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A comprehensive algorithm for approval of health technologies with, without, or only in research: the key principles for informing coverage decisions

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ABSTRACT

Objectives: The value of evidence about the performance of a technology and the value of access to a technology is central to policy decisions regarding coverage with, without, or only in research and managed entry (or risk-sharing) agreements. We aim to outline the key principles of what assessments are needed to inform 'only in research' (OIR) or 'approval with research' (AWR) recommendations, in addition to approval or rejection.

Methods: We develop a comprehensive algorithm to inform the sequence of assessments and judgements which lead to different types of guidance: OIR, AWR, Approve or Reject. This algorithm identifies the order in which assessments might be made, how similar guidance might be arrived at through different combinations of considerations, and when guidance might change.

Results: The key principles are: whether the technology is expected to be cost-effective; whether the technology has significant irrecoverable costs; whether additional research is needed; whether research is possible with approval and whether there are opportunity costs which once committed by approval cannot be recovered; and whether there are effective price reductions. Determining expected cost-effectiveness is only a first step. As well as AWR for technologies expected to be cost-effective and OIR for those not expected to be cost-effective, there are other important circumstances when OIR should be considered.

Conclusions: These principles demonstrate that cost-effectiveness is a necessary but not sufficient condition for approval. Even when research is possible with approval, OIR may be appropriate when a technology is expected to be cost-effective due to significant irrecoverable costs.

1 INTRODUCTION

The value of evidence about the performance of a technology and the value of access to a technology is central to policy decisions regarding coverage with, without, or only in research and managed entry (or risk-sharing) agreements. Decisions about health technologies are increasingly being made close to licence when the evidence base to support the technology is least mature. This is partly linked to changes in the regulatory landscape where regulators and payers have produced new approaches in an effort to provide patients with timely access to new medicines. For example, the European Medicines Agency has introduced the "Adaptive Pathways" approach which is open to interventions in the early stages of development (1, 2). Inevitably this means that coverage decisions in many different jurisdictions and healthcare systems are being made when there may be substantial uncertainty surrounding the technology's effectiveness, cost-effectiveness and potential for harm. In these circumstances, further evidence may be particularly valuable as it can lead to better decisions which improve patient outcomes and/or reduce resource costs. Establishing the key principles for 'only in research' (OIR), defined as when a technology is only approved within the context of a suitable research study, and 'approval with research' (AWR), which refers to approval while research is being conducted, will enable coverage decisions to be addressed in an explicit and transparent manner. This has wide relevance to different types of health care systems, helping to inform the questions posed by coverage with evidence development and managed entry agreements (3-6).

If the resources available for health care are limited, then approving a more costly technology will displace other activities that would have otherwise generated improvements in health for other patients (7). If the objective of a health care system (HCS) is to improve health outcomes across the population it serves then 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 costs, i.e. a cost-effective technology will offer positive *net health effects*

(8-10). 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 additional health care costs together with some assessment of what health is likely to be forgone as a consequence (the cost-effectiveness threshold) (11). In health systems without administrative budgets there are often constrains on the growth in health care expenditure. Even where there are no constraints the same principles are likely to apply but the opportunity costs may manifest in terms of non-health expenditure, e.g. through increased insurance premiums, co-payments or taxation.

Such assessments are inevitably uncertain and without sufficient and good quality evidence, subsequent decisions about the use of technologies will also be uncertain. 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 (12-14). 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 (15). In these circumstances there will be a trade-off between the net health effects to current patients from early access to a cost-effective technology and the health benefits to future patients from withholding approval until valuable research has been conducted (16).

Research also consumes valuable resources which could have been devoted to patient care or to other more valuable research priorities. Uncertain events in the near or distant future may also change the value of the technology and the need for evidence (17). In addition, implementing a decision to approve a new technology may commit resources which cannot subsequently be

recovered if guidance changes in the future (18-22). Guidance about the use of health technologies will depend on 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 uncertainty are resolved.

