National Trauma Research Institute

ISCRR Institute for Safety, Compensation and Recovery Research

Transport Accident Commission & WorkSafe Victoria

Evidence Service

Non-Established, New or Experimental Treatments (NENET)

Evidence Summary

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INTRODUCTION

> ***"Policy makers are often expected to make coverage decisions based on the "best available" evidence, which can, at times, be inadequate. By having a "yes" or "no" decision as the only options, promising technologies may be rejected or ineffective (or unsafe) ones adopted, depending more on political and other pressures than evidence. This finding can perpetuate the problems of scientific uncertainty, underuse and overuse of services, and failure to resolve uncertainty through further evidence generation [6]." (1)***

When evidence is lacking or inadequate, decision makers need to weigh up the potential risk of providing coverage for ineffective or harmful treatments (Type I error) against denying coverage for treatments that are "beneficial and efficient" (Type II error).(1) Factors such as Australia's history with thalidomide, and potential 'cost blowouts' associated with new technologies could make decision-makers more likely to lean towards 'no' decisions that avoid Type I error, which has the potential to create a system with "an unacceptable level of denying access to medical procedures that are beneficial and efficient (Type II errors) [4]".(1)

As an alternative to strict 'yes' or 'no' decision-making, where evidence may be inadequate, the TAC has developed a policy for Non-Established, New or Experimental Treatments (NENET).(2) In this policy, non-established, new or experimental treatment includes equipment, medication, procedures, prostheses, surgery or treatment that:

- is still undergoing clinical trials
- has no MBS item number (for medical treatment, procedures and surgery)
- has no relevant articles published in the peer-reviewed journals
- does not have the support of the majority of medical practitioners in the relevant field
- is being used in a way other than the technique published in the peer-reviewed journals
- is being used in a different body area to the data published in the peer-reviewed journals. For example, where a provider may request funding for joint fluid therapy to an area other than the knee joint.
- is prescribed off-label, i.e. the intended use differs from that prescribed on the product information sheet or label (medications where the use differs in the form of dose, age, indication or route).(2)

Currently there seems to be debate and uncertainty around the best way to make decisions around the use or reimbursement of treatments for which there is little or no evidence. Other organisations have policies for making decisions about funding for clinical interventions with a limited or non-existent evidence base; these are summarized below and outlined in greater detail in the table that follows.

DECISION-MAKING MODELS

Off-label use of medications

A framework for assessing the appropriateness of off-label medication use by Madlen Gazarian was used by the TAC in the formulation of their NENET policy. This was published as a paper in the Medical Journal of Australia,[3] and then later presented as a discussion paper to the World Health Organisation (WHO).[4]

Coverage with Evidence Development (CED) Approaches

A "coverage with evidence development" type approach has been adopted in several different countries, examples of these are presented below:

Medicare (USA)

In America, the public health insurer Medicare has been using a 'Coverage with Evidence Development' (CED) policy. This policy allows the reimbursement of promising new technologies for which there is not a strong enough evidence base, on the proviso that the patient receives the treatment as part of a trial or register, with the aim of building the evidence base so that eventually their recommendations/decisions can be based on the evidence. The NHS in Scotland is considering taking this approach as well.

MSAC (Aus)

Coverage with Evidence Development, or interim funding, has been used in Australia for several years. Since April 1998, the Medical Services Advisory Committee (MSAC) has granted interim listing on the Medicare Benefits Schedule (MBS) to fifteen applications (as at October 2008).[1] O'Malley et al. have written a case study that discusses the practical application of a CED decision for a particular medical device, how this process worked, and lessons learned along the way.[1]

NICE (UK)

When appraising health interventions such as health technologies, health promotion and disease prevention programmes, screening and diagnostic tests and surgical procedures for use under the the NHS, the National Institute of Health and Clinical Excellence (NICE) can recommend: routine use of an intervention in the NHS, that the intervention is not used in the NHS, or use of the intervention in the NHS only in the context of appropriate research. [5]

Chalkidou et al (2007) write about how NICE deals with uncertainty, how it issues recommendations for interventions to be used only in the context of research, and how these recommendations are implemented.[5]

NICE has an Interventional Procedures Programme, with the remit of evaluating clinical interventional procedures for coverage by the NHS. The Programme develops guidance documents for use of the procedure within the NHS. They have a structured decision making framework for their recommendations, and they often deal with emerging technologies where little evidence exists[6]

Other Approaches

PBAC (Aus)

