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8 'International Lessons in New Methods for Grading and Integrating Cost Effectiveness Evidence into Clinical Practice
9 Guidelines'

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Abstract

Economic evidence is influential in health technology assessment world-wide. Clinical Practice Guidelines (CPG) can enable economists to include economic information on health care provision. Application of economic evidence in CPGs, and its integration into clinical practice and national decision making is hampered by objections from professions, paucity of economic evidence or lack of policy commitment. The use of state-of-art economic methodologies will improve this.

Economic evidence can be graded by 'checklists' to establish the best evidence for decision making given methodological rigor. New economic evaluation checklists, Multi-Criteria Decision Analyses (MCDA) and other decision criteria enable health economists to impact on decision making world-wide. We analyse the methodologies for integrating economic evidence into CPG agencies globally, including the Agency of Health Research and Quality (AHRQ) in the USA, National Health and Medical Research Council (NHMRC) and Australian political reforms. The Guidelines and Economists Network International (GENI) Board members from Australia, UK, Canada and Denmark presented the findings at the conference of the International Health Economists Association (IHEA) and we report conclusions and developments since.

The Consolidated Guidelines for the Reporting of Economic Evaluations (CHEERS) 24 item check list can be used by AHRQ, NHMRC, other CPG and health organisations, in conjunction with the Drummond ten-point check list and a questionnaire that scores that checklist for grading studies, when assessing economic evidence. Cost-effectiveness Analysis (CEA) thresholds, opportunity cost and willingness-to-pay (WTP) are crucial issues for decision rules in CEA generally, including end-of-life therapies. Limitations of inter-rater reliability in checklists can be addressed by including more than one assessor to reach a consensus, especially when impacting on treatment decisions. We identify priority areas to generate economic evidence for CPGs by NHMRC, AHRQ, and other agencies. The evidence may cover demand for care issues such as involved time, logistics, innovation price, price sensitivity, substitutes and complements, WTP, absenteeism and presentism. Supply issues may include economies of scale, efficiency changes, and return on investment. Involved equity and efficiency measures may include cost-of-illness, disease burden, quality-of-life, budget impact, cost-effective ratios, net benefits and disparities in access and outcomes..

Priority setting remains essential and trade-off decisions between policy criteria can be based on MCDA, both in evidence based clinical medicine and in health planning.

Introduction

112 Economic evidence is becoming influential in health technology assessment (HTA) world-wide. However, most health
113 care practices and procedures are not subjected to HTAs, thereby limiting the impact of economic evidence. CPGs offer
114 the potential for economists to be centrally involved in increasing the cost-effectiveness of health care provision.
115 However, examples of the use of economic evidence in such guidelines, and the subsequent integration of such
116 evidence into clinical practice and national decision making are limited. This may be because of resistance from the
117 professions, paucity of economic evidence or lack of policy commitment.

118 Important components of the evidence used in the development of CPGs include the use of systematic reviews of the
119 literature, decision rules, WTP, opportunity costs, and end of life/social value judgement along with techniques to grade
120 the economic evidence. Such evidence can be graded by guidelines or 'checklists' to establish which evidence should be
121 used to inform decisions based on the rigor of the methodology. New developments in all of these areas are cutting
122 edge techniques that provide a platform for improved contribution by health economists in decision making world-wide
123 and are considered in this paper. The principal purpose of this paper is to address the implications of these
124 methodologies for the integration of economic evidence into CPG agencies world-wide and their implications for
125 Australian reforms by the Parliament, governments and health services. These issues were discussed by Board
126 members of the Guidelines and Economists Network International¹ (GENI) in presentations at the 9th IHEA World
127 Congress.

128 The GENI is an international association which enables health economists, epidemiologists, clinicians and medical
129 experts world-wide to work with prominent international bodies, health services and governments. GENI's agenda is to
130 facilitate the effective integration of CPGs, economic and clinical evidence into national decision making and clinical
131 practice in the health sector. GENI aims to forge linkages with bodies that set the standards for appropriate treatment
132 under different conditions that may link to contracts or regulatory processes such as insurers and national government
133 funding systems. Linkages to Evidence Based Medicine (EBM), service delivery and related government regulatory and
134 funding systems are central. GENI's has twelve international board members and a large twenty nine member
135 management team comprising CEO, Medical Advisory Committee, Directors, senior managers and researchers, with
136 over 830 GENI LinkedIn Group affiliates.

137

138 At the 9th IHEA Congress, five of GENI's Board members from America, UK, Australia, Canada and Denmark
139 discussed new methodologies and economic guidelines or 'checklists' for incorporating economic evidence into CPGs,
140 clinical practice and national decision making. The session considered guidelines recently developed for the conduct

¹ <http://geni-econ.org/>

141 and reporting of economic evaluations. These guidelines assess studies for decision-making in technology assessment
142 for reimbursement or developing CPGs. The session also discussed use of CEA evidence in CPG processes in
143 Australia by NHMRC, three Local Hospital Networks (LHNs) in Victoria and implications for related national and
144 state health policy reforms led by the Council of Australian Governments (COAG) and reviewed by the Australian
145 Parliament. An impetus for the international discussion at IHEA was a request from the NHMRC for input from GENI
146 about the Council's review of its processes to develop and approve guidelines in Australia using the costs and benefits
147 evidence and also socio-economic evidence. The focus on these Evidence Based Medicine (EBM) approaches
148 involving CPGs and CEA evidence has also been an important feature in some reforms by the Australian Parliament,
149 Governments and health services. The methodologies discussed in this paper may further assist this reform agenda,
150 along with the deliberations of the NHMRC and other regulatory bodies that approve CPGs world-wide.

151 Firstly, we discuss Australian health policy reforms in Commonwealth-State health agreements involving, *inter*
152 *alia*, national implementation of LHN governance structures and hospital Activity Based Funding (ABF) based on
153 the Victorian model. Recommendations were provided to COAG and the Senate based on Victorian evaluations of
154 applications of NHMRC's CPG methods using CEA in Victorian LHNs and the risk adjustment of ABF, given
155 relevance to legislation for health agreements and related authorities. The Senate also considered reforms for
156 palliative care, rural health and the Aged Care Quality Agency and recommendations were submitted to the Senate
157 about crucial CPG and CEA issues. COAG's 2016 Heads of Agreements on Public Hospital Funding will reduce ABF
158 for specified adverse events, ineffective or harmful treatments and readmissions from July 2017. Recommendations to
159 the Senate about risk adjusting ABF and measurements of quality outcomes and disseminating NHMRC's EBM
160 methods Australia-wide are also discussed. The NHMRC's CPG development process review is then considered.

161

162 That is followed by consideration of the CHEERS Task Force which has consolidated guidelines for assessing health
163 economic evaluation studies and recently published a consensus statement, along with the checklist. Recent
164 developments for MCDA that broaden the objectives of evaluation in health care are considered along with the
165 International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) MCDA Emerging Good
166 Practices Task Force that has developed a common definition for MCDA in health care and good practice
167 guidelines for conducting MCDA. The Hopkins Review is then discussed which examines if and how economic
168 evidence impacts on health policy, including clinical guidelines, in the USA. It also examines the strengths and
169 weaknesses of existing checklists used to assess best practices in economic evaluations. The review of studies also
170 addresses the use of economic outcomes in policy and decision making. Finally, we conclude with implications of
171 these deliberations world-wide for health services, governments and agencies that develop CPGs such as National

172 Institute of Health and Care Excellence (NICE), US Guidelines clearing house, NHMRC and the USA Centre for
173 Disease Control and Prevention (CDC).

