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COMMENTARY

Has NICE got it right? An international perspective considering the case of Technology Appraisal No. 98 by the National Institute for Health and Clinical Excellence (NICE)

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ABSTRACT

Background: The National Institute for Health and Clinical Excellence (NICE) has been widely recognised as setting an international standard for high-quality health technology assessments (HTAs) including economic evaluation.

Scope: A previous critical analysis of NICE Technology Appraisal No. 98 (TA98), evaluating methylphenidate, dexamphetamine and atomoxetine for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children, revealed a number of issues, which must cast doubt on the robustness of the NICE approach when addressing a complex clinical decision problem. The exploration of potential underlying problems will be followed by a discussion of lessons for international healthcare policy-makers, and is intended to be an invitation to further debate and inquiry, not a presentation of definitive conclusions.

Symptoms: Pertaining to the technology assessment report, potential problems were identified relating to an unnecessarily narrow scope, data search and selection strategy, the distinction between efficacy and effectiveness, data synthesis across studies and clinical effect measures, and limitations of the economic model. The appraisal process moderated the asserted 'clear conclusions' of the assessment but could not compensate for some of its gaps.

Conclusions: It is suggested that key issues contributing to these problems may have included a separation of clinical and economic perspectives, a highly standardised reference case analysis that was followed schematically, the absence of an effective system for quality assurance of technology assessments, and transparency deficits of the economic evaluation. Further considerations for international policy-makers looking at NICE as a potential role model for HTAs are discussed, such as institutional context, the objectives of collectively financed healthcare and related value judgments, the reliance on QALYs as a universal and comprehensive measure of health benefits, the appropriate perspective for analysis, and process-related implications.

Introduction

If collectively financed healthcare cannot fund all 'effective' clinical interventions in the face of limited resources, choices are inevitable, and the need arises to determine which services are most worthwhile. International healthcare policy-makers have increasingly turned to cost–effectiveness analysis (CEA), which promises to inform about the trade-offs involved in an explicit, quantitative, and systematic way. Following the early examples of Australia[1] and Canada[2], many jurisdictions have mandated the use of such evaluation in decisions about the reimbursement of medical technologies, often pharmaceuticals[1–3].

The National Institute for Health and Clinical Excellence (NICE), which was established as a Special Health Authority within the United Kingdom National Health Service (NHS) in April 1999, features prominently among these initiatives[3–8]. Using a range of anomalies observed in a recent analysis of NICE Technology Appraisal No. 98[8–10] as a starting point, the present Commentary will explore potential underlying problems and suggest lessons for international policy-makers. Keeping in mind the limitations of qualitative research, this exploration should be interpreted as an invitation to further debate and inquiry, not as a presentation of definitive conclusions.

NICE as an international role model

While leading health economists have expressed concern that economic evaluation may not be used to its full potential[11,12], NICE has been acclaimed for representing 'the closest anyone has yet come to fulfilling the economist's dream of how priority-setting in healthcare should be conducted'[13]. It has been suggested that 'NICE tends to concentrate on the difficult choices, where there are usually trade-offs between increased benefit and increased costs', representing 'these situations where economic analysis is likely to have the greatest added value, including the quantification of the uncertainty surrounding the decision'[11].

A key role of technology appraisals is to provide the basis for NICE to issue guidance about the optimal use of a health technology[14]. NICE claims that its guidance 'ends the uncertainty' over the value of a technology[15] and 'helps to standardise access … across the country'[15]. Implementation of NICE guidance is mandatory for the NHS in England and Wales, although its actual implementation has been subject to debate[16–18]. Within the context of NICE this guidance is also expected to inform the development of clinical guidelines by National Collaborating Centres and Guideline Developers[19–21]. NICE guidance should be reproduced unchanged within clinical guidelines and should be given the highest ranking for strength of evidence[19], implying the assumption that highest quality standards will be attained consistently.

A review team of the World Health Organization (WHO) commissioned by NICE to appraise the methods and processes of its technology appraisal program 'was impressed by the commitment to using rigorous methodology throughout the process of technology assessment'[22]. A number of 'particularly valuable achievements' were noted including transparency of the process, intensive participation of stakeholders, responsiveness to change, commitment to using the best available evidence, and use of academic centres of excellence for independent technology appraisal. The review team observed that 'published technology appraisals are already being used as international benchmarks'[22]. The WHO team also made a number of recommendations 'to further enhance the operations of NICE' and, explicitly, to 'assist organisations with similar responsibilities in other countries to deal with their difficulties and meet their expectations'[22]. Although limited to 'consideration of the methods and scientific robustness' of technology appraisals, the WHO report was interpreted by observers as largely affirming NICE as 'a leading organisation internationally in the use of evidence about clinical and cost-effectiveness to inform decisions in the health sector'[23].

Accordingly NICE has been recommended as a role model for other jurisdictions[22,24–27]. This has not been without effect. For instance the remit of the German Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 'IQWiG'), which was initially limited to comparable effectiveness reviews, has now been extended to include cost-effectiveness reviews 'following international standards' with explicit reference to NICE[28]. Debate in the United States also includes consideration of the experiences in the United Kingdom[29]. The troubled start of the new Medicare drug benefit (Medicare Part D) has contributed to renewed interest in alternative approaches in order 'to make drug choices … on the basis of evidence about efficacy, safety, and economic value'[30], and the development of an independent information infrastructure has been proposed to disseminate data on pharmaceutical cost-effectiveness[31,32]. Leading NICE representatives have claimed, 'the conditions … seem ripe for a NICE in the United States'[27].

