# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

# Briefing paper for methods review working party on uncertainty and only in research recommendations

The briefing paper is intended to provide a brief summary of the issues that are proposed for discussion by the Methods Review Working Party to inform an update to the Institute's Guide to Methods of Technology Appraisal. It is not intended to reflect a comprehensive or systematic review of the literature. The views presented in this paper are those of the authors and do not reflect the views of the Institute.

## 1 Review of the 'Guide to Methods of Technology Appraisal'

The Institute is reviewing the 'Guide to the methods of technology appraisal', which underpins the technology appraisal programme.

The original Methods Guide was published in February 2001, and revised versions were published in 2004 and 2008. The Methods Guide provides an overview of the principles and methods used by the Institute in assessing health technologies. It is a guide for all organisations considering submitting evidence to the technology appraisal programme and describes appraisal methodology.

The revised draft of the Methods Guide will be available for a 3-month public consultation, expected to begin in June 2012. We encourage all interested parties to take part in this consultation.

# 2 Background

## *2.1 Relevance of topic to NICE technology appraisals*

The NICE technology appraisals programme makes recommendations about health technologies close to regulatory approval through the single technology assessment (STA) process. Inevitably these decisions are made when there may be substantial uncertainty about their clinical effectiveness and cost-effectiveness. In these circumstances the acquisition of further evidence could lead to better decisions in the future. The decision to recommend a technology for use in the NHS could have an impact on the prospects of acquiring further evidence because the incentives on researchers, including those from marketing authorisation holders, are diminished once the technology has been recommended. Therefore, it has been suggested that the decision to recommend a technology should account for the potential costs to future NHS patients in terms of the value of evidence that may be forgone by early adoption.

## *2.2 What the current Methods Guide advises with respect to 'only in research' recommendations*

Sections 6.2.11 and 6.2.12 set out the discussion of 'only in research' recommendations in the 2008 Methods Guide in terms of factors to be consider by the Appraisal Committee, but no detailed criteria or thresholds for making such decisions are provided. The concept of 'approval with research' does not feature in the 2008 Methods Guide.

*6.2.11 When evidence of effectiveness is either absent or weak, the Appraisal Committee may recommend that particular interventions are used within the NHS only in the context of research. Factors that will be considered before issuing such recommendations include the following.*

- *The intervention should have a reasonable prospect of providing benefits to patients in a cost-effective way.*

- *The research can realistically be set up, is already planned, or is already recruiting patients.*
- *There is a real prospect that the research will inform future NICE guidance.*
- *The broad balance of the benefits and costs of conducting the research are favourable.*

*6.2.12 Recommendations on the use of technologies only in the context of research will not include consideration of which organisation (public or private) will fund the research.*

### *2.3 Relevant methodological research*

The MRC and NIHR 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 (Claxton K., Palmer, Longworth L., et al. 2011).

This paper categorised previous NICE technology appraisal guidance with a research element as either 'only in research' (OIR) recommendations (interpreted for the purposes of this briefing as meaning that the technology is recommended to be used **only** in the context of research, the nature of which is specified in the guidance) or 'approval with research (AWR) recommendations (that is, the technology is recommended alongside a further recommendation for research or data collection).

The executive summary of the CHE publication of this research (HTA monograph forthcoming) is appended to this document (Appendix A).

## 3 Proposed issues for discussion

In consideration of the developments in this area resulting from the MRC project, the current Methods Guide and the requirements of the Institute's

Technology Appraisal Programme, it is proposed that the following key areas are discussed by the working party.

## *3.1 Uncertainty about clinical effectiveness*

Currently the recommendations in the methods guide focus on situations where *"evidence of effectiveness is either absent or weak".*

- Should this focus of on the estimate of effectiveness remain, or should other aspects of uncertainty in the estimates of cost effectiveness be considered.

## *3.2 Key principles and assessments needed for OIR recommendations*

Should the methods guide recommend a more formal method of assessing the need for further research in the conduct of technology appraisals? The MRC researchers suggest the use of checklists as an aid to these judgments (see Appendix B).

- Are the checklists outlined in section 3 of the CHE research paper in Appendix B useful for committee decision making
- What additional information and analysis – over and above that already conducted in the course of an appraisal – might be required to allow the committee to be more systematic in its exploration of the value of undertaking further research
- How can research commissioners be involved when the Appraisal Committee are considering AWR/OIR recommendations ?