174

175 **Review**

176 **Lessons for Australian Parliament, National Health and Medical Research Council, Governments and Health** 177 **Services**

178 **Australian Commonwealth-State Health Agreements and Reforms**

179

180 In Australia, there are several agreements between Commonwealth and State governments through the Council of
181 Australian Governments (COAG), that specify health policy and reform directions, including the National Healthcare
182 Agreement (NHA), the National Health Reform Agreement (NHRA), National Partnership Agreements and the
183 Intergovernmental Agreement on Federal Financial Relations. Further, the April 2016 Heads of Agreement on Public
184 Hospital Funding forms the basis of negotiations leading towards a time-limited addendum of the NHRA, in the form
185 of an additional schedule, to commence on 1 July 2017.

186

187 This suite of Agreements is designed to set out the architecture for a nationally unified and locally controlled health
188 system. They also encourage improved quality of care and the cost-effective use of guidelines, clinical pathways and
189 other EBM initiatives (COAG 2011) [1].

190

191 Antioch briefed COAG during 2008, 2009 and 2010 about the new health agreements. She also briefed the Australian
192 Senate from 2010 to 2013 on COAG Agreements and related authorities and, in 2016, on new COAG Heads of
193 Agreements. Some briefs included evidence that implementing NHMRC methodologies for CPG implementation with
194 economic and clinical evidence in Victorian LHNs resulted in cost effective service provision in the context of ABF.
195 She recommended the development of *State Centres of EBM Health Services and Workforce Redesign*, use of NHMRC
196 and international methods with economic and clinical evidence. an International Centre of EBM and Health Economics
197 and the need for adequate risk adjustment of ABF (Antioch 2008, 2009, 2010a) [2, 3 ,4].

198 Antioch's (2008) [2] COAG brief addressed a reform agenda for the 2009 Australian Healthcare Agreements (AHA)
199 re-negotiation involving two areas. Firstly, she proposed new state centres to integrate the economic and clinical
200 evidence and CPGs into clinical practice using methods by the NHMRC (1999, 2000a, 2000b, 2000c, 2001) (5, 6, 7, 8,
201 9), Antioch Jennings and Botti (2002) [10], Drummond, Schulpher Torrance et al (2005) [11] and organisations such

202 as GENI. Secondly, she argued the equity of the AHCA formulae and index can be improved using risk adjustment to
 203 align funding with health need by using either Diagnostic Cost Group – Hierarchical Condition Categories (DCG-HCC)
 204 relative risk scores or Diagnostic Related Group (DRG) cost weights, Evidence she published in European Journal of
 205 Health Economics concerning risk adjustment requirements for the ABF formulae in Victoria relating to severity
 206 markers for state-wide referral services eg transplantation, major trauma was also referenced [2, 12].
 207 Antioch's (2009) [3] COAG brief outlined national cost savings of \$273.524m pa (2006 prices) and \$1,367.620m over
 208 five years via implementation of the proposed State Centres, modelled on cost savings achieved by reductions of
 209 adverse events and length of stay in the Victorian hospital experience. That brief attached advice from the Northern
 210 Territory (NT) Health Minister who expressed interest in risk adjustment for ABF implementation given the
 211 demographic and geography of NT are such that the use of a standard Australian profile runs a severe risk of the
 212 jurisdiction being disadvantaged (Antioch 2009) [3]. The ABF formulae subsequently developed by the Australian
 213 Government included a risk adjustment to the formulae called 'indigenous adjustment' which still remains along with
 214 other adjustments (IHPA, 2015) [13]
 215
 216 Antioch's COAG brief (2010a), which was also published by the Senate Standing Committee on Finance and Public
 217 Administration Inquiry into COAG Reforms relating to Health and Hospitals [4], stated that some Health Ministers
 218 advised that their Departments were considering her reform proposals for their implementation of the National Health
 219 Agreements and Partnership programs, with one large jurisdiction indicating that the State planned to introduce a State
 220 Centre similar to her proposed State Centres. The brief also recommended the establishment of an International Centre
 221 of Evidence Based Medicine and Health Economics
 222
 223 Antioch's COAG and Senate submissions indicated that the 'State Centres' recommendation arose from national
 224 stakeholder engagement during her 2007 presentations in all Australian States and Territories and NZ about the
 225 implementation and evaluation of the initiatives she led in the Victorian LHNs and subsequent liaison with the Federal
 226 Health Ministers' Office. The national presentations were sponsored by the Australian Health Care and Hospital
 227 Association and the Women's and Children's Hospital Australasia in the context of the renegotiation of National Health
 228 Agreements. She provided a Cost Benefit Analysis (CBA) of national implementation of the State Centres in her
 229 invited submission to the Senate Inquiry concerning the establishment of the National Health Performance Authority
 230 and also the Independent Hospital Pricing Authority which calculated net benefits of \$269.6m per annum (2006
 231 prices) (Antioch, 2011a, 2011b) [14, 15]. The CBA was modelled on the evaluation of the Victorian LHN initiatives.
 Many features of the national reforms by COAG, and under consideration by then Australian Parliament, were based on

232 the Victorian health system including ABF and new hospital network governance through LHNs. Evidence of cost
233 effective EBM implementation in Victoria was of interest.

234

235 **Australian Parliament Inquiries on Health Agreement Legislation and Health Policy Reforms**

236 Parliamentary Inquiries since 2010 made recommendations about policy and legislation to implement elements of the
237 Health Agreements and other health policy. The Senate Report on the Federal Finance (National Health and Hospitals
238 Network) Bill (2010) (Economics Legislation Senate Committee, 2011) [16] cited Victorian health system
239 effectiveness and efficiency evidence provided by Antioch (2010b) [17] in support of the new national arrangements.
240 The Committee recommended that the Senate pass the Bill and recognized the Bill is 'a vital piece of legislation which
241 will enable the implementation of significant elements of the health and hospital reforms agreed by COAG in April
242 2010'. (Economics Legislation Senate Committee, 2011) [16]. More recently, various State governments are
243 implementing State Centres to facilitate best practice and innovation in NSW, Victoria and Queensland². The
244 methodologies in this paper and deliberations of more recent Senate Inquires in 2012, 2013 and 2016 outlined below
245 could assist such State Centres along with Australian governments, health services and the NHMRC.

246 The Senate Inquiries during 2012 into Palliative Care in Australia and Factors Affecting the Supply of Health Services
247 and Medical Professionals in Rural Areas addressed CPGs and the use of health economics to improve efficiency,
248 outcomes and prioritization of health technologies and service delivery. Stakeholders in the Palliative Care Inquiry
249 advocated urgent updated CPGs for palliative care, advanced care directives, dementia diagnosis, pain management
250 and case management to enable improvements in cost effective service provision and continuum of care. Antioch
251 recommended that CPG updates by COAG, Federal Department of Health and NHMRC could use CPGs by NICE and
252 Agency for Healthcare Research Quality (AHRQ) USA CPG Clearinghouse concerning opioids, advanced care
253 directives/planning and radiotherapy. She advocated that CEA evidence for new Australian CPGs in palliative care
254 should be based on NHMRC methodologies (Antioch 2012a) [18]. The Senate report on Palliative Care in Australia
255 recommended that COAG should consider developing and implementing a case management model; and a uniform
256 national palliative care pathway that clarifies when general palliative care moves into specialist palliative care, and
257 maps the diagnosis and referral process to ensure that a palliative patient's journey involves coordinated access to all
258 necessary services. It also recommended that a national model legislation for advanced care planning should be
259 developed and the NHMRC should report its work on alternative therapy claims in relation to palliative care and [19].
260

² This includes the Agency for Clinical Innovation (ACI) and Centre for Health Care Redesign in NSW and the Centre for Health Care Improvement in Queensland. In Victoria the Commission for Hospital Improvement and the Health Innovation and Reform Council were created. More recently the Victorian Commission was disbanded and replaced by Better Care Victoria

Stakeholders in the 2012 Rural Health Senate Inquiry argued for urgent mechanisms for rapid EBM translation of CEA evidence and CPGs into rural practice with the input of economists. They also advocated improved Evidence Based Planning (EBP) to identify rural supply and demand factors and prioritisation. Antioch (2012b) [18] recommended that the Federal government undertake a national review of EBM translational work to prevent duplication, with a consolidated and rapid disseminate EBM evidence to rural areas. For EBP she recommended the uptake of evidence concerning disease burden, epidemiological data and CEA of interventions, for demand and supply modelling. Any gaps in the evidence identified in the national review should be addressed by Federal and State governments, NHMRC and all States (Antioch 2012b) [20]. A key Senate Committee recommendation was for the Department of Health and Ageing to prepare a brief for COAG's Standing Council on Health on existing or emerging gaps affecting the delivery of health services to rural and remote communities caused by mis-alignment between Commonwealth and state policy, including options for measures to remediate such gaps [21].