Scope and symptoms

Technology Appraisal No. 98 (TA98)

A qualitative study of a recently completed technology appraisal[8–10] casts doubt on the robustness of the NICE technology appraisal process. Specifically it revealed for NICE Technology Appraisal No. 98 (TA98), which had been concerned with methylphenidate, dexamphetamine and atomoxetine for treatment of attention-deficit hyperactivity disorder (ADHD) in children and adolescents, a variety of issues related to (1) its narrow scope, including substantive gaps in scope between the technology appraisal and the related development process of clinical guidelines, (2) the search for and selection of evidence for assessment[33], (3) the distinction between efficacy and effectiveness and the role of treatment compliance in ADHD, (4) data synthesis across heterogeneous effectiveness measures and study types, (5) an economic model extrapolating long-term outcomes on the basis of a small number of short-term studies, and (6) some process-related issues, notably concerning certain aspects of its transparency and relevance[34] (see Appendix, Table A1). The ADHD health technology assessment therefore is open to criticism regarding all four essential components of a review question[35], namely the population studied, the choice of interventions, the clinical (quantitative and qualitative) and economic outcomes criteria used, as well as the study designs and selection criteria. As noted earlier[8,9], final appraisal determination[36] and guidance[37] by NICE did not endorse the 'clear conclusions' of the technology assessment but stated that 'given the limited data used to inform response and withdrawal rates, it is not possible to distinguish between the different strategies on the grounds of cost-effectiveness'[36,37]. The case analysis suggested that, collectively, these anomalies resulted in an incomplete assessment of available information and that the identified gaps constituted a source of distorted, potentially biased conclusions[9,10].

At first glance it might seem easy to relegate the qualitative study of TA98[8,9] to the growing inventory of controversial criticisms that a priority-setting body like NICE has to expect[38,39]. Why bother with one outlier when there is so much praise for the approach adopted by NICE? After all, isn't the feasibility of the case study testimonial of a transparent appraisal process? There are a number of reasons, however, why its findings should not be so quickly dismissed. First, agencies like NICE are most likely to draw fire from interested parties when their recommendations imply restrictions of use or denial of reimbursement[16,40–43], which does not apply to the present case[8,9,37]. (Others however have questioned NICE's ability to say 'no', except in obvious cases[16,44–46], or even the appropriateness of cost–effectiveness analysis since it does not fully consider opportunity cost (or 'affordability')[47–52]. Second, even if the case study dealt with an exceptional outlier, its findings were still relevant, as they would indicate an unsatisfactory robustness, suggesting difficulties when dealing with a complex clinical decision problem. These might have potentially far-reaching implications for the comparability of appraisals across a wide range of indications and interventions, which are intended to form the basis of decisions affecting large numbers of patients. Third, qualitative methods in health and health services research can 'reach the parts other methods cannot reach'[53], and as such can complement quantitative studies: case study research has been recognised to be especially useful to explore contemporary phenomena not amenable to quantitative analysis, for instance where complex interrelated issues are involved[53]. Furthermore, such analyses appear unlikely to be repeated on a large scale as they are demanding and require thorough examination of a broad range of data; in the present case, the assessment report alone was a 605-page document[54]. Indeed independent in-depth analyses of technology appraisals have been rare[22,55–57].

Potential underlying problems

The anomalies observed prompt the intriguing question whether a causal relationship may exist with structural characteristics of the specific NICE approach to health technology assessments (HTAs).

Separation of clinical and economic perspectives

The frequent occurrence of substantial gaps between the scopes of clinical guidelines and technology appraisals has been identified earlier[13]. In TA98, this gap related to the management of ADHD in adults, the place of non-drug treatment (especially psychological interventions, which are recommended by European clinical guidelines[58]), the influence of illness subtypes including hyperkinetic disorder (the bulk of clinical data came from studies applying DSM-IV-based diagnostic criteria), and the management of comorbidities[59,60]. This gap may be attributable to the overall approach adopted by NICE, which allowed two very different streams of work (i.e., technology appraisal and clinical guideline development) to develop. It appears that NICE has not (yet) succeeded in integrating economically-driven technology-related guidance development and clinically-driven guideline development[13]. Even within its narrow scope, however, the assessment[54] did not address important aspects specified in advance[59,61], notably outcome measures

related to core symptoms in the economic model (for effectiveness review, hyperactivity – but not inattention and impulsivity – was included), coexistent problems, and treatment in the presence of co-morbid disorders.

It seems conceivable that the separation of clinical and economic perspectives at NICE might also account, at least in part, for a range of specific observations related to TA98, including: (a) the complete absence of a discussion of the literature on clinical effect measures (and their psychometric properties) used in ADHD treatment studies[9], (b) the almost complete absence of consideration of the role of treatment compliance for clinical effectiveness in general, and its particular importance in ADHD[9], and (c) the peculiar interpretation of the 3-weeks' minimum duration criterion for study inclusion, combined with the absence of a discussion of carryover effects in crossover studies included in the review[9]. It seems likely that injection of a stronger dose of clinical expertise at the stage of the assessment process might have served to ameliorate if not prevent these issues. Except for one clinical specialist, who provided input and comments, the assessment group was exclusively composed of staff from the Centre for Reviews and Dissemination (CRD) and the Centre for Health Economics (CHE), both within the University of York[54]. Thus the assessment team's expertise was predominantly in the areas of review methodology and health economics, whereas the clinical subject area of interest was underrepresented.