## *3.3 The concept of approval with research*

The methods guide does not currently include the concept of AWR.

- Is the concept of AWR, or a similar concept, useful in circumstances where the committee is considering use of the technolgy in the context of research

# 4 References

Claxton K., Palmer.S, Longworth L., et al. Uncertainty, evidence and irrecoverable costs: Informing approval, pricing and research decisions for health technologies? University of York; CHE Research Paper 69; 2011.

Claxton K., Palmer S., Longworth L., et al.. 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. Health Technology Assessment forthcoming.

# 5 Author/s

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# Appendix A

## *Executive summary of CHE Research Paper 69*[1]

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. This research was commissioned to inform when NICE should approve health technologies only in research (OIR) or with research (AWR). It has implications 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). However, establishing the key principles of what assessments are required and how they might be informed has much wider relevance beyond NICE and the UK NHS (e.g., informing the questions posed by coverage with evidence development initiatives).

### Key principles and assessment needed

The key principles and assessments needed 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 and whether the type of research required can be conducted once a technology is approved for widespread use; iii) whether there are sources of uncertainty which cannot be resolved by research but only over time; and iv) whether there are significant (opportunity) costs which will be committed and cannot be recovered once the technology is approved.

Decisions (NICE 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

[1] Claxton K., Palmer.S, Longworth L., et al. Uncertainty, evidence and irrecoverable costs: Informing approval, pricing and research decisions for health technologies? University of York; CHE Research Paper 69; 2011. Available from URL: http://www.york.ac.uk/che/publications/in-house/. Other related documents available from URL: http://www.york.ac.uk/che/research/teams/teehta/workshops/only-in-research-workshop/

other sources of uncertainty are resolved. The sequence of assessment and judgments required is represented as an algorithm, which can be summarised as a simple seven point checklist.

Each sequence of assessment and decision, leads to different categories of guidance (e.g., Approve, AWR, OIR or Reject) for technologies with differing characteristics, indications and target populations. Different 'types' of apparently similar guidance can be identified. This illustrates how the same category of guidance might be arrived at in different ways, helping to identify the particular combination of considerations which might underpin decisions.

The principles suggest that restricting approval to OIR, or making it conditional on research through AWR, has wider application than is reflected in previous NICE guidance. For example, OIR may be appropriate when a technology is expected to be cost-effective. Even when research is possible with approval, OIR or even Reject maybe appropriate if there are significant irrecoverable costs. Therefore, the full range of categories of guidance 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 and lack of cost-effectiveness is neither necessary nor sufficient for rejection.

Distinguishing principles (what assessment are needed) from methods of analysis (how they might be informed) allows potentially wide application of principles embodied in the algorithm and associated checklist, whist recognising that how the assessment might be made is likely to differ in different contexts.

**Implications for value based pricing**

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 value based pricing scheme) will affect the key assessments, leading to different categories of guidance. The price at which a technology is just expected to be cost-

effective is commonly regarded as its value based price. This describes the threshold price below which Approve rather than Reject would be appropriate if OIR or AWR are not available as policy options. However, if they are available there are often a number of relevant price thresholds. Once uncertainty, the need for evidence and the impact of irrecoverable costs are recognised, the threshold price that would lead to Approval rather than OIR will always be lower than a single value based price based on expected cost-effectiveness alone, i.e., disregarding uncertainty in costs and effects.

Even if price negotiation becomes possible alongside NICE appraisal, it will be important to retain OIR and AWR as available categories of guidance for two reasons: i) 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 ii) there may be many circumstances when no effective price reduction which would make Approval appropriate, e.g., Reject or OIR guidance may 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.

**Incentives for evaluative research**

An explicit assessment of OIR and AWR provides clear signals and an incentive to ensure the type of evidence, requiring research that cannot be conducted once approved for NHS use, is available and is sufficient at launch (e.g., relative effectiveness and subtle but important differences in side effect profiles). Therefore, a predictable OIR and AWR policy signals what type of evidence is likely to be most important at an early stage. It offers manufacturers a choice, to either: i) accept OIR Guidance at a higher price but restricted volume; ii) reduce the effective price to achieve Approval, or AWR where that is possible; or iii) conduct the evaluative research at an earlier stage so that additional evidence is available at launch.