Antioch (2013b) [22] recommended to the 2013 Senate Inquiry on the Aged Care Quality Agency Bill 2013 that the Agency, which is the new accreditation body, should include health economists and indigenous health experts and should collaborate with the NHMRC, GENI, Australian Commission on Safety and Quality in Health Care (ACSQHC), Cochrane Collaboration, Guidelines International Network (GIN), National Guideline Clearing House AHRQ, NICE, NHS Economic Evaluation Database (NHS EED), NHS Evidence, WHO Health Economics Network and the CDC. That Committee considered five Bills on Aged Care of which the Quality Agency was one. The Senate Committee's Report recommended monitoring the impacts of fee scales on client welfare and providers, and new supplements for the homeless and workforce. The report addressed guidelines from the perspective of home care packages based on clinical need, accreditation of residential care services, workforce supplements and pricing [23].

Under the April 2016 COAG Heads of Agreement, which cover public hospital funding from 2017 to 2020, the Commonwealth will provide \$2.9b in additional funding but growth is capped at 6.5% with some funding linked to quality outcomes. The Agreements will reduce payments for specified adverse events, ineffective interventions, procedures known to be harmful and readmission rates and the Independent Hospitals Pricing Authority (IHPA) is working with the ACSQHC and COAG to develop implementation details [24], Antioch (2016a) [24] recommended the risk adjustment of all comparative hospital data to capture, inter alia, the impact of state-wide referral services on case-mix severity and emphasised that reductions in funding can unfortunately further exacerbate adverse quality outcomes for some conditions such as certain infections. The Committee concluded that 'the gap in health and education funding remains. The Government remains committed to policies that deprive these areas of the much needed funds'[25].

292 In response to the Senate Select Committee on Health Inquiry on Health Policy, Administration and Expenditure in
293 2016 , Antioch (2016b) [26] recommended that, in conjunction with the COAG 2016 Health Agreements and
294 associated ABF linking risk adjusted quality outcomes to funding, COAG should facilitate dissemination of
295 NHMRC's methods for using the costs and benefits evidence in CPGs Australia-wide and the revised methods once
296 finalised (Antioch, 2016b) [25]. The Inquiry recommended that the Government should determine that the
297 implementation mechanisms for ABF should not be dismantled and a body similar to the National Health and
298 Hospitals Reform Commission should be reconstituted (Senate Select Committee on Health, 2016) [27] We now
299 turn to the NHMRC review of CPG development processes in Australia..

300

301 **NHMRC review of Australian clinical practice guideline development and approval methodologies**

302

303 NHMRC is reviewing its CPG development and implementation methods, including the use of economic evidence and
304 requested advice from GENI on use of the costs and benefits and socio-economic evidence. The advice was provided to
305 the NHMRC in September 2013 and was based on the issues cited herein to 2013. More recent issues covered can
306 further facilitate NHMRC's review which is still underway. The NHMRC (2011) [28] 'Procedures and Requirements
307 for Meeting the 2011 NHMRC Standard for Clinical Practice Guidelines document provides direction for CPG
308 developers who must initially register their guidelines in the NHMRC Development Register and include evidence
309 about needs analysis, disease burden and the clinical problem to be addressed. NHMRC then notifies the Australian
310 Health Ministers Advisory Council if CPGs have been accepted for consideration. The CPG drafts are assessed using
311 the AGREE II tool. The CPG drafts are forwarded to the Therapeutics Goods Administration (TGA), Pharmaceutical
312 Benefits Advisory Committee (PBAC), Medical Services Advisory Committee (MSAC) and Health Departments for
313 comment. The NHMRC's current review of its CPG processes and standards aims to improve development and
314 implementation of CPGs, public health guidelines, systematic reviews and decision making. This review involves
315 NHMRC Principal Committees, NHMRC Synthesis and Translation of Research Evidence Advisory Group 2014-16
316 with Working Groups formed from NHMRC's Research Translation Group (RTG) Advisors List. The current
317 NHMRC standards (2011) [28] handbooks on CPGs (NHMRC, 1999, 2000a, 2000b, 2000c, 2001, 2002, 2009) [5, 6,
318 7, 8, 9, 29, 30] and methodological guidance by AHRQ and NICE will be considered. The NHMRC (2011) [28]
319 Standards refer to the publication 'NHMRC additional levels of evidence and grades of recommendations for
320 developers of guidelines' (NHMRC 2009) [30]. However, NHMRC (2009) [30] does not address the economic
321 evidence. Rather, economic evidence is only addressed in 'How to compare the costs and benefits: evaluation of the
322 economic evidence (NHMRC, 2001) [9]. The NHMRC's (2011) [28] standards state that the NHMRC desires input on
323 CEA of interventions to be included in guidelines. Hence, economic issues are important. NHMRC Standard C. 3.4

states the evidence review should involve search strategies for cost effectiveness, and resource implications of practice. NHMRC Standard D.9.2 indicates that guideline recommendations should consider resource implications and cost effectiveness of recommended practice compared to current practice. NHMRC Standard G.4 indicates that resources for guideline implementation should be considered. The NHMRC (2001) [9] handbook on how to evaluate the economic evidence uses Drummond et al's "10 point" check list (Drummond et al, 2005) [11] and assesses whether there is a well-defined question, a comprehensive description of alternatives is provided, effectiveness is established. all relevant cost and consequences are included along with appropriate measurement. It also assesses credible valuation, differential timing, incremental costs and consequences, and whether allowance is made for uncertainty and appropriate interpretation of results (NHMRC, 2001) [9]. The matrix in table 1 is used to make decisions about the new technology given the strength of evidence for outcomes and costs [9]. The methods for the economic evaluation of health care programmes and treatments have also been discussed in the requirements of other decision-making bodies, such as the National Institute of Health and Care Excellence (NICE) in the UK, which uses the NICE Reference Case, considered in more detail later. The reporting of economic evaluations of health interventions is challenging because substantial information must be provided to enable the scrutiny of findings. Despite a growth in published reports in recent years, reporting guidelines have not being widely adopted. There has been a need to consolidate and update existing guidelines in a user-friendly manner. Checklists can assist peer reviews, authors, and editors, to use consistent guidelines to improve reporting. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS statement consolidates and updates previous health economic evaluation guidelines into one current, useful reporting guidance. The ISPOR 2013 CHEERS 24 item check list, discussed more fully in the next section , can be used by the NHMRC, in conjunction with Drummond et al's 10 point check list, when assessing the economic evidence. A questionnaire by Antioch, Jennings, Botti et al (2002) [10] published in the *European Journal of Health Economics*, that scores Drummond et al [11] 10 point check list, has been used in Australia since 2000 to grade the cost effectiveness evidence using NHMRC methods and CEA thresholds for making recommendations about changes to clinical guidelines and for implementing evidence in three Victorian Local Hospital Networks. Since 2013, that questionnaire [10] has been used in Australia in conjunction with CHEERS assessments which enables an in-depth analysis of issues covered in the Drummond's 10-point checklist. This work on grading the CEA evidence in systematic reviews to evaluate CPGs for diseases such as diabetes type 2 and cystic fibrosis involves senior members of public and private hospitals, national associations, universities, and GENT's senior management team.