The purpose of this paper is to outline the key principles of what assessments are needed to inform coverage decisions. The starting point is an assessment of expected cost-effectiveness from an underlying extra-welfarist approach, which identifies improvements in health as an important objective of health care provision (23). This is the approach that has been adopted by major decision making bodies such as the National Institute for Health and Care Excellence (NICE) in the UK, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia and the Canadian Agency for Drugs and Technologies in Health (CADTH). These principles do not presuppose how the assessments might be informed in terms of the methods of analysis or how different aspects of health gained and forgone might be measured and valued. This distinction between principles and methods of analysis is important since different healthcare systems (or decision making bodies) are likely to vary in terms of the social values they apply as well as the time and resources available to carry out an appraisal of a health technology and may adopt different methods of analysis to inform the same question. Based on these principles, we present a comprehensive algorithm which demonstrates how the sequence of assessments and judgements can lead to different types of guidance: OIR, AWR, Approve (without research) or Reject (without research). Full details on the development of this comprehensive framework and algorithm have been described elsewhere (24) and we refer the reader to this fuller description for a deeper insight. An illustration of how the assessments can be informed in terms of the methods of analysis is also presented elsewhere, with application to a number of case studies (24, 25).

2 KEY PRINCIPLES AND ASSESSMENTS NEEDED

The key principles fall into a number of broad areas: i) whether the technology is expected to be cost-effective; ii) whether the technology has significant irrecoverable costs; iii) whether additional evidence/research is needed; iv) whether research is possible with approval and whether there are significant (opportunity) costs which once committed by approval cannot be recovered; and v) whether there are any effective price reductions offered. These key principles can be represented by a sequence of assessments and judgements, which are summarised as a 7-point checklist (24, 25):

1. Is the technology expected to be cost-effective?
2. Are there significant irrecoverable costs?
3. Does more research seem worthwhile?
4. Is the research possible with (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 opportunity costs?

Based on estimates of expected net health effect (NHE) at each point of this checklist, a judgement Yes or No can be made. For example, a judgement at point 1 uses standard cost-effectiveness analysis to estimate the NHE, a judgement at point 2 assesses the impact of irrecoverable costs on NHE, a judgement at points 3 and 4 uses probabilistic sensitivity analysis and methods of value of information analysis (the reader is referred to McKenna et al, 2015 (25) for the methods of analysis for each point of the checklist). Guidance will depend on the combined effect of these assessments. In some cases all 7 assessments may not be necessary as earlier decisions lead directly to guidance.

Figures 1 to 3 show the sequence of assessments and decisions which lead to a particular category and type of guidance, represented as a comprehensive algorithm. Four broad categories

of guidance are represented within the algorithm: Approve, AWR, OIR and Reject. Each different type of guidance illustrates how similar guidance might be arrived at in different ways, helping to identify the particular combination of considerations which underpin the guidance. Figure 1 is for technologies without significant irrecoverable costs, while Figures 2 and 3 are for technologies with significant irrecoverable costs. Figures 2 and 3 are separated further based on whether the technology is expected to be cost-effective and research is needed (Figure 2) or whether it is not expected to be cost-effective and research may or may not be needed (Figure 3). The key principles underpinning each of these assessments are now described in the sections which follow. The reader is referred to Claxton et al (2012) for a more detailed explanation (24).

<<Insert Figures 1 - 3 >>

2.1 Technologies without significant irrecoverable costs

Although some element of cost which once committed cannot be subsequently recovered is almost always present in the evaluation of technologies, the sequence of assessments and decisions for these technologies is relatively straightforward compared to other technologies judged to have 'significant' irrecoverable costs associated with approval. Significant irrecoverable costs depend on the commitment of upfront costs and whether there is sufficient flexibility in when a patient can initiate treatment (e.g., if treatment can be delayed until uncertainty is resolved then the commitment of these irrecoverable costs can be avoided). Technologies without significant irrecoverable costs are considered first as the simpler case (see Figure 1).

2.1.1 Technologies expected to be cost-effective

The sequence of assessment is assumed to start with cost-effectiveness and expected incremental net health effect for the technology relative to its comparators since this is the starting point used by many decision making bodies such as NICE, PBAC and CADTH. In order to avoid binary decisions of Approve or Reject under conditions of uncertainty, the need for additional evidence

should be assessed. An assessment is also required of whether the research needed to provide this evidence is possible if the technology is approved for widespread use while the research is being conducted.

