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The DH Register of Cost-Effectiveness Studies: A Review of Study Content and Quality.

James Mason
Michael Drummond

DISCUSSION PAPER 128

THE DH REGISTER OF COST-EFFECTIVENESS STUDIES: A REVIEW OF STUDY CONTENT AND QUALITY.

James Mason

Michael Drummond

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The Authors

James Mason is a Research Fellow and Michael Drummond is Professor of Economics at the Centre for Health Economics, University of York.

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Abstract

The Department of Health has recently published a register of economic evaluations of health care treatments and programmes. The objective of the register is to assist health care decision makers in assessing the value for money from alternative ways of allocating scarce resources. If the register is to be useful, it is important that decision makers have an appreciation of the methodological quality of the studies contained in the register, and hence the confidence that can be placed in the results.

This discussion paper gives details of an approach for assessing the methodological quality of economic evaluations. A worked example of a search in the register is presented and discussed. Some summary findings of the studies contained in the first published version of the register are presented together with a listing of the studies included. The interpretation of the existing register and the future reporting of economic evaluations are discussed.

Introduction

An important information requirement for health care decision making is evidence on the relative value for money from health care interventions. Such evidence is provided by economic evaluations of health care programmes and treatments, which compare their relative costs with their relative consequences (Drummond, Stoddart and Torrance, 1987). Now that more economic evaluations have been conducted, it has become common to compare the cost-effectiveness of different interventions in terms of the cost per life-year or cost per quality-adjusted life-year (QALY) gained.

The growing trend in making such comparisons has led to considerable discussion and debate (Birch and Gafni, 1992; Gerard and Mooney, 1993; Mason et al., 1993; Drummond et al., 1993; Gafni and Birch, 1993; Laupacis et al., 1993; Johannesson and Weinstein, 1993; Birch and Gafni, 1993; Birch and Gafni, 1994; Mason 1994). In particular there are concerns about constructing rankings, or 'league tables' since these have led to simplistic judgements about the superiority of one programme or treatment over another.

However, decisions have to be made and it would make sense to retain and strengthen economic considerations: scarce resources must be used wisely. Therefore, it is important that decision makers gain as much as possible from published economic evaluations and are able to use the available economic data intelligently. This includes knowing when not to use the available data and when to commission work addressing local circumstances more directly.

The Economics and Operational Research Division of the Department of Health assembled a register of cost-effectiveness studies containing details of over 200 economic evaluations. The Centre for Health Economics at the University of York was commissioned by the Department to review these studies. Consequently, the Department of Health has published a pilot Register of Cost-Effectiveness studies (RCES) containing details of 147 economic evaluations (Department of Health, 1994). The availability of the RCES was announced in an NHS Executive Letter (NHS Executive, 1994) on 28th September 1994. Copies of the register have been distributed to Regional General Managers, Regional Directors of R&D and Regional and District Directors of Public Health.

The RCES is presented not as a ranking or 'league table' but as an alphabetical listing of studies. If the RCES is to be useful, it is important that decision makers have an appreciation of the methodological quality of studies contained in the register, and hence the confidence that

can be placed in the results. This discussion paper gives details of an approach for assessing the methodological quality of economic evaluations and applies it to the studies contained in the RCES. Use of the register is illustrated by a search for studies addressing lung cancer.

Study Assessment

There are a number of textbooks on the methodology of economic evaluation in health care (Drummond et al., 1987; Luce and Elixhauser, 1990) and basic methodological principles have emerged. Often these are presented in the form of a checklist of questions to ask about published studies (Drummond et al., 1987). These checklists were not directive enough for the purpose of assessing the studies in the register and so an assessment template was devised. An abbreviated version of the assessment scheme is set out in Table 1. The focus of assessment was to extract from each paper the data and methods that comprise the analysis and to summarize consequent limitations. All studies were reviewed by the primary investigator (JM) with confirmatory reviews provided by health economist colleagues (see acknowledgements): conflicts were resolved by discussion.