Table 1 Assessing CEA evidence using shadow prices in Australia: NHMRC [9]

Ranking of evidence on costs	Ranking of evidence on effects	
	High	Low
Strong	Recommend if: < \$70,000 per life-year	Recommend if < \$30,000 per life-year
	Do not recommend if > \$100,000 per life-year	Do not recommend if > \$70,000 per life-year
Weak	Recommend if < \$30,000 per life-year	Recommend if < \$30,000 per life-year
	Do not recommend if > \$70,000 per life-year	Do not recommend if > \$30,000 per life-year

We outline below international findings that can also guide NHMRC's review of CEA thresholds for CPG development and approval. CEA studies should identify the health benefits offered by an intervention; the additional costs imposed on a limited healthcare budget; and the opportunity costs (i.e. health benefits forgone) from commitment of resources to an intervention. An intervention can be considered cost-effective if its benefits outweigh the opportunity costs of health benefits forgone. The opportunity costs in terms of forgone health benefits are reflected in most CEAs by using a cost-effectiveness threshold (CET) [33].

When the maximum acceptable trade-off between costs and effectiveness is known, CEA can inform whether a program providing a trade-off between its costs and its effectiveness should be implemented. By using the maximum WTP per Quality-Adjusted Life Year (QALY), one can establish a decision rule for CEA. This view emanates from welfare economics, which states that welfare is maximized if goods are exchanged when there is a maximum WTP that exceeds the opportunity cost of the good (Polsky, 2005) [31]. The NHMRC (2001) defines its CEA threshold or 'shadow prices' as is the predetermined maximum WTP for health gains [9].

CEA used by NICE is an assessment of whether the health expected to be gained from using a new medical technology exceeds the health likely to be forgone as other NHS activities are displaced to accommodate the additional costs of the new technology. The CEA threshold therefore represents an estimate of the health forgone as services are displaced [32].

The challenge for decision makers is to determine and use CETs that reflect supply-side constraints. However, there are few empirically estimated supply-side CETs. One exception is Claxton et al (2015) [33] study that estimated the marginal productivity of the UK National NHS and produced a best estimate of the supply-side CET of £12,936, about half of UK GDP pc. [33]

376 Claxton et al (2015) [33] estimated the effects of changes in NHS expenditure on the health of all NHS patients and
377 found that NICE's CEA threshold used to assess new drugs is too high. The approval of new drugs is therefore causing
378 more harm than good to NHS patients overall given the NHS is paying too much for new drugs. NICE has applied
379 £30,000 per QALY threshold to determine whether health benefits of a new drug are greater than the health likely to be
380 lost because the additional resources required are not available to offer effective treatments to other NHS patients.
381 Claxton et al (2015) [33] found that the threshold is too high as their best empirical estimates, based on a number of
382 assumptions, was £12,936 (rounded £13,000) of NHS resources adds one QALY to the lives of NHS patients. Greater
383 harm is therefore being done to other NHS patients when NICE approves costlier drugs. The approval of a new drug
384 that costs the NHS an additional £10m per annum would offer benefits of 333 QALYs. It would also lead to the loss of
385 773 QALYs for other NHS patients with increased mortality in circulatory, cancer, gastro-intestinal or respiratory
386 diseases and reduced quality of life in mental health and neurological diseases. This represents a net loss of 440 QALY
387 for every £10m of additional NHS costs. Further, devoting £280m to the Cancer Drugs Fund in 2014/15 has been
388 associated with a loss of 21,645 QALYs for other NHS patients [33, 34].

389 NHMRC (2001) [9] includes additional criteria which allow higher prices for CEA thresholds for criteria such as:
390 quality of life for patient and/or family; survival improvement; functional status; condition is severe, rare,
391 preventable, or leads to permanent effects in youth; no other health care options available and intervention prevents
392 adverse flow-on effects into other sectors with equity implications. Health care options might require further
393 consideration with regard to these social values if they fall in the range \$70,000–\$ 100,000 per life-year saved and
394 rank highly for evidence on costs and effects, or if they are in the range \$30,000–\$70,000 per life-year saved and
395 rank highly on one but not the other [9].

396

397 Other developments about CEA thresholds in Australia are important to consider. Australia has public insurance
398 coverage for drugs through the Pharmaceutical Benefits Scheme (PBS). Harris et al (2008) [35] found that the
399 Pharmaceutical Benefits Advisory Council (PBAC) decided drug approval coverage from 1994 to 2004 without
400 reference to a public CEA threshold for the cost per LYG or QALY. WTP and decisions were based on the clinical
401 significance, CEA results, cost to government and disease severity. Clinical significance increased the probability of
402 recommending coverage by 0.21 and a drug for a 'life threatening' condition increased that probability by 0.38.
403 Increases of \$A10,000 from an incremental cost per QALY of \$A46,400, reduced the probability of listing by 0.06
404 (Harris, 2008) [33]. Harris et al (2016) [36] analysed 1993 to 2009 PBAC funding decisions. They found that an
405 A\$10,000 increase in cost per QALY reduces average probability of funding from 37% to 33 %. For life threatening

406 conditions or where the drug has no active comparator, odds of positive recommendation are 3.18 and 2.14 greater. If
407 both conditions are met, the odds are increased by 4.41 times [36].

408

409 Shiroiwa, Sung and Fukuda et al (2010) [37] note that although CEA thresholds for medical interventions are assumed
410 to be \$50 000-\$100 000 in the US and 20 000- 30 000 UK pounds in the UK such values are unjustified, given lack of
411 evidence. They measured WTP for one additional QALY gained to determine the threshold of the incremental cost-
412 effectiveness ratio. They compared WTP for the additional year of survival in a perfect status of health in Japan, the
413 Republic of Korea (ROK), Taiwan, Australia, the UK, and USA. A double-bound dichotomous choice was used, and
414 analysis by the nonparametric Turnbull method. WTP values were JPY 5 million (Japan), KWN 68 million (ROK),
415 NT\$ 2.1 million (Taiwan), 23 000 UK pounds (UK), AU\$ 64 000 (Australia), and US\$ 62 000 (US). The discount rates
416 of outcome were estimated at 6.8% (Japan), 3.7% (ROK), 1.6% (Taiwan), 2.8% (UK), 1.9% (Australia), and 3.2%
417 (US). They recommended a new classification of cost-effectiveness plane and methodology for decision making
418 (Shiroiwa et al. 2010) [37].

419 Importantly, Drummond de Pouvourville, Jones, et al (2014) [38] note that NICE has developed supplementary
420 guidance for 'end of life' therapies in the circumstance where the therapy is for a small patient population with life
421 expectancy of less than 24 months and where the therapy adds three months or more to life expectancy. In this
422 scenario, QALYs gained should assume full quality-of-life in the added months. In addition, the Committee can
423 consider that the QALYs gained should be weighted sufficiently high for the therapy to be approved, given NICE's
424 current threshold. These findings along with Harris et al (2008, 2016) [35, 36], Shiroiwa et al (2010) [37] could inform
425 NHMRC's consideration of revised thresholds for CEA in its review of CPG processes and in other countries.