Need for evidence

Some initial assessment about whether further research might be potentially worthwhile is important because a 'No' at this point can avoid further 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 effect is positive. In these circumstances, further research may not be worthwhile so guidance to approve could be issued (e.g. Approve [4] in Figure 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 is likely to be conducted if approval is granted (24, 26).

Where research is possible with approval

If research is possible with approval, some assessment of the long term benefits of research is required, including: i) the likelihood that the type of research needed will be conducted; ii) how long the results of research will take to report; and iii) how much of the uncertainty might be resolved by the research (15). 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 (17). These sources of uncertainty will influence the future benefits of research. For example, if the price of the technology is likely to fall significantly before or shortly after research reports then the 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 1 dependent on 'Yes' and 'No' respectively.

Where research is not possible with approval

The type of research needed may not be possible once a technology is approved for widespread use, e.g. randomised clinical trials (RCTs) may not be possible due to ethical concerns, recruitment problems and limited incentives for manufacturers. In these circumstances the expected benefits of approval to current patients must be balanced against the benefits to future patients from withholding approval until the research is conducted. The same assessments of the long term value of research and the impact of other sources of uncertainty is still required. 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 1). However, judging that research is worthwhile at this point is not sufficient for OIR guidance. An assessment of whether the benefits of early approval are expected to be greater than the opportunity costs of research that may be forgone to future patients is required. If the expected benefits are judged to be less than the opportunity costs then OIR guidance would be appropriate (OIR[1] in Figure 1), whereas if they are judged to be greater, then approval would be appropriate (Approve[2] in Figure 1).

2.1.2 Technologies not expected to be cost-effective

A technology which is not expected to be cost-effective based on existing evidence is expected to impose negative net health effect if it is approved. In these circumstances Approve can be ruled out, but depending on the level of uncertainty in the current evidence and other changes that may occur, subsequent assessments and decisions are required before guidance is reached (see Figure 1).

Need for evidence

Even if the technology is not expected to be cost-effective, the assessment may be uncertain; therefore it remains a possibility that the technology might offer positive net health effect. Again, the scale and consequences of uncertainty must be considered and whether additional research might potentially be worthwhile. If it is not, then the technology can be rejected (Reject [4] in Figure 1). 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.

Where research is possible without approval

Generally, most types of research (including RCTs) will be possible without approval. The long term value of research and the impact of other sources of uncertainty are required. 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 1). 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 1).

Where research is not possible without approval

In some circumstances it is possible that certain types of evidence might only be acquired once a technology is in widespread use, e.g., linking surrogates to longer term outcomes, longer term (or rare) adverse events, learning and incremental improvements, or identifying particular types of patients that might benefit most (27). 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 1). Alternatively, if research is judged worthwhile an additional assessment of whether the benefits of approval exceed the costs

is required. In this case, approval will impose opportunity costs (negative expected NHE 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 would have been worthwhile (Reject $_3$ in Figure 1). Alternatively, if the net benefits of research more than offsets the opportunity costs then AWR would be appropriate even though the technology is expected to be cost-ineffective (AWR ^{2} in Figure 1).

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.

2.2 Technologies with significant irrecoverable costs

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. In most appraisals these types of cost are first annuitized and then allocated pro-rata to the number of patients likely to be treated during the lifetime of the equipment. If guidance remains unchanged throughout this period (i.e., research does not report or other sources of 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 which was allocated to them cannot be recovered.

Even in the absence of capital investment costs, most new technologies impose initial per patient treatment costs which exceed the immediate health benefits. 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). Therefore, a technology expected to be cost-effective may only accumulate sufficient 'gains' to compensate earlier 'losses' after some considerable time. Whether this type of irrecoverable opportunity cost is significant (i.e., might influence decisions) depends on 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 patient with a technology cannot be reconsidered at a later date, whereas for a chronic condition the decision to treat can be delayed until uncertainty is resolved. Therefore, the commitment of irrecoverable opportunity costs (negative NHE) can be avoided (21). In these circumstances, OIR or reject avoids this commitment and preserves the option to approve the technology at a later date when its purchase represents a 'less risky investment' (21).