Basic study description

We recorded the full study title, the names of the authors and the journal (source) in which the study was published. Apart from enabling the user to locate the original paper, these details may give some clues to the quality of the work. However, a 'good quality' journal does not necessarily imply a 'good quality' study, as many medical journals have not been very well equipped to referee economic studies until recently.

We also recorded the source of funding for the study when this was mentioned, because of possible sponsorship bias (Hillman et al., 1991). However, many published studies do not give the funding source: this is likely to be rectified in the future (International Committee of Medical Journal Writers, 1993).

Studies were categorised by disease, intervention type and ICD-9 code. In future the now available morbidity related ICD-10 coding should prove a superior alternative to ICD-9.

Alternatives assessed

Cost-effectiveness estimation involves the relative performance of a health care intervention and an alternative (comparator). Good studies always give an adequate description of both the intervention and the comparator, but this is sometimes lacking. Often the implicit comparison may be 'doing nothing' or 'current care'. Apart from being a methodological deficiency, inadequate description of the alternatives greatly reduces the usefulness of a published study, since the user needs to know whether the results of the evaluation relate to his or her own setting. Sometimes the same study considers a wide number of alternatives.

TABLE 1: Analysis assessment scheme (abbreviated)

Section	Notes/Coding
1 Source	
Item number	For paper, article, study etc
Number of entries	A paper may contain more than one scenario, each scenario is assigned an entry number
Entry number	
Reviewer	
Author(s)	
Title	If book: Chapter heading, in... book title, editor(s)
Journal	In full, If book then Publisher
Date	
Volume; Number :Pages	If book, Chapter: pages.
Funding Source	C Commercial; F Foundation; G Government agency; H Charity; I Insurance company; R Research council; V University; O Other
2 Medical area	
Disease field	Broad terms: blood, circulatory, congenital, digestive, endocrine, general, genitourinary, immune, infectious, injury, mental, metabolic, musculoskeletal, neoplasm, nervous, parasitic, perinatal, poisoning, respiratory, sensory, skin, symptoms
ICD-9 code	
Intervention type	Broad terms: care, counselling, dentistry, diagnosis, dialysis, drug, education, immunization, physical therapy, prevention, radiotherapy, screening, surgery
3 Medical evidence	
Outcome model/type of study	X Randomized Controlled Trial (RCT); P Other prospective controlled trial (CT); F Meta-analysis of RCTs; I Informal Meta-analysis of RCTs; E Epidemiological cohort model (model of survival and disease); R Retrospective case-control study; O Other
Treatment description	Who got what, when and where?
Control description	
Nationality	Of the outcome study/model
Single/Multi- Centre	
Duration	Of follow-up of the treatment cohort
Selection	Is there evidence that the initial study sample is representative for the clinical study question?
Power calculations	Have these determined sample size?
Refusal to participate	What % of patients refused to participate, at invitation stage
Randomization	F Formal; H Haphazard; M Method not recorded; N None
Trial size	Number of patients Overall, in Intervention group, in Control group
Drop out rates	% Overall, % in Intervention group, % in Control group
Blinding	P Patient; C Clinician; A Analysis; R Randomization; B Review; N None
Hypothesis	H Hypothesis driven; P Post hoc analysis
Analysis	I Intention to treat; T Treatment completers
Group comparability	At analysis, are groups shown, or adjusted to be, comparable in age, sex and prognostic features.
Primary outcome	e.g. CHD deaths prevented
p-value	Of primary outcome
4 Economic question	
Intervention description	Includes treatment, patient sample characteristics and setting of treatment
Intervention description (cont.)	
Comparator description	
QALY, LY, LS Outcome in summary cost-effectiveness ratio	Q QALY (Quality-adjusted Life Years) gained; L Life years gained; N No summary ratio; S Lives saved
Type of change	A augmentation; C current practice; E programme expansion/retraction; N new field of medicine; R replacement
Comparator type	C current practice; M minimum practice; H historical practice; N none; P placebo
Technology date	i.e. date to which patient and treatment data relates

