected to conduct the research specified in AWR or OIR guidance and as long as incentive consistent contractual arrangements can be set in place, i.e., those that can be monitored and enforced with credible penalties to ensure any agreed research is conducted in the way intended. Alternatively, manufactures might be expected to make some contribution to the costs of publically funded research which may untimely benefit their product.

It is important that policy provides (or at least does not undermine) appropriate incentives for manufacturers to conduct the type of research needed to support NICE guidance at launch. The use of OIR and AWR Guidance, as described in the Algorithm provides clear signals and incentives. For example, the threshold price for Reject/OIR and Reject/AWR will be higher than for OIR/Approve and AWR/Approve. Therefore, manufactures may choose to either i) accept OIR and AWR Guidance at a higher price; ii) reduce the effective price to achieve Approval, where that is possible; or iii) conduct the evaluative research at an earlier stage so that cost-effectiveness is not uncertain at launch. In addition,

[5] See footnotes 1, 3 and 5.

a predictable OIR and AWR policy also signals what type of research is most important at an early stage. Although the threshold price for OIR/Approve will tend to be higher than AWR/Approve, guidance restricted to OIR offers very limited NHS volumes and revenue to manufacturers. This provides a strong incentive to ensure the type of evidence, that would require research that cannot be conducted once approved for NHS use, is sufficient at launch (e.g. relative effectiveness and subtle but important differences in side effect profiles).

Other things being equal, those new technologies which are supported at NICE Appraisal by more, better quality and relevant evidence will be more likely to be approved (rather than OIR or AWR) and at higher prices than those that are not, because additional evidence is less likely to be needed. Therefore, greater consideration of OIR and AWR will tend to reward those manufactures who have invested in good quality and relevant evidence, with earlier approval of their technology. In addition, the effect of price on OIR and AWR recommendations suggests that those technologies supported by better evidence will tend to get approval at higher effective prices, providing an incentive for manufacturers to invest in the type of evidence needed earlier in the development process.

2.2.3 Assessing the prospects of research

When considering OIR or AWR guidance there must be some assessment of: i) the type of research needed to address the key uncertainties; ii) whether this will be regarded as ethical and can be undertaken while the technology is approved for use; iii) whether it is likely to be a priority for public funding and be commissioned; and iv) when it is likely to report.

Although the NICE appraisal process maybe well suited to identifying the need for evidence when assessing cost-effectiveness, these other critical assessments are not necessarily ones for which NICE and its advisory committees, as currently constituted, have particular expertise, not least because they reflect the decisions of those responsible for research design, prioritisation and commissioning. Without sufficient coordination between these communities there is a danger that OIR or AWR could be issued when either the type of research required would not be regarded as ethical or feasible, or not of sufficient priority compared to other competing research needs to be commissioned. Since publically funded research is also budget constrained, it is perfectly possible that research which might be valuable from a wider NHS perspective might nevertheless not be a priority if other more valuable research might be displaced. This might be a particular concern if there is a possibility that the research could be undertaken by the manufacturer rather than displacing other research without proprietary interest. Therefore, a decision of whether OIR or AWR research should be undertaken by the manufacturer or through publically funded research is one that NICE cannot properly take alone.

Although some judgement about how the research community might respond to OIR or AWR recommendations when NICE is formulating guidance is clearly possible, more informed judgements

and better decisions might be possible though greater involvement of the research community. For example, a research advisory committee could be constituted which could consider provisional OIR or AWR guidance, making recommendations about the type of research needed, its ethics, feasibility and likely priority during the consultation period before final appraisal and guidance. It might also make recommendations about whether research should be publically funded or undertaken by the manufacturer with appropriate contractual arrangements. There are of course many different ways in which greater coordination might be achieved. However, since some of the assessments that NICE must make in formulating OIR or AWR guidance are, in fact, research decisions which fall outside its remit, it would seem sensible to draw on the expertise of those involved in, and responsible for, these types of research decisions to help make these assessments.

2.3 Social value judgements and ethical principles

An OIR decision will benefit future patients but in some circumstances impose opportunity costs on current patients by withholding early approval of a technology which on balance is expected to be cost-effective. Equally, an AED decision will benefit future patients but at the expense of other current NHS patients if it is not expected to be cost-effective. Therefore, OIR and AWR decisions impact on different populations of patients: i) the current patient population who could benefit from the technology, a subset of whom might enrol in research; ii) the future patient population who will benefit from the results of research and iii) other unidentified NHS patients (current or future) who will forgo health if a more costly technology is approved. The ethical implications are explored by examining whether the different types of OIR and AWR decisions described in 2.1 conflict with 4 ethical principles: i) known and unknown lives; ii) current and future patients; iii) do no harm and iv) mere means.

2.3.1 Known and unknown lives

An established starting point for NICE appraisal is that improving health is an important objective of the NHS and that all health impacts whether they accrue to identifiable individuals who might benefit from the technology being appraised or other unidentified NHS patient who might forgo health are of equal significance. This principle does conflict with common emotional reactions favouring known individuals. However, such sentiment may not provide a sound ethical, or coherent, basis for social decisions, because who happens to be known in any particular instance is a matter of perspective, time and ignorance. That is, those unknown to the decision maker will be known to others and, with enough information or simply with sufficient time, those currently unidentified could become known. Therefore, decisions made on behalf of everyone served by the NHS should not distinguish between those who happen to be identified and unidentified at the time a particular decision is made.

2.3.2 Current and future patients

A similar ethical question is whether health impacts for future patients should be regarded as of equal importance and given equal weight (subject to discounting) as current patients. NICE and other NHS

decisions implicitly accept that future health benefits might come at the expense of current patients, e.g. a new technology maybe approved if the future health benefits offset the opportunity costs imposed on current (albeit unknown) patients due to high initial costs. Investment in facilities, public health, prevention and clinical research are examples where the benefits accrue to future patient populations.

These two ethical principles were taken as the starting point in developing the key assessments in Section 2.1. The first is clearly embodied in the assessment of health forgone as a consequence of additional NHS costs and the second in the assessment of whether the benefits of early approval exceed the opportunity costs (see Figures 2.1 and 2.2). Therefore, unless other ethical principles are deemed relevant, the implications ought to be acceptable unless an argument can be made to disregard or down weight benefits to future patients or favour known over unknown patients. Assuming these two principles are acceptable there may, however, be conflict with other established ethical principles which might also be applied.

2.3.3 Do no harm

A principle of 'do no harm' could define harm as compared to: i) current state; ii) some minimum standard or ii) what patients could have had (counterfactual harm). Some type of harm maybe unavoidable but must be justified by benefits or avoidance of harm to others. For technologies expected to be cost-effective, AWR would not harm current patients using any of these definitions. An OIR decision would not harm the current population compared to their current state or a minimum standard because they will continue to receive current NHS treatment. However, there will be counterfactual harm (the technology could have been approved). The question is whether this harm can be justified. In Section 2.1, OIR would only be appropriate if the expected net benefits of research to future patients exceed the opportunity cost (counterfactual harm) to current patients. This justification is consistent with i) and ii) above. Also the alternative to OIR (Approve) will not avoid harm either, because approval of this technology will harm other NHS patients compared to their current state (justified by the benefits to current and future patients). For technologies not expected to be cost-effective, an OIR decision would not harm current patients, however, an AWR decision would harm other NHS patients (compared to current state) and this would only be justified by the net benefits to future patients when the research reports.

In general, the ethical implications of OIR and AWR decisions appear uncontroversial. In many circumstances OIR or AWR does not impose harm (however defined) on the current population and if there is harm, the key principles ensure it must be justified. Some form of harm to some population is often unavoidable and where OIR or AWR is appropriate, the alternatives (Approve or Reject) impose more significant and less justified harm.

2.3.4 Mere means

A key ethical principle, based on the nature of the action rather than its consequences, is to avoid using individuals as a mere means to an end, i.e., without their consent. This principle of informed consent is central to the ethics of clinical research. Here we focus on OIR or AWR decisions made by NICE, assuming that any research following OIR or AWR guidance will only be conducted if deemed ethical by the clinical and research communities.

Patients are unlikely to give informed consent to participate in an RCT when they already have access to a new technology which is expected to be more effective. For this reason the type of research needed might not be possible once approval is granted, so withholding approval to allow research (OIR) might be appropriate. The question arises of whether the population of current patients are being used as a 'mere means' because access to the new technology is being withheld simply to make research possible (encourage informed consent) to the benefit future patients. Equally AWR, when a technology is not expected to be cost-effective, might be considered as using other NHS patents who will forgo health care, as a mere means of benefiting future patients. There are a number of responses to this problem:

i) Absurd implications

The implications of the principle suggest it is not very useful, e.g. the alternative to OIR - approval of the new technology - would deprive other (albeit unknown) patients of health care. That is, other NHS patients would be used as a 'mere means'. The consistent application of this ethical principle implies that only technologies which saved NHS costs in each period could ever be ethically approved.

ii) Consent

The question of 'mere means' is one of consent. Although individuals do not consent to particular NICE guidance they do consent to use the NHS, accepting that their individual interests will not always be met because decisions within collectively funded health care must balance the interests of current, future and other patient populations. Informed consent would still be required for many types of research to be regarded as ethical in the context of OIR.

iii) Double effect

The only intention of OIR guidance is to improve net health benefits for future patients by improving the evidence base for future clinical practice. If a technology is expected to be cost effective this will have the unintended but foreseeable consequence that current patients will not benefit from the technology until the research reports. However, should circumstances change (e.g. if research becomes possible with approval) the technology would be approved for current patients.

iv) Equipoise

The problem of 'mere means' in clinical research (some patients are not allocated to the treatment expected to be 'best') is overcome by invoking the notion of equipoise; that any difference in the effectiveness of the technologies is 'sufficiently uncertain' that it is 'not possible' to judge which is better, i.e. patients are not being used as 'mere means' because it is 'not known' which is more effective. The notion of equipoise, if applied to NICE decisions, would define 'better' as the overall impact on health (i.e. expected cost-effectiveness). Whether expected cost-effectiveness is 'sufficiently uncertain' is really a question of whether further evidence is needed and research is worthwhile. Therefore, if OIR or AWR was deemed appropriate (using the principles in Section 2.1) NICE could also be described as in equipoise. Therefore, whether or not the new technology will improve or reduce overall health is unknown so withholding approval is not using current patients as 'mere means'.

The notion of equipoise used in clinical research defines 'better' in terms of effectiveness rather than the overall impact on the NHS. Therefore, even when OIR or AWR is appropriate and regarded as ethical, research may nevertheless not be considered ethical if equipoise (in effectiveness) cannot be established and if consent would not be given by informed patients. Therefore, some consideration of whether particular types of research are likely to be considered ethical by clinical and research community is needed, including whether guidance is likely to influence this ethical judgement. An important question is whether clinical and research communities will regard research as ethical in the context of OIR where informed consent would be given but evidence suggests that the technology, which is not currently approved and available for widespread NHS use, is more effective, i.e. individual clinical equipoise cannot be established, but a collective notion of equipoise can.

If the principle that all health impacts whether to identifiable or unidentified patients or current and future patients should be regarded as of equal importance and given equal weight is accepted, then the ethical implications of OIR and AWR guidance are in general uncontroversial. An OIR decision when a technology is expected to be cost-effective does, however, pose the question of whether current patients are being used as a mere means to benefit future patients (similarly, an AWR decision when the technology is not cost-effective poses the question of whether other NHS patients are being used as a mere means to benefit future patients). However, closer examination of this principle of action suggests there are a number of reasons why this potential concern might be set aside.

3 Informing the assessments

The key principles and assessments which are needed when considering OIR or AWR guidance have been outlined Section 2. How these assessments might be made and whether the existing methods of appraisal are sufficient, or whether addition information, evidence and analysis might be useful, was not addressed. In this section we outline additional information and evidence which might be useful and a range of methods of analysis which could be used to inform each of the assessments and decisions within the algorithm. We take existing methods of NICE appraisal as an accepted starting point and focus instead on what additional information and analysis might feasibly be included in appraisal and how it might be interpreted to inform the judgements required We also consider whether this type of additional information and analysis might be routinely required within appraisal or only conducted when OIR or AWR appear to be particularly relevant, e.g., more sophisticated additional analysis might only be required if it is established tfurther research might in principle be worthwhile.

3.1 A checklist of assessment

The possible sequences of assessments and decisions which lead to a particular categories and types of guidance were represented as an algorithm in Figures 2.1 and 2.2 and Parts I to III in Appendix A. The sequence of judgements required can be summarised as a simple checklist that could be considered by the TAR team/ERG and AC as well as manufacturers during appraisal. There are two checklists: one for technologies expected to be cost-effective (Table 3.1a) and one for those not expected to be cost-effective based on the balance of existing evidence and current effective prices (Table 3.1b). The only difference between the checklists is at point 4, where, for technologies expected to be cost effective, the judgment is whether the research is possible *with* approval whereas a judgment of whether research is possible *without* approval is required if the technology is not expected to be cost-effective.

Each of the seven points on the checklist relate to the sequence of decision nodes that fully describe the algorithm in Appendix A. Therefore, each sequence of Yes or No judgements defines a single pathway leading to a particular type and category of guidance (the type and category of guidance implied by each combination is described in Table B1, Appendix B). However, all 7 assessments do not necessarily need to be undertaken because sometimes earlier decisions will lead directly to guidance. For example a ‘No’ at point 3 always leads directly to either Approve or Reject and hence further assessment is unnecessary. Similarly, a ‘No’ at point 6 also leads directly to Approve or Reject if there are no significant irrecoverable costs associated with the technology (See Table B1, Appendix B).

Table 3.1a **Checklist for OIR and AWR** (technologies expected to be cost-effective)

Point	Assessment	Judgement Yes	No
1	Is it cost-effective?	Yes	
2	Are there significant irrecoverable costs?		
3	Does more research seem worthwhile?		
4	Is the research possible with approval?		
5	Will other sources of uncertainty resolve over time?		
6	Are the benefits of research greater than the costs?		
7	Are the benefits of approval greater than the costs?		

Table 3.1b **Checklist for OIR and AWR** (technologies not expected to be cost-effective)

Point	Assessment	Judgement Yes	No
1	Is it cost-effective?		No
2	Are there significant irrecoverable costs?		
3	Does more research seem worthwhile?		
4	Is the research possible without approval?		
5	Will other sources of uncertainty resolve over time?		
6	Are the benefits of research greater than the costs?		
7	Are the benefits of approval greater than the costs?		

3.2 Introduction to case studies

The objective of developing a series of case studies was to: i) demonstrate how the key principles and assessments might inform the development of guidance through application of the checklist and ii) establish whether existing methods of appraisal are sufficient, or whether (and when) additional information and analysis might be useful.

3.2.1 Selection of case studies

Case studies were selected to ensure that the full range of possible analysis was feasible within the time and resource constraints of this research project, while exploring situations where OIR or AWR might be particularly relevant and challenging. Therefore, de novo or substantial re-analysis of original assessments is not possible. Nor would it be necessary or informative, since one of the objectives is to explore what *additional* information and analysis might be required. For this reason candidate case studies which met the following feasibility criteria were considered: i) the economic analysis was regarded as a suitable basis for developing guidance; ii) an analysis of uncertainty in expected cost-effectiveness (PSA as specified in the NICE reference case) was conducted and iii) ready access was available to the electronic versions of the models which informed guidance.

There are three groups of potential case studies where the key principles and assessment described above might have influenced guidance: i) where OIR or AWR was included in the FAD; ii) where OIR or AWR was considered during appraisal (e.g., included in ACD or section 6 of TA Guidance); and iii) where OIR or AWR was not obviously considered at any stage. As well as examples of AWR for technologies expected to be cost-effective and OIR for those not, there are also a number of particularly interesting ways in which guidance might be influenced by these additional considerations. For technologies expected to be cost-effective these include: i) OIR rather than Approve when research *is not possible* with approval; and ii) OIR or even Reject rather than AWR or Approve even if research *is possible* with approval because there are significant irrecoverable costs.

To fully explore the implications of these principles and assessments it is useful to select case studies which reflect the range of possible and interesting characteristics. For example, i) technologies which are and are not expected to be cost-effective; ii) with and without irrecoverable costs; iii) where other sources of uncertainty are and are not present; iv) where the research needed is and is not possible with approval; v) consideration of non pharmaceutical interventions and vi) those appraised under the MTA and STA process. Four studies will not be enough to demonstrate the full range of possible combinations of interesting characteristics or illustrate all of the potential impacts of interest. Therefore, in selecting case studies there was a need to balance feasibility and those characteristics of greatest interest.

3.2.2 Background to the case studies

The following four case studies were selected. A range of additional information was sought, and further analysis conducted, to inform the sequence of assessment and judgements required when completing the OIR/AWR checklist in Tables 3.1a and 3.1b.

i) Clopidogrel for the management of patients with non-ST-segment elevation acute coronary syndromes (CLOP)

The use of CLOP (for up to 12 months) in combination with low dose aspirin was recommended by NICE following an MTA appraisal for patients with non-ST-segment-elevation acute coronary syndrome (NSTE-ACS) presenting with a moderate to high risk of ischemic events (TA80 in 2004 and updated in 2010 in CG94) . In TA80 the AC considered 12 month or lifetime treatment with CLOP, but recommended research to inform optimal treatment duration. The original AR had included an analysis of shorter treatment durations (<12 months) and the NIHR-HTA programme subsequently commissioned additional re-analysis based on this original work to inform this research recommendation in 2009. This case study is based on the re-analysis of TA80 undertaken in 2009 which included standard therapy compared to 4 alternative treatment durations of clopidogrel of 1, 3, 6, and 12 months. Importantly, while the case study is based on the later re-analysis of TA80, the analysis considered here has been undertaken from the standpoint of the originalTA80 appraisal asking, what assessments might have been made at that time when standard therapy was low dose aspirin?

The research recommendation was made in Section 6 of TA80, therefore, CLOP is not an example of AWR at FAD, but where AWR was considered during appraisal. The possible pathways through the algorithm that the CLOP case study illustrates are reported in Figure C1 in Appendix C, where the new technology is expected to be cost-effective and with no significant irrecoverable costs. The CLOP case study also illustrates a number of other important characteristics, including: (i) the impact that other sources of uncertainty (price change following patent expiry) can have on the value of further research; (ii) the interpretation of analyses where there are multiple alternatives; and (ii) the use of scenarios to represent alternative but credible assumptions.

ii) Enhanced External Counterpulsation for chronic stable angina (EECP)

The NIHR-HTA programme identified EECP as an important topic and commissioned a short report to examine the clinical effectiveness and cost-effectiveness of EECP as an adjunct to standard therapy in patients with chronic stable angina. Although the topic was not ultimately considered by NICE it was commissioned in the same way and with the same resources as other assessment reports which inform NICE guidance. The assessment followed the NICE reference case and is consistent with the type of analysis which would have been required in an MTA appraisal. Like other MTA ARs it was published in full as a HTA monograph.