426 We now consider the CHEERS guidelines, which consolidate previous health economic evaluation guidelines.
427 Requirements of other decision making bodies such as NICE, which uses the NICE Reference Case are also considered
428 and may be instructive for deliberations of other CPG Agencies, including the NHMRC.

429

430 **Consolidated Guidelines for the Reporting of Economic Evaluations: The CHEERS Task Force - Reporting** 431 **Guidelines for Economic Evaluation**

432

433
434 The '*CHEERS Elaboration and Explanation Report of the ISPOR Health Economic Evaluation Publication Guidelines*
435 *Good Reporting Practices Task Force*' facilitates the use of the CHEERS statement by providing examples and
436 explanations for each recommendation (Husereau, Drummond and Petrou, 2013) [39].

437 If economic considerations are to be incorporated into clinical guidelines, the guidelines need to reflect the current
438 knowledge on the cost-effectiveness methodology. Therefore, guideline developers need to consult the existing
439 literature on economic evaluation of health care treatments and programmes. The methods for the economic evaluation
440 of health care programmes and treatments have been discussed in the academic literature [11] and in the requirements
441 of decision-making bodies, such as NICE in the UK which uses the NICE Reference Case [40]. The NICE Reference
442 Case requires submission for product review to conform to the following standards: a decision problem defined by
443 NICE scope; comparator therapies listed in NICE scope; inclusion of all direct health effects for patients and caregivers;
444 costs incurred by NHS and Personal Social Services (PSS), cost-utility analysis with full incremental analysis; time
445 horizon long enough to reflect all important differences in costs and outcomes between technologies being compared;
446 claims for health effects based on systematic review; health effects expressed as QALYs with EQ-5D the preferred
447 instrument; data for health related quality of life measurement reported by patients and/or caregivers; preference data
448 for valuation of changes in health related quality of life obtained from a representative sample of UK population;
449 QALYs all have equal equity weight; resource use and costs valued using prices relevant to NHS and PSS; costs and
450 benefits should be discounted at same annual rate (3.5%) (NICE, 2013 [40]; Langley, 2016) [42].

451

452 Application of these standards for chronic disease interventions involves modelling the natural disease progression and
453 the impact of competing interventions over the patient's lifetime or similar long-term time horizon. Disease progression
454 stages can involve a Markov process to track a hypothetical cohort of patients through disease stages. Each health state
455 is defined via associated utilities and costs, with results expressed as cost per QALY (Langley, 2016) [42]. The Markov
456 process often involves two methods of evaluation. *Cohort simulation* tracks a hypothetical cohort of patients
457 simultaneously through the model. *Monte Carl simulation* randomly selects a patient from the cohort and each patient
458 transits through the model one at a time (Drummond and McGuire, 2006) [43]. By application of a WTP threshold cost
459 per QALY, products are judged acceptable, rejected or accepted after agreement on a the actual price set (Langley
460 2016)[42].

461

462 Although various aspects of the methods of economic evaluation are a continuing source of debate, there is much more
463 agreement about the need for reporting standards for studies. That is, although different studies may use different
464 methods, all researchers should have an obligation to report their studies in a transparent fashion. This will help
465 guideline developers and other users of economic evaluations to benefit the most from the existing literature. The most
466 recent attempt to specify reporting guidelines for economic evaluations is the CHEERS initiative [39].

467 The CHEERS Standards were developed by the Good Research Practices Task Force established by the International
468 Society for Pharmacoeconomics and Outcomes Research (ISPOR). The Task Force comprised specialists in the
469 economic evaluation of health care programmes and the editors of journals publishing cost-effectiveness studies of
470 health care interventions. The reporting guidelines were developed through a process consistent with that of the
471 CONSORT initiative for developing guidelines for the reporting of clinical trials [41].

472 The CHEERS guidelines shown in Appendix 1 assess studies with regard to conflict of interest and funding sources in
473 addition to traditional components of published health economic evaluations that involve the title, abstract,
474 introduction, methods and discussion. Economic evaluation methods are assessed with regard to the target population
475 and sub-groups, setting and location, study perspective, comparators, time horizon, discount rate, choice of health
476 outcomes, measurement of effectiveness and evaluation of preference based outcomes, estimates of resource and costs,
477 currency, price date, conversions, choice of model, assumptions and analytic methods. Results are assessed in terms of
478 study parameters, incremental costs and outcomes and characterising uncertainty and heterogeneity. Research findings,
479 limitations, generalisability and current knowledge are assessed in the study's discussion [41].

480 One point to note is that, on occasions, the guidelines differ for economic evaluations conducted alongside a single
481 clinical study (e.g. a clinical trial) and those conducted as part of a decision analytic model, involving the synthesis of
482 data from a number of sources. Several issues arose during the development of the CHEERS guidelines. The main issue
483 related to whether reporting guidelines should merely require the authors of a study to describe their methods, or
484 whether authors should describe *and explain* why they had adopted a particular approach. A good example of this is the
485 selection of comparators. The CHEERS group felt that, in addition to describing the comparators included in their
486 study, authors should also give their rationale for the selection eg One rationale would be to include the current standard
487 of care in the jurisdiction where the study was conducted [39] The CHEERS checklist enables detailed analysis of the
488 items in Drummond's 10 point checklist thereby facilitating comprehensive scoring of Drummond's checklist using
489 the EJHE questionnaire [10] to grade the evidence.

490 **Structuring Complex Evidence and Values Using Multi-Criteria Decision Analysis (MCDA)**

491 During the 1970s and 1980s there was debate in the economics and ethics literature about relevant criteria for making
492 resource allocation decisions in health care. At that time the focus was on clinical and cost-effectiveness. During the
493 subsequent two decades, health technology assessment bodies emerged. There was growing recognition that other criteria
494 are important, relating to equity, acceptability, burden and sustainability. More recently during the 2010s there has been
495 growing interest in decision analytic methods for considering multiple criteria, driven primarily by NICE in the UK and
496 shifts to Value-Based Pricing. MCDA is a methodology designed to help decision-makers when making complex choices

497 – first developed in the 1960s and 1970s (Peacock et al, 2013) [44]. Health care decisions are complex and often
498 involve trade-offs between conflicting and multiple objectives. Decision making involving either
499 committees or individuals can involve difficulty in systematically evaluating all the relevant information. The MCDA
500 confronts trade-offs between alternatives under consideration and each decision maker prioritizes the most important.
501 Where a group is involved, the priorities of decision makers can conflict, rendering the decision-making process very
502 complex. Reliance on informal processes during decision making can result in suboptimal decisions. A formal process
503 such as MCDA is therefore required to evaluate alternatives and priorities to avoid inconsistency, variability, or a lack
504 of predictability on the importance of specific factors or criteria in the decision. MCDA provides clarity on which
505 criteria are relevant, their relative importance and how the information can be used in a framework for assessing
506 available alternatives. It is an extension of decision theory that covers any decision with multiple objectives (See
507 Thokala et al,2016 [45] for a review).

508 Whilst MCDA is used extensively in other sectors, recently health care applications have increased. During
509 2014, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) established an
510 MCDA Emerging Good Practices Task Force to establish a common MCDA approach in health care and
511 develop associated good practice guidelines. MCDA is applied in various types of decision making in
512 health care, including benefit risk analysis, health technology assessment, resource allocation, portfolio
513 decision analysis, shared patient clinician decision making and prioritizing patients' access to services. It
514 allows for the inclusion of preferences and social values (Thokala, Devlin, and Marsh, et al 2016) [45].

515

516 **MCDA Approaches**

517 MCDA approaches can be classified into value measurement models, outranking models, and reference-level
518 models (Thokala and Duenas, 2012) [46].