2.2.1 Technologies expected to be cost-effective

The presence of irrecoverable costs for 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 1) because the impact of irrecoverable costs must also be considered. Now OIR may be more appropriate than AWR (e.g., the choice between OIR^{4} and AWR^{4} in Figure 2), 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 the case when there are also other sources of uncertainty which might resolve while the research is being conducted as it increases the chance that guidance will be revised (e.g., OIR^{3} or AWR^{3} in Figure 2).

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 Figure 2). 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 Figure 2).

If research is not judged worthwhile, approval does not necessarily follow as previously (e.g., Approve[1, 3, 4] in Figure 1). 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 irrecoverable costs can be reconsidered once the other sources of uncertainty have resolved (e.g., Reject[5, 6] in Figure 2).

2.2.2 Technologies not expected to be cost-effective

The presence of irrecoverable costs for technologies not expected to be cost-effective means that reject is more likely to be appropriate than AWR when research is not possible without approval (see AWR[5] in Figure 3). This is because a decision to reject, although it may be revised to approve, generally does not commit irrecoverable costs. There may be circumstances when implementing guidance to reject a technology also requires resources if it has already been diffused into clinical practice. If these are significant they should be taken into account in the same way as other irrecoverable costs, tending to make AWR more likely to be appropriate.

2.3 Changes in effective price of a technology

Any change in the effective price of the technology will affect the key assessments, leading to different categories of guidance. For example, OIR 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 the value of additional evidence will tend to be lower (e.g., from OIR [1] to Approve [2] in Figure 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 1). Therefore, consideration of the effect of price changes on OIR and AWR is needed when assessing the potential impact of discount schemes and more direct price negotiation (24).

Even if direct price negotiation is possible through a value based pricing scheme (10), it will be important to retain OIR and AWR as possibilities because there is no guarantee that manufacturers will always agree to the lower price below which Approval rather than OIR or AWR would be appropriate, and there may be many circumstances when there is no effective price reduction which would make Approval appropriate. 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.

3 DISCUSSION

Each sequence of assessment and decision leads to a different category and type of guidance for technologies with differing characteristics, indications and target populations. The different types of guidance illustrate how similar guidance might be arrived at but in different ways, adding to the transparency of the appraisal and helping to be explicit about the particular combination of considerations which underpin the guidance. There are many circumstances when AWR and OIR are applicable. For example, there are 5 different types of OIR which may be appropriate

when a technology is expected to be cost-effective. Even when research is possible with approval, OIR is appropriate if there are significant irrecoverable costs. 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. It is only approval that can be ruled out if a technology is not expected to be cost-effective, i.e., cost-effectiveness is a necessary but not sufficient condition for approval but lack of cost-effectiveness is neither necessary nor sufficient for rejection. There are circumstances when AWR may be appropriate even when a technology is not expected to be cost effective. Importantly, the category of guidance only partly depends on an assessment of expected cost-effectiveness. A number of other key assessments are required: the need for evidence; whether the type of research required is possible with approval; the expected longer term benefits and costs of research that is likely to be conducted; the impact of other sources of uncertainty which will resolve over time; and the significance of any irrecoverable costs.

This paper has set out the key principles of what assessments are needed for coverage decisions. It has not specified how these assessments might be informed as this can differ across different jurisdictions. The explicit framework for OIR and AWR decisions is likely to have a number of implications for policy (e.g., drug pricing and incentives for evaluative research), as well as the process of appraisal (e.g., greater involvement of research commissioners) and the methods of appraisal (e.g., additional information, evidence and analysis that might be required).

Coverage decisions which are based on some assessment of the likely health opportunity costs, whether or not a 'threshold' is explicitly stated, sends a signal of how much health care systems can afford to pay for the benefits that new technologies offer. Manufacturers inevitably respond to these incentives through their pricing and investment decisions. Not only is price endogenous

(29) but the effects and the costs of developing and producing new technologies are endogenous as well. Therefore, the role of reimbursement agencies can be seen as signalling collective demand for the health benefits that new technologies offer, reflecting the social choices of how much resource is to be made available for health care. The endogeneity of price aligns the dynamic incentives for research and development with the needs and resource constraints of health care systems that reflects social values and mirrors how temporary monopolists with patent protection respond to demand in other markets (30). The principles of how the need for evidence might influence coverage decisions and the implications that it has for pricing decisions by manufacturers enables greater subtlety in the signal sent and a better alignment of incentives for the development of new technologies and evaluative research available to support their use.