High level of standardisation

A second potential reason to explain a number of problematic issues observed is the high level of standardisation of technology assessments by NICE[14,62–67], which necessitates making clinical problems fit to a pre-determined solution strategy. A key element of standardisation applied by NICE is the definition of the 'reference case' by NICE (Table 1), which prescribes – *inter alia* – systematic reviews and the use of meta-analyses for synthesising evidence on treatment outcomes and the use of QALYs (using preferences elicited by a choice-based method as opposed to a rating scale) for valuation of health effects[62]. It should be noted however that NICE permits a qualitative overview 'where sufficient relevant and valid data are not available'[62], and it does nor preclude assessment groups from conducting additional analyses, providing these are justified and clearly distinguished from reference case analysis[62]. Interestingly, (different from technology appraisals) the clinical guideline development process is more flexible in this regard. The respective NICE methods guidance of February 2004 and March 2005 explicitly encouraged that cost–effectiveness analyses using 'alternative measures of effectiveness' should be considered[19] (i.e., other than QALYs), although the preference for QALYs as an outcome measure has been somewhat strengthened with the April 2006 update of the NICE Guidelines Manual[20].

Table 1. *NICE specifications for reference case analysis*

Problem definition	Scope from NICE
Comparator(s)	Routine therapies in NHS
Evidence on outcomes	Systematic review
Economic evaluation	Cost–effectiveness analysis (CEA)
Perspective on outcomes	All health effects on individuals
Perspective on costs	National Health Service (NHS) and Personal Social Services (PSS)
Discount rate	3.5% p.a. on both costs and health effects
Addressing uncertainty	Probabilistic sensitivity analysis
Measure of health benefits	Quality-adjusted life years (QALYs)
Source of preference data	Representative sample of the public
Health state valuation method	Choice-based method (such as standard gamble [SG] or time trade-off [TTO])
Description of health states for calculating QALYs	Using a standardized and validated generic instrument
Equity position	Each additional QALY has equal value

Major changes that NICE introduced in April 2004 included the definition of an explicit "reference case", the abolishment of differential discounting on costs and health benefits, the mandatory use of probabilistic sensitivity analysis to address decision uncertainty, and explicit consideration of subgroup analyses[62].

The extensive standardisation of technology assessments, and the appraisal process in general, has been driven by a desire to achieve consistency between submissions and evaluations, to ensure that measures of health-related benefits are comparable across evaluations, and perhaps to serve as a substitute for knowledge of the analysts[35,38,62,68–73]. It has been asserted that government and industry interests 'have ensured that [health] economic evaluation is a heavily regulated environment,' and it has been further argued that 'under-education and over-regulation' may not only be detrimental to the further evolution of the discipline but also place junior health economists at risk of 'becoming the 'worker bees' of a heavily regulated industry'[74]. From a welfare theoretic perspective it has been further remarked that 'one key advantage of taking an artificially determined objective function, such as cost per QALY, is that many … (real-world) complications are avoided'[74]. While others have taken alternative positions relating to the extrawelfarist logic of cost-effectiveness (cf. below, Implications), in the present context it is probably most important to acknowledge that a fundamental motivation underpinning cost per QALY evaluations, as the standard form of cost–utility analyses (CUAs), has been the application of a comprehensive and universal measure of health benefits.

In TA98 a rich clinical evidence base was reduced to a limited number of short-term studies reporting clinical global impressions, which was motivated to enable cost per QALY calculations[9,33]. Adhering by the book to the reference case prescribed by NICE, the assessment did not address important caveats surrounding the use of QALYs in pediatric[75,76] and psychiatric[77] populations[9]. Psychiatric research has been dominated by the short-term measurement of symptoms[77]. As a consequence it became impossible to differentiate between treatments on the grounds of clinical effectiveness, and the resulting economic model was ultimately driven by drug cost differentials[8,9,54].

While there is virtue in process standardisation as a means to achieve procedural justice[78], over-restrictive use of available evidence and reliance on secondary endpoints of a small number of short-term studies[9] may be a cause of bias and misleading results of data synthesis. These issues are exaggerated if sources of heterogeneity, such as the pooling of efficacy and effectiveness studies, are not addressed[9,79–84]. It has therefore been recommended that a formal meta-analysis should be conducted only after it has been determined 'whether quantitative synthesis is at all possible and if so whether it would be appropriate'[35]. Other scholars have observed that, even the most advanced, sophisticated 'statistical tests cannot compensate for lack of common sense, clinical acumen, and biological plausibility in the design and protocol of a meta-analysis'[85], and according to a paper supporting a recent consensus statement on 'decision analytic modelling in the economic evaluation of health technologies'[81], the structural quality of a model should be judged by two attributes: (1) it should be consistent with the stated decision problem, and (2) its 'structure should be dictated by a theory of disease, not by data availability'[86].