EECP is a non-invasive procedure (adjunct to standard therapy) used to provide symptomatic relief from stable angina. The analysis compares EECP to standard therapy alone. RCT evidence suggests an improvement in HRQL with EECP at 12 months. To characterise the uncertainty associated with possible longer durations of treatment effect, formal elicitation of expert clinical judgement was

undertaken. This provided an estimate of the probability, with uncertainty, of continuing to respond to treatment with EECP in subsequent years.

The possible pathways through the algorithm that EECP illustrate are reported in Figure C2 in Appendix C. In this case study the new technology is expected to be cost-effective but with potentially significant irrecoverable costs. These irrecoverable costs include both: i) long lived costs associated with the purchase of equipment; and ii) large initial per patient treatment costs, combined with a chronic condition where a decision not to treat a particular patient with EECP can be changed at alter date (decisions are not irreversible) when research reports or other events occur. Consequently these irrecoverable costs might influence the category of guidance, e.g., OIR rather than Approve. EECP also provides an opportunity to explore the impact of research design (length of follow-up) on guidance and to examine the potential role of elicitation rather than extreme scenarios to characterise uncertainty.

iii) Omalizumab for the treatment of severe persistent allergic asthma in children aged 6 to 11 years (OMAL)

The use of OMAL for the treatment of severe persistent allergic asthma in children aged 6 to 11 years was not recommended by NICE following an STA appraisal (TA201 in 2010). The analysis compared OMAL as an add-on to standard care versus standard care alone. The primary analysis was based on a pre-specified severe asthma population within an international, multicentre, placebo-controlled RCT. However, a high-risk subgroup within this population (recent hospitalisation for an asthma exacerbation) was also identified post-hoc.

Omalizumab was not found to be cost effective in either the severe or severe/high risk populations. However, an RCT was recommended comparing OMAL to oral corticosteroids (OCS) in children to establish reduction in OCS use. This was made in Section 6 of TA201; therefore, OMAL is not an example of OIR at FAD, but where OIR was considered during appraisal. The possible pathways through the algorithm that OMAL illustrate are reported in Figure C3 in Appendix C, where the new technology is not expected to be cost-effective and with no significant irrecoverable costs. OMAL also illustrates assessment in small patient populations (rare disease) for the assessment and how sub group analysis can be considered.

Following an MTA appraisal (TA199 in 2010), the use of biologic treatment with etanercept, infliximab and adalimumab was recommended by NICE for patients with active and progressive PsA and who have an inadequate response to standard treatment, including two conventional disease-modifying antirheumatic drugs (DMARDs). However, the guidance also recommended that treatment should start with the least expensive biologic, taking account of dose, route of administration and price. This guidance updated an earlier MTA appraisal in 2006 (TA104), which had recommended etanercept and

restricted guidance on the use of infliximab to only those patients shown to be either intolerant or contraindicated to etanercept.[6] The analysis in this case study is from the standpoint of TA199, using the updated model which included new evidence and adalimumab as an additional comparator. At this point NICE guidance recommended etanercept, so the first question posed in the checklist can be interpreted as, are the other technologies available (infliximab, adalimumab or palliative care) expected to be cost-effective compared to etanercept?

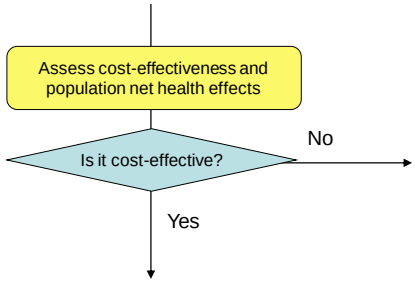
In Section 6 of TA199 the importance of data on long term outcomes and adverse events from patient registries was highlighted. Therefore, PsA is not an example of AWR at FAD, but where AWR was considered during appraisal. The possible pathways through the algorithm that PsA illustrate are reported in Figure C4 in Appendix C. In this case study the alternatives to etanercept are not expected to be cost-effective. However, etanercept as well as infliximab and adalimumab have potentially significant irrecoverable costs because of the high initial per patient treatment costs, combined with a chronic condition where treatment decisions are not irreversible. PsA, like EECP, also provides an opportunity to examine the potential role of elicitation in the appraisal process.

3.3 Is it cost effective and what are the risks?

The judgements made at points 1 and 2 of the checklist are critical because, although neither leads directly to a particular category of guidance, they do determine the subsequent path that might be taken, sometimes avoiding further and potentially complex assessments. For example, the absence of significant irrecoverable costs means that only 4 out of the 12 possible pathways require all 7 assessments to be made (see Table B1, Appendix B).

3.3.1 Point 1 - Is it expected to be cost effective?

The sequence of assessments starts with cost-effectiveness and the expected impact on population net health effects. i.e., at the following point in the algorithm:



This requires an assessment of expected cost-effectiveness based on the balance of the evidence and analysis currently available. Methods to estimate expected cost-effectiveness are well established

[6] TA104 included an AWR recommendation in the ACD but this was removed in the FAD. The recommended research was to enter patients into the BSR register, on the grounds of the possibility of severe side effects and little information on the use of these agents beyond the duration of RCTs

within the NICE appraisal process and are extensively described in the Guide to Methods of Technology Appraisal. [7] Commonly, expected cost-effectiveness is summarised and presented using incremental cost-effectiveness ratios (ICERs). Equivalently, but more usefully in this context, cost-effectiveness can be expressed in terms of expected net health effects (NHE), which can be expressed per patient treated or for a population of patients. This is especially important when later assessments require a comparison of benefits to current or future patient populations and when assessing the significance of irrecoverable costs (see Section 3.3.2). All the information required to express expected cost-effectiveness in these ways is already available during appraisal. .

i) Cost-effectiveness at the patient level

Estimates of the expected NHS costs and QALYs for each patient treated over an appropriate time horizon - the 'patient time horizon' [8] - can be summarised as an ICER, which must be compared to a cost-effectiveness threshold to judge cost-effectiveness. Equivalently, this can be expressed as the per patient NHE of each intervention, i.e., the difference between any health gained and health forgone elsewhere. [9]

Technologies expected to be cost effective

The results for EECP are summarised in Table 3.2a. There are only two alternatives (EECP and standard care, so only one ICER. EECP is just expected to be cost-effective at a threshold of £20,000 per QALY.[10] Consequently the NHE of EECP are greater than standard care but the difference per patient treated (the incremental NHE) is small.

[7] Throughout the case-studies, estimates of expected costs and QALYs reported and used in subsequent analysis are the mean costs and QALYs derived from probabilistic analysis using Monte Carlo simulation. The costs and QALYs from a deterministic analysis will be incorrect unless the model is multi-linear with independent parameters.

[8] This is the time horizon over which costs and benefits are likely to differ for an individual patient (commonly termed the model time horizon). In many some circumstances (e.g., where there is a mortality effect) this will be the lifetime of the patient. Expected costs and QALYs each period are the expectations (means) from the results of probabilistic analysis. All future costs and QALY (per patient or population) are discounted at 3.5% throughout.

[9] The expected per patient net health effects for each intervention (*i*) is the difference between the expected health (QALYs) with the intervention (*hi*) and the health likely to be forgone elsewhere are a consequence of the costs of the intervention (*ci*), which requires an estimate of the cost-effectiveness threshold (*k*). Therefore, the per patient expected net health effects of each intervention (*NHEi = hi - ci/k*) can be expressed using the same information required to present the more familiar ICERs. It can also be expressed in terms of the NHS resources required to generate the NHEi (*k.hi-ci*) The intervention which is expected to be cost-effective is the one with the highest expected net health effects. This is entirely equivalent to drawing conclusions about cost-effectiveness based on ICERs but has many advantages once an assessment of uncertainty and it consequences is required. It is also needed when considering the impact of irrecoverable costs and is especially important when decisions require a trade-off to be made between benefits to current or future patients.

[10] All analysis has been conducted at the upper and lower bound for the range NICE has adopted for the threshold. However, unless otherwise stated results in the text relate to a threshold of £20,000 per QALY.

Table 3.2a Expected cost-effectiveness of EECP per patient treated

				Cost-effectiveness threshold at:			
				£20,000 per QALY		£30,000 per QALY	
Treatment	**Costs**	**QALYs**	**ICER**	**NHE,** QALY (£)	**Incr NHE,** QALY (£)	**NHE,** QALY (£)	**Incr NHE,** QALY (£)
EECP	£4,744	7.6045	£19,391	7.3673 (147,346)	0.0074 (£149)	7.4464 (£223,391)	0.0865 (£2,595)
Std	-	7.3598	-	7.3598 (147,197)	-	7.3598 (£220,795)	-

It is also important to consider how NHE accumulate over time or the 'investment profile' per patient treated with EECP. Figure 3.1a illustrates the cumulative incremental NHE over the patient time horizon. The initial per patient costs of EECP are high and are far in excess of the immediate health benefits in the initial period of treatment. These negative NHE are gradually offset by positive NHE in later periods. In this case, it is only after 14 years that the initial losses are compensated by later gains. i.e., EECP doesn't 'breakeven' until 14 years from initial treatment. It is only beyond 30 years that the modest incremental NHE reported in Table 3.2a are eventually achieved.

Figure 3.1a Cumulative incremental NHE of EECP over the patient time horizon

Multiple alternatives

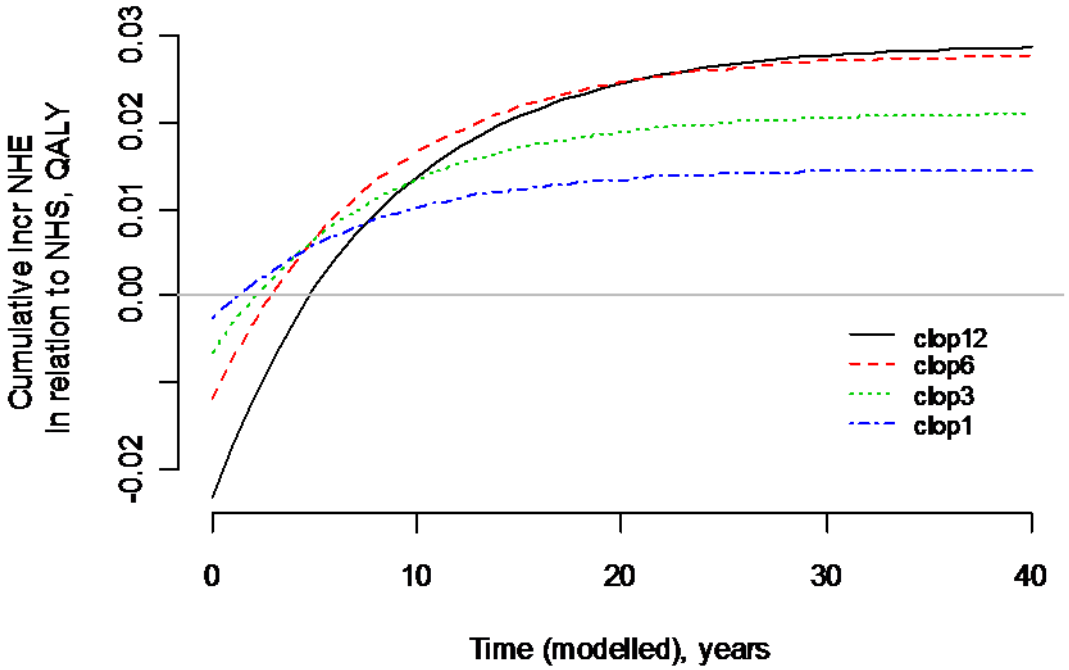
Similar analysis can be conducted when there are more than two alternatives. For example, in CLOP four treatment durations as well as current NHS treatment (aspirin alone) were considered at the time of TA80. The results in Table 3.2b indicate that 12 month treatment with CLOP is expected to be cost-effective, although the difference in NHE between 12 and 6 months treatment duration is small.

Table 3.2b Expected cost-effectiveness of CLOP per patient treated

				Cost-effectiveness threshold at:	
				£20,000 per QALY	£30,000 per QALY
Treatment	**Costs**	**QALYs**	**ICER**	**NHE,** QALY (£)	**NHE,** QALY (£)
clop12	£20,127	8.122	£18,663	7.115 (142,307)	7.451 (223,525)
clop6	£19,860	8.107	£10,477	7.114 (142,288)	7.445 (223,362)
clop3	£19,712	8.093	£9,396	7.108 (142,154)	7.436 (223,087)
clop1	£19,598	8.081	£4,961	7.101 (142,025)	7.428 (222,837)
NHS	£19,502	8.062	-	7.087 (141,734)	7.412 (222,353)

The 'investment profile' of CLOP, per patient treated, is illustrated in Figure 3.1b. The per patient costs of CLOP are in excess of the health benefits during the period of treatment. These negative NHE are eventually offset by positive NHE in later periods. In this case, it is only after 5 years that 12 months of treatment with CLOP 'breaks even' against current NHS care and it is not until 21 years that it is better than a shorter treatment duration of 6 months. Notice that shorter treatment durations with CLOP offer a much less 'risky profile', e.g., the breakeven point for one month of treatment is 2 years against current NHS care.

Figure 3.1b Cumulative incremental NHE of CLOP over the patient time horizon



Technologies not expected to be cost effective

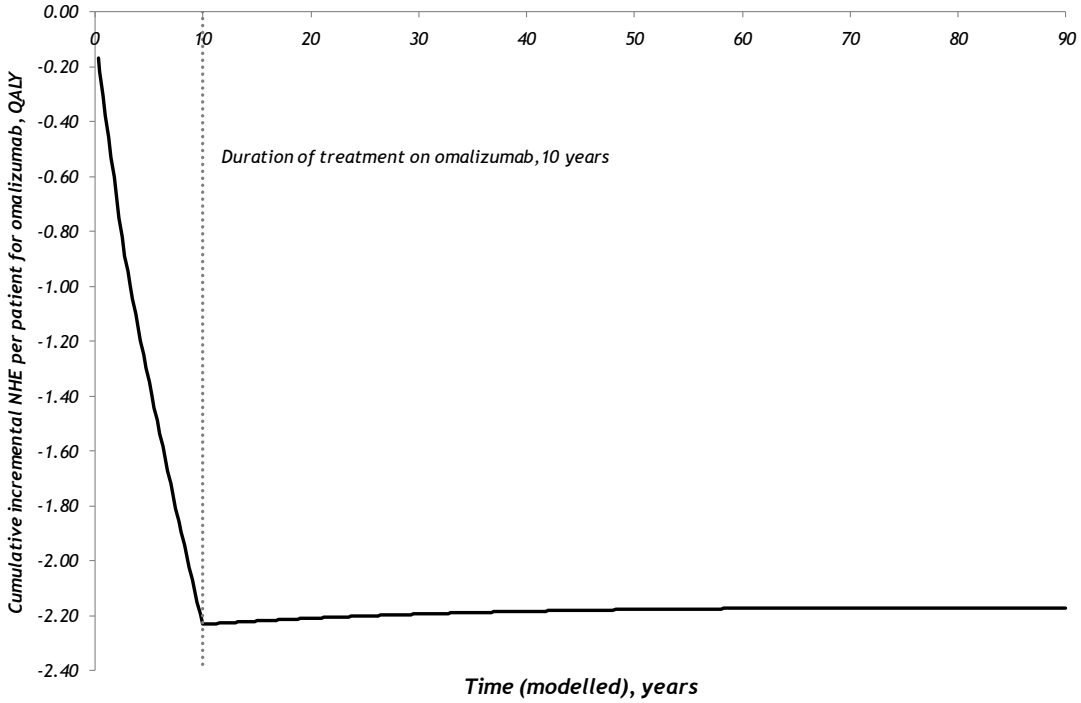
The ICER for omalizumab in Table 3.2c is greater than the threshold so it is not expected to be cost-effective compared to standard care alone. Consequently the incremental NHE of OMAL is negative.

Table 3.2c Expected cost-effectiveness of OMAL per patient treated

				Cost-effectiveness threshold at:			
				£20,000 per QALY		£30,000 per QALY	
Treatment	**Costs**	**QALY**	**ICER**	**NHE,** QALY (£)	**Incr NHE,** QALY (£)	**NHE,** QALY (£)	**Incr NHE,** QALY (£)
Omal + Std	£94,992	16.64	£93,844	11.8861 (237,721)	-2.1908 (-43,815)	13.4693 (404,078)	-1.2627 (-37,882)
Std	£39,310	16.04	-	14.0768 (281,536)	-	14.7320 (441,960)	-

The per patient 'investment profile' for OMAL is illustrated in Figure 3.1c and shows that it is always expected to offer negative NHE compared to standard care over the entire patient time horizon, i.e., the high costs of treatment are never compensated by future health gains. In this example, the initial treatment costs with OMAL continue for 10 years (10 years is assumed to represent the duration a patient would continue to receive treatment with OMAL) with health effects predominately while on treatment. Therefore, OMAL is not so much a 'risky purchase' but one that is simply not cost-effective at its current price.

Figure 3.1c Cumulative incremental NHE of OMAL over the patient time horizon



Multiple alternatives

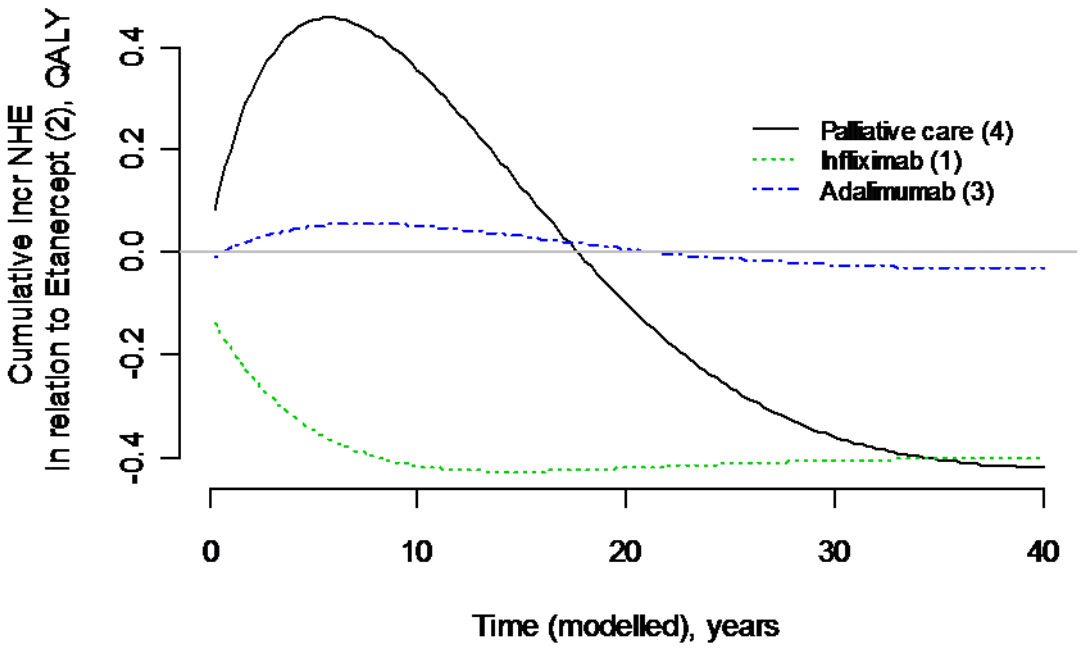
PsA offers an example where the alternatives to the treatment already recommended by NICE (etanercept at the time of TA199) are not expected to be cost-effective, i.e., the results in Table 3.2d indicate that etanercept is expected to be cost-effective. Notice that although adalimumab is less effective than etanercept it is also cheaper. However, the resources savings it offers do not compensate for the reduction in health benefits.