- 519 • *Value measurement models* develop and compare numerical scores to determine the extent to
520 which one decision alternative is preferred over another. They often involve additive models -
521 "weighted-sum" models, or "additive multi-attribute value models". These multiply a numerical
522 score for each alternative on a specific criterion by the relative weight for the criterion and then
523 sum those weighted scores to determine a "total score" for each alternative.
- 524 • *Reference-level modelling* searches for the alternative that is closest to attaining pre-defined
525 minimum levels of performance on each criterion, using linear programming techniques and
526 aspiration or goal methods.

- *Outranking methods* make pair-wise comparisons of alternatives on each criterion which are combined to measure support for each alternative being judged the top-ranked alternative. Outranking algorithms include the Elimination and Choice Expressing Reality (ELECTRE) methods, Preference Ranking Organization Method for Enrichment of Evaluations (PROMETHEE), and geometrical analysis for interactive aid (GAIA) (See Thokala, Devlin, and Marsh, et al 2016 for a review) [45].

Value measurement approaches are the most widely used approach in health care. However, determining which MCDA model is most appropriate depends on the analysis and decision maker preferences. (Thokala and Duenas, 2012) [46].

Decision-makers in the health sector face a global challenge: how do we develop robust, evidence-based, scientific methods for priority setting? This challenge is often most evident in decisions concerning the coverage/reimbursement of new drugs and technologies. Peacock, Mitton and Cromwell et al (2013) [44] indicated that a range of different criteria may be relevant for such decisions, including the effectiveness, cost-effectiveness and budget impact of the new drug; the incidence/prevalence and severity of the disease; the population group affected; the availability of alternative drugs/technologies; and, the quality of the available evidence [44].

When comparing new versus existing drugs/technologies these criteria will often need to be traded-off against one another. For example, a new drug may be more effective, but it may be costlier and targeted towards a smaller sub-population. MCDA can assist decision-makers make trade-offs when resources are constrained. When such trade-offs exist, MCDA offers a structured approach to evaluating and identifying a preferred option by scoring and weighting the various attributes and deriving an aggregate 'value'. This is in contrast with more traditional committee based approaches, where trade-offs either not discussed or are explored in a more qualitative manner.

Some key methodological issues and challenges identified by Peacock, et al 2013 [44]. There are two main stages associated with MDCA, i.e. problem structuring and model building. Problem structuring involves generating a set of alternatives and a set of criteria against which the alternatives are evaluated and compared. Model building involves constructing some form of model which represents decision-makers' objectives and their value judgements. A key consideration is the methods used to describe decision-makers preferences and 'importance' weights for decision-making criteria and the type of aggregation model used to combine criteria scores.

A simple model is:

$$WBS_j = \sum_{i=1}^n w_i s_{ij}$$

Equation 1

Where:

$i = 1, \dots, n$ criteria

w_i = criteria weights

j represents alternatives

s_{ij} = scores for alternatives for different criteria

WBS = Weighted Benefit Score

Priority setting can be conceptualized as a continuous quality-improvement reiterative process involving the following sequential steps: define the aim and scope; form an advisory panel of stakeholders; establish a program budget, develop the decision criteria; identify and rank options; make decisions and specify the rationale; undertake a decision review process and finally, evaluate and improve. The economic evidence and MCDA are applied at the decision criteria development stage through to decision making and rationale specification stage. A review of the literature identified 52 different criteria listed in fourteen studies, with the most commonly occurring criteria, in descending order, including accessibility, reducing inequalities, effectiveness, alignment with strategic plan and policies, value for money, affordability and integration with other programs. Peacock, et al [44] compared criteria used in Australia and Canada for cancer control and also for HTA agencies in Australia and the UK. These criteria are in Table 2.

Table 2: Criteria developed by Cancer Control and HTA Agencies

Cancer Control initiatives	National HTA Agencies
National Cancer Control Initiative (Australia) <ul style="list-style-type: none"> Health gain – Disability Adjusted Life Years (DALYs) (Vertical) equity – reducing inequalities in mortality rates in vulnerable populations Size of health burden – disease burden in DALYs and cost to health system Acceptability and feasibility 	NICE (England and Wales) <ul style="list-style-type: none"> Clinicaleffectiveness Cost-effectiveness Feasibility and impact Equity and equality Acceptability and appropriateness
British Columbia Cancer Control decision-makers (Canada) <ul style="list-style-type: none"> Health gain – Quality Adjusted Life Years (QALYs) Resource impact – budget constraints Resource impact – resource constraints Availability/advisability of alternatives 	Pharmaceutical Benefits Advisory Committee (Australia) <ul style="list-style-type: none"> Gap in current coverage Cost-effectiveness Effectiveness and safety Community need

584 A review of the literature concerning criteria weights in MCDA methods found that four studies did not report weights
585 and seven studies used allocation of points (direct rating). Two studies used a combination of ratio estimation and direct
586 rating. One study used indifference methods (DCEs). Previous studies have also used swing weights (hybrid of
587 indifference method). No studies have used gambles – all choices riskless [44].

588

589 With regard to MCDA methods for aggregation rules, Peacock et al (2013) [44] found that where the aggregation rule
590 was presented almost all (ie nine) applications used an additive functional form. Three did not state the functional form
591 used. One used an exponential function and another used a variant of the multiplicative function. Peacock et al (2013)
592 found that the choice of functional form was rarely justified [44].

593 MCDA is useful from several perspectives. The primary aim of MCDA is to develop models of decision-maker
594 objectives and their value trade-offs so that alternatives under consideration can be compared with each other in a
595 consistent and transparent manner. The process is often more important than the numbers. It involves value focussed
596 thinking and values clarification. MCDA practice suggests preferences are constructed as part of the decision-making
597 process, not endowed. It is consistent with deliberative-analytic methods.

598 There are several issues that have arisen involving international consistencies and controversies in the decision criteria
599 used in priority setting, the methods used to elicit criteria weights, and the complexity and transparency of the
600 decision-making process. These fall into four broad methodological challenges. Firstly, how do we decide which
601 stakeholder's criteria will count - society, governments, private sector, patients, families, health providers, or other
602 decision-makers? Second, which methods should be used to elicit and describe decision-makers preferences, including
603 the relationship between objectives and criteria. Further, the methods used to elicit importance weights for decision-
604 making criteria can be controversial along with the type of aggregation model used to combine criteria scores.

605

606 Is there any common ground? Economics has often focussed on prescriptive behavioural rules, based on utility
607 maximisation and game theory. On the other hand, psychology has sought to explain actual individual behaviour, and
608 why it can deviate from prescriptive rules. Interestingly, decision analysis, including MCDA, endeavours to combine
609 elements of both approaches through both 'prescription' with 'practicality'. These approaches all share a common
610 heritage from von Neumann and Morgenstern [44].

611

612 ISPOR's 2016 second Task Force report provides good-practice guidance on the implementation of
613 MCDA for health care decisions. It incorporates a checklist to support the design, implementation and

review of an MCDA; guidance to support checklist implementation; the sequencing of implemented steps and describes the incorporation of budget constraints into an MCDA. It also covers the skills and resources, including software, required to implement MCDA; and canvasses future research directions. ISPOR's MCDA Good Practice Guidelines checklist is shown in table 3 below. ISPOR also provides general guidance on the validation process in each step and on how to implement the other recommendations in the checklist (Marsh, IJzerman and Thokala et al, 2016) [47].

Table 3 – ISPOR MCDA Good Practice Guidelines Checklist.