Section	Notes/Coding
5 Benefit description	
Description of health states	e.g. Rosser classification, author description
Health State Valuation Whose, and how many, values	A Author; C Clinician; H other Health worker; L Literature; P Patient; R Relative; S Society
When valued?	
Where valued?	e.g. postal or telephone survey, interview
Valuation tool	CR Category rating; ME Magnitude estimation; SG Standard gamble; TTO Time trade off
Health utility valuation	e.g. Amended Rosser, McMaster scale, Quality of Wellbeing Scale, Rosser 1, Sackett and Torrance
Incremental benefit?	y/n
Intervention	
Lives saved	
Life-Years and discount rate (rb)	e.g. 100 (0), 78 (5), 63, (15)
QALYs and discount rate (rb)	
Comparison treatment	
Lives saved	
Life-Years and discount rate (rb)	
QALYs and discount rate (rb)	
Incremental benefit	
ΔLives saved	(Δ = Incremental)
ΔLife-Years and discount rate (rb)	
ΔQALYs and discount rate (rb)	
Programme scale	e.g. /patient, /programme, /1000 invitations to screen
Duration of intervention benefits	Used in the economic analysis: the duration of benefit to the patient
Health omissions	Are there broader health effects missing, or have benefits been unsatisfactorily truncated? Discussed in notes section if necessary.
Side-effects of treatment	Are these in the estimates, or not relevant? Discussed in notes section
6 Cost description	
Published cost date	The date to which costs were reflated (if different from cost date)
Cost date	Date when costs were estimated from resource use
Resource date	Date when resources were quantified. Range of years quoted if necessary
Cost inclusions	Direct Health Costs { H = Health service; P = Patient; A = Other agencies; R = Relatives }, I = Indirect (Production gains)
Incremental cost?	y/n
Currency	e.g. US $, Yen
Intervention cost and disc. rate (rc)	Recorded in original currency.
Comparator cost and disc. rate (rc)	
ΔCost and discount rate (rc)	(Δ = Incremental)
Programme scale of cost	e.g. /patient, /programme, /1000 invitations to screen
Duration of intervention cost	Used in the economic analysis: duration of cost implications of the intervention for the patient..
Duration of comparator cost	Used in the economic analysis: duration of cost implications of the comparator treatment for the patient.
Are all relevant costs included?	y/n Discussed in notes section if necessary.
Adverse/ knock-on costs?	y/n Are these dealt with in the costing, or not relevant ? Discussed in notes section if necessary.
7 Allowance for uncertainty	
Sensitivity analysis	S Single parameter variation; M Multiple parameter variation; P Probabilistic variation; T Threshold analysis; N None
Was it adequate?	Were the parameters selected and ranges of values adequately justified?
Range ΔCost/Life Saved and discount rate (rc)	Baseline (discount rate cost), lowest, highest values + e.g. 100 (5), 25, 250
Range ΔCost/Life-Year and discount rates (rc,rb)	Baseline (discount rate cost, discount rate benefit), lowest, highest values +
Range ΔCost/QALY and discount rates (rc,rb)	Baseline (discount rate cost, discount rate benefit), lowest, highest values +
Sensitive parameters?	Any influential parameters discovered are noted.
	+ As presented in the original study, and converted to UK £s Sterling using GDP Purchasing Power Parities, reflated to 1991 (pay and prices).
8 Summary findings	
ΔCost/Life Saved and discount rate (rc)	+ e.g. 10000 (5), 15000 (0)
ΔCost/Life-Year and discount rates (rc,rb)	+ e.g. 1000 (5,0), 1500 (5,5)
ΔCost/QALY and discount rates (rc,rb)	+
9 Entry specific notes	
1 Resources costed 2 Notes on health effects 3 Notes on costs 4 General	
10 General study notes	
1 Resources costed 2 Notes on health effects 3 Notes on costs 4 General	These notes are common to all entries for a particular item

Our original intention was to develop a classification scheme for the interventions and alternatives used in studies. This would have two elements. The first would relate to the type of change being examined i.e. did the evaluation concern the replacement of existing care, augmentation of what was currently available, programme expansion/retraction or a completely new field? The second element would relate to the type of alternative assessed: current practice, minimum practice, a placebo, another new technology, or 'doing nothing' In practice this classification was unworkable since interventions and comparators could often legitimately be coded in several ways, and our coding could therefore mislead decision makers for whom current practice is different. Instead we decided to give a full description of intervention and comparator programmes. This should enable a decision maker to assess the relevance of the study.