Instead, recipients of an analysis might be led astray by 'clear conclusions' supported by mathematically precise computations – in TA98, utility differences extending to the third or fourth decimal place only – suggestive of levels of reliability that cannot reflect the quality of data accrued from a seven-point clinical global impressions subscale (consisting of one question only), which was reported as secondary endpoint of a small subset of clinical trials[9,54].

Technical quality of assessment

A third potential reason relates to the apparent absence of an effective quality assurance system for assessments that can be inferred from the limited technical quality of the TA98 assessment report. While reviews of economic evaluations have suggested a high prevalence of serious methodological flaws[56,87–90], this is surprising here given (a) the efforts of NICE to standardise assessments (see above), which, in the case of TA98, apparently failed to ensure consistent quality, and (b) the fact that NICE assessment groups are recruited from some of the leading health economics research centres worldwide.

It should be emphasised here that these issues are not simply attributable to a failure of the assessment group. For instance, some technical issues might be attributable, at least in part, to insufficient access to clinical expertise (a problem for which structural reasons may be suspected at NICE). As discussed earlier, limited use or availability of clinical input may be reflected by the hardly appropriate treatment of compliance issues[9], the interpretation of the 3-weeks' duration cut-off as a study selection criterion, the exclusion of treatment effects on the core symptoms of impulsivity and inattention in the effectiveness review, and/or the absence of a meaningful discussion of the various effectiveness measures used in ADHD or of the substantial long-term sequelae associated with the disorder[8–10].

As one would expect, the assessment group provided justifications and caveats for many of its assumptions and assertions. A closer inspection of these reveals a number of problems related to the internal and external consistency of the assessment[9]. Further problems of a predominantly technical nature fall under the responsibility of the review team, such as the departure from search criteria pre-specified in the assessment protocol, discount rates deviating from NICE reference case recommendations, heterogeneity of trials and endpoints pooled, and lack of preparedness

to incorporate into the evaluation model the well-established distinction between clinical efficacy and effectiveness. Also for these problems, however, contradictions between the assessment report and existing economic expert consensus or statements made elsewhere by its senior author[9,10,54,84] are suggestive of process-related issues: another contributing factor might have been insufficient resources available to the assessment group, for instance in terms of time (given the complexity of the task at hand) and/or in terms of sufficient involvement of senior experts).

Process-related issues

The process adopted by NICE was discussed earlier in light of TA98[8]. This review was guided by the accountability for reasonableness (A4R) framework developed by Norman Daniels and James Sabin[91–93], who proposed that 'fair-minded people' should accept A4R based on the idea that there exists a core set of reasons, that all centre on fairness, on which there will be no disagreement. A4R is strongly focused on a fair institutional process and comprises four conditions: publicity, relevance, appeals, and enforcement. Fulfilment of these conditions has been suggested to give legitimacy to resource allocation decisions.

The analysis of the TA98 technology assessment[9] may add some interesting aspects to this discussion[8,34] (cf. Appendix, Table A2): First, a high level of standardisation has been identified as a potential reason underlying some of the problems of the assessment (see above). Standardisation certainly contributes to the predictability and reliability of appraisal time schedules[8] and thus facilitates stakeholder participation and minimises surprises. Yet in terms of time and resources allotted to assessment groups the NICE technology appraisal process resembles a 'one size fits all' approach. It appears conceivable that an unintended effect of standardisation is a loss of flexibility to adapt the process (e.g., resources and time) to the level of complexity of the assessment at hand. Resource constraints had already been identified by the WHO review[22], in particular it was noted that 'the late deadline for stakeholder submissions puts unreasonable time pressure on the Technical Assessment Groups'[22] and that 'the quality of reports may be compromised by late arrival of stakeholder submissions'[22]. The detrimental effect of such pressures may be exacerbated when the clinical problem is as complex and challenging as ADHD[8], and may be a hindrance for assessment groups to conduct additional evaluations beyond those stipulated by the NICE reference case.

Second, it was noted earlier that economic models are considered confidential and protected by intellectual property rights[8,34]. The relevance of this observation is underscored by the review of the ADHD technology assessment, as there is no opportunity for observers to uncover important elements of the model; in the present case, for instance, to find out which clinical trials were actually included[9]. Insofar as not only the publicity condition of A4R is not met for an essential part of the NICE appraisal process[34], but also a key characteristic of good modelling practice is missed[81–83]. Publicity and the resulting exposure of models to scrutiny by third parties might also assist effective quality assurance. This corresponds to the conclusion of Jefferson and colleagues[88] who 'believe that urgent action should be taken to address the problem of poor methods in economic evaluations. First, absolute transparency of reporting is needed. … Economic models used in evaluations should be readily accessible to reviewers and readers. … Editorial teams, regulatory institutions, and researchers should implement and assess quality assurance'[88].

This consideration leads directly to a third observation related to A4R. Discussing the enforcement condition of A4R, it was noted earlier that there is no indication that NICE has implemented an effective quality assurance system for health technology assessments[8], the design of which would have to take into account that conventional peer-review may not be up to the task[56,81]. Given the technical anomalies and inconsistencies identified in the ADHD technology assessment, there appears to be a need for NICE to reconsider current arrangements with the assessment groups in that respect[22], as they apparently stand in the way of full publication of models[94]. Thus the current policy constitutes a peculiar contrast with broadly accepted quality criteria for economic models[81,83].