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Figure 1: An algorithm for only in research and approval with research decisions – Technologies without significant irrecoverable costs

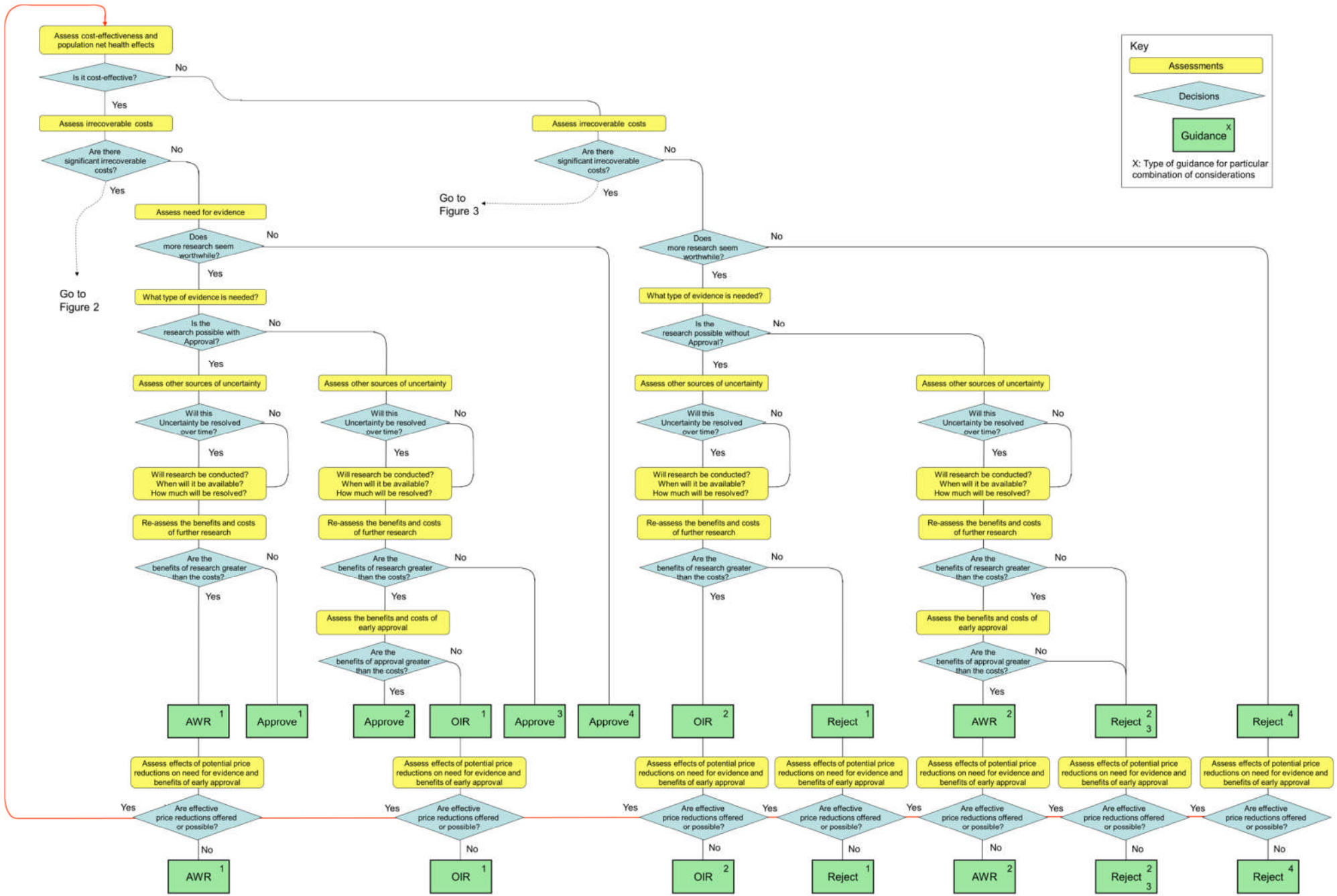

Figure 2: An algorithm for only in research and approval with research decisions – Technologies with significant irrecoverable costs, expected to be cost-effective and research is needed