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 or contribute to the costs of publicly funded research which may ultimately benefit their product. The

success of AWR when manufacturers are asked to conduct the research will depend on whether appropriate contractual arrangements can be established, i.e., those that can be monitored and enforced with credible penalties to ensure agreed research is conducted and in the way intended. At present, NICE does not have a credible mechanism since removing approval of a technology simply because recommended research had not been conducted was not considered an ethical or credible threat.

The assessments required can be used to consider the value to the NHS of: i) being able to conduct research while a technology is approved (value of AWR); ii) making evidence that is needed by the NHS available at launch; and iii) being able to acquire evidence more quickly. This can inform investments in better data collection, registries or information systems that might make AWR possible. The value to the NHS of having access to the evidence needed at launch can inform a range of policies, such as early advice, public investment in transitional and evaluative research earlier in the development process or other incentives for research and development. Understanding the relationship between the time taken for research to report and the value of the evidence to future populations can help to inform: i) investments which might make research findings more quickly available; ii) the trade-off implicit in the choice of alternative research designs; and iii) those areas where if research is to be undertaken there must be confidence that it can report quickly.

The value of early evidence at launch and AWR can also be considered from the perspective of the manufacturer and inform whether they or the NHS might be expected to conduct the research needed. In principle, AWR and OIR research could be publicly funded rather than undertaken by manufacturers if the costs of research could be recovered directly from manufacturers or indirectly through other price discounts. Since the costs of public research are likely to be substantially lower than for manufacturers this might be mutually beneficial in many circumstances; providing appropriate support to innovation, while allowing wider access to the data generated and more transparency and accountability in the conduct of the research.

**How should the assessment be undertaken?**

The order of the assessments in the checklist relate to the sequence of decision nodes that fully describe the algorithm in Appendix A. This order of considerations means that all 7 assessments do not necessarily need to be made when an earlier judgement can lead directly to guidance. Therefore, one model for an efficient process of assessment would be to consider points 1-5 routinely. The Appraisal Committee would then be in a position to either rule out OIR or AWR and issue guidance in the usual way or indicate in the appraisal consultation document (ACD) that OIR or AWR was provisionally recommended subject to advice from a research advisory committee and subsequent analysis to support an assessment of points 6 and 7 of the checklist prior to FAD. This model would avoid unnecessary analysis and incorporate the judgments of the research community without necessarily delaying appraisal.

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 is required. Although the NICE appraisal process may be well suited to identifying the need for evidence, these other critical assessments (the type of research and its priority) are not necessarily ones for which NICE and its advisory committees, as currently constituted, have particular expertise. Informed judgements and better decisions might be possible through greater involvement of the research community. For example, a research advisory committee could be constituted which could consider provisional OIR or AWR guidance (at ACD), 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 publicly funded or undertaken by the manufacturer with appropriate contractual arrangements (which may require the involvement of DH at some stage).

**What additional information and analysis might be required?**

In the assessments, cost-effectiveness was presented as net health effects per patient treated and for the population of patients over time. This provides information in a way that is directly relevant to the assessments that need to be made using information generally already available during appraisal.

An early indication of potential importance of irrecoverable costs can be based on their scale relative to expected net health effects, the point at which any initial losses are expected to be compensated by later gains, whether treatment decisions are reversible and what opportunities to improve health might be forgone by a delay to initiating treatment.

The question of whether further research might be worthwhile requires some assessment 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. This can be made in a series of steps each presenting what is already available within current methods of appraisal but in ways that can more directly inform the assessment required. How the consequences of uncertainty between as well as within scenarios can be presented and interpreted is also explored.

An assessment of the type of evidence needed 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? The methods of analysis presented in Section 3 take these steps in turn; presenting what is available within current appraisal but in ways that more directly inform the assessment required. It is only when assessing the consequences of uncertainty associated with particular parameters that additional analysis is required to provide quantitative estimates.

The current appraisal process generally already provides the information and much of the analysis required to complete all the quantitative assessment reported in Section 3. However, the information required to assess whether other sources of uncertainty will resolve over time requires information that is not commonly sort as part of NICE appraisal. NICE many need to consider how access to this type of information can be provided or whether it should extract this type of information itself at an earlier stage of appraisal.