Table 3.2d Expected cost-effectiveness in PsA per patient treated

				Cost-effectiveness threshold at:	
				£20,000 per QALY	£30,000 per QALY
Treatment	**Costs**	**QALYs**	**ICER**	**NHE,** QALY (£)	**NHE,** QALY (£)
1: Infliximab	£90,343	7.269	£60,965	2.752 (5504)	4.258 (8516)
2: Etanercept	£78,150	7.069	£17,733	3.161 (6322)	4.464 (8928)
3: Adalimumab	£72,972	6.777	£14,622	3.129 (6258)	4.345 (8690)
4: Palliative care	£51,800	5.329	-	2.739 (5478)	3.602 (7204)

Consequently the 'investment profile' of the alternatives to etanercept, illustrated in Figure 3.1d, differs in appearance. However, all the biologic treatments for PsA have high initial costs which are only gradually compensated by later health benefits. All three ultimately offer positive NHE compared to palliative care but only breakeven at 17, 17.5 and 34.5 years for adalimumab, etanercept and infliximab respectively. Adalimumab offers a slightly less risky profile than etanercept, so it is only at 21.25 years that etanercept is expected offer the highest NHE.

Figure 3.1d Cumulative incremental NHE in PsA over the patient time horizon



ii) Cost-effectiveness at the population level

Per patient NHEs can also be expressed for the population of current and future patients. This requires information about prevalence and future incidence of the target population (already required in appraisal). It also requires a judgement about the time horizon over which the technology will be used This 'technology time horizon' ought to reflect the period over which the technology is likely to be part of

clinical practice and generate the expected NHEs.[11] An estimate of the scale of the total population NHEs and how they cumulate over time is important for subsequent assessments ,including: i) where the NHE for current patient populations must be compared with the benefits to future patients; and ii) where the treatment decision can be changed so the irrecoverable costs of initially negative NHE become significant.

For example, there is a large prevalent population eligible for EECP relative to future incident populations in this chronic condition. The total population NHE, assuming the technology will be used to treat prevalent and incident patients over 10 years, are reported in Table 3.3a. Expected cost-effectiveness is unchanged (ICER is the same as Table 3.2a) but the incremental NHE although small per patient, is more significant at a population level.

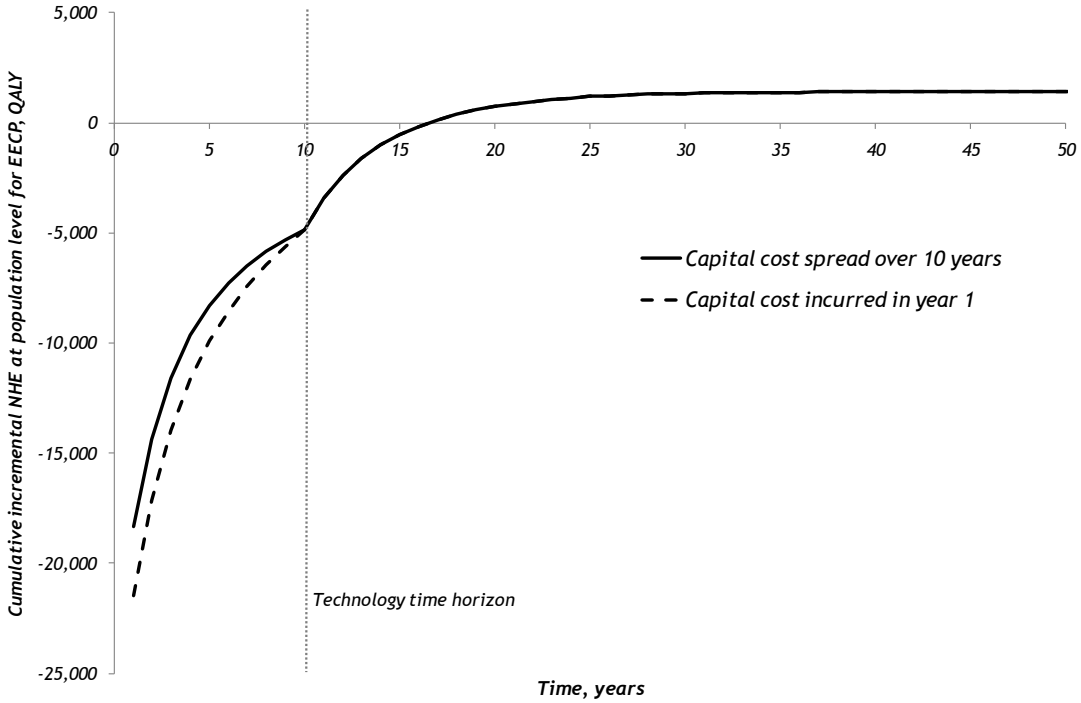
Table 3.3a Expected cost-effectiveness of EECP for the population

				Cost-effectiveness threshold at:			
				£20,000 per QALY		£30,000 per QALY	
Treatment	**Costs** (£m)	**QALY**	**ICER**	**NHE** QALY (£m)	**Incr NHE,** QALY (£m)	**NHE** QALY (£m)	**Incr NHE,** QALY (£m)
EECP	896	1,435,787	£19,391	1,391,001 (27,820)	1,405 (28)	1,405,930 (42,177)	16,334 (490)
Std	-	1,389,596	-	1,389,596 (27,792)		1,389,596 (41,688)	

The 'investment profile' for EECP when used to treat patients over 10 years is illustrated in Figure 3.2. At a population level it is not until 17 years (rather than 14 years at a patient level) that initial losses are compensated by later gains and EECP 'breaks even'. In other words, EECP appears a more risky investment when evaluated at a population rather than individual level. This is because, although each patient treated with EECP is expected to offer the same profile of NHEs shown in Figure 3.1a, the negative NHE associated with patients' incident and treated in year 10 won't be offset by later gains until year 24. The population level 'investment profile' would exhibit greater risk (breakeven later) if the prevalent population was smaller relative to the incident population and/or the technology time horizon was longer. For example the breakeven point extends to 23 years when the technology time horizon is increased to 20 years.

[11] The time horizon for the technology might be longer or shorter than the patient time horizon. Technology time horizons might be based on historical evidence of the obsolescence of health technologies but any estimate will be a proxy for a complex and uncertain process of future changes in new technologies, prices and evidence. Therefore the impacts of different technology time horizons have been explored.

Figure 3.2 Cumulative incremental NHE of EECP for the population



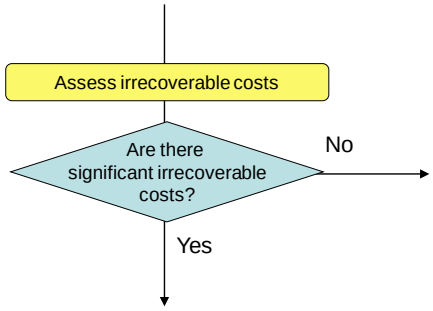
The effect on the other case studies of assessment at the population level is similar to EECP. It simply increases the magnitude of differences in per patient NHE (to a greater extent for longer technology time horizons), but leaves expected cost-effectiveness unchanged. However, the 'investment profiles' at a population level also differ, exhibiting greater 'risk' indicated by later breakeven points for the same reasons as EECP. For example, the breakeven points for CLOP when evaluated at a population level are reported in Table 3.3b. At a technology time horizon of 10 years it is only at 11 years, rather than 5 years for a single patient, that 12 months of CLOP treatment 'breaks even' against current NHS care and not until 27 years (rather than 21 years) that it is better than a shorter treatment duration of 6 months. Even the shorter durations of treatment offer a 'risky profile', e.g., the breakeven point for one month of treatment is 4 years (rather than 2 years).

Table 3.3b Expected cost-effectiveness of CLOP for the population

			Breakeven points (years)		
Technology time horizon	**Treatment**	**Incr NHE,** QALYs (£m)	**12 months vs 6 months**	**12 months vs NHS**	**1 month vs NHS**
5 years	1: clop12 2: clop6 3: clop3 4: clop1 5: NHS	269 (5.4) 1,881 (37.6) 1,804 (36.1) 4,073 (81.5) -	24	8	4
10 years	1: clop12 2: clop6 3: clop3 4: clop1 5: NHS	495 (9.9) 3,465 (69.3) 3,324 (66.5) 7,502 (150) -	27	11	4
15 years	1: clop12 2: clop6 3: clop3 4: clop1 5: NHS	686 (13.7) 4,799 (96) 4,603 (92.1) 10,389 (207.8) -	30	12	4
20 years	1: clop12 2: clop6 3: clop3 4: clop1 5: NHS	846 (16.9) 5,921 (118.4) 5,680 (113.6) 12,820 (256.4) -	33	12	4

3.3.2 Point 2 - Are there significant irrecoverable costs?

The second point on the checklist requires: i) an assessment of whether there are irrecoverable costs and ii) a judgement of their potential significance, i.e., at the following point in the algorithm



Irrecoverable costs are those which once committed cannot be recovered if guidance is changed at a later date. Irrecoverable costs are most commonly thought of as 'up-front' or capital costs of new facilities or equipment with long life expectancy (they might also include any practitioner training and the costs of implementation efforts). In NICE appraisal these types of cost are first annuitized [12] and then allocated pro-rata to the number of patients likely to be treated during the lifetime of the equipment. That is, capital costs are treated as if they are paid per patient treated over the life time of the equipment. If guidance remains unchanged throughout this period (i.e., research does not report or other sources of

[12] The annual payments required each year over the life time of the equipment (discounted at 3.5%) which would be equivalent to the capital cost at the start of the 1st year.

uncertainty resolve) then this common assumption has no influence. However, should guidance change (initial approval is withdrawn) before the end of the lifetime of the equipment then, although future patents will no longer use the technology, the cost of the equipment allocated to them cannot be recovered. The possibility that initial guidance might change and its impact on expected costs needs to be considered before costs are made irrecoverable through approval or AWR. The impact of irrecoverable costs will tend to be greater if they represent a greater proportion of the total costs, if guidance is more likely to change and to change in the near future.

EECP is the only case study in which these types of cost are present to any great extent because treatment requires capital investment in the EECP machines themselves. The expected per patient and population costs reported in Tables 3.1a and 3.2b allocated this capital cost in the usual way (i.e., annuitized over the 10 year life time of the machines and allocated to the number of patients treated each year). The irrecoverable costs are reported separately in Table 3.4 and represent 19% of the total. However, this will have no influence on expected cost-effectiveness so long as guidance does not change during the lifetime of the equipment.

Table 3.4 Capital costs associated with EECP

					Cost-effectiveness threshold	
					£20,000 per QALY	
Treatment	**Capital costs**	**Non capital costs**	**QALY**	**ICER**	**NHE** QALY (£m)	**Incr NHE** QALY (£m)
EECP	£170,304,591	£725,408,798	1,435,787	£19,391	1,391,001 (27,820)	1,405 (28)
Std	-	-	1,389,596	-	1,389,596 (27,792)	-

'Investment profile' of NHE

Even in the absence of capital costs of equipment and facilities, NHE accumulate over time both at a patient and population level. With the possible exception of OMAL [13] the analysis in Section 3.3.1 indicates a common pattern of initially negative NHE that are only gradually offset by positive NHE in later periods. Therefore, approval or AWR commonly commits opportunity costs of negative NHE which are irrecoverable.

[13] The profile of NHE at a patient level did not exhibit significant irrecoverable opportunity costs. Assessment at a population level and for longer technology time horizons simply increases the magnitude of the expected negative NHE. Therefore, there are no irrecoverable costs in this case study

i) Are they likely to be significant?

Whether or not irrecoverable costs are significant (i.e., might influence guidance) depends critically on whether guidance is likely to change and whether that is more likely in the near or distant future. That will depend on whether research is likely to be undertaken and when it is likely to report, as well as other events that might occur, e.g., a change in price following patent expiry. These are assessed later, at points 5 and 6 on the checklist. However, the *potential* significance of any irrecoverable costs can be assessed at this point. For example, capital costs can be judged based on the proportion of total population cost which are irrecoverable for this reason as well as their scale relative to the additional population NHE offered (e.g., see Table 3.4).

Judging the potential significance of the investment profiles of NHE is more nuanced. It depends whether treatment decisions for individual patients are irreversible, which in part depends on the nature of the disease. For example, in an acute condition the decision to treat a particular presenting patient with a technology cannot be reconsidered at a later date – it is irreversible. Of course it is possible that the later benefits are not realised but it is also possible that they will realise more (the profiles of NHE in Figure 3.1a to 3.1d are the average over these possibilities). Similarly the possibility that guidance might change in the future (e.g., research suggest that the longer term benefits will not offset initial losses), will not influence the irreversible decision to treat a presenting patient with a technology that is expected to be cost-effective prior to the research reporting.

Implication for the case studies

For example, CLOP is a treatment for acute coronary syndromes and, although decisions about treatment and its duration are not irreversible in the short run, over the time scales more likely for research being conducted (and reporting) or other events occurring, which would change guidance, they can be regarded as such. Therefore, although the investment profile of CLOP (at a patient and more so at a population level) exhibits irrecoverable costs these should not be judged significant in the sense that they have little potential to influence guidance. There are also no significant irrecoverable costs associated with OMAL but for different reasons; treatment decisions are reversible in this chronic condition but any irrecoverable costs appear very limited (see Figure 3.1c).

Both EECP and the biologics in PsA are for chronic conditions where the decision to treat a particular patient can be changed at some later date (decisions are not irreversible). Therefore, the type of investment profile of NHE at a patient and population level is significant because, instead of committing irrecoverable costs by deciding to use technologies expected to be cost-effective now, the decision and commitment of costs can be made later, after research reports, other events occur and/or guidance changes. Of course, proper account must be taken of the impact of withholding initiation of treatment on expected health benefits and costs (see Section 7).

EECP is the only case where both types of irrecoverable costs are potentially significant. Figure 3.2 illustrates the impact of accounting for the actual timing of expenditure on EECP machines rather than treating it as if it was paid when each patient was treated, i.e., expenditure is treated like a consumable cost by spreading the capital cost over 10years.[14] If approval of EECP might be withdrawn before 10 years, the potential losses in NHE will be greater than initially indicated in Figure 3.2 because the equipment costs allocated to treating future patients cannot be recovered. The earlier such a change might occur the greater the additional loss. The impact of these possibilities should be considered at point 7 of the checklist before guidance to approve or AWR commits both types of irrecoverable costs.

Pricing and irrecoverable costs

The importance of irrecoverable treatment costs when they maybe potentially significant should also consider the scale of initially negative NHE and the duration of such losses, i.e., how long until the use of the technology 'breaks even' for an individual patient and for the population of patients who are likely to be treated if it is approved. Health technologies with patent protection are more likely to be priced close to the point at which the expected incremental NHE are close to zero, i.e., where the ICER is close to or equal to the threshold. A value based pricing scheme would formalises these existing incentives. The use of a technology which is only just expected to be cost-effective will not breakeven until close to the end of the patient time horizon for an individual patient and much longer for the population of patents likely to benefits from its use (the time horizon *plus* the patent time horizon) . Therefore, those technologies already priced close to the threshold, and all new technologies considered in a value based pricing scheme, will tend to increase the scale of irrecoverable costs committed by approval, making OIR or Reject more likely even when a technology is expected to be cost-effective at point 1 of the checklist.[15]

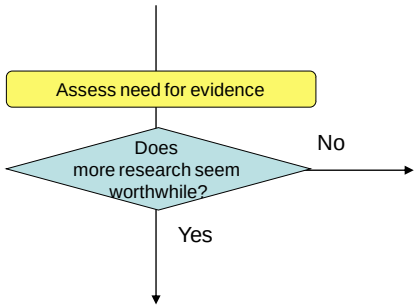
3.4 Is further research required?

The judgements made at points 3 and 4 of the checklist are critical because if more research is not judged to be worthwhile no further assessments are required (unless there are significant irrecoverable costs, see table B1 in Appendix B). If research is worthwhile, then what type of evidence is needed and whether the research required to generate it can be conducted while the technology is approved will determine whether AWR or OIR are possibilities.

[14] In Figure 3.2 the technology time horizon happens to coincide with the life time of the equipment but it need not
[15] It is also important to consider the risk profile of the health technologies and activities likely to be displaced. Insofar as additional NHS costs do not just displace new technologies the net effect will still tend to increase 'risk' – see technical appendix in the Addendum to the main report.

3.4.1 Point 3 – Does more research seem worthwhile?

The third point on the checklist requires an assessment of the potential benefits of conducting further research, i.e., at the following point in the algorithm:



This requires judgements about: i) how uncertain a decision to approve or reject a technology might be based on the estimates of expected cost-effectiveness; and ii) whether the scale of the likely consequences of this uncertainty might justify further research. Some assessment of the potential consequences of uncertainty is important because it indicates the scale of the population NHE, over the technology time horizon, that could be gained if the uncertainty surrounding this decision could be resolved immediately, i.e., it represents an expected upper bound on the benefits of more research.[16] If the potential benefits of further research are unlikely to justify the costs, then a judgement that more research does not seem worthwhile will lead directly to guidance in the following circumstances (extracted from Table B1 in Appendix B):

	Assessment	1	2	3	4	5	6	7	Guidance
Pathway number	6	Yes	No	No	-	-	-	-	Approve 4
	12	No	No	No	-	-	-	-	Reject 4
	35	No	Yes	No	-	-	-	-	Reject 11

i) Assessing the consequences of uncertainty

Some assessment is required of: i) how uncertain a decision based on expected cost-effectiveness might be; and ii) what the consequences, in terms of population NHE, are likely to be if an incorrect decision is made.