NICE Technology Appraisal No. 98 – a unique outlier?

Clearly, despite the caveats provided earlier, there is a risk of implicit overgeneralisation of observations based on one case study only. International observers, including this author, have been suitably impressed by the attempts of NICE to ensure rigorous systematic reviews, objective economic evaluation, stakeholder participation and transparency of process, as well as value judgments[8,10,22,26]. This notwithstanding, even a single outlier must cast doubt on the attained robustness of its technology assessment process, which is an important requirement for sustained widespread acceptance. It appears impossible to rule out that certain problems identified with the ADHD technology appraisal might be less unique than one would hope.

There is little if any dispute about the need to integrate clinical and economic evidence for health technology assessments to be meaningful in the context of a priority-setting body like NICE. Apart from the emergence of two streams of work – technology appraisals and clinical

guideline development – that have developed very differently[13], others have observed that there are some difficulties 'in ensuring that all academic centres [which provide the assessment groups] have the appropriate combination of clinical and economic expertise'[22].

Within the realm of technology assessments, problems seem to be more common in reconciling clinical data availability for systematic effectiveness review and the perspective of cost–utility analysis requiring units of outcome that facilitate the calculation of QALYs. For instance, for the recent economic evaluation of newer drugs for epilepsy in adults, effectiveness data, usually reported in terms of the reduction of seizures over a defined time period, were transformed into the categories of full (seizure-free) or partial (≥ 50% reduction in seizure frequency) responders, which were subsequently combined with utility estimates for each state. This approach did not enable incorporation of side effect profiles[95] (which has generally proven difficult[10,96]) and no significant effectiveness differences could be confirmed in the systematic review. A meta-analysis performed on this basis, in order to produce economic model inputs, showed a difference in expected QALYs of only 0.025 between the drugs studied[95]. Different from the conclusions of NICE[97], clinical guidelines developed by the Scottish Intercollegiate Guidelines Network (SIGN) without formal consideration of cost-effectiveness included two of the newer compounds (lamotrigine and oxcarbamazepine) for first-line treatment of partial and secondary generalised seizures[98], and the American Epilepsy Society even recommended four of the newer compounds for newly diagnosed epilepsy[99].

Although post-hoc departures from pre-defined search strategies for data on the clinical or cost effectiveness of interventions[10,100] should be a rare occurrence, it is clear that abstracts and conference proceedings represent a challenge to review teams. While the critique of the ADHD assessment[9] illustrates their importance in HTAs of rapidly evolving technologies, this is a time- and resource-consuming endeavour that often requires efforts to obtain further information from the authors. In this respect, there have been 'variations in policy and practice' of assessment groups[101].

Next, the health economics literature[70,80,81,84] suggests a broad consensus about the fundamental distinction between efficacy, effectiveness, and cost-effectiveness. Dealing with results of randomised clinical trials, the question for the economic analyst is 'what does this mean in practice?'[79]. It is less evident how this insight has translated into real-life decision-making, since pragmatic open-label trials are frequently considered of lower quality than well-controlled double-blind studies[20,35], seen to provide evidence of a lower hierarchy level, 'and so should be interpreted with caution'[100,102]. Specifically concerning treatment compliance, which may differ greatly between settings, analysts and decision makers face pertinent issues related to the appropriate criteria to distinguish between mere convenience and clinical relevance. Challenges include what type of evidence to expect and how to weight it, from models driven by assumptions or expert consensus, over randomised pragmatic clinical trials (usually open-label!), to observational studies and retrospective database analyses.

Finally, transparency of economic models appears to be an issue far exceeding a single technology assessment. Lack of transparency may not only impede effective stakeholder participation, but might even violate legal provisions. Two pharmaceutical companies whose appeal against a recent NICE appraisal determination had been dismissed[103], took NICE to court on grounds that its conclusions were 'irrational' and 'not supported legally', and that NICE 'refused to disclose a fully-working version of the cost–effectiveness model used'[103,104]. After an initial ruling largely in favour of NICE, the companies have applied for permission to appeal against the court's decision[105].

Collectively, these random observations suggest that many of the issues identified with TA98 may be less unique than one might have hoped.

Implications for international healthcare policy-makers

The approach taken to HTAs differs internationally perhaps most markedly with respect to the use of economic evaluation[7]. Some organisations, including the Centers for Medicare and Medicaid Services (CMS) and the Veterans Administration (VA Technology Assessment Program, VATAP) in the United States, the German IQWiG, and the Spanish Agency for Health Technology Evaluation (Agencia de Evaluación de Tecnologías Sanitarias, AETS), do not (yet) use formal economic analyses[5,106,107]. With the limitations of reviews focused on effectiveness only being increasingly realized, interest has been growing in economic evaluations, which clearly have the potential to add important information on the trade-offs associated with prioritisation decisions[3–7,10,11,24–29,31,32,38,39,70,82,84,93].