Place and date

It is important to assess whether a particular study is likely to be past its 'sell-by' date. Health technologies change over time, affecting both costs and benefits.

Potentially there are three dates relating to cost data in an economic study: these are:

(1) the date of resource measurement;

(2) the date of costing of resources; and

(3) the date to which costs are reflated to arrive at a common year for internal consistency and publication purposes (the 'published cost').

Ideally one would like to record the technological date of the medical evidence used in studies. However, studies seldom reported this information. Since many studies included epidemiological data of some kind, such data could relate to decades before the study. Trial data generally has a date of origin within a decade of publication date: with other study designs this can not be presumed.

Despite these limitations, the publication and cost dates give information on the context in which a given study was undertaken. We believe that the age of studies has been largely neglected by compilers of cost-effectiveness rankings in the past, with many of the studies included being well past their 'sell-by' date. A user may be further misled because of the common practice of reflating costs to a recent year when publishing rankings of study findings. A simplistic updating of costs for inflation will only suffice when relative costs of health resources do not change and when technological change is absent.

The classification of place of study was confined to the country (or countries) in which the major data collection took place. This is not always straightforward; some economic studies may use clinical data generated in another country and then apply local cost data. We believe the problems of transferability to be greater for economic data than for clinical data, although they are not absent in either case. There are also wide variations in clinical practice or health service organization within countries.

However, it is known from the limited number of studies already carried out that the cost-effectiveness of interventions vary by location (Drummond et al., 1992). In an ideal world published studies would give much more information about local practice patterns, resource availability, demography and relative prices. This is largely lacking at the moment. Therefore users should not simply accept or reject studies from other countries without careful consideration of the likely differences between settings.

Comparison involving cost data from different countries also raises the additional issue of exchange rate conversions. Simple published exchange rates are subject to fluctuations and may be misleading. Adjustments should be made using purchasing power parities (PPPs). Some analysts argue that, where possible, PPPs should be specific to medical goods and services (Gray, 1989). However, it is arguable that health PPPs are still at a developmental stage and unreliable since they feature an inadequate selection of services. A further methodological concern is that while health PPPs capture the relative cost of health technology purchases between countries they fail to capture relative wealth (and thus ability to pay, which diffusely influences price) reflected in Gross Domestic Product (GDP) PPPs. A comparison of health and GDP PPPs indicates that the choice may be important. Table 2 shows the conversion factors for expressing health care expenditures from three sample countries in £, sterling (derived from OECD, 1993).

	1980		1985		1990		1980-90
Adjustment:	GDP PPP	Medical PPP	GDP PPP	Medical PPP	GDP PPP	Medical PPP	GDP/Medical
Canada	0.409	0.252	0.426	0.349	0.462	0.362	1.37
France	0.092	0.075	0.083	0.071	0.091	0.093	1.12
United States	0.520	0.260	0.550	0.321	0.600	0.337	1.83

TABLE 2: PPP Conversions to £, sterling.

Averaging data over the three years available, GDP PPPs value an American dollar spent on health 1.83 times higher than that obtained by health PPPs, when expressed in £s sterling. A further issue here is that each particular health technology reported in a study involves a small bundle of goods and services: PPPs may be very imprecise at this level while accurately reflecting a macroeconomic picture.

Our primary reporting of study results was in the local currency and at the published cost date (see page 5, item 3) used in the study itself. However, in order to facilitate appropriate comparison between studies we adjusted the local currency to £s sterling using GDP PPPs (OECD, 1993) and then reflated the estimates to mid-1991 prices (NHSME, 1993).