Any additional analysis to support a more explicit consideration of OIR and AWR would need to be included in manufacturers' submissions and be reviewed by the ERG. Although the additional analysis itself is limited (most is already required but sometimes presented in different forms), more explicit consideration of OIR and AWR and their link to price would make the critique of how uncertainty and its consequences has been characterised more important. An assessment of whether the point estimate of cost–effectiveness is reasonable is inevitably a more limited task than also assessing whether the uncertainty surrounding that assessment is credible. Any additional burden on ERGs (and manufacturers) might be eased with clear guidance on the details of how analysis should be conducted and presented, what common assumptions are deemed reasonable and provision of additional information by the Institute as well as only considering points 6 and 7 on the checklist after ACD and following advice from a research advisory committee.

# Appendix B

The following checklists and algorithm are reproduced from CHE Research paper 69[2]

**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? | | |

**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? | | |

[2] Claxton K., Palmer.S, Longworth L., et al. Uncertainty, evidence and irrecoverable costs: Informing approval, pricing and research decisions for health technologies? University of York; CHE Research Paper 69; 2011. Available from URL: http://www.york.ac.uk/che/publications/in-house/

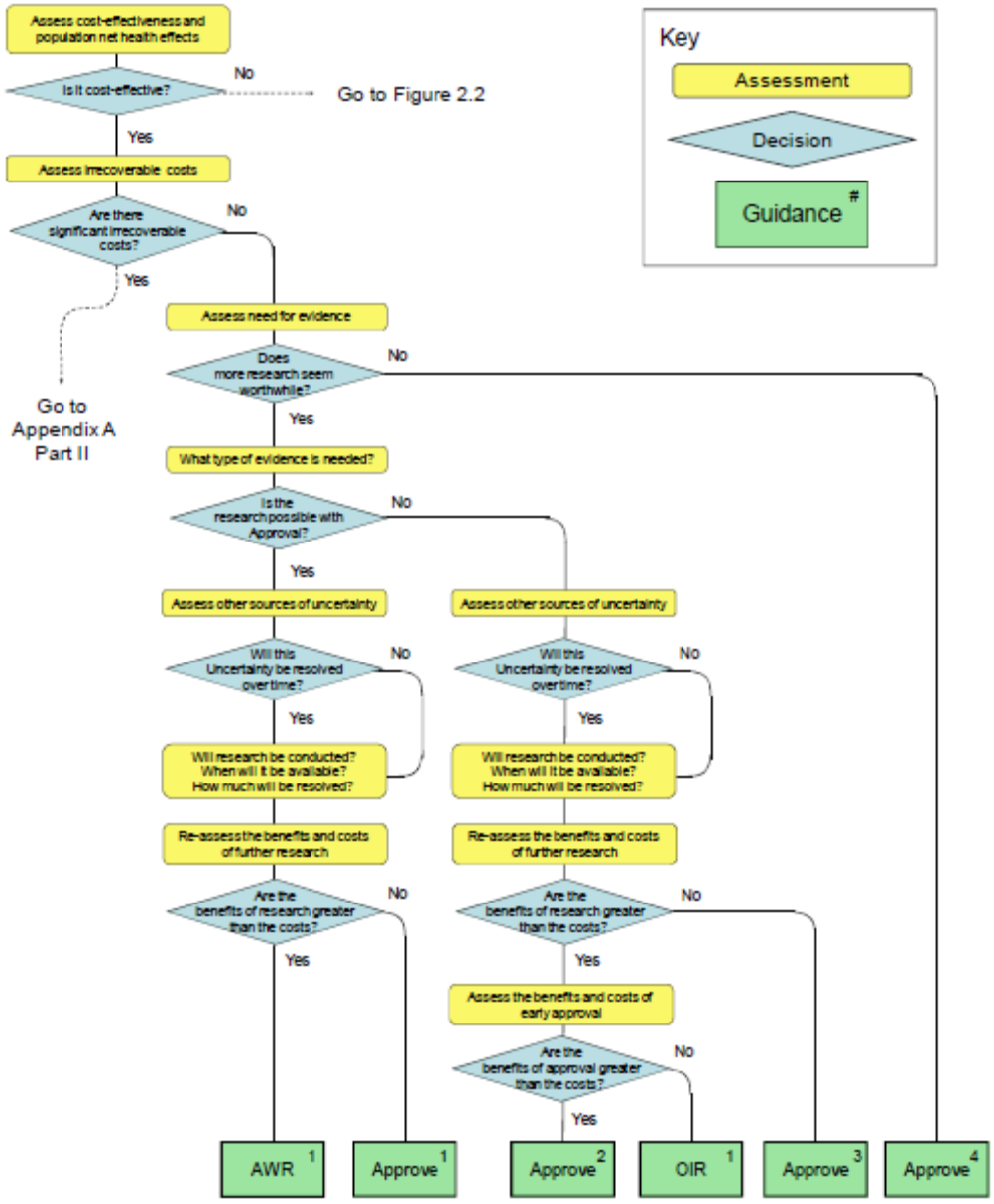


**Figure 2.1** **Technologies expected to be cost-effective**

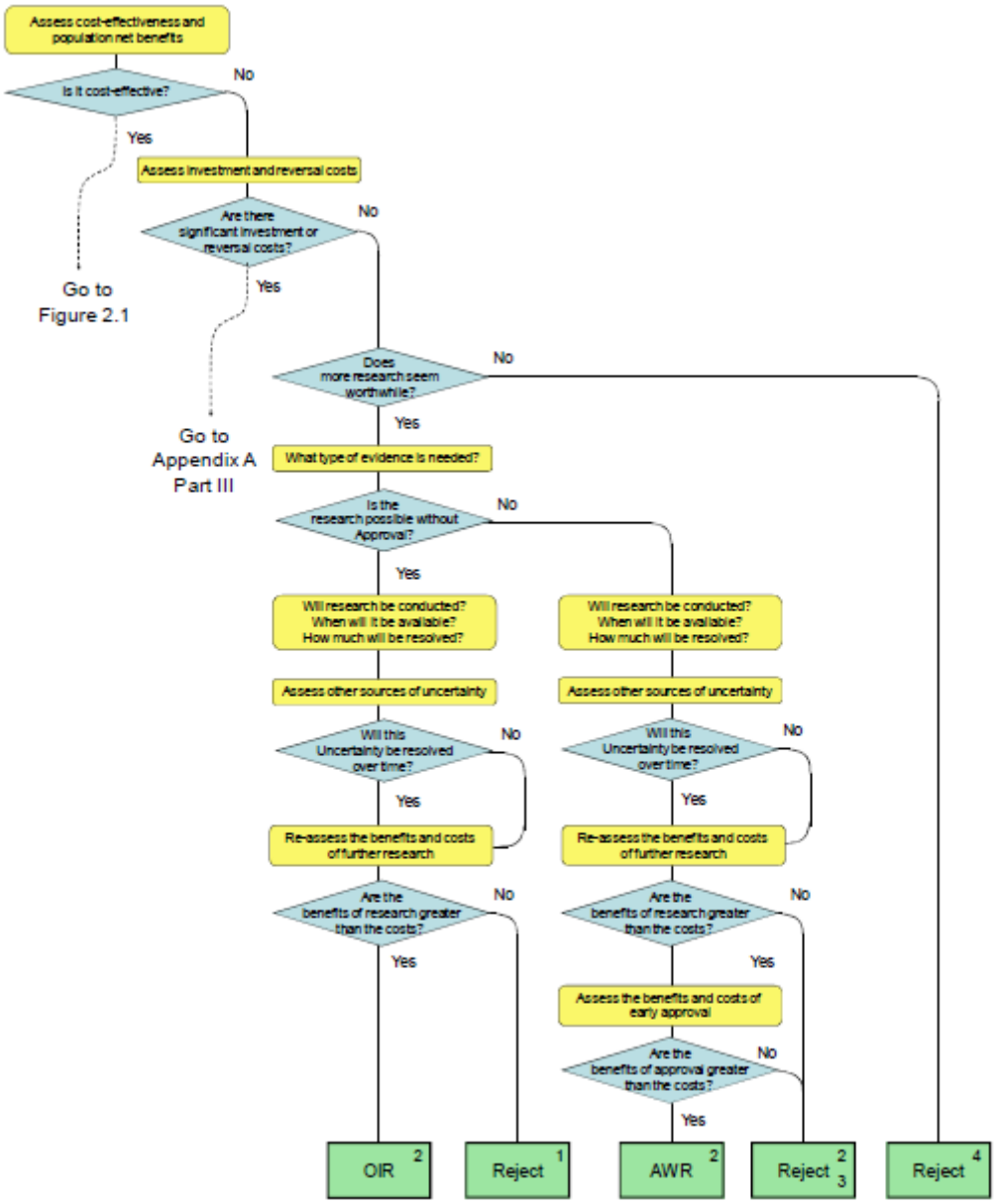


**Figure 2.2** **Technologies not expected to be cost-effective**