First and foremost, expectations for cost–effectiveness evaluation should be realistic. For example, international experience, including Australia and Canada, indicates that implementation of cost–effectiveness analyses tends to increase spending[12,108,109]; it does not (and was never conceptualised to[70]) provide for a cost-containment device. In England, prescription drug spending increased from £5.58bn in 2000 to £7.94bn in 2005, i.e., by a compound annual growth rate of 7.4%, and NICE guidance has

been seen by many analysts as one important underlying reason[46,110,111]. According to recent internal estimates from NICE, full implementation of NICE guidance from 1999 through 2004 would have an annual cumulated budgetary impact on the NHS of £800 million, equivalent to one percent of total NHS spending[112].

Institutional context

Institutional context will have to be taken into account in various ways. One aspect relates to specific features of healthcare systems, such as centralisation (NHS model) versus decentralisation (e.g., competition in the United States system), which will influence the optimal way of implementation of economic evaluations, obviously without invalidating the principal usefulness of the discipline. Also the level of decision-making will matter. At the central or macro level, usually an agency is entrusted with the task of making decisions for the whole healthcare system. At the local or micro level (sometimes referred to as 'meso' level, as opposed to the 'micro' level of bedside decisions), for instance Regional Health Authorities or hospitals, various constraints (e.g., budget pressures, limited available health economic expertise, etc.) may dictate different approaches. Moreover, local implementation of central guidance rests – among other factors – on alignment between recommendations and funding[18, 112].

More importantly, legal environments will impose constraints on prioritisation decisions. A well-known incident in the United States was the revisions of the Oregon Health Plan required in 1992 by the Department of Health and Human Services (HHS) to comply with the Federal Americans with Disabilities Act (ADA) of 1990[113]. QALYs value life as a function of health status[114–117]. However, any discrimination of (groups of) patients on grounds of their reduced capacity to gain 'quality of life', for instance the disabled or the chronically ill (people in so-called 'double-jeopardy')[118,119], would still have to stand the test of the declaration of human rights, stating that 'recognition of the inherent dignity and of the equal and inalienable rights of all members of the human family is the foundation'[120]. In many jurisdictions, there exist constitutional provisions that set limits to a utilitarian or quasi-utilitarian approach that is exclusively or primarily concerned with maximising the distribution-independent sum of individual utilities, as 'distribution indifference does not take the distinction between persons adequately seriously'[121,122].

Objectives of collectively financed healthcare

Keeping the specific legal context in mind as a constraint, it is a fundamental principle of decision analysis that 'the identification and structuring of *objectives* essentially frames the decision being addressed. It sets the stage for all that follows'[123].

The pursuit of efficiency

Most health economists assume that, because healthcare produces health, the objective of collectively financed healthcare should be to maximise either (a) the aggregate of ordinally measured individual utilities (with health being one out of many arguments of the utility function)[124–127] or (b) cardinally measured health gains (i.e., treating health as an independent argument of the utility function)[128–132]. In its pure form, this view results in an '*efficiency-only*' approach, with efficiency being defined either (a) based on the welfare theoretic principles of Pareto and Kaldor-Hicks[133,134] or (b) their extrawelfarist variant seeking to produce the maximum amount of QALYs (or a comparable construct) for a given budget[131,132,135,136]. Then, the tools to determine efficiency are cost–benefit or cost–utility analysis, respectively. While the debate between the proponents of either approach continues[48,52,137,138], it is noteworthy here that both approaches represent attempts to maximise an average expected consequence irrespective of its actual distribution across individuals, and have been criticised for overlooking the frequent impossibility of compensating 'losers' for health benefits foregone[132–134,139–141]. Apart from normative concerns, the quasi-utilitarian QALY aggregation rule has been shown to be empirically flawed, i.e., it does not adequately reflect prevailing social value judgments[119,132,142,143].

The approach adopted by NICE may be characterised as '*efficiency-first*'[6,27,131], following the extrawelfarist proposition and using a cost–effectiveness benchmark of 'a most plausible' £20 000 to £30 000 per QALY gained[62] while rejecting an absolute threshold[27,131], specifying that it would also consider other factors including 'the particular features of the condition and population receiving the technology'[62], which may include social value judgments such as 'special considerations of equity'[131]. NICE established a Citizens Council to provide input 'on the topics it wants the council to discuss', in order 'to ensure that these values resonate broadly with the public'[131], while maintaining that guidance 'is based on clinical and cost–effectiveness evidence'[144]. The Citizens Council endorsed NICE's approach, concluding that 'cost–utility analysis is necessary but should not be the sole basis for decisions on cost-effectiveness'[145]. A concern has been raised that the NICE approach in practice may result in 'the marginalisation of factors other than clinical and cost-effectiveness as outside NICE's terms of reference'[57,146]. A related concern found by the WHO review team has been the lack of transparency regarding considerations other than cost-effectiveness[22], which led to second-

guessing and inquiry by academic researchers[147–149]. NICE has rejected speculation that it considers the budgetary impact[27,131] despite indications to the contrary[149], which has caused critique from a theoretic perspective[47,50,52,138] as well as for its practical consequences[46]. The WHO team recommended that 'NICE codifies and justifies the specific criteria used in decision-making'[22]. Other observers analyzed NICE's positive appraisal of riluzole for motor neuron disease on the basis of an ICER of a cost per QALY of £34 000 to £43 500[150], which had initially been estimated at £58 000[151] and had later been brought down to £16 500 to £20 000[152]. Independent analyses demonstrated substantial uncertainty surrounding these estimates[153], and it was argued that NICE 'should not need to fabricate an efficiency criterion to support the reimbursement of riluzole' because it 'tried to resolve two impossible statements', (a) 'uncertainty on effectiveness' and (b) 'a cost per QALY in a tightly circumscribed range'[154]. They concluded that it might 'be better to accept that resources are more reasonably and appropriately allocated on the basis of the rule of rescue or fair innings rather than a strict efficacy [note added: *efficiency?*] criterion'[154].