EECP is expected to be cost-effective compared to standard care (see Tables 3.2a and 3.5a) but the estimates of cost and QALYs are uncertain so there is a chance that a decision to approve EECP based on existing evidence will be incorrect, i.e., standard care might offer greater NHE. Some assessment of the likely consequences of approving EECP when standard care might be better could be based on the difference in expected NHE, i.e., the expected incremental population NHE reported in Tables 3.3a and 3.5a). This is illustrated in Figure 3.3a where a judgement about the probability that a decision based

[16] In mathematics and economics this is referred to as expected opportunity loss. In decision theory and its applications including economic evaluation it is referred to as the expected value of perfect information (EVPI). It is also directly related to option value in financial economics.

on expected cost effectiveness is correct translates into expected consequences based on the expected incremental population NHE. For example, if the decision was judged to be 100% certain then there are no consequences and so there would be nothing to be gained by more research. However, as the probability that the decision is correct becomes less certain, the expected consequences (and hence potential value of more research) increase.

This judgment, of how uncertain a decision might be, can be informed by the probabilistic analysis (PSA) already used to estimate costs and QALY and is required as part of the NICE reference case. The probability that EECP is cost effective is 0.428 (see Table 3.5a),[17] which would translate into approximately 800 QALYs (see Figure 3.3a) over the technology time horizon,[18] based on the expected or average difference between NHE. However, the difference in NHE when EECP is not the correct decision is not necessarily the average. In fact, it is very unlikely to be the average and such estimates may substantially under or overestimate the expected consequences of uncertainty.[19]

Table 3.5a Expected consequences of uncertainty for EECP

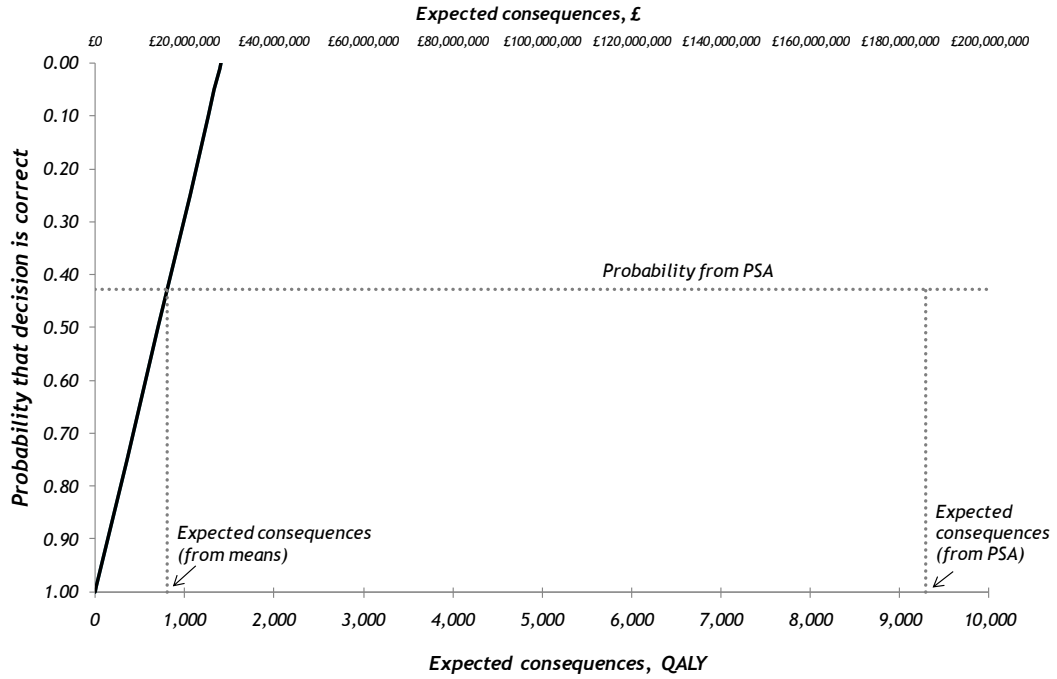
		Cost-effectiveness threshold at:					
		£20,000 per QALY			£30,000 per QALY		
Treatment	**ICER**	**Incr NHE** QALY (£m)	**Probability cost-effective**	**Expected consequences,** QALY (£m)	**Incr NHE,** QALY (£m)	**Probability cost-effective**	**Expected consequences,** QALY (£)
EECP	£19,391	1,405 (28.1)	0.428	9,287 (185.7)	1,405,930 (490)	0.7	2,774 (83.2)
Std		-	0.572		-	0.3	

[17] The alternative which is expected to be cost effective may not have the highest probability of being cost-effective if, as in his case, the distribution of NHE are skewed, i.e., when the NHE of EECP are greater than std they are much greater but when std offers higher NHE they are only a little higher than EECP.

[18] The time horizon over which evidence generated by research about a technology might be valuable may be longer (or shorter) than the period over which the technology is used. Therefore there is a distinction between the technology time horizon and the time horizon for the benefits of research. To simplify the exposition in this summary of the case studies they are assumed to be equal but other credible assumptions are explored in the full analysis reported in the addendum to the main report.

[19] If an assessment of expected consequences based on mean NHE was always an underestimate this would be a useful, simple assessment of a lower bound to the potential benefits of research. However, such estimates can also overestimate expected consequences, e.g., in the analysis of EECP at a threshold of £30,000. Unfortunately such circumstances cannot be specified in advance without conducting a proper analysis of the expected consequences antway (see Appendix to the addendum to the main report).

Figure 3.3a Probability that EECP is cost-effective and the consequences of uncertainty



The same probabilistic analysis can be used to record the difference between the NHEs of EECP and standard care and the frequency of such errors. This distribution of consequences is illustrated in Figure 3.4a. Commonly there are no consequences, because EECP is the correct decision (42.8%). However, when EECP offers lower NHE than standard care the consequence of error may be relatively small, e.g., 9% are less than 5,000 QALYs. However, they may be very large, although less likely, e.g., there is a small chance (5.7%) that they are greater than 30,000 QALYs. The average over this distribution provides the expected consequences of uncertainty, which in this case is 9,287 QALYs.[20]

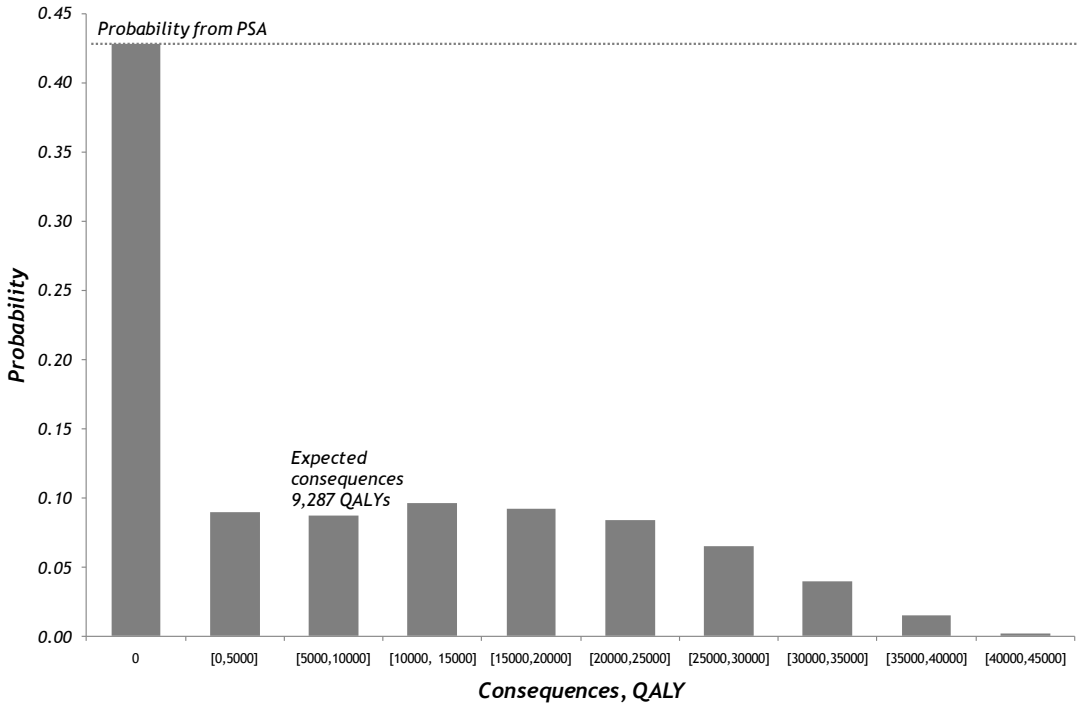
These expected consequences can be interpreted as an estimate of the population NHE over the technology time horizon that could be gained if the uncertainty surrounding this decision could be resolved immediately, i.e., it indicates an expected upper bound on the benefits of more research.[21] The consequences can also be expressed as the equivalent NHS resources required to generate the same population NHE (£185.7m in Table 3.5a). They will increase with the size of the patient population and the technology time horizon. In the case of EECP the consequences fall with the cost-effectiveness threshold because a decision to approve EECP will be less uncertain (see Table 3.5a). A

[20] This is substantial greater than the estimate of 800 QALYs based on mean incremental population NHEs, demonstrating that such simple estimate may be misleading - see Figure 3.3a.

[21] It should be noted that these estimates of QALYs that might be gained are for the population over the time horizon for the benefit of research (in this case equal to the technology time horizon – see foot note 17) if all sources of uncertainty could be immediately resolved. It includes both improvements in health outcomes for this population but also NHS resource saving that could be made and used to generate QALYs elsewhere.

judgment at this point that more research might be worthwhile seems reasonable, since the upper bound on its potential benefits exceed the likely costs.

Figure 3.4a Distribution of the consequences of uncertainty for EECP



Multiple alternatives

Similar analysis can be conducted when there are more than two alternatives but greater difficulties are encountered unless the results of PSA are used to assess both uncertainty and its consequences. For example, in the CLOP case study, 12 month treatment duration with CLOP is expected to be cost-effective but this is also uncertain. A judgement is required about the chance that 12 months of treatment is incorrect and if so which of the other four alternatives are likely to offer higher NHE, and how much higher. In other words, for decisions involving multiple alternatives, a judgement is required on the level of uncertainty surrounding the decision, how this uncertainty is distributed across the various alternatives and what the consequences are likely to be. The results of PSA can inform this judgement. The probabilities that each of the 5 alternatives is cost-effective are reported in Table 3.5b. This indicates that 12 months treatment is uncertain (probability that it is incorrect is 0.476). However, much of this probability of error is allocated to 6 months treatment with CLOP (0.18) where the difference in NHEs is likely to be relatively modest.

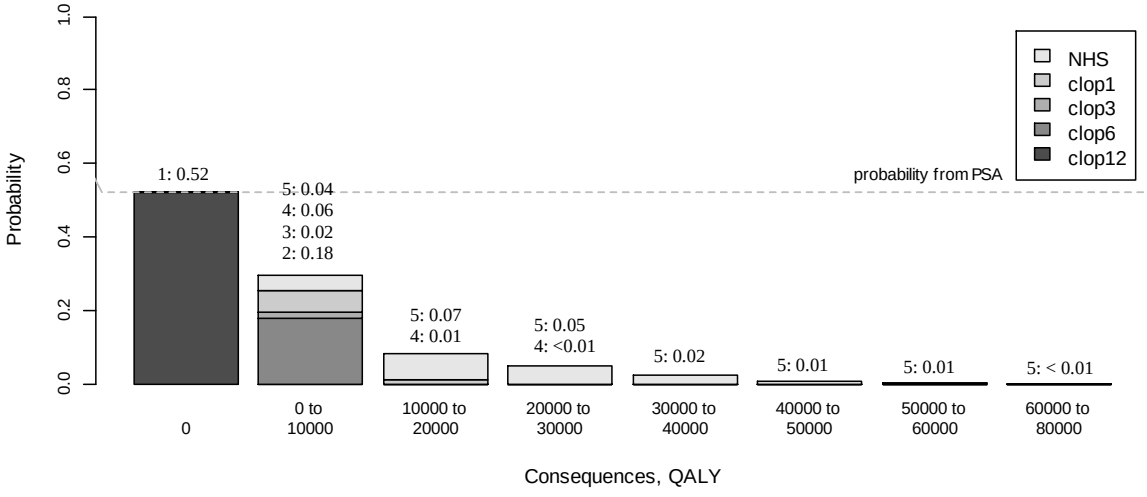
Table 3.5b Expected consequences of uncertainty for CLOP

		Cost-effectiveness threshold at:					
		£20,000 per QALY			£30,000 per QALY		
Treatment	**ICER,**	**Incr NHE *** QALY (£m)	**Probability cost-effective**	**Expected consequences** QALY (£m)	**Incr NHE *** QALY (£m)	**Probability cost-effective**	**Expected consequences** QALY (£m)
1: clop12	£18,663	495 (9.9m)	0.524	5,194 (103.9)	2,798 (56.0m)	0.677	3,657 (109.7)
2: clop6	£10,477	3,465 (69.3m)	0.180		4,736 (94.7m)	0.092	
3: clop3	£9,396	3,324 (66.5m)	0.018		4,305 (86.1m)	0.009	
4: clop1	£4,961	7,502 (150.0m)	0.075		8,327 (166.5m)	0.052	
5: NHS	-	-	0.202		-	0.170	

* The mean additional population NHE of moving from the least to most effective alternative, i.e., the incremental NHE of 12 month compared to NHS is the sum of these increments (14,786 QALY or £295.7m at £20,000 per QALY)

The distribution of consequences is illustrated in Figure 3.4b. Most commonly (52.4%) there are no consequences, because 12 months duration of treatment with CLOP is the correct decision. When it is not, there is a greater chance of relatively small consequences (30% are less than 10,000 QALYs) which occur predominantly when 6 months treatment duration offers the highest NHE. But there is a small chance of larger consequences (less than 5% chance that they are greater than 30,000QALYs) when standard NHS treatment offers the highest NHE, i.e., there remains important uncertainly about the cost-effectiveness of treatment itself, not just its duration. The expected consequence of uncertainty (5,194 QALYs) is simply the average over this distribution. Again this can be interpreted as an estimate of the population NHE that could be gained, over the time horizon of this technology, if the uncertainty about treatment and its duration could be immediately resolved. Therefore, like EECP, a judgement at this point that more research might be worthwhile seems reasonable, since the potential benefits exceed the likely costs.

Figure 3.4b Distribution of the consequences of uncertainty for CLOP



PsA provides a similar picture to CLOP, where approval of the alternative which is expected to be cost-effective (etanercept) is uncertain (probability that approval is incorrect is 0.557), but in this case most of this probability of error is associated with palliative care (probability of 0.4 that it is cost effective). Again, there is a greater chance of relatively small consequences (19% are less than 28,000 QALYs), most of which occur when adalimumab has the highest NHE, but a smaller chance of very large consequences (4.7% chance that they are greater than 138,000 QALYs), which occur when palliative care offers the greatest NHE. The expected consequences of uncertainty and the upper bound on the population NHE that might be gained by immediately resolving uncertainty (35, 342 QALYs or £707m over the technology time horizon) supports a judgement that more research maybe worthwhile.

ii) Analysis of subgroups

OMAL was not expected to be cost-effective based on existing evidence. The ICER in Table 3.2c was substantially greater than the threshold and a decision to reject this technology does not appear uncertain. This judgement is supported by the results of PSA (the probability that OMAL is cost effective is zero in Table 3.5c). Therefore, a decision to reject (Reject [4] in the algorithm) is not uncertain; there are no consequences of uncertainty and nothing to be gained by more research. However, it is possible to consider a high risk subgroup within this population. Subgroups, once credibly defined, need to be considered in the same way; starting at point 1 on the checklist, i.e., entering at the top of the algorithm. Although the ICER for this high risk subgroup is somewhat lower, it is still significantly higher than the threshold. The result of PSA suggest that at even at a threshold of £30,000 the probability that OMAL is cost-effective is very small and the upper bound on the gains from more research are very limited (10.61 QALYs). Therefore, even after an analysis of subgroups OMAL is not expected to be cost-effective and more research does not seem worthwhile. OMAL can be rejected at this point and no further assessment is required.

Table 3.5c Expected consequences of uncertainty for OMAL

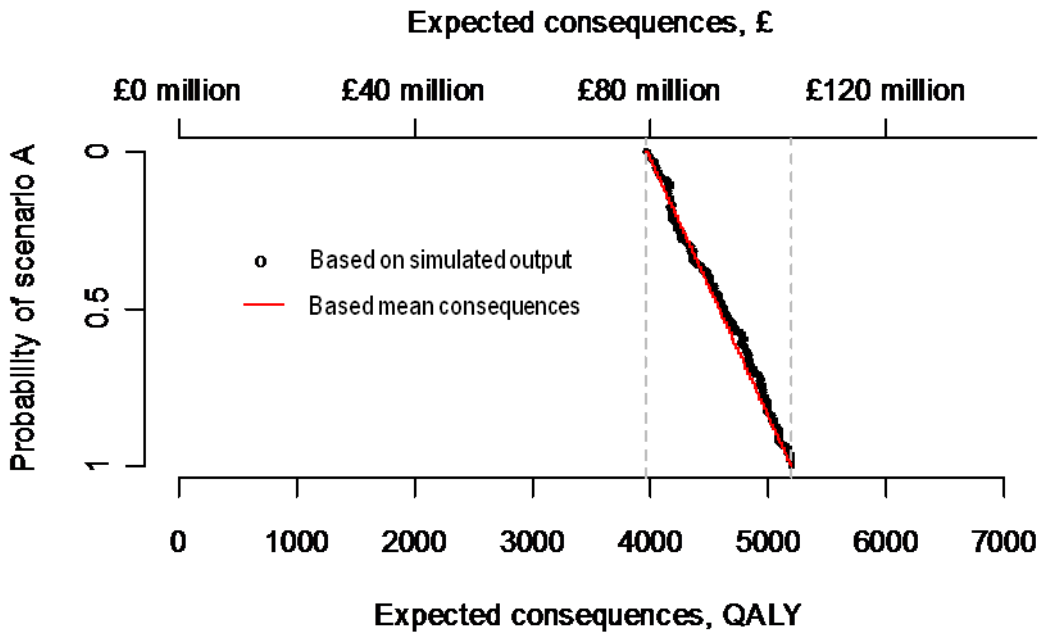
Severe population		**Cost-effectiveness threshold at:**					
		£20,000 per QALY			**£30,000 per QALY**		
Treatment	**ICER**	**Incr NHE** QALY (£m)	**Probability cost-effective**	**Expected consequences** QALY (£)	**Incr NHE** QALY (£m)	**Probability cost-effective**	**Expected consequences** QALY (£)
Omal + Std	£93,844	-5,789 (-116)	0.0	0	-3,337 (-100)	0.0	0.0
Std		-	1.0		-	1.0	
High risk subgroup		**Cost-effectiveness threshold at:**					
		£20,000 per QALY			**£30,000 per QALY**		
Treatment	**ICER**	**Incr NHE** QALY (£m)	**Probability cost-effective**	**Expected consequences,** QALY (£)	**Incr NHE** QALY (£m)	**Probability cost-effective**	**Expected consequences,** QALY (£m)
Omal + Std	£69,463	-3,851 (-77)	0.0	0	-2,048 (-61)	0.013	10.61 (0.32)
Std		-	1.0		-	0.987	

iii) Alternative scenarios

There are often alternative views about the quality and relevance of evidence as well as other assumptions that might be made when estimating expected costs and QALYs. These are commonly presented as separate scenarios, with estimates of costs and QALY presented for each. Much of the deliberation by the AC often surrounds the scientific value judgments required to judge the credibility of the alternative assumptions represented by the scenarios. The type of probabilistic analysis reported represents the uncertainty within each scenario and will be sufficient to indicate the potential benefits of research when only one scenario is regarded as credible. However, when more than one scenario might be credible and carry some 'weight', there will be uncertainty *between* as well as *within* scenarios. The 'weighting' of scenarios can be made explicit by assigning probabilities to represent how credible each is believed to be. The weighted average of costs and QALY across scenarios can easily be calculated. It is also tempting to take a simple weighted average of the expected consequences of uncertainty across these scenarios as well. However, a simple weighted average may under or overestimate the combined consequences of uncertainty within and between scenarios. The correct estimate requires the probabilities (weights) to be applied directly to the simulated output from PSA rather than to the mean values. Although this doesn't require additional simulation and is quick and easy to implement, it does require that either the probabilities are made explicit in advance or for estimates to be presented for a range of probabilities that might represent the judgement of the AC following deliberation.