Australia's Pharmaceutical Benefits Advisory Committee (PBAC) are in charge of making decisions about which products are listed on the Pharmaceutical Benefits Scheme. Recommendations made by PBAC are listed on the Australian Government Department of Health and Ageing website. The recommendations are either positive, negative, or to defer decision making.[7]

ACC (NZ)

When deciding whether to fund an intervention, the Accident Compensation Corporation (ACC) of New Zealand's Evidence Based Healthcare group works with their Purchasing Guidance Advisory Group (PGAG) to make a recommendation. Purchasing recommendations are developed through a considered judgement process that involves evaluating evidence and consulting with clinical experts. This process is captured in a considered judgement form, which outlines the factors taken into consideration. These forms are usually produced to accompany an evidence based review or brief report.[8]

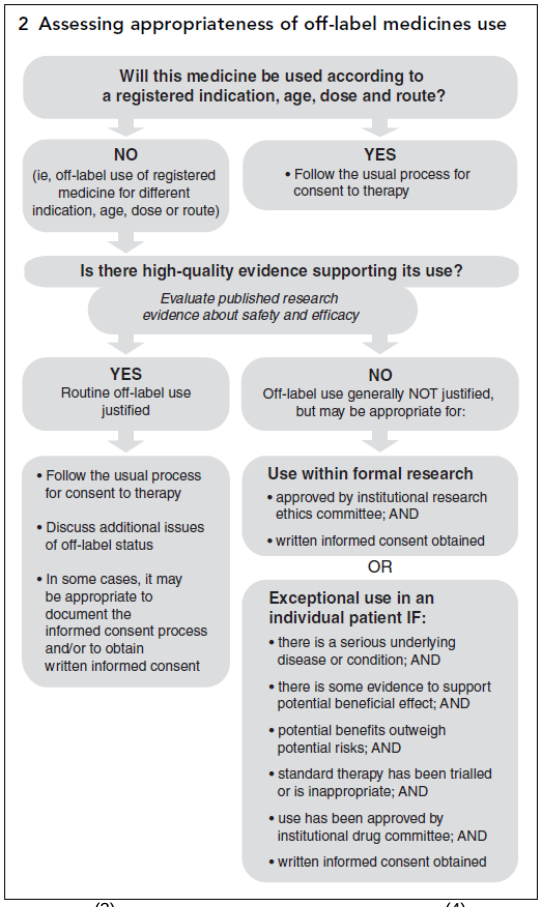
Canada

"Little is available in peer-reviewed literature about how HTA is actually used in decision-making across Canada. In fact, little is known about decision-making processes, both at the national and local levels. The lack of transparency has become particularly frustrating for patients and manufacturers searching for answers to why certain technologies received negative recommendations or decisions [14]. The CDR is taking steps to "open up" its process through the appointment of members of the public to CEDAC."[9]

SUPPORT Tools for evidence-informed health Policymaking (STP)

This is a series of articles written for people responsible for making decisions about health policies and programmes and for those who support these decision makers. The series is intended to help such people ensure that their decisions are well informed by the best available research evidence. Article 17 of this series addresses the issue of decision making for policymakers in situations where there is insufficient evidence to know the likely impacts of a health policy or programme option.[10]

APPROACHES TO DECISION MAKING AROUND TREATMENTS FOR WHICH THERE IS LITTLE OR NO EVIDENCE

Description	Decision making process/outcome
Off label use of medications policy[3, 4] The Gazarian MJA paper[3] that the existing TAC policy[2] is based on includes a framework for making coverage decisions, and the information that is needed to make decisions. A follow-on 2007 discussion paper for WHO[4] by the same author states that: • "there has been a virtual silence in terms of specific guidance to assist clinicians, guideline developers and policy makers trying to make decisions about the appropriateness of such [off-label] prescribing" • "for those organisations that do provide information about off-label uses, there does not appear to be an explicit or consistent process by which recommendations are developed"[4]	 Source: Gazarian MJA paper[3] and WHO discussion paper[4]
Description	Decision making process/outcome