The pursuit of fairness

It has been argued, however, that the primary objective of a collectively financed health scheme (and therefore the relevant unit of analysis) is *not* the maximisation of an aggregate of utility or population health *but* that it includes prominently the provision to give *individuals* the chance to achieve a 'decent basic minimum' of health[155] or the 'capability' of achieving good health[122,156], in order to gain 'a normal range of opportunities' to pursue their individual conceptions of the 'good'[121,155]. This would imply an explicit '*fairness-first*' approach to healthcare resource allocation decisions, which would make treatment of motor neuron disease or reimbursement coverage for expensive drugs for rare diseases ('orphan drugs', the development of which is encouraged by European policy[157]) not *necessarily* (!) 'a small extravagance'[158], which is (still) tolerated owing to its limited budgetary impact (sic!) but not justifiable on the grounds of cost-effectiveness[142,157,159–166]. Assigning a higher priority to the objective of fairness compared to efficiency may have both normative and empirical support[114–122,132,140–143,154,155,167], but it would absolutely not abolish the need for economic analysis to moderate fairness-driven reasoning. Importantly, however, it has been argued that current standards of health economic evaluation might need re-interpretation, concerning both the appropriate valuation of benefits[132,156,167–171] and the determination of relevant costs[172]. This represents an equally intriguing and important area for further scientific endeavour and debate.

A broader perspective

NICE evaluates medical technologies from the perspective of the National Health Service (NHS)[62]. This perspective is narrow on two grounds. First, it imposes a consequentialist notion of health benefits, conceptualised as QALYs gained and requiring some kind of (largely context-independent) cost per QALY benchmark[173–176], thereby neglecting other sources of utility, such as the process leading to a certain health outcome. (In the example of ADHD, many patients and caregivers have expressed a preference for non-psychopharmacological interventions[177].) Second, it also implies a restrictive view of costs, limiting consideration to expenditures incurred by the NHS and for 'personal social services', a residual category covering both social work and 'social care' outside the remit of health services[62,178]. This departure from economic welfare theory, which requires a broad societal perspective for costing[127], results in distinct difficulties associated with the treatment of 'indirect costs', i.e. productivity losses caused by poor health[84,179–181]. These difficulties are echoed in international guidelines for cost–effectiveness analyses, comparison of which indicates that payers tend to exclude indirect costs, whereas the scholarly methods found in the literature favour their inclusion[182]. Cost–benefit analysis (CBA), more firmly grounded in economic theory and applying (maximum) willingness-to-pay (WTP) as a comprehensive measure of utility, would elegantly overcome this difficulty[127]. However, in the context of an NHS, CBA would have to adequately reflect the discrepancy between individual WTP for one's own life and 'social WTP' of an individual acting as a citizen and taxpayer[183]. Clearly this implies extending the conceptual underpinnings of cost–benefit analysis in order to accommodate concerns for fairness, which currently represents a frontier of scientific inquiry and debate. It has been argued that, at this point, 'a separate kind of analysis is required to weigh rights and equal treatment'[184].

(Almost) exclusive reliance on QALYs?

A key motive for the widespread use of QALYs has been the wish to make comparisons across a wide range of morbidities supported by a universal and comprehensive measure of health outcomes with interval scale properties. *Any* relaxation of, or deviation from, the extrawelfarist approach would immediately alleviate the limitations associated with an (almost) exclusive reliance on QALYs as the outcome measure of interest. As has been seen in the case of TA98, this narrow analytical focus was a prime reason for the highly selective use of clinical data and the resulting

neglect of existing relevant, rich clinical and cost–effectiveness information[33].

However, even if acceptability on grounds of 'efficiency' was established by some cost per (weighted or unweighted) QALY ratio, current limitations of the methods used to derive utility estimates[132,185–187], including the availability (or lack) of suitable clinical data, might still encourage policy-makers to have such evaluations complemented by appropriate examinations using other techniques, for instance, cost–effectiveness analysis. Instead of relying on restricted data sets, this might enable utilisation of the best available clinical evidence and would imply greater flexibility in use of analytic approaches compared to the NICE reference case. Indeed, other agencies concerned with the evaluation of medical interventions – such as the Australian Pharmaceutical Benefits Advisory Committee (PBAC) and the Scottish Medicines Consortium (SMC), both applying cost–effectiveness analysis and considering a broader range of clinical effect measures compared to NICE – had been able to identify differences between the treatment options assessed with TA98[33,188–191] .