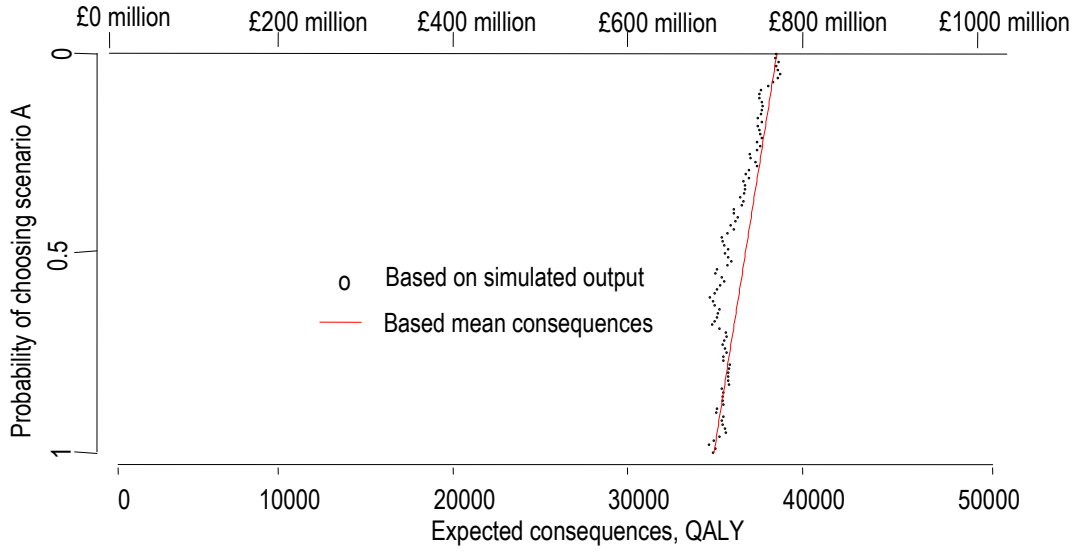
For example, the CLOP analysis presented above assumes a constant relative treatment effect for different durations of treatment (scenario A). An alternative assumption (scenario B) was that the relative treatment effect also differed by duration based on the data reported in the SIGN guidelines. This alternative assumption made longer durations less cost-effective and reduced the expected consequences of uncertainty from 5,195 to 3,969 QALYs. Although scenario A was regarded as more credible by the AC, scenario B might nevertheless carry some weight or have some probability associated with it. In this case the simple weighted average of expected consequences (linear combination of mean estimates) is very similar to the correct estimate based on weighting the output of PSA in Figure 3.5a. This figure also shows how these estimates can be presented for a range of probabilities.

Figure 3.5a Expected consequences of uncertainty with alternative scenarios (CLOP)



An alternative assumption of a common class effect across the three biologics was considered in the PsA case study (scenario B), but was judged less credible than the analysis which allowed differential effects (scenario A). The alternative scenario made etanercept less likely to be cost effective and increased the expected consequences of uncertainty from 34,930 to 38,521 QALYs (see Figure 3.5b). In this case a simple weighted average of expected consequences based on the probability assigned to each scenario is, in general, lower than the correct estimate of expected consequences based on the output from PSA.

Figure 3.5b Expected consequences of uncertainty with alternative scenarios (PsA)

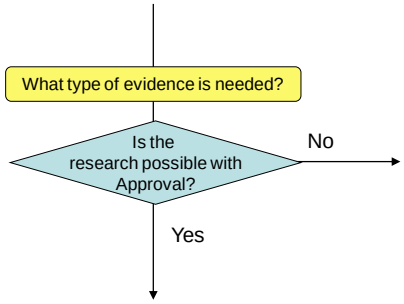


Elicitation

The single RCT of EECP showed evidence of improvements in quality of life at 12 months; however, the degree to which these are sustained in the long run is uncertain. Rather than make alternative assumptions and present extreme scenarios, formal elicitation of the judgements of clinical experts about the likelihood of QALY gains in subsequent years was undertaken.[22] The uncertainty in these elicited values is included in the estimates of the expected consequences of uncertainty reported in Table 3.5a, which might otherwise have been represented by alternative scenarios. For example: no QALY benefits beyond 12 months could be assumed for scenario A; benefits sustained for a patient's life time for scenario B; and sustained for 4 years for scenario C. The results of elicitation implied probabilities of: 0.243; 0.353; and 0.404 associated with each of these scenarios respectively. A simple weighted average of the expected consequences within each scenario using these probabilities (1,442 QALYs) significantly underestimates both the estimate of expected consequences based on the all the information from elicitation (9,287 QAYs) and the estimate based on weighting the simulated output rather than the mean estimates (13,081 QALYs). This illustrates that: i) a simple weighted average of expected consequences may be misleading; and ii) that elicitation may provide a richer characterisation of uncertainty as well the probabilities associated with alternative assumptions.

3.4.2 Point 4 - Is research possible with approval?

The fourth point on the check list requires an assessment of what type of evidence is needed and a judgement of whether the research required to generate it can be conducted while the technology is approved, i.e., at the following point in the algorithm:



Although the decision at this point does not lead directly to guidance, it does determine whether AWR or OIR are possibilities. This judgement will depend, in part, on whether the type of evidence that is needed will require experimental research design. For example, more precise estimates of relative

[22] Five experts with experience and knowledge of EECP in the UK, independently completed an Excel based exercise. The uncertainty associated with any judgement is critical, so a frequency chart format, where experts place 20 crosses on a frequency chart to represent a distribution was adopted. The results from each expert were linearly pooled, with equal weight, providing the probability of continuing to respond to treatment in each subsequent year. The uncertainty associated with these pooled estimates was characterised by fitting Beta distributions to pooled responses.

treatment effect are likely to require an RCT if the dangers of selection bias are to be avoided. However, further RCTs for this particular indication and patient group are unlikely to be possible once a technology is approved for widespread NHS use.

This requires judgements about: i) how important particular types of parameters (inputs to the economic model) are to estimates of cost and QALY; ii) what values these parameters would have to take to change a decision based on expected cost-effectiveness; iii) how likely is it that parameters might take such values and iv) what would be the consequences if they did, i.e., what might be gained in terms of population NHE if the uncertainty in the values of these parameters could be immediately resolved?

Assessing the importance of parameters

The type of economic model used to estimate expected cost-effectiveness in NICE appraisal specifies the relationship between the inputs (the parameters) and outputs (costs and QALYs). A simple summary of the direction and strength of these relationships can be provided by calculating elasticities for each, i.e., the proportionate change in the NHE of each alternative, and differences in NHE, due to a one percent change in the value of the parameter, e.g., those parameters with high elasticities (especially with respect to differences in NHE) might be regarded as more 'important'. These elasticities are presented for each case study in the addendum to the main report. Although these measures of importance are more instructive than a series of arbitrary one way sensitivity analysis, it does not directly help the assessment of what values parameters must take to change decisions and how likely such values might be. A simple summary of the values particular parameters must take to make each of the alternatives cost-effective can also be provided (see the addendum to the main report). However, although instructive, such 'threshold values' do not indicate how likely it is that threshold will be crossed or the combined effect of groups of related parameters.

Assessment of uncertainty

The judgement about how likely it is that parameters might take values which will change the technology expected to be cost effective can be informed by the results of probabilistic analysis. This is because the distributions assigned to parameters in PSA describe how uncertain the parameter estimates are, such that they ought to reflect the amount and quality of exiting evidence. The probability that each parameter might take values which would lead to each of the alternatives being cost-effective are reported for the CLOP case study in Table 3.6a. This, essentially, decomposes the overall probabilities reported in Table 3.5b into the contribution that each parameter makes[23]. Interestingly, it indicates that it

[23] The probability of error associated with 12 month of treatment reported in table 3.5b will, in general, not equal the sum of probabilities of error across the parameters, because the overall probability from PSA takes account of the joint effect of uncertainty in all parameters simultaneously. Even if parameters are independent they will be

is uncertainty in the estimates of relative effect (RR_Death) that contributes most to the probability of error associated with 12 months of treatment. It is the only parameter which might take values which could make any of the other alternatives cost-effective. It is also worth noting that there is a very small chance that cost in the 'well state' (C_Well) might be sufficiently high that standard NHS care would be cost-effective.

What type of evidence is needed?

Although an understanding of uncertainty and importance of parameters separately is helpful, an assessment of the likely consequences of this uncertainty, and therefore what might be potentially gained, in terms of population NHE, if uncertainty could be immediately resolved, is required. This assessment can directly inform the judgement of what evidence is needed and whether the type of research required to generate it will be possible with approval. In a similar way to Section 3.4.1, the results of PSA can inform this judgement since estimates of the expected consequences of uncertainty associated with each parameter combines both uncertainty in its potential values and their importance in terms of changing decisions and differences in NHE. The expected consequences of uncertainty associated with each parameter in CLOP are reported in Table 3.6b. This decomposes the overall expected consequences reported in Table 3.5b into the contribution that each parameter makes and which other alternatives might offer higher NHE than 12 month treatment.[24] It confirms that it is uncertainty in the estimates of relative effect (RR_Death) that contributes most and where there is potentially the most to be gained by resolving this uncertainty through additional research (4,433 QALYs or £88.7m). Since more precise estimates of relative effects are likely require a RCT, a judgement that the type of research need will not be possible if 12 month treatment duration is approved may be reasonable. However, the potential benefits of resolving the uncertainty associated with other groups of parameters, e.g., costs (547 QALYs or £10.9m) and the natural history (369 QALYs or £7.4m), might mean that other types of cheaper, non experimental research could be worthwhile as well.[25]

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related to differences in NHE in different ways (indicated by the sign and magnitude of the elasticities), so sometimes the effect of uncertainty in one may, to some extent, 'substitute' or 'complement' the effect of uncertainty in others.

[24] For similar reason to foot note 23 the overall expected consequences of uncertainty reported in table 3.5b (5,194 QALYs) will not, in general, equal the sum of the expected consequences for each of the parameters separately (5,432 QALYs).

[25] The sequence in which research might be conducted can also be considered. This is discussed at greater length and more formally in the technical appendix to the main report, i.e., OIR for treatment effects followed by AWR for natural history if that research continues to be necessary once research recommended in OIR reports. It is feasible to withdraw approval of a technology that is expected to be cost-effective to allow research to be conducted then in this case AWR followed by OIR if necessary is likely to offer greater expected population NHE.

Table 3.6a Probabilities associated with parameter values (CLOP)

	Parameter	Clop12	Clop6	Clop3	Clop1	NHS
Natural history	1 P_die_0.1	1	-	-	-	-
	2 P_NFMI_0.1	1	-	-	-	-
	3 P_die_1.3	1	-	-	-	-
	4 P_NFMI_1.3	1	-	-	-	-
	5 P_die_3.6	1	-	-	-	-
	6 P_NFMI_3.6	1	-	-	-	-
	7 P_die_6.12	0.65	0.35	-	-	-
	8 P_NFMI_6.12	0.91	0.09	-	-	-
	9 TP_AC	1	-	-	-	-
	10 TP_AD	0.83	0.17	-	-	-
	11 TP_CD	1	-	-	-	-
	12 TP_BD	0.85	0.15	-	-	-
Utilities	13 U_Well	1	-	-	-	-
	14 U_Well1	0.94	0.06	-	-	-
	15 U_NFMI	1	-	-	-	-
	16 U_POSTMI	1	-	-	-	-
RE	17 RR_death	0.55	0.18	0.01	0.10	0.16
	18 RR_NFMI	0.97	0.03	-	-	-
Costs	19 C_Well	0.78	0.19	-	-	0.03
	20 C_MI_LT	1	-	-	-	-
	21 C_PostMI	0.89	0.11	-	-	-
	22 TC_Well_Dead	1	-	-	-	-
	23 C_t1	0.95	0.05	-	-	-
	24 C_t2	0.99	0.01	-	-	-
	25 C_t3	1	-	-	-	-
	26 C_t4	1	-	-	-	-
	27 C_t5	1	-	-	-	-

Table 3.6b Consequences of uncertainty associated with parameter values (CLOP)

		Expected consequences (QALYs)					
		Decomposed by treatment choice					
	Parameter	clop12	clop6	clop3	clop1	NHS	Overall
Natural history*	1 P_die_0.1	0	-	-	-	-	0
	2 P_NFMI_0.1	0	-	-	-	-	0
	3 P_die_1.3	0	-	-	-	-	0
	4 P_NFMI_1.3	0	-	-	-	-	0
	5 P_die_3.6	0	-	-	-	-	0
	6 P_NFMI_3.6	0	-	-	-	-	0
	7 P_die_6.12	0	250	-	-	-	250
	8 P_NFMI_6.12	0	9	-	-	-	9
	9 TP_AC	0	-	-	-	-	0
	10 TP_AD	0	47	-	-	-	47
	11 TP_CD	0	-	-	-	-	0
	12 TP_BD	0	35	-	-	-	35
Utilities*	13 U_Well	0	-	-	-	-	0
	14 U_Well1	0	10	-	-	-	10
	15 U_NFMI	0	-	-	-	-	0
	16 U_POSTMI	0	-	-	-	-	0
RE	17 RR_death	0	284	16	518	3614	4433
	18 RR_NFMI	0	3	-	-	-	3
Costs*	19 C_Well	0	153	-	-	321	474
	20 C_MI_LT	0	-	-	-	-	0
	21 C_PostMI	0	8	-	-	-	8
	22 TC_Well_Dead	0	-	-	-	-	0
	23 C_t1	0	8	-	-	-	8
	24 C_t2	0	0	-	-	-	0
	25 C_t3	0	-	-	-	-	0
	26 C_t4	0	-	-	-	-	0
	27 C_t5	0	-	-	-	-	0

* Expected consequences for groups of parameters are: natural history 369 QALY (7.4m); RE 4,504 QALYs (£90.1m); 15 QALYs (£0.3m) and costs 547 QALYs (£10.9m). These are not equal to the sum of expected consequences for component parameters for the reasons explained in footnotes 23 and 24.

EECP provides a similar pattern of results, with the most significant consequences of uncertainty associated with parameters related to relative treatment effect; suggesting that the research needed might not be possible following approval of EECP or etanercept. Interestingly, although the probability of sustaining the QALY benefits of EECP in the long run is very uncertain, the greater part of potential value is in more precise estimates of QALY gains in the first 12 months (2,709 QALYs or £54m and 8,511 QALYs or £170m respectively).

In PsA, on the other hand, the greater potential value is associated with uncertainty in natural history of HAQ progression (8,697 QALY or £17.4m) rather than relative treatment effect (1,201 QALYs or £2.4m). Although this might suggest that AWR, which recommended research on HAQ progression is possible and worthwhile, the combined potential benefits of resolving uncertainty associated with natural

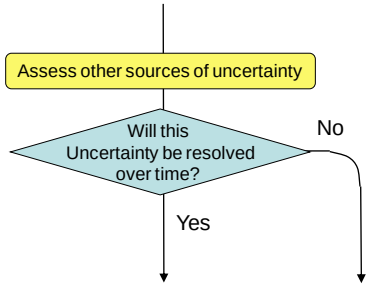
history and treatment effect together is much greater than the 'sum of its parts'.[26] This suggests that both types of research could be conducted while etanercept continues to be approved but infliximab and adalimumab are not, i.e., a possible OIR rather than reject for infliximab and adalimumab but AWR for etancercept..

3.5 Do the benefits of research exceed the costs?

The judgements made at points 5 and 6 of the check list are critical because if the benefits of research are not judged to exceed the costs then no further assessment are required (unless there are significant irrecoverable costs, see table B1 in Appendix B). If they are and research can be conducted with approval, then AWR would be appropriate. However, other sources of uncertainty need to be assessed first, as they will influence the potential benefits of research and, even when research is not conducted, they will also influence the appropriate category of guidance when there are significant irrecoverable costs.

3.5.1 Point 5 – Will other sources of uncertainty resolve over time?

The fifth point on the check list requires an assessment of whether changes are likely to occur in the future which will influence the cost-effectiveness of the alternative technologies and the potential benefits of research, i.e., at the following point in the algorithm:



The judgement made at this point will influence the potential benefits of research and therefore subsequent decisions which lead directly to a particular category of guidance (see point 6 in Section 3.5.2 below). Even when research was not considered worthwhile (at point 3) the presence of other sources of uncertainty will determine whether significant irrecoverable costs are likely to influence the category of guidance. In some circumstances it can lead directly to guidance, i.e., if there are no other sources of uncertainty even significant irrecoverable costs will have no influence and a technology which is expected to be cost effective can be approved:

Pathway number	Assessment	1	2	3	4	5	6	7	Guidance
	29	Yes	Yes	No	-	No	-	-	Approve 12

[26] These values represents an upper bound on what might be gained be resolving each alone. The potential value of resolving these uncertainties together is much greater for the reasons give in footnote 23 and 24.