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Coverage with Evidence Development: (Medicare USA)[11] This guidance document describes national coverage determinations (NCDs) that include, as a condition of payment, the development and capture of additional patient data to supplement standard claims data.[11]	Coverage with evidence development option (due to lack of evidence): "**B. Coverage with Study Participation (CSP)** CSP will allow coverage of certain items or services for which the evidence is not adequate to support coverage under section 1862(a)(1)(A) and where additional data gathered in the context of clinical care would further clarify the impact of these items and services on the health of Medicare beneficiaries. In the past, this level of evidence would have prompted non-coverage decisions."[11]
Coverage with Evidence Development: discussion paper (NHS Scotland)[12] NHS Scotland discussion paper for a stakeholder workshop held in November 2008. A 'coverage with evidence development' model is currently being investigated by the NHS Scotland as a way of funding promising health interventions while more conclusive evidence is gathered to address uncertainty regarding its clinical or cost effectiveness. This paper discusses the experiences of the use of similar policies by Medicare (USA), NICE (UK), Ontario Health Technology Advisory Committee (Canada), and the Dental and Pharmaceutical Benefits Agency (Sweden)	The framework and model are still being developed. This discussion paper talks about the experiences of the different countries using 'coverage with evidence development' models.
Coverage with Evidence Development: MSAC example[1] "Where the evidence is inconclusive, but MSAC concludes that the service is likely to be safer, more effective, and more cost-effective than currently funded services, MSAC may advise the Minister that interim funding to enable data collection and further evaluation may be appropriate."[13] "Since its inception in 1998, MSAC has recommended interim funding for fifteen applications with a data collection proviso for most of them. In only two cases was the collection of data funded by the government ...In other cases, data have not	A CED ruling was made for a capsule endoscopy device, with interim funding granted for 3 years. The funding was conditional on the collection of Australian data on the long-term safety, effectiveness, and cost-effectiveness of capsule endoscopy. A capsule endoscopy register for this device was run from 2004-2007, collecting data on 4,099 patients. Based on these data, MSAC recommended that full public funding be supported under the MBS. This procedure is preferred by patients and has the potential to reduce the number and cost of previous investigations.[1] The O'Malley et al. paper reviewed how the data were collected, the methodological difficulties associated with the collection and analysis of the data, and the outcomes of the data. "The experience of the PillCam R _ Capsule Endoscopy Register in Australia has demonstrated that data collection can be an effective solution to the unique problems associated with gathering evidence to support medical procedures. This experience has also highlighted several possible

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been collected and have resulted in a renewal of interim funding or the provision of permanent funding based on the evidence accumulated from other sources during the time that interim funding was available."[1] This article describes a case study of the CED ruling for a specific medical device, how this process worked (i.e. funding, data collection, analysis and reporting), and lessons learned along the way.[1]	improvements in the system."[1] "The financial burden of the register was shared between (i) the Australian Federal Government providing MBS Funding; (ii) Given Imaging, the manufacturer of PillCam R _ providing the administrative support; (iii) the Gastroenterological Society of Australia (GESA) and key clinical experts designing the data collection forms and overall supervision of the data collection; and (iv) the practicing physicians spending their time completing the forms."[1] "Increased use of Coverage with Evidence Development (CED) has the potential to make beneficial new technology available earlier and potentially decrease the probability of Type II errors based on insufficient evidence. The interim funding of PillCam R _ Capsule Endoscopy is an example of a successful application of CED in Australia. However, the use of CED has at least one major problematic policy implication. What action could and should be taken if the evidence generated does not demonstrate the long-term safety, effectiveness, and cost-effectiveness of the procedure?"[1]
NICE general recommendations – Only in Research (OIR) recommendation[5] Summary: "NICE guidance is based on the best available evidence; however, there are several situations in which there may be significant uncertainties about the intervention under consideration. In these cases, recommending the use of the intervention in the context of research can help fill the evidence gaps, while ensuring the efficient use of resources and encouraging innovation that adds value. Making OIR recommendations has been a policy option for NICE since it was established in 1999. However, setting out clear and consistent criteria leading to such decisions and ensuring that the recommended research is undertaken in a timely and responsive manner are challenging tasks. Through reviewing the cases where NICE has issued OIR recommendations, this paper reinforces the importance of acknowledging uncertainty and highlights the difficulties in implementing this policy option within the NHS."[5]	NICE can recommend: • The routine use of an intervention in the NHS (either for all or specific licensed indications or patient subgroups); • That the intervention is not used in the NHS (because of inadequate evidence of effectiveness, or more frequently cost-effectiveness); or • The use of the intervention in the NHS only in the context of appropriate research. This would be appropriate in the case of promising interventions not yet supported by sufficiently robust evidence to justify an unqualified recommendation. In those cases, NICE would 'recommend that further research is carried out to see whether the potential promise of the intervention can be realized, indicate in broad terms the questions this research should address and advise clinicians that, in the meantime, they should only use the new intervention as part of a well-designed programme of research intended to answer these questions' [5] To ensure the OIR option is used in a pragmatic way, NICE is exploring the decision-making trail leading to and the criteria underpinning these decisions. These criteria should ideally reflect how well NICE and the NHS tolerate uncertainty. A number of questions need addressing: • How much uncertainty should there be before a recommendation is issued that a technology be used only in the context of research? • How would this vary (if at all) when there is no ongoing or planned research? • Should the focus be solely on the quality of the evidence or should the potential