1. Defining the decision problem	a. Develop a clear description of the decision problem b. Validate and report the decision problem
2. Selecting and structuring criteria	a. Report and justify the methods used to identify criteria b. Report and justify the criteria definitions c. Validate and report the criteria and the value tree
3. Measuring performance	a. Report and justify the sources used to measure performance b. Validate and report the performance matrix
4. Scoring alternatives	a. Report and justify the methods used for scoring b. Validate and report scores
5. Weighting criteria	a. Report and justify the methods used for weighting b. Validate and report weights
6. Calculating aggregate scores	a. Report and justify the aggregation function used b. Validate and report results of the aggregation
7. Dealing with uncertainty	a. Report sources of uncertainty b. Report and justify the uncertainty analysis
8. Reporting and examining of findings	a. Report the MCDA method and findings b. Examine the MCDA findings

Source: Marsh, IJzerman and Thokala et al (2016) [47]

Several areas for further research have been identified by Marsh, IJzerman and Thokala et al (2016) [47] to address the challenges associated with the technique, including the level of precision required of an MCDA; the cognitive challenges facing different types of stakeholders and the support that can overcome these challenges; decision makers' preferences for the theoretical foundations of MCDA methods; which value functions best describe stakeholders preferences; and the best methods for incorporating uncertainty and budget constraints into an MCDA. Further, constructing a cost-benefit ratio using MCDA outputs faces several challenges. including the different scales that are used to measure benefits and costs. (Marsh, IJzerman and Thokala et al, 2016) [47]

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Inclusion of Economic Evidence in Systematic Reviews: Recommendations after reviews on health policy impact and best practices

Systematic reviews are important in improving understanding of comparative effectiveness and relative value of medical interventions in health policy decisions and health guidelines (Niessen et al (2013) [48]. A study by the Hopkins AHRQ project team addressed the appropriateness of incorporating economic data into systematic reviews of medical interventions in America. First, it examined if and how economic evidence impacts on health policy, including clinical guidelines, in the USA. It examined strengths and weaknesses of existing checklists used to assess best practices in economic evaluations. Finally, it reviewed studies addressing the use of economic outcomes in policy and decision making. The work is reported in publications by Niessen, Bridges and Lau et al (2012) [49]; Walker, Wilson and Sharma et al (2012) [50] and Frick, Niessen, and Bridges et al (2012) [51].

The review on *economic evidence impacts on policy including clinical guidelines*, used original studies applying quantitative or qualitative methods providing empirical data, in any country. The team excluded opinion or experienced-based articles without newly generated data. They defined ‘best-practice’ checklists as any original listing of recommendations that the authors used in economic evaluation. MEDLINE, EconLit, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase®, and ISI Web of ScienceSM searched 1991 to January 2012. The literature was searched for articles on economic evaluations, outcomes, and guidelines for the decision maker. Paired reviewers independently determined whether articles met eligibility criteria and then extracted data.

Reviewers assessed the quality of each reporting study on policy impact using the standard grading recommendations (GRADE). Of 19,127 titles initially screened, 43 studies on policy impact were included, with all but five published since 2000. The most frequently studied countries were the United Kingdom (15), and Australia, Canada, and the United States (5 each). Most studies (27 studies) considered national-level policy and examined the key health actors involved. Important topics were reimbursement and health package decisions, and priority setting in programming. Thirty studies found evidence that use of economic evidence had a substantial impact on health care policy making, 27 of which emphasized at least one other criterion, such as equity considerations, usually ill-defined (14 studies), clinical effectiveness, budget impact, ethical reasons, and advocacy arguments. The thirty studies confirmed the acceptance of economic evidence as having an impact on either general policy or specific decisions, such as reimbursement decisions. Of 37 observational studies on policy impact, 11 (30%) received a favourable rating on more than three of the 8 items

on the GRADE quality checklist. Five studies were graded of intermediate quality evidence (Niessen, Bridges, Lau et al 2012) [49].

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The study concerning best practices for conducting economic evaluations in health care was a systematic review of quality assessment tools (Walker, Wilson and Sharma et al (2012) [50]. The objective was to describe strengths and weaknesses of checklists for conducting and reporting on economic evaluations in health care. The authors defined checklists as the original listings of specific items recommended in the conduct or reporting of an economic evaluation. The study involved a review of the criteria for judging that an economic evaluation is of sufficiently high quality to be useful. It also considered the importance of different aspects of the evaluation; and the extent to which high quality on one aspect of an evaluation can compensate for lower quality items. The methods involved a systematic search until January 2012 for articles and guidelines for decision makers. In MEDLINE, EconLit, CINAHL, Embase, and ISI Web of Science. They found that ten peer-reviewed journal articles reported an original checklist. The first in 1992 and last in 2011 (EVEREST and CHEERS in 2013). The number of items ranged from 11 to 57. Perspective was a criterion in all 10. The ten checklists reviewed included those by Adams, 1992. Gerard, 1992. Sacristan, 1993, Clemens, 1995. The U.S. Panel, The British Medical Journal (BMJ) Checklist, The Paediatrics' Quality Appraisal Questionnaire (PQAQ). The Quality of Health Economic Studies (QHES) List. The Consensus on Health Economic Criteria (CHEC) List. and A Checklist to Frame Health Technology Assessments for Resource Allocation Decisions. (Grutters, 2011).[52-62].

Eleven criteria were in 7 to 9 lists: including target population, alternatives, study question, design, measurement, valuation, outcome identification, outcome measurement, time adjustment, sensitivity and uncertainties, presentation of results, generalizability, and incremental analysis. Four had evidence of excellent test-retest reliability: none had evidence of excellent inter-rater reliability in two or more studies. Three had evidence of excellent criterion validity, comparing checklists or expert ratings. They concluded that several well-developed checklists exist for investigators, reviewers, and journal editors to use in efforts to ensure more informative and transparent evidence (Walker, Wilson and Sharma et al (2012)[50].

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They also analysed the usefulness of economic evaluation data in systematic reviews of evidence (Frick, Niessen, Bridges et al 2012). [51] This addressed the question: How useful is incorporating economic evaluation data into systematic reviews of medical interventions? The method used was a consensus process with outside experts to develop a conceptual framework.

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693 They found that all stakeholders, including insurers are interested in economic data and the perspectives of patients,
694 providers, and manufacturers. Patients and providers determine the demand for care and manufacturers determine the
695 supply. Decisions are to be based on incremental cost, magnitude of the incremental effect, and the probability that
696 economic evidence will change a decision. There is a high priority for evidence if there is a small effect at a high level
697 of expenditure with a high probability of influencing a decision.

698

699 Economic data are of interest at many policy levels including approval and monitoring of services, formulary inclusion,
700 insurance coverage, reimbursement rate, preferred practice guideline, technology adoption or non-adoption, or clinical
701 management. They may include information on cost-effectiveness, productivity changes related to disease, price data,
702 responses to price changes. The following areas were of greatest interest: demand for care: time, distance, innovation
703 price, price sensitivity, substitutes and complements, WTP, absenteeism and presentism. Supply of care was of interest
704 including economy of scale, efficiency changes and return on investment. The equity and efficiency measures of
705 particular interest were cost of illness studies; disease burden, Quality of life, budget impact, CEA ratio, net benefits
706 and disparities. Existing economic data may be sufficient. Occasionally, it may be necessary to perform new
707 evaluations in case of inadequate data (Frick, Niessen, Bridges et al 2012) [51].