Technology appraisal processes

In particular the processes of NICE have been understood by observers to set a new standard internationally[6,8,22]. This accomplishment has been supported by a high level of standardisation, which in turn has contributed to a lack of flexibility to adapt the analytic process to the complexity of the specific decision situation. It would probably be more appropriate if the assessment strategies pursued were adapted to the problems at hand. A number of issues may be straightforward, not requiring application of the full analytic arsenal, such as probabilistic sensitivity analysis, and hence be less resource-consuming[6,192]. On the other hand, there may be challenges (such as in TA98) that can be met only if sufficient resources (time, manpower, budget, access to expertise) are available and that demand a problem-solving strategy different from the currently prescribed standard.

Flexibility

A less schematic evaluation process might also allow for more than one stage of assessment, contingent on the problem. A meaningful approach could be to invite assessment groups to submit proposals; this could be organised as a competitive process among a selected group of academic centres with established excellence. Within the predefined scope, such proposals would usefully present 'convincing arguments that the objectives of the review have been understood (and refined if necessary)', demonstrate the necessary range of expertise of the assessment group, describe an appropriate and feasible methodology for undertaking the review, and cover the resources (funds and time scales) required[35]. If and when a process consisting of more than one stage was considered adequate, the principal objective of a first phase could be to determine the social desirability of funding a technology; this would sensibly include, but not be limited to, consideration of allocative efficiency[114–122,132,140–143,154,155,193]. These criteria would need to be codified[22]. A subsequent phase of evaluation might address the issue of technical efficiency, which would offer an opportunity for a more complete review of available evidence, including a more cautious use of quantitative meta-analysis and not necessarily limited to cost–effectiveness analysis using clinical endpoints considered meaningful.

Timing of technology appraisals

It is well understood that the cost-effectiveness of technologies does change over time. Regarding TA98, the rapid evolution of our understanding of the economic implications of ADHD[8–10,194] underscores the relevance of this observation. There is no ideal solution to the resulting dilemma, for which the term Buxton's law has been coined, '*It's always too early [to evaluate] until, unfortunately, it's suddenly too late*'[195]. This difficulty is exacerbated by the well-known phenomenon that the cost-effectiveness of interventions may change substantially over time[196]. If anything, the dilemma is further aggravated by the fact that sound economic evaluations of complex clinical problems require substantial resources, including time, especially when they are embedded in truly participatory processes. In the ADHD case, it took 33 months from initial scoping to the issue of NICE guidance[8], and it seems quite possible that the 6 months allotted for assessment were too short to complete the task[9,10]. In an attempt to address the problem, NICE recently announced the introduction of a new process allowing more rapid appraisal of important new technologies[197,198]. It will be interesting to see how NICE is going to deal with the challenging task of ensuring a sufficiently broad scope and high quality of such rapid reviews[199].

Multidisciplinary assessment teams

Technology appraisals address clinical problems, which may be complex, and are expected to derive meaningful conclusions, which are intended to impact clinical decision-making. The case of TA98 lends support to the conjecture that it is unlikely that complex problems can be handled successfully by either discipline – the

medical profession or economists – largely working in isolation. The desirable (if not necessary) integration transcends the link between clinical guideline development and technology appraisals. Beyond sharing expertise, a higher level of integration of the key disciplines involved in technology assessments and clinical guideline development might also assist in addressing the differences between the professions in terms of attitudes, values, and beliefs relevant to prioritisation problems in healthcare.

Effective quality assurance

High levels of standardisation do not suffice to ensure consistent quality of technology assessments. There seems to be a need for some kind of enforcement (as postulated by Daniels and Sabin[91–93]). This would extend to the technical quality of reviews. Beyond full disclosure of potential conflicts of interest and effective peer review processes, absolute transparency of methods used for modelling might be useful.

Implementation

Economic evaluations are useless unless their results can be applied in clinical practice. The implementation of NICE guidance within the UK National Health Service to date has been mixed[18]. In principle, there are several possible approaches to improve implementation, discussion of which is beyond the scope of this paper. In the present context it will of interest that guidance seems 'more likely to be adopted when there is strong professional support, a stable and convincing evidence base, … Guidance needs to be clear and reflect the clinical context'[18].

Conclusions

Reviews indicate that NICE has set standards for health technology appraisal processes including economic evaluation, and thus has attracted a high level of attention internationally. A qualitative case study of its recent appraisal of medications for attention-deficit/hyperactivity disorder (TA98) indicated that technology assessments may not consistently attain highest quality standards, raising doubt about the robustness of the NICE process. Suggested problems potentially contributing to this suboptimal performance include the integration of clinical and economic perspectives, a high level of standardisation including an overly rigid focus on QALYs as an effectiveness measure, and the apparent absence of effective provisions for quality assurance of economic evaluations, which may be aggravated by a distinct lack of transparency of economic models. With respect to the ADHD case study, it should be noted that during appraisal the conclusions of the technology assessment, which appeared questionable, were moderated, whereas the appraisal could not compensate for the gaps left by the assessment report. International healthcare policy-makers looking at NICE as a potential role model may prefer to learn from NICE as opposed to copying it. This will almost certainly include careful consideration of the social value judgments by NICE, which they may or may not share.

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Appendix

The following tables are available as electronic supplementary data (doi:10.1185/030079908X280437) published with the online version of this article.

Table A1. *Summary critique of Technology Appraisal No. 98*

Table A2. *NICE technology appraisal process: accountability for reasonableness (A4R) revisited*

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