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	budgetary impacts and clinical importance of the practice be considered when issuing an OIR recommendation? • How can these decisions be made in a transparent, consistent and methodologically sound way across NICE? Implementing the OIR option in the NICE and broader NHS context has been challenging, due to a lack of formal arrangements for such an implementation between NICE, industry and the clinical research community, including the NHS and patient organizations. The NICE Citizen's Council met in January 2007 to discuss NICE's approach to uncertainty. They unanimously endorsed OIR as a valuable decision option for NICE and identified the following key considerations: • The extent to which further research is likely to reduce current uncertainty; • The value-for-money of the research; • The implications of a positive recommendation on the evidence base and the NHS budget when this is made inappropriately in place of an OIR decision; • The existence of an ongoing study or the feasibility setting one up study within a realistic time frame; • Issues of patient access to the study across different geographical areas. OIR recommendations can be viable and workable decision options as long as there is some co-ordination between the research and decision-making communities.[5]
NICE Interventional Procedures Programme methods guide[6] This document contains details of the types of recommendations made by NICE's multidisciplinary Interventional Procedures Advisory Committee regarding the use of a clinical interventional procedures under the NHS (section 6.2)[6]	The main types of recommendations made by the committee are: **'Normal' arrangements:** the evidence should be adequate in the following respects. • It should be valid, relevant and of good quality. • It should be available in sufficient quantities for the Committee to make a positive decision. • It should be sufficiently consistent in nature.*etc...(see document for full details, section 6.2.1)* **'Special' arrangements** In instances where any of the above conditions are not fulfilled, recommendations are made for clinicians to use the procedure only with special arrangements for consent and/or audit and/or research. It is also stipulated that the clinical governance leads of trusts should be notified. This recommendation is often made when the procedure is considered to be emerging practice in the NHS.

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	'Research only' In some circumstances, the Committee recommends that the procedure should be carried out only in the context of formal research studies approved by a research ethics committee. This recommendation is often made where: • the procedure is still considered to be experimental in nature • the level of uncertainty about the efficacy and/or safety evidence is such that it is considered to be in the best interest of patients to recommend controlled investigation of the procedure under the scrutiny and protection of a research ethics committee • resolution of substantial uncertainties about its efficacy and/or safety would be fundamental to its routine use. **'Should not be used'** The Committee may recommend this for a procedure where the evidence suggests that it has no efficacy and/or poses unacceptable safety risks.
Pharmaceutical Benefits Advisory Committee (PBAC) (Australia) Australia's Pharmaceutical Benefits Advisory Committee (PBAC) are in charge of making decisions about which products are listed on the Pharmaceutical Benefits Scheme.	Recommendations made by PBAC are listed on the Australian Government Department of Health and Ageing website. The recommendations are either: • Positive recommendations • Decisions not to recommend, or • Deferrals.[7] When decision making is deferred, this is generally done so to allow correspondence with the sponsor/applicant or to allow them to generate or provide further evidence.[7] In its interim report to Government in July 2008, the Access to Medicines Working Group (AMWG) discuss the topic of uncertainty and transparency in PBAC decision making. They describe uncertainty as "areas where the evidence, results or conclusions provided are unclear, ambiguous or open to various or different interpretations"[14] The AMWG describe four types of uncertainty that can impact evaluation and decision making

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	process: • Clinical uncertainty – there may be uncertainty about whether a new medicine will effectively meet the clinical need it is proposed to treat. • Economic uncertainty –uncertainties around its value, i.e. value that patients place on the extra health outcomes to be gained, costs of administration, the wider impacts on the use of other health care resources, etc. • Utilisation uncertainty – the extent to which the medicine will be used in practice in the Australian community may be unclear. • Financial uncertainty – in some ways linked to utilisation uncertainty, uncertainty may exist around the overall cost of the medicine to the PBS and perhaps even greater uncertainty about the overall impact of the medicine on other areas of the Government's health budget.(14) In terms of PBAC's decision making process, it is in the Terms of Reference of the AMWG to work with PBAC to develop and articulate a set of principles for assessing evidence and information relating to new medicines and for improving the transparency of the decision making process.(14)
ACC Considered Judgement Form	
When considering whether to 'purchase' an intervention, the ACC's Evidence Based Healthcare group works with the Purchasing Guidance Advisory Group (PGAG) through a considered judgement process, which involves evaluating evidence and consulting with clinical experts. This process is documented in a considered judgement form. (8)	***Checklist of issues that may be considered by the Purchasing Guidance Advisory Group when making recommendations***
	1. Volume of evidence *Comment here on any issues concerning the quantity of evidence available on this topic and its methodological quality.*
	2. Consistency *Comment here on the degree of consistency demonstrated by the availability of evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence.*
	3. Applicability *Comment here on the extent to which the evidence is directly applicable in the New Zealand setting. Comment here on how reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline.*
	4. Clinical Impact *Comment here on the potential clinical impact that the intervention in question might have – e.g. size of patient population; magnitude of effect; relative benefit over other management options;*