This assessment requires information about: i) changes in prices of the technology and its comparators; ii) the emergence of new technologies which might make existing ones obsolete or change their cost-effectiveness; and iii) other relevant research reporting. A number of potential sources of information and evidence were examined to inform this assessment for each case study (the full details of the sources and searches conducted are reported in the addendum to the main report). However, many potentially useful sources wereeither proprietary or public access was restricted, making it surprisingly difficult to inform these assessments with publically available information. When information and estimates were available they were often not directly relevant to a UK context.

i) Changes in the price (the technology and its comparators)

Changes in prices not only influence expected cost effectiveness but also uncertainty and the potential benefits of research to future patients, e.g., if the price of a technology expected to be cost-effective is likely to fall significantly just before research reports the potential benefits will not be realised because approval of the technology will be less uncertain and there may be much less or little to gain from the results of the research. This assessment requires information about when major changes in prices are likely and some evidence about the likely extent of the change. A major event in the life cycle of a pharmaceutical technology is the date at which the patient expires and cheaper generic versions of the brand become available. Although the date of patient expiry is, of course known, it is surprisingly difficult to obtain the relevant date for particular products in the UK from publically available sources. Evidence of the extent to which the price of generic versions are below the original brand price are also difficult to obtain and are likely to differ by health care system, type of technology, indication and time since patient expiry. Therefore, the estimate, reported by the Office of Fair Trading, that on average generic prices tend to be 25% of the original price was used in the subsequent analysis.

At the time of TA80 the patent for CLOP was expected to expire 7 years later and subsequent analysis assumes that at that time equivalent generic prices will be 25% of the original price of CLOP at the time of TA80.[27] Although it was possible, for the PsA case study, to find patent expiry dates for Etanercept (Enbrel), Infliximab (Remicade) and Adalimumab (Humira) in the US (2012, 2014 and 2017 respectively) they were not available for the UK on the National Patent Database (IPO). It is even more difficult to locate patient information relevant to devices, such as EECP, since a device may only have a CE mark, which, unlike a patent, does not offer protection and can be renewed every 10years. Any patent is likely to relate to some aspect of the device rather than the device itself. Although, prices may change over time they can also be relatively stable but with incremental innovation of the original device. Again this is likely to differ by health care system, technology and indication. For these reasons

[27] This assumes that either prescribing will switch from the brand to equivalent generic (brands tend to maintain, or even increase premium prices in some health care systems, after patient expiry) or that any new branded technologies will be appraised using generic versions of the old brand as a comparator.

future changes in prices are only quantitatively explored in subsequent analysis in CLOP in Section 3.5.2. There is a need to consider how access to the type of information required during NICE appraisal can be provided and how estimates of likely changes in prices relevant to the UK can be made readily available, if these assessments are to be routinely made.

ii) Entry of new technologies

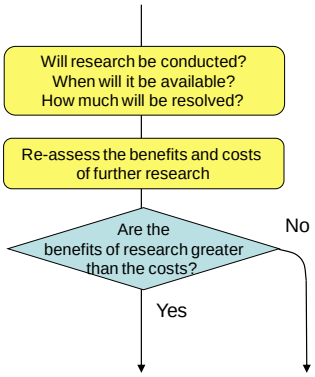
The entry of a new technology may make the existing technology that is expected to be cost-effective obsolete (no longer the most cost-effective alternative). Even when it does not, it will tend to change the relative cost effectiveness of the alternatives, influencing how uncertain a decision to approve the original technology will be for future patients and the potential gains from research. A number of potential sources of information were examined to identify new technologies relevant to the indications which were likely to become available. These included a variety of sources related to NICE topic selection, information about licence applications, clinical research in phase I, II and III as well as evidence of the probability that earlier phase research leads to entry (probability of successful licence) and the likely time of entry (time to launch from initiating phase I, II and III research). Again this information and evidence is fragmented, and in some cases restricted, e.g., NHS Horizon Scanning. Nevertheless, the information that was available indicated that one new technology relevant to CLOP and one relevant to PsA might have been expected to enter. Information about these technologies was limited so scenarios are used to explore the implication for CLOP and PsA in Section 3.5.2.

iii) Other research reporting (the technology and its comparators)

Research which is already underway, commissioned or likely to be undertaken whether in the UK or elsewhere, is relevant for two reasons. Firstly, if it is research based in the UK then guidance might impact on recruitment and the successful completion of this research (see Section 3.6). Secondly, when this research reports there is a chance that it will change the estimates of cost-effectiveness and resolve some of the current uncertainties. In other words, there is little to be gained by recommending OIR or AWR if the uncertainty is likely to be resolved in the near future when other research reports. A number of potential sources of information were examined to identify clinical research underway at the time of the relevant appraisal, including: national and international trial registries; as well as other databases which report NHS funded research and not just clinical trials (e.g., NRR and UKCRN). Despite an assiduous search no records relevant to the case studies were identified. This may suggest that no other research was ongoing or expected for these comparators in these indications, or it may indicate that currently available sources are fragmented, incomplete and/or difficult to access.

3.5.2 Point 6 – Are the benefits of research greater than the costs?

The sixth point on the checklist requires a re-assessment of the potential benefits of conducting further research which were initially considered at point 3 (see Section 3.4.1), and a judgment of whether the benefits of research are likely to exceed the costs i.e., at the following point in the algorithm:



A judgment about whether the potential benefits of research identified in Section 3.4 will be realised requires an assessment of: i) whether the type of research that is required is likely to be conducted; ii) if conducted, when the results are likely to be available; iii) how much uncertainty is likely to be resolved and iv) the likely impact of the other sources of uncertainty identified in Section 3.5.1 on the longer term benefits of research.

The decision at this point may not necessarily lead directly guidance. For example, where the benefits of research exceed the costs but research is not possible with approval or there are significant irrecoverable costs. Which category of guidance will ultimately be appropriate will depend on whether the benefits of approval are judged to exceed the costs, i.e., point 7 of the checklist in Section 3.6. However, in many other circumstances the decision at this point will lead directly to a particular category of guidance. These circumstances or pathways through the algorithm are detailed below (extracted from Table B1 in Appendix B):

	Assessment	1	2	3	4	5	6	7	Guidance
Pathway number	1	Yes	No	Yes	Yes	Yes/No	Yes	-	AWR 1
	2	Yes	No	Yes	Yes	Yes/No	No	-	Approve 1
	5	Yes	No	Yes	No	Yes/No	No	-	Approve3
	7	No	No	Yes	Yes	Yes/No	Yes	-	OIR 2
	8	No	No	Yes	Yes	Yes/No	No	-	Reject 1
	11	No	No	Yes	No	Yes/No	No	-	Reject 3
	19	Yes	Yes	Yes	Yes	No	No	-	Approve 6
	26	Yes	Yes	Yes	No	No	No	-	Approve 10
	30	No	Yes	Yes	Yes	Yes/No	Yes	-	OIR 7
	31	No	Yes	Yes	Yes	Yes/No	No	-	Reject 8
	34	No	Yes	Yes	No	Yes/No	No	-	Reject 10

The expected consequences of uncertainty reported in Section 3.4.1 represented the NHE that could be gained over the lifetime of the technology if the uncertainty surrounding the decision based on expected cost-effectiveness could be immediately and completely resolved. This represents an upper bound on the potential benefits of research for a number of reasons: i) research, although recommended, might not be commissioned and/or recruit and report; ii) any research will take some time to complete before results are available; and iii) not all of the uncertainty is likely to be resolved. In addition, future events (identified in Section 3.5.1) might change the NHE expected to be gained by future patient populations. Finally, the expected benefits of research once properly re-assessed must be compared to the likely costs.

i) Will the research be conducted?

Even if research is recommended in OIR or AWR, it might not be undertaken by manufacturers or commissioned by research funders. Even if undertaken or commissioned, there is no guarantee that research will be able to recruit or it may not complete for other reasons. The expected consequences of uncertainty for CLOP and EECP reported in Section 3.4.1 are illustrated for a range of probabilities that research will be successfully undertaken in Figures 3.6a and 3.6b respectively. This indicates that the potential gains depend on a judgment of whether the research recommended as part of OIR or AWR will be successfully completed. They also illustrate that the cost of research (in this case considered to be either £1.5m or £10m) can be compared directly to the potential benefits by either expressing the potential gains in population NHE as the equivalent NHS resources (i.e., the resources that would be required to generate the same NHE) or expressing the cost of research in terms of the QALYs that could be gained elsewhere in the NHS by using the same resources to provide access to health care.

Figure 3.6a Expected potential benefits of research (CLOP)

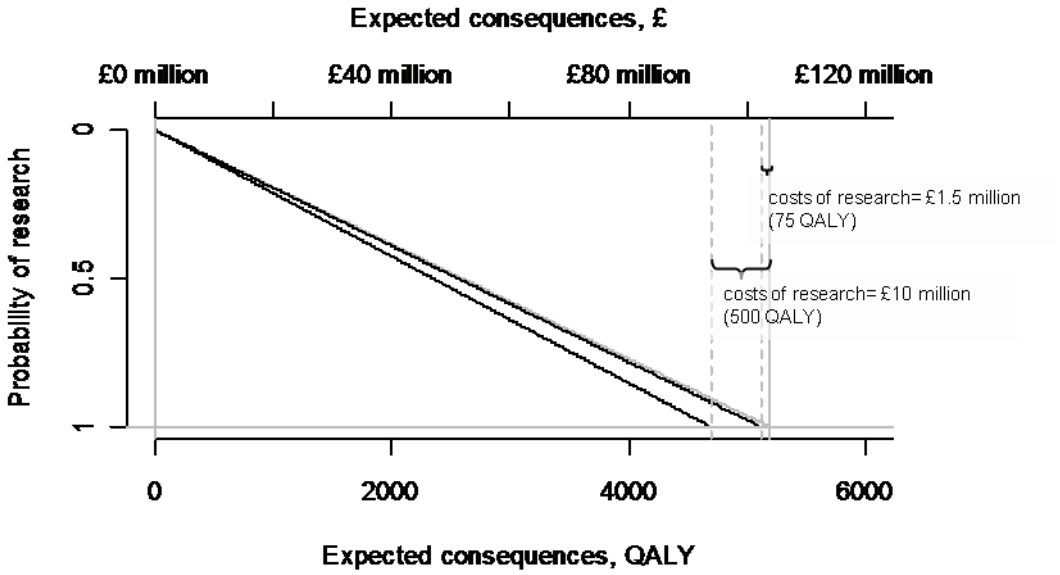
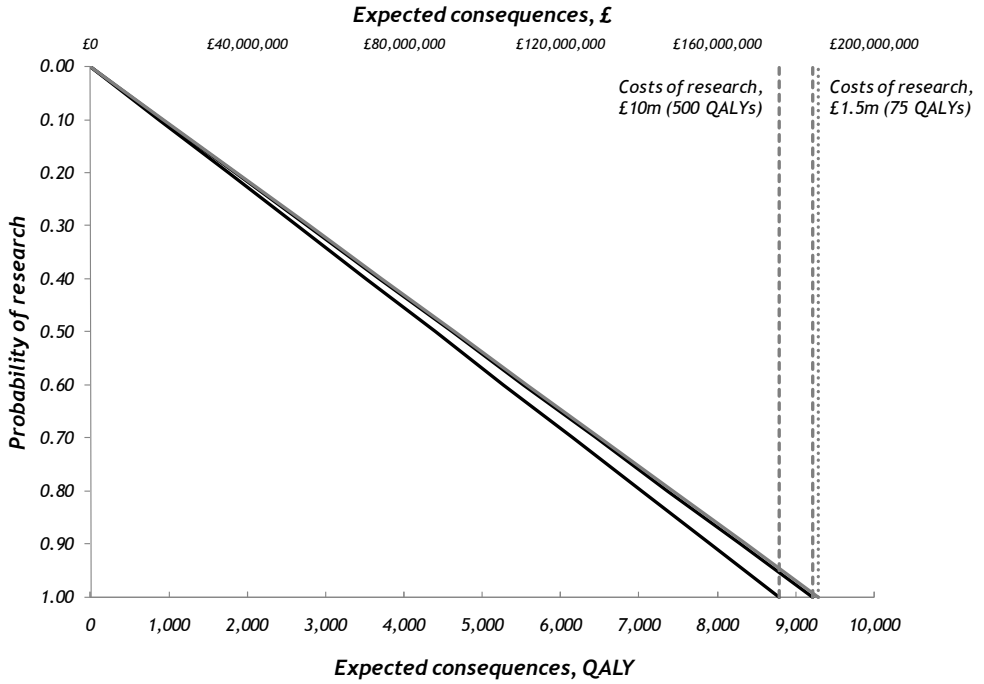


Figure 3.6b Expected potential benefits of research (EECP)



ii) When will it be available?

Research, even if commissioned and successfully completed, will take time to complete and report. Therefore, any assessment of the potential benefits should account for the fact that patient populations will not benefit from the results of research until they are available. Whether those patients who are prevalent while research is underway will be able to benefit from the results will depend on whether treatment decisions for presenting patients are irreversible or not (see Section 3.3.2). If treatment decisions are irreversible, e.g., in CLOP which is an acute indication, then it is only those patients' incident after the research reports that will realise any of the potential benefits. In contrast, treatment

decisions in EECP are not irreversible (since it is a chronic condition), so although patients prevalent while research is undertaken will not benefit immediately, those that survive can benefit from the results once the research is completed. How long research might take to report will depend in part on the design (follow-up, sample size and endpoints), recruitment rates and size of the eligible patient population, as well as how efficient the organisation and data collection might be. The potential value of research in CLOP and EECP over a range of possible time horizons is reported in Figures 3.7a and 3.7b respectively. In both cases the potential value of further research declines with the time to research reporting. This relationship gives some indication of the value of improving the timeliness of research though, for example, investment in research infrastructure or adopting a research design, which, although offering less potential benefits, can be conducted more quickly.

Figure 3.7a Potential value of research and time to report (CLOP)

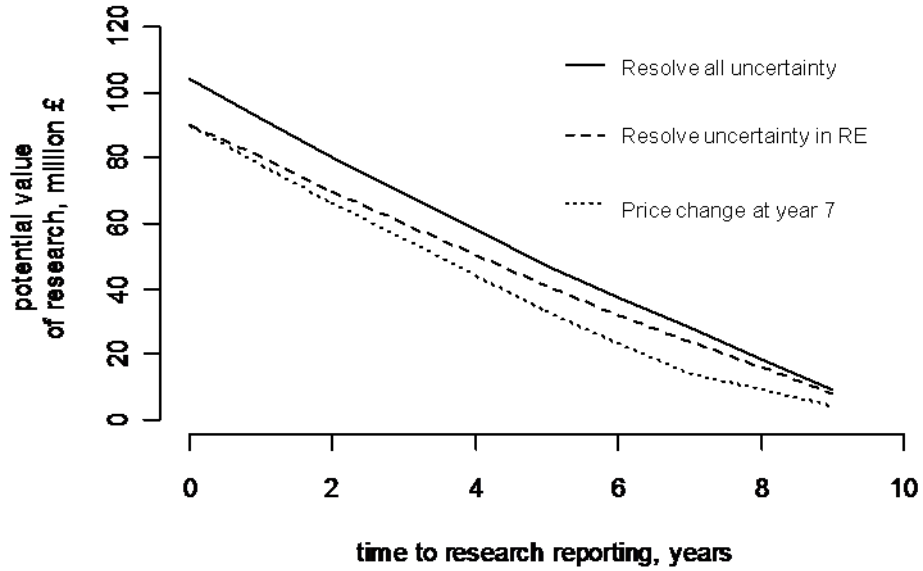
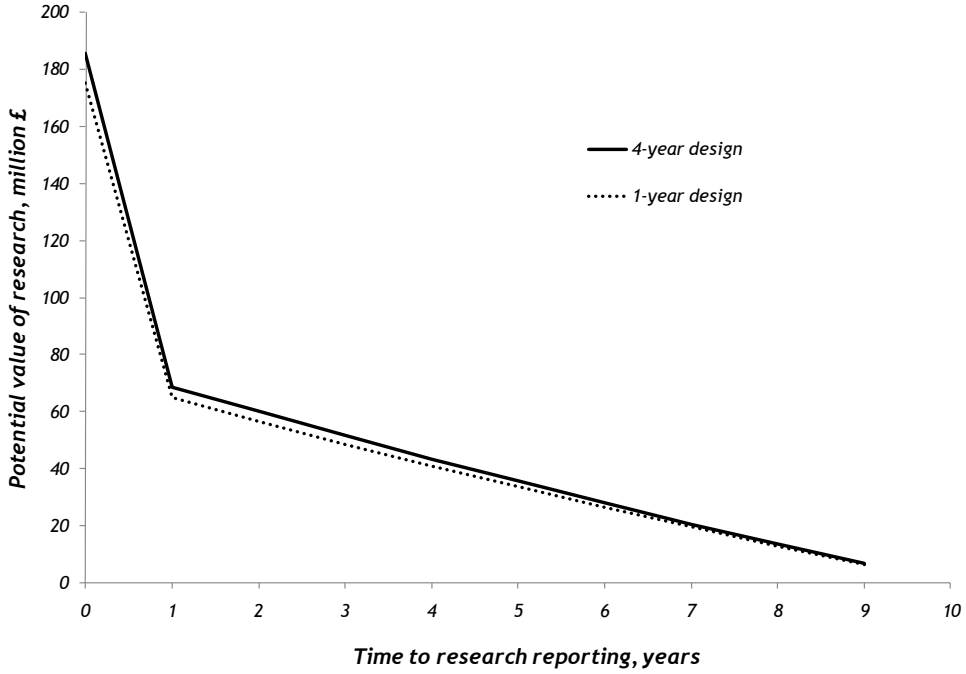


Figure 3.7b Potential benefits of research and time to report (EECP)



iii) How much will be resolved?

Most research will not inform all the parameters that determine expected cost and QALYs but usually a subset of them. Therefore, the potential benefits of research that might be conducted will not be the total expected costs of uncertainty surrounding expected cost-effectiveness, but some part of it. In Section 3.4.3 the potential benefits of different types of evidence was assessed. In CLOP it was additional evidence about relative treatment effects that were most valuable and therefore experimental research may be required to provide more precise estimates of RR_Death. The potential value of research, which only resolved uncertainty about this relative treatment effect over a range of times to report, is also represented in Figure 3.7a (denoted by the legend 'resolve uncertainty in RE'). Although the potential value of research is lower at every time point, unless research is likely to take more than 8 years, the potential value is still likely to exceed the costs. In EECP there was most benefit to be gained by resolving the uncertainty in the improvement in quality of life at 12 months, which in common with CLOP, is likely to require experimental design. Figure 3.6b represents the potential benefits of alternative trial designs with either one or four years of follow-up (1, 2, 3 and 4 year follow-up designs were evaluated, see addendum to the main report). Although longer follow-up offers greater potential benefits they are relatively small compared to the loss of potential value if longer follow-up delays the time until research findings are available, i.e., a 4 year design will require a minimum of 4 years to complete. Again, as long as research reports before 8 years, the potential benefits are likely to exceed the costs

iv) What is the impact of other source of uncertainty?