708

709 **Conclusion**

710 There is some evidence that Drummond's 10-point checklist [11], when used in conjunction with Antioch et al's [10]
711 questionnaire that scores Drummond's checklist, has resulted in cost-effective health care. These were used to grade
712 economic evaluations, while integrating economic evidence into CPGs by the Australian Local Hospital Networks that
713 use both NHMRC and international methodologies. That checklist and questionnaire can be used, in conjunction with
714 the CHEERS 24 item checklist by health services, governments, NHMRC, other CPG organisations, and the ACSQHC
715 for grading the economic evidence. Whilst the ten checklists reviewed by AHRQ are very useful, their limitations of
716 inter-rater reliability can be addressed by including more than one assessor to reach a consensus on assessments.
717 especially when impacting on treatment decisions. Further research could assess the impact of such checklists on the
718 cost effectiveness of health services where they have been used to assess evidence for CPGs and treatment decisions.
719 Antioch et al's [10] questionnaire involves consensus by two assessors, given the impacts on treatment decisions. The
720 issues discussed concerning CEA thresholds, decision rules, opportunity costs, WTP and end of life therapies are also
721 instructive world-wide. Priority setting is important and where trade-off decisions between criteria are required and
722 MCDA is useful for Evidence Based Medicine and Evidence Based Planning. The Hopkins review identifies key
723 priority areas for studies including the demand for care issues which can investigate time, distance, innovation price,

724 price sensitivity, substitutes and complements, WTP, absenteeism and presentism. Supply of care issues can explore
725 economies of scale, efficiency changes, and return-on-investments, equity and efficiency measures can include cost of
726 illness studies, disease burden, quality of life, budget impact, CEA ratios, net benefits and disparities.

727 COAG, AHMAC, IHPA, ACSQHC and the Australian Department of Health could expedite the Australia-wide
728 dissemination of NHMRC's methods on using the costs and benefits in CPGs and the subsequent revised methods. This
729 may assist the health industry prepare for implementation of COAG's 2016 Heads of Agreements on Public Hospital
730 Funding which reduces ABF for specified adverse events, ineffective or harmful treatments and readmissions from
731 July 2017. IHPA, ACSQHC and COAG can risk adjust ABF and quality outcome measurement, through analysis of
732 complexity markers for state-wide referral services such as transplantation, major trauma and cystic fibrosis. to enable
733 equity.

734 **Competing interests**

735 The authors declare that they have no conflict of interest.

736 **Authors' contributions**

737 *Antioch* prepared the paper in close consultation with co-authors who had all participated in presenting the paper at the
738 9th International Health Economists Association (IHEA) Congress, Organised Session: "*Economic Guidelines for*
739 *Clinical Guidelines*". In addition to specific sections of the 'Review' section specified below, *all authors* contributed to
740 the 'Abstract' (page 3), 'Introduction' (page 3) and 'Conclusion' (page 22). *Drummond* presented and prepared section
741 'Consolidated Guidelines for the Reporting of Economic Evaluations: The CHEERS Task Force - Reporting Guidelines
742 for Economic Evaluation' (page 13 to 14). *Antioch* prepared the section 'Structuring Complex Evidence and Values
743 Using Multi-Criteria Decision Analysis (MCDA) which had been presented by Peacock (pages 14 to 19). *Niessen*
744 presented and prepared (with Antioch) 'Inclusion of Economic Evidence in Systematic Reviews? Recommendations
745 after reviews on health policy impact and best practices' (pages 19 to 22). *Antioch* presented and prepared 'Lessons for
746 Australian Parliament, NHMRC, Governments and Health Services' (pages 5 to 12) and did overall editing of the
747 document (pages 1 to 23) and prepared the bibliography (pages 24 to 29). *Vondeling* chaired the session at IHEA and
748 contributed to overall editing of all sections (pages 1 to 23). He also prepared the original glossary. This paper was
749 presented at the 9th IHEA Congress by all authors. Dr Antioch also presented the paper during October and November,
750 2016 involving stakeholders from all Australian States and Territories participating in the 'ABF Reform Toolkit
751 Workshop' conducted in NSW and WA, and at another workshop at the Joint Asia Pacific Australasian College of
752 Health Services Management (ACHSM)/ ACHS Congress, Queensland, October, 2016.

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754 **Data Availability**

755 Data sharing not applicable to this article as no datasets were generated or analysed during the current
756 study.

757

758 **Ethics Approval and Consent to Participate**

759 Not applicable.

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761 **Consent for publication**

762 Not applicable.

763

764 **Funding**

765 None.

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767 **List of Abbreviations**

768		
769	ABF	Activity Based Funding
770	AHCA	Australian Health Care Agreements
771	AHRQ	Agency of Health Research and Quality
772	CAHRD	Centre for Applied Health Research and Delivery
773	CBA	Cost Benefit Analysis
774	CDC	Centre for Disease Control and Prevention
775	CEA	Cost-effectiveness analysis
776	CHEC	Consensus on Health Economic Criteria List.
777	CHEERS	Consolidated Health Economic Evaluation Reporting Standards
778	CINAHL	Cumulative Index to Nursing and Allied Health Literature (CINAHL),
779	COAG	Council of Australian Governments
780	COHERE	Center for Health Economic Research
781	CPG	Clinical Practice Guidelines
782	DALY	Disability Adjusted Life Year
783	DCG-HCC	Diagnostic Cost Group – Hierarchical Condition Categories
784	EBM	Evidence-based Medicine
785	ELEC TR E	Elimination and Choice Expressing Reality
786	GAIA	Geometrical analysis for interactive aid
787	GENI	Guidelines and Economists Network International
788	GIN	Guidelines International Network
789	GRADE	Grading of Recommendations Assessment, Development and Evaluation
790	IHEA	International Health Economics Association
791	ISPOR	International Society for Pharmacoeconomics and Outcomes Research
792	LHN	Local Hospital Networks
793	MCDA	Multi-Criteria Decision Analysis
794	NHMRC	National Health and Medical Research Council's
795	NHS	National Health Services
796	NHSEED	National Health Services Economic Evaluations Database
797	NICE	National Institute for Health and Care Excellence
798	PQAAQ	Paediatrics Quality Appraisal Questionnaire (PQAAQ).
799	PROMETHEE	Preference Ranking Organization Method for Enrichment of Evaluations
800	QALY	Quality Adjusted Life Year
801	RTG	Research Translation Groups
802	WTP	Willingness-to-pay

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Table 2 – CHEERS checklist—Items to include when reporting economic evaluations of health interventions.

Section/item	Item no.	Recommendation	Reported on page no./line no.
Title and abstract			
Title	1	Identify the study as an economic evaluation, or use more specific terms such as “cost-effectiveness analysis” and describe the interventions compared.	_____
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base-case and uncertainty analyses), and conclusions.	_____
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	_____
Methods			
Target population and subgroups	4	Describe characteristics of the base-case population and subgroups analyzed including why they were chosen.	_____
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	_____
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	_____
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	_____
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	_____
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	_____
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	_____
Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	_____
	11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for the identification of included studies and synthesis of clinical effectiveness data.	_____
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	_____
Estimating resources and costs	13a	<i>Single study-based economic evaluation:</i> Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	_____
	13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	_____
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	_____
Choice of model	15	Describe and give reasons for the specific type of decision-analytic model used. Providing a figure to show model structure is strongly recommended.	_____
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytic model.	_____
Analytic methods	17	Describe all analytic methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (e.g., half-cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	_____

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Table 2 – continued

Section/item	Item no.	Recommendation	Reported on page no./line no.
Results			
Study parameters	18	Report the values, ranges, references, and if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	_____
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	_____
Characterizing uncertainty	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for estimated incremental cost, incremental effectiveness, and incremental cost-effectiveness, together with the impact of methodological assumptions (such as discount rate, study perspective).	_____
	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	_____
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	_____
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	_____
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other nonmonetary sources of support.	_____
Conflicts of interest	24	Describe any potential for conflict of interest among study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors' recommendations.	_____
Note. For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist.			

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1122 Source: Husereau, D., Drummond, M.F., Petrou S. et al. (2013) [3], table 2, pages 235, 236

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