<table>
<tr><th>Description</th><th colspan="3">Decision making process/outcome</th></tr>
<tr><td></td><td colspan="3">resource implications; balance of risk and benefit.</td></tr>
<tr><td></td><td colspan="3">5. Other Factors
Indicate here any other factors that you took into account when assessing the evidence base.</td></tr>
<tr><td></td><td>6. Evidence Statement (IPM Advisory Group)
Please summarise the development group's synthesis of the evidence relating to this key question, taking all the above factors into account, and indicate the evidence level which applies.</td><td>Weight and consistency of evidence*</td><td>Evidence Level**</td></tr>
<tr><td></td><td>7. Recommendation (IPM Advisory Group)
What recommendation(s) does the guideline development group draw from this evidence? Please indicate the grade of recommendation(s) and any dissenting opinion within the group.</td><td colspan="2">Grade of Recommendation***</td></tr>
<tr><td></td><td>8. Purchasing Recommendation (PGAG)</td><td colspan="2"></td></tr>
<tr><td></td><td colspan="3"><u>PGAG Discussion</u>
<u>*weight and consistency of evidence:</u>
+ good ~ moderate - poor
<u>**Evidence level:</u>
+ strong studies where all or most of the validity criteria are met
~ studies where not all the of the criteria are met but the results of the study are not likely to be affected
- weak studies where very few of the validity criteria are met and there is a high risk of bias
<u>***Grade of recommendation:</u>
A= The recommendation (course of action) is supported by good evidence
The evidence consists of results from studies of strong design for answering the question addressed
B = The recommendation (course of action) is supported by fair evidence
The evidence consists of results from studies of strong design for answering the question addressed but there is some uncertainty attached to the conclusion either because of inconsistencies among the results from the studies or because of minor flaws; or the evidence consists of results from weaker study designs for the question addressed but the results have been confirmed in separate studies are reasonably consistent. There is fair evidence that the benefits of the course of action being proposed outweigh the harms.
C = The recommendation (course of action) is supported by expert opinion only
For some outcomes, trials or studies cannot be or have not been performed and practice is informed by only expert opinion
I = No recommendation can be made because the evidence is insufficient
Evidence for a course of action is lacking, of poor quality or conflicting and the balance of benefits and harms cannot be determined.</td></tr>
<tr><td>SUPPORT Tools for evidence-informed health Policymaking (STP) 17: Dealing with insufficient</td><td colspan="3">In this article, we focus on decision making undertaken in instances in which there is insufficient evidence available to be able to know whether an option will have the impacts intended, or</td></tr>
</table>

Description	Decision making process/outcome
research evidence[10] This article addresses the issue of decision making for policymakers in situations where there is insufficient evidence to know the likely impacts of a health policy or programme option. The authors suggest four questions that can be considered when there may be insufficient evidence to be confident about the impacts of implementing an option.[10] While this paper discusses individual interventions, it may be more relevant to making decisions about health policies and programs.	whether it may have unintended (and undesirable) impacts. Common mistakes made when there is insufficient evidence at hand include making assumptions about the evidence without a systematic review, confusing a lack of evidence with evidence of no effect, assuming that insufficient evidence necessarily implies uncertainty about a decision, and the assumption that it is politically expedient to feign certainty. We present four questions in this article that can help to avoid these. **Questions to consider** If there is insufficient evidence at hand to allow one to be confident about the impacts of implementing a policy or programme option, the following questions can be considered: 1. Is there a systematic review of the impacts of the option? 2. Has inconclusive evidence been misinterpreted as evidence of no effect? 3. Is it possible to be confident about a decision despite a lack of evidence? 4. Is the option potentially harmful, ineffective or not worth the cost?[10]

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