In Section 3.5.1 the information that was publically available identified that the patent for CLOP was due to expire 7 years after the appraisal. Based on the OFT estimate that generic prices tend to be 25% of the original brand price, this other source of uncertainty which will resolve over time can be integrated quantitatively when estimating the potential value of research over the life time of the technology. In this case a significant fall in price in year 7 will substantially reduce the reduce uncertainty surrounding 12 months of treatment with CLOP. Therefore after year 7 there is less to be gained from resolving uncertainty, so the potential and value of research findings for patients' incident after year 7 are thereby reduced. The effect of a price change on research which could potentially resolve uncertainty in cost natural history, and utilities as well as relative effect is also illustrated in Figure 3.6a. The potential value of the research is lower whenever the research reports, because it includes the value to future as well as current patient populations. Nevertheless, even if research didn't report until 7 years the potential value is likely to exceed the costs (see Figure3.7a). The expected price reduction reduces the potential value of research at each time point for both scenarios, e.g., for scenario B from 174,519 QALYs when research is immediately available (see Figure 3.8a) to 165,701 with a price change at year 7.[28]

There was some evidence of possible entry of a new technology (comparator) in the indication described in the CLOP case study. However, there was limited information on its characteristics. Therefore two alternative but somewhat extreme scenarios are illustrated in Figure 3.8a. In scenario A the new technology enters at years 5 and makes CLOP entirely obsolete, i.e., not cost-effective and not uncertain – equivalent to a shorter technology horizon of 5 years. At this point there is no value in the evidence generated by research about CLOP.[29] In these circumstances the potential value of research is only likely to exceed its costs if it reports quickly. In scenario B the new technology has similar NHE to 12 month of treatment with CLOP[30] and the uncertainty surrounding its expected cost-effectiveness is also similar. Now research about CLOP has more potential value in the future since it will also help resolve some of the uncertainty in the choice between CLOP and the new technology for patients that become incident after that time. Although there was no evidence of new technologies emerging in EECP, the same scenarios are explored as the development and launch of new devices are more difficult to identify in advance. The impact on the potential value of research is illustrated in Figure 3.8b and demonstrates similar qualitative effects as CLOP. In scenario A (EECP becomes obsolete) the potential benefits of further research about EECP are only likely to exceed the costs if the research

[28] These much higher values of immediate research than the 4,495 QALYs or £89.9m in Figure 3.7a without the entry of a new technology but with a similar price change.
[29] There may continue to be value if evidence about CLOP remains is an important link in mixed or indirect treatment comparisons required to evaluate the new technology.
[30] This is likely to be an increasingly common scenario if value based pricing effectively makes all branded technologies equally cost-effective.

reports quickly. Nevertheless, even in this extreme scenario the benefits of research with only 1 year follow-up are likely to exceed the costs so long as it reports before 4 years.

The potential value of research presented in these figures, even after accounting for the type of evidence, follow-up and time until research reports, should still be regarded as an upper bound to the value that is likely to be realised by actual research for two reasons: i) even well designed research with large sample sizes will not fully resolve the uncertainty in the value that a parameter might take, especially in specific target populations and in a particular (future) contexts; and ii) insofar as implementation of NICE guidance is not 'perfect' and all clinical practice might not immediately respond to the results of research, the full benefits will only be realised over time or with additional implementation efforts. For these reasons a judgment of whether benefits of research are likely to exceed the costs might be made conservatively, requiring evidence that, even in pessimistic scenarios, the research would still worthwhile.

Figure 3.8a Potential value of research and other sources of uncertainty (CLOP)

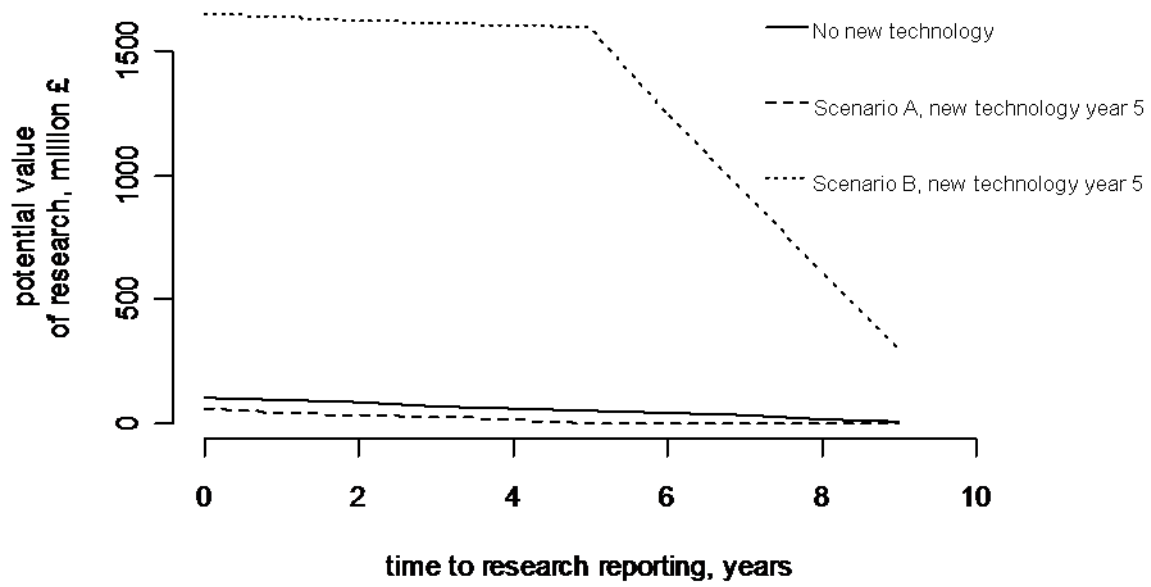
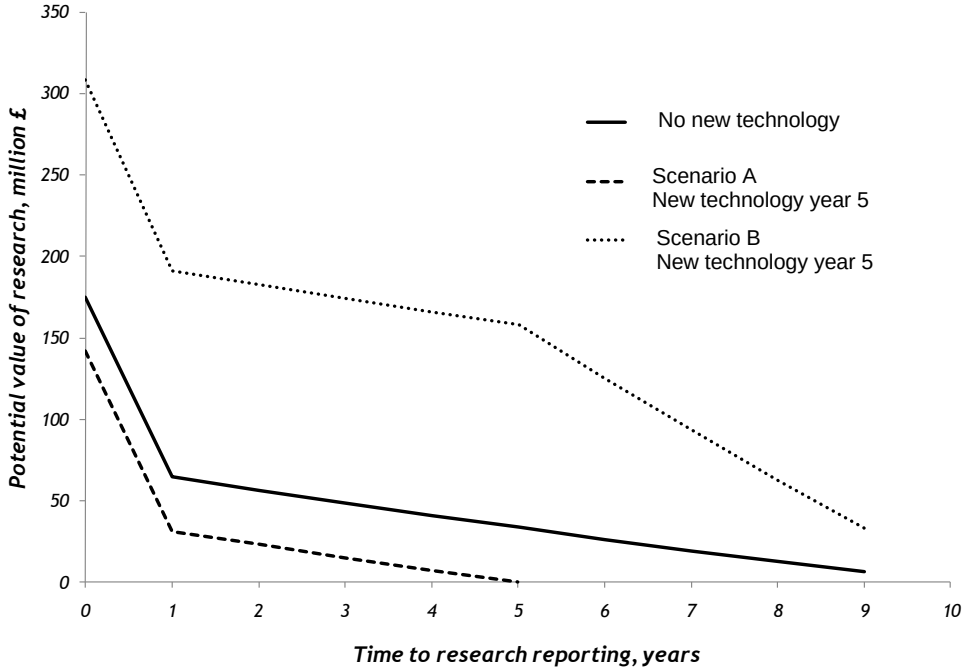


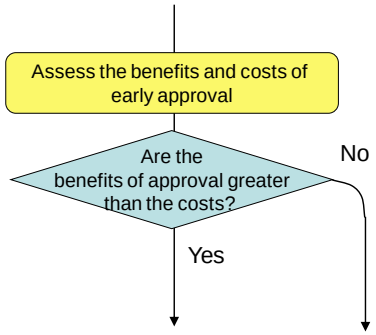
Figure 3.8b Potential value of research and other sources of uncertainty (EECP)*



* These potential values are based on a 1 year follow-up design

3.6 Point 7 – Are the benefits of approval greater than the costs

The seventh and final point on the checklist requires an assessment and comparison of the benefits and costs of early approval. The costs of approval, are not financial ones, but opportunity costs, and will include the potential value of any research that maybe forgone as a consequence, e.g., if the research needed cannot be conducted once the technology is approved for use. It will also include any costs that are irrecoverably committed by approval. As well as the capital costs of equipment and facilities (or training and learning), they will also include the irrecoverable opportunity costs of initially negative NHE (if treatment decisions are not irreversible - see the discussion in Section 3.3.1 and 3.3.2). A judgment of whether the benefits of approval and early access for current patients are likely to exceed the opportunity costs for future patients is required i.e., at the following point in the algorithm:



The decision at this point always leads directly to guidance; allocating all remaining possible pathways to a particular type and category of guidance. These remaining (20) pathways through the algorithm are detailed below (extracted from Table B1 in Appendix B):

Pathway number

Assessment	1	2	3	4	5	6	7	Guidance
3	Yes	No	Yes	No	Yes/No	Yes	Yes	Approve 2
4	Yes	No	Yes	No	Yes/No	Yes	No	OIR 1
9	No	No	Yes	No	Yes/No	Yes	Yes	AWR 2
10	No	No	Yes	No	Yes/No	Yes	No	Reject 2
13	Yes	Yes	Yes	Yes	Yes	Yes	Yes	AWR 3
14	Yes	Yes	Yes	Yes	Yes	Yes	No	OIR 3
15	Yes	Yes	Yes	Yes	Yes	No	Yes	Approve 5
16	Yes	Yes	Yes	Yes	Yes	No	No	Reject 5
17	Yes	Yes	Yes	Yes	No	Yes	Yes	AWR 4
18	Yes	Yes	Yes	Yes	No	Yes	No	OIR 4
20	Yes	Yes	Yes	No	Yes	Yes	Yes	Approve 7
21	Yes	Yes	Yes	No	Yes	Yes	No	OIR 5
22	Yes	Yes	Yes	No	Yes	No	Yes	Approve 8
23	Yes	Yes	Yes	No	Yes	No	No	Reject 6
24	Yes	Yes	Yes	No	No	Yes	Yes	Approve 9
25	Yes	Yes	Yes	No	No	Yes	No	OIR 6
27	Yes	Yes	No	n/a	Yes	n/a	Yes	Approve 11
28	Yes	Yes	No	n/a	Yes	n/a	No	Reject 7
32	No	Yes	Yes	No	Yes/No	Yes	Yes	AWR 5
33	No	Yes	Yes	No	Yes/No	Yes	No	Reject 9

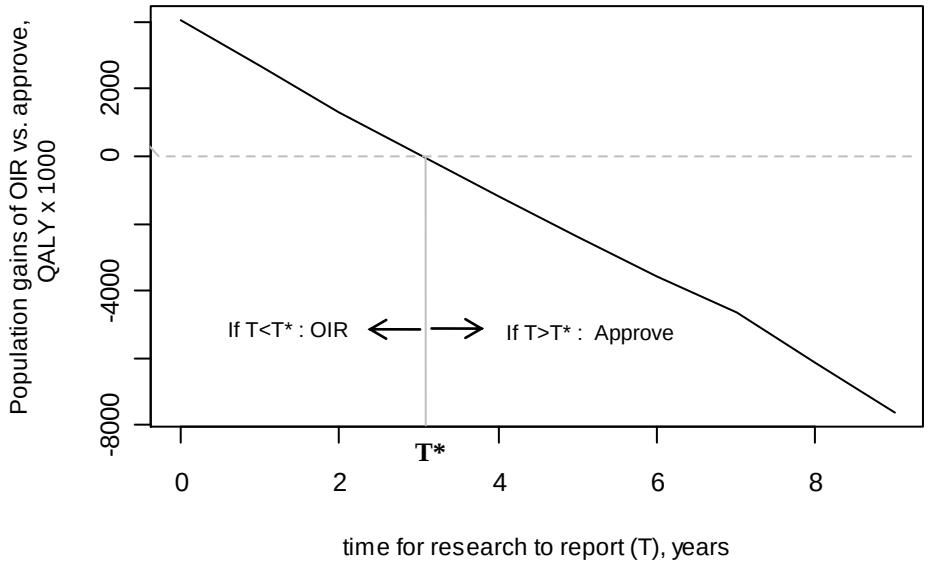
Significant irrecoverable costs

3.6.1 Technologies without significant irrecoverable costs

Only four of the 20 possible pathways illustrated above are associated with technologies without significant irrecoverable costs. In these four pathways, research was either: i) not considered possible *with* approval for those expected to be cost effective (i.e., Approve[2] or OIR[1]); or ii) research was not possible *without* approval for those not expected to be cost effective (i.e., AWR[2] or Reject [2]). CLOP provides as example of the former. It is research that would provide more precise estimates of the relative effect of CLOP and of shorter treatment durations, which is potentially valuable (see Section 3.4.2). As a consequence, the type experimental design that is likely to be needed is unlikely to be possible if 12 months of treatment with CLOP is already approved for widespread NHS use. Although treatment with CLOP does commit initially negative NHE that are irrecoverable, these should not be regarded as significant since the treatment decision for a presenting patient is irreversible in relevant time frames (see Section 3.3.2). Therefore, AWR may not be possible, so the benefits of early access to 12 months of treatment with CLOP (Approval) must be compared to the potential value of OIR.

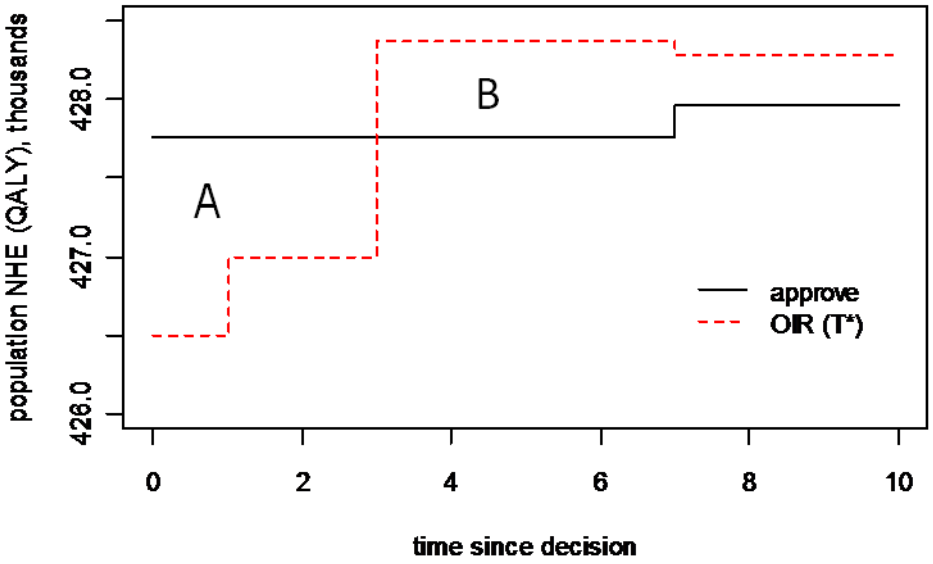
OIR is more likely to offer greater expected NHE than Approve if the research can be conducted quickly and report sooner, since fewer patients forgo access to CLOP and more can have treatment choice informed by the research finding. This is illustrated in Figure 3.9a which reports the difference between Approve and OIR in population NHE over a range of times for when the research recommended in OIR might report. This takes account of both the expected changes in price at year 7 and research costs of £10m. It shows that OIR will only be appropriate of the research reports within 3 years of appraisal (T* = 3) because beyond this time the NHE forgone by withholding access to CLOP will exceed the potential gains to future patients.

Figure 3.9a Population NHE of Approve and OIR for time to research reporting (CLOP)



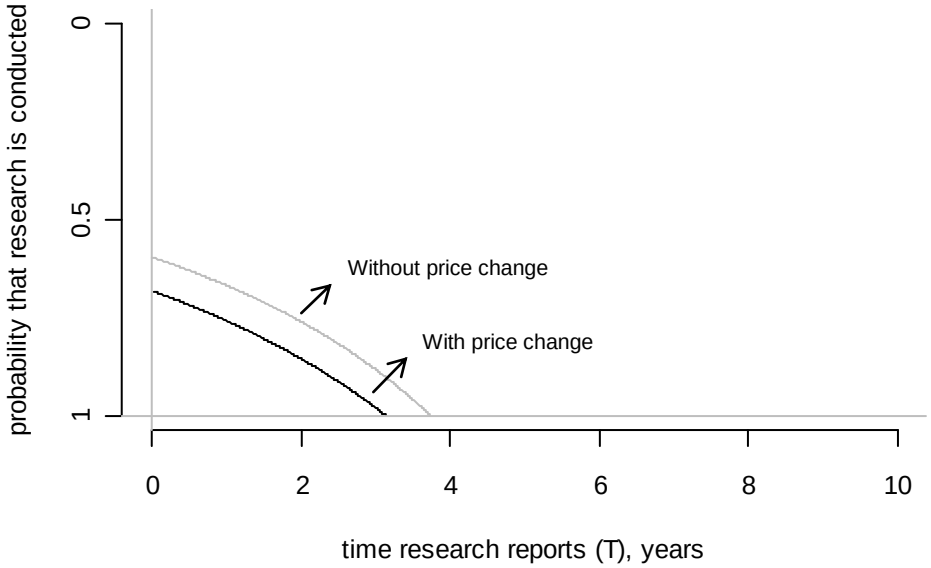
The trade-off between NHE for current and future patients which lies behind Figure 3.9a is illustrated in Figure 3.10 using undiscounted values for ease of exposition. It illustrates the (per period) population NHE of approval and OIR, if the research recommended as part of OIR reports at year 3. At this point, the initial losses of NHE, caused by restricting access to CLOP (area A), start to be offset by the potential gains from the research findings (area B). The price change at year 7 increases the NHE of approval (i.e., CLOP is more cost-effective) but on balance reduces the NHE of OIR, i.e., although CLOP is more cost-effective and offers greater NHE the evidence generated by the research reporting is less valuable because the choice of treatment and duration is less uncertain (see sections 3.5.1 and 3.5.2). With research reporting at 3 years the initial losses of OIR (area A) are just offset by the later gains (area B), so T* = 3. If research reported earlier than 3 years (area A > area B) and OIR would be appropriate but if later than 3 years (area A > area B) and Approve would be more appropriate.