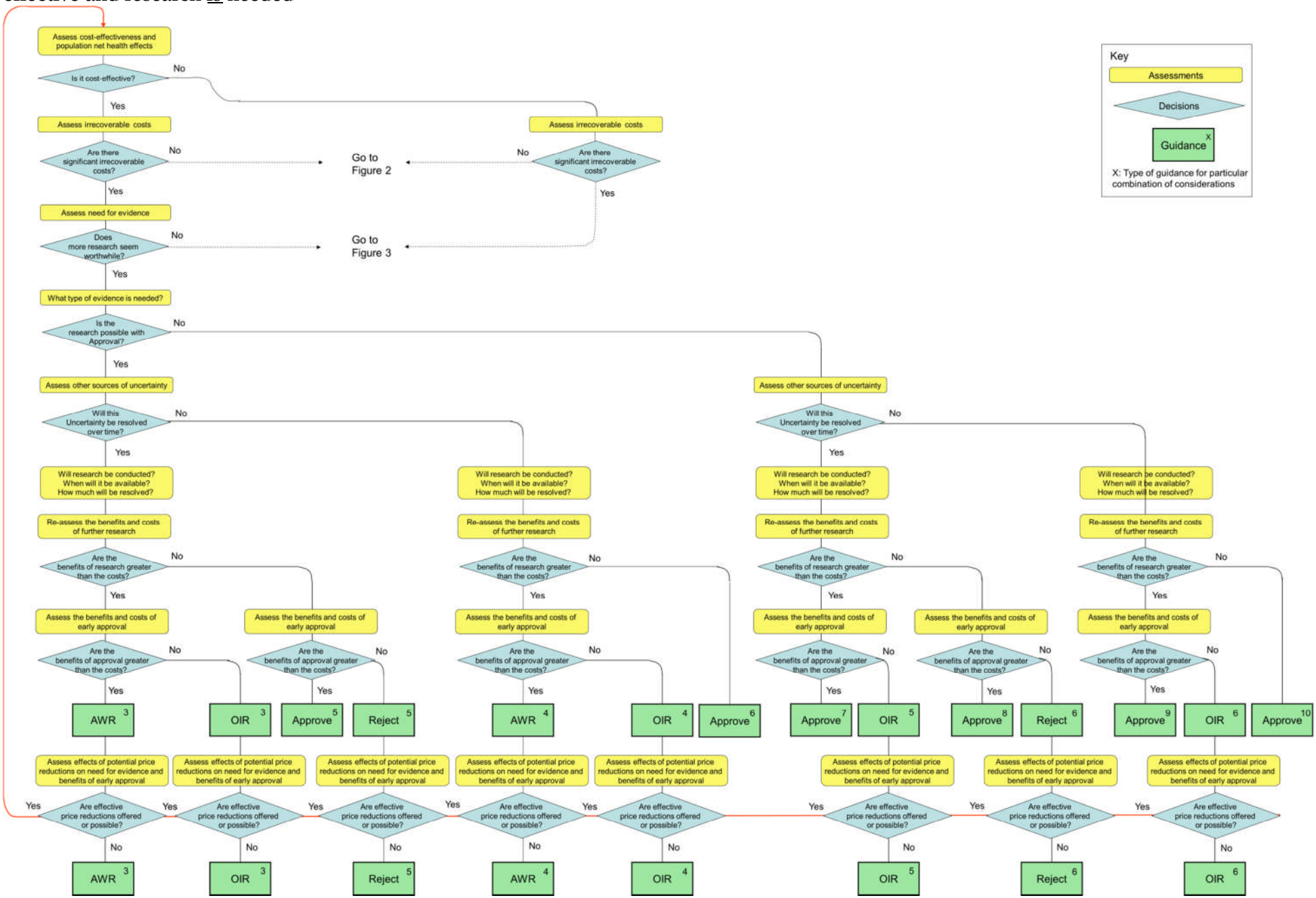

Figure 3: An algorithm for only in research and approval with research decisions – Technologies with significant irrecoverable costs, not expected to be cost-effective and research is not needed