Figure 3.10 Population NHE of Approve and OIR at T* (CLOP)



However, there is no guarantee that the research recommended as part of OIR guidance will be conducted by manufacturers or commissioned by research funders. Even if it is, it is not certain that it will be successfully completed (see discussion in Section 3.5.2). Therefore, the probability that research will report at a particular time also needs to be considered. The implications of considering whether the recommended research will be conducted and when it might report are illustrated in Figure 3.11a, which presents a boundary for when OIR might be appropriate or when approval should be granted. For example, if research is certain to report but will take 4 years, or when it will only take 1 year but with only a 50% chance of reporting, then OIR would not be appropriate and 12 month treatment of CLOP should be approved, i.e., these points fall to the north east of this boundary. Points to the south west of the boundary indicate that OIR might be appropriate.

Figure 3.11a An OIR or Approve boundary (CLOP)



However, the estimates of the potential value of research on which these boundaries are based are still likely to overestimate the value that will be realised by research (see discussion in Section 3.5.2); they represent a necessary condition for OIR. Therefore, OIR guidance should require a conservative judgment that the point is almost certain to be below the boundary, rather than on balance close to it. For the same reason, points anywhere above the boundary represent a sufficient condition for approval. The boundary when the change in price is included is to the south west; reflecting the lower potential value of research, and OIR guidance, once CLOP becomes more cost-effective. In this case it seems unlikely that the type of research required could report quickly enough and with sufficient confidence that OIR would be appropriate. Therefore, these assessments would support a judgment that the benefits of approval are likely to exceed the opportunity costs, and Approve[2] (pathway 3 for CLOP) would be more appropriate.

The assessments that have been undertaken for CLOP can be bought together to consider: i) what would be the value of being able to conduct research while CLOP is approved and ii) what would be the value of making evidence that is needed by the NHS available at launch. These questions can be informed by the results (already presented elsewhere) but also reported in Table 3.7a.

Table 3.7a Population NHE over the technology time horizon for different policies (CLOP)

	Approve	OIR	AWR*	Reject	Value of AWR	Uncertainty resolved at launch	Value of evidence at launch
Expressed in QALY							
T<T* (T=2)	3,680,187	3,681,480	3,682,995	3,671,660	1,515	3,684,181	2,701
T>T* (T=7)	3,680,187	3,675,487	3,680,362	3,671,660	175	3,684,181	3,994
NHE expressed in £m							
T<T* (T=2)	73,604	73,630	73,660	73,433	30	73,684	54
T>T* (T=7)	73,604	73,510	73,607	73,433	4	73,684	80

The difference in population NHE between AWR (if it had been possible) and the next best feasible policy (i.e., OIR for T<T* = £30m and Approve T>T*=£4m) represents the value to the NHS of being able to conduct research while CLOP is approved for use, e.g., informing whether investment in better data collection, registries or information systems that might make this possible.[31] The difference in population NHE when all uncertainty had been resolved prior to appraisal (at launch) and the next best available policy (i.e., OIR for T<T* = £54m and Approve for T>T*=£80m) represents the value to the NHS of having access to the evidence needed at launch. This can inform policies which might make better and more relevant evidence available.

It is also possible to consider the commercial and well as NHS value in each of the cells of this table. The value of early evidence at launch can then be considered from the perspective of the manufacturer (the expected revenue streams), taking account of prices (see discussion of price in Section 2.2.1 and 2.2.2) and expected volumes over the remaining patent life and technology time horizon. Together with estimates of the costs of conducting research by manufacturers or though public funding, this assessment might inform when manufacturers might be expected to conduct the research needed (high commercial value that exceeds the cost to manufacturers) and when the NHS might be expected to undertake it (low commercial value but high potential value to the NHS that exceeds the costs to the NHS). In many circumstances both the commercial and NHS values will exceed their respective costs. In these circumstances the question of who should conduct, or pay for, the research might be informed by which sector has the comparative advantage, i.e., which has the highest 'relative efficiency' in generating social value? Of course, the value to the NHS and to manufacturers will depend; to a large extent, on what type of flexible pricing arrangements and value based pricing scheme might be in place (see discussion in Section 2.2.1 and 2.2.2). The question will also turn on how any agreements can be made and incentive consistent contracts written and enforced.

[31] Even with such investment AWR might not be possible if there is insufficient variation in treatment assignment and no robust way of controlling for unobserved characteristics through, for example instrumental variables.

3.6.2 Technologies with significant irrecoverable costs

Only 16 of the 20 possible pathways illustrated above are associated with technologies with significant irrecoverable costs. This is because even when research is possible with approval (or even when not needed), the impact of committing irrecoverable cost through AWR (or approval) must be considered, so OIR (or reject) remains a possibility. EECP provides an example of this; where research that would provide more precise estimates of the effect of treatment on quality of life accounts for all the potential value (see Section 3.4.2). EECP does commit both capital costs associated with long lived equipment, as well as initially negative per patient NHE. Unlike CLOP these irrecoverable opportunity costs at a patient level are significant because treatment choice for a presenting patient is not irreversible over relevant time frames (see Section 3.3.2). As a consequence, even if research possible with approval it is not clear that AWR would be appropriate, because OIR avoids the commitment of irrecoverable costs until research finding are available and a more informed decision can be made.

Research is possible with approval

Even when research is possible with approval OIR offers greater expected NHE than AWR as long as research reports before 9 years in Figure 3.9b. This is because the consequences (losses of population NHE) of committing both aspects of irrecoverable costs through AWR are greater than the NHE forgone by restricting access to EECP through OIR. The costs of research have not been included because they are incurred with both AWR and OIR guidance.[32]

As previously for CLOP, there is no guarantee that the research recommended as part of OIR or AWR guidance will be conducted and research report. A boundary for when OIR rather than AWR might be appropriate is illustrated in Figure 3.11b for 4 research designs with differing follow-up. A one year follow-up will generate evidence with the lowest potential value (so the boundary is to the south west) but it is likely to report sooner. Therefore, OIR might be appropriate even if the probability that the research will be conducted and report is relatively low. In this case it seems likely that the type of research required could report quickly enough and with sufficient confidence that OIR would be appropriate even though the research could be conducted while EECP is approved. Therefore, these assessments would support a judgment that the benefits of approval (through AWR) are unlikely to exceed the opportunity costs (the NHE of OIR), so OIR[4] (pathway 18 for EECP) rather AWR[4] (pathway 17 for EECP) would be more appropriate.

[32] Any difference in costs of research under AWR or OIR guidance can easily be integrated into these assessments.

Figure 3.9b Population NHE of Approve and OIR for time to research reporting (EECP)

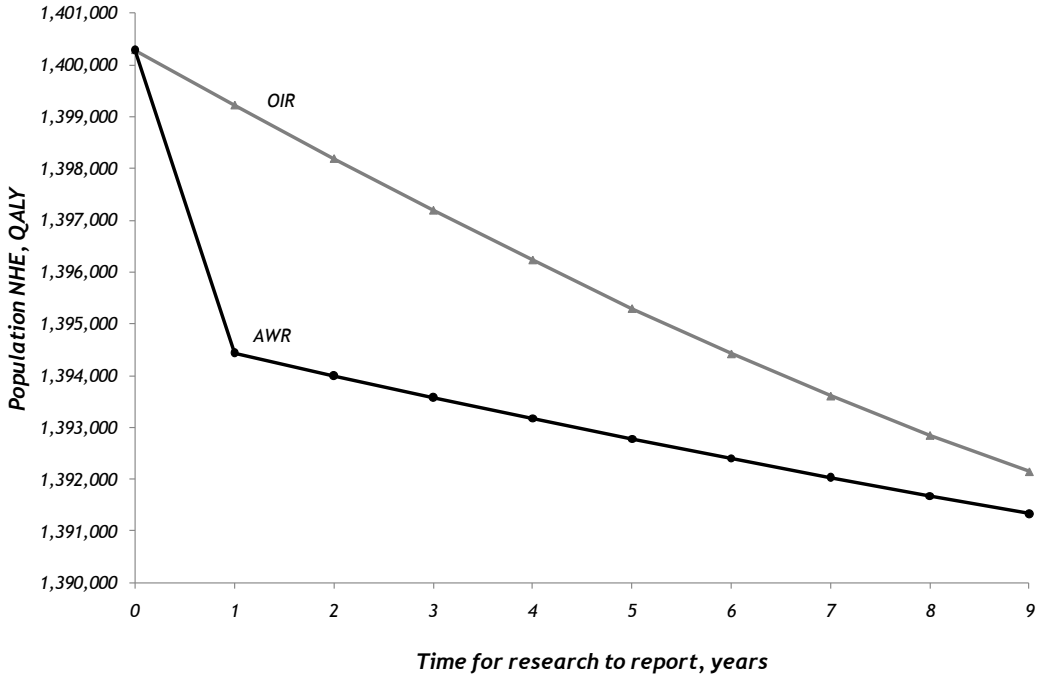
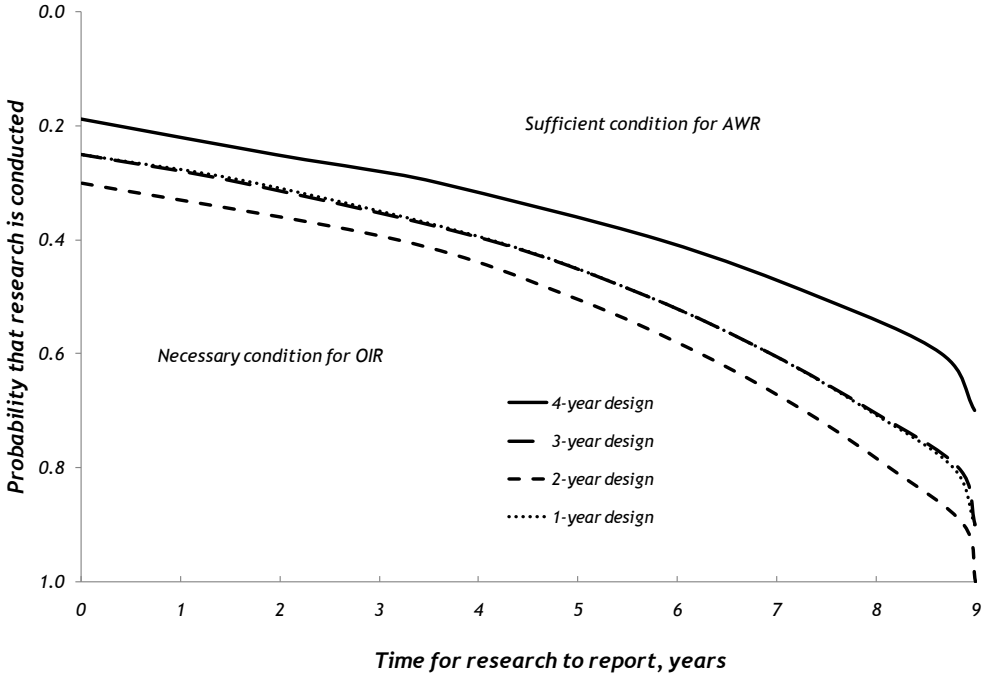


Figure 3.11b An OIR or AWR boundary (EECP)



Research is not possible with approval

For the general reasons discussed in Section 2 and those specific to EECP discussed in Section 3.4.2, the type of experimental research required to robustly estimate the effect of EECP on quality of life is unlikely to be possible one it is approved and in widespread use. Now approval (now through Approve

rather than AWR) not only commits the type of irrecoverable costs discussed above it also means that the potential value of evidence to future patients must also be forgone. This is reflected in Figure 3.9c where the difference between OIR and approve are always greater than between OIR and AWR in Figure 3.9b. It suggest that as long as the cost of the research exceed the difference between OIR and approve, when it is expected to report, OIR rather than approve would be appropriate. This is also reflected in the boundaries for OIR and Approve reported in Figure 3.11c. These boundaries are always to the north east of the OIR/AWR boundaries reported in Figure 3.11b, again reflecting the fact the approval not only commits irrecoverable costs but also forgoes the potential value evidence that might have been generated through an OIR recommendation. These assessments would support a judgment that the benefits of approval are unlikely to exceed the opportunity costs (the NHE of OIR), so OIR[6] (pathway 25 for EECP) rather than Approve[9] (pathway 24 for EECP) would be more appropriate.

Figure 3.9b Population NHE of Approve and OIR for time to research reporting (EECP)

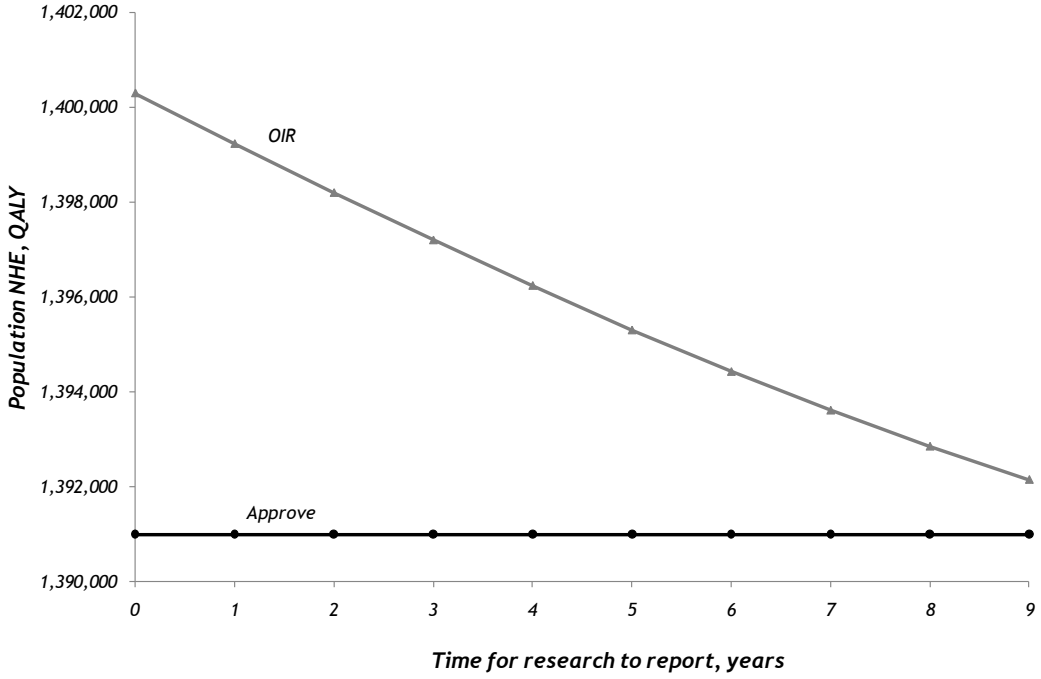
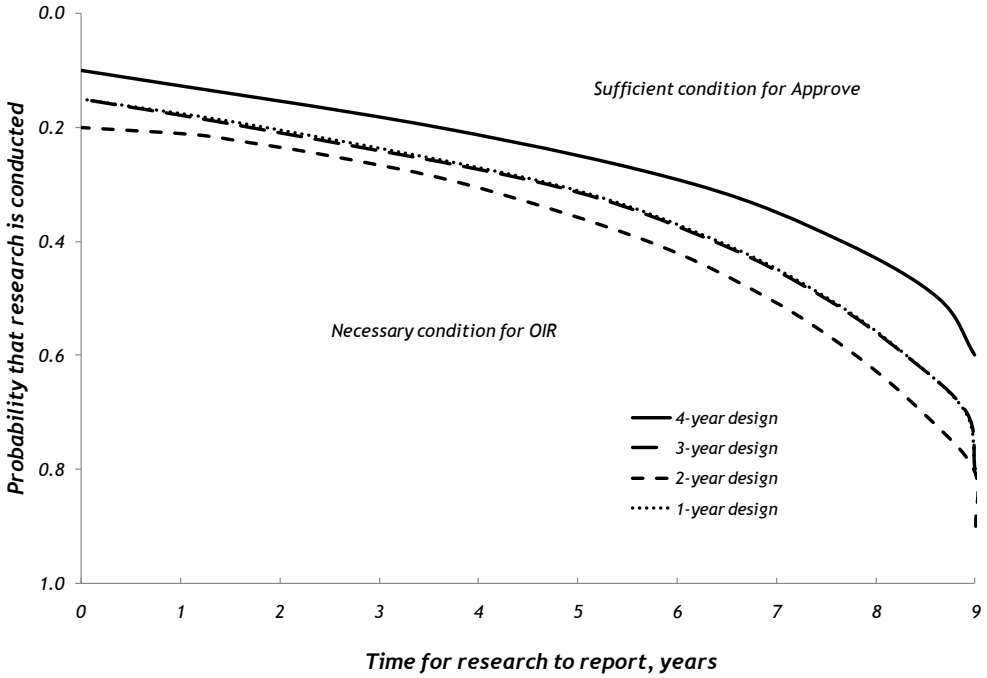


Figure 3.11b An OIR or AWR boundary (AWR)



As with CLOP, the assessments that have been undertaken for EECP are bought together in Table 3.7b and can help inform the same policy questions: i) what would be the value of being able to conduct research while EECP is approved and ii) what would be the value of making the evidence that is needed by the NHS available at launch. In this case, due to the irrecoverable costs associated with EECP, there is no value to the NHS of being able to conduct research while EECP is approved for use. In fact these figures are negative; indicating that even if AWR was possible it would not be appropriate. However, like CLOP there is value to the NHS of having the evidence needed prior to appraisal. The value, expressed in the equivalent NHS resources, depends on how long it would otherwise have taken for an OIR recommendation to deliver the same evidence e.g., £62m if 3 years and £134m if 7years. As with CLOP these assessments can also inform policies which might make better and more relevant evidence available and the question of how and who might contribute most to providing the evidence needed at the right time.

Table 3.7b Population NHE over the technology time horizon for different policies (EECP)

	Approve	OIR	AWR	Reject	Value of AWR	Uncertainty resolved at launch	Value of evidence at launch
Expressed in QALY							
T=3	1,391,001	**1,397,192**	1,393,578	1,389,596	-3,614	1,400,288	3,096
T=7	1,391,001	**1,393,608**	1,392,030	1,389,596	-1,578	1,400,288	6,680
Expressed in £m							
T=3	27,820	**27,944**	27,872	27,792	-72	28,006	62
T=7	27,820	**27,872**	27,841	27,792	-32	28,006	134

4 Implications for policy, process and methods

It is intended that this section of the main report will be informed by the discussion and feedback from the floor and in small groups at the workshop. Therefore, here we only outline the sections of how that feedback and discussion might be usefully organised. We hope that the output of the workshop will constitute a range of possible recommendations that might be considered by NICE and other relevant bodies.

A list of questions under the following headings will be circulated prior to the workshop with hard copies available on the day.

4.1 Implications for policy

4.1.1 Policy issues directly relevant to the NICE remit

4.1.2 Other broader policy issues

4.2 Implications for the process of appraisal

4.3 Implications for methods of appraisal