Medical evidence

It is obvious that an economic evaluation is only as good as the medical evidence on which it is based. Therefore we included a detailed classification of medical evidence where the information in the published studies permitted.

The main classification related to the basic type of clinical evidence. Economic evaluations draw variously on data from randomized controlled trials (RCT), formal meta-analyses (Sacks et al., 1987) of RCTs (with comprehensive literature search and clear admission criteria), informal meta-analyses (of studies immediately to hand), epidemiological cohort models, prospective (non-randomized) controlled trials, retrospective case control studies and other sources.

Some studies use a mixture of evidence. For example, the study by Schulman et al. (1991) on drug therapy for people with asymptomatic HIV infection used RCT data on disease progression, extrapolated to survival by use of an epidemiological model. In our classification this was placed under 'epidemiological cohort model' since the RCT evidence did not relate to the final endpoint used in the economic evaluation. However, sometimes classification was difficult since it is common for an economic evaluation, even when based on an RCT, to extrapolate survival data, add assumptions or generally broaden the scope of the assessments made. Therefore the economic assessments seldom exactly match the clinical data.

Where the economic study was based on a prospective clinical study, usually an RCT, further information was recorded when this was available. Items included the adequacy of patient selection, single or multicentre location, the percentage of non-respondents, the randomization method, the size of the trial, the drop out rate, the adequacy of statistical power, the type of blinding, the comparability of treatment groups at baseline, the primary outcome measure (with

p value if given) and the type of analysis (i.e. intent-to-treat or treatment-completers). Few published economic evaluations presented these data, and this section was completed for only a few studies in the RCES.

Resources included in the costing were listed where the study gave details. Giving full details of the (quantities of) resources used in an evaluation is desirable since it may permit validation and recosting by decision makers in other settings.

Benefit measurement and valuation

On some occasions the medical evidence from clinical studies is a direct input to the economic evaluation. This would be the case for a trial of a lifesaving intervention where the main clinical endpoint was length of survival. However, in most cases the derivation of a measure of economic benefit requires further analysis. For example, intermediate clinical endpoints are often used to predict, by modelling techniques, the number of life years gained; descriptive quality of life data are sometimes used to construct a health status index; and health status indices are used, in conjunction with survival data, to calculate the number of quality-adjusted life-years (QALYs) gained from therapy.

We documented the methods used in the economic studies to derive measures of benefit, either from the clinical data, or by the collection of additional information. For example, we recorded whether the main economic benefit measure was lives saved, life years gained or quality-adjusted life-years gained. We also documented the use of any descriptive health status (quality of life) measures, such as the Nottingham Health Profile.

Where health status preference values (or utilities) were calculated, we recorded the source of health state valuation (e.g. patients, clinicians, general public) and whether the associated health state utilities were obtained by direct measurement, derived from the literature, or obtained from a published value matrix (e.g. that developed by Rosser). If direct measurement was used, the measurement approach (e.g. time trade-off, visual analogue scale) was recorded. Finally, the benefits were reported, where available, for the different discount rates used in the study.

Cost measurement and valuation

There are a number of important methodological features of the costing employed in published studies. First, the cost boundary can consist of health care costs falling on health services only, or include those health costs falling on other agencies; the patient and their family), or include indirect costs arising from production losses. The relevant range of costs depends on the perspective, or viewpoint, of the study. Where the range in a study was unusual this was

commented on in the study notes.

Secondly, the years of data collection, relating to both resource quantities and costs, were recorded and a note made of any adjustment of cost estimates for inflation. Thirdly, the costs were reported, where available, for the different discount rates used in the study. Finally, costs were reported in their original currency and a note made of any other methodological issues relating to costing.

Allowance for uncertainty in estimations

Estimates in economic evaluations are often subject to uncertainty, because assumptions have to be made, because estimates are imprecise, or because of methodological controversy. Uncertainty is usually dealt with in economic evaluations by undertaking a sensitivity analysis, where the values of parameters are varied to see whether they greatly affect study results.

We recorded whether a sensitivity analysis was performed, the method used, and the ranges (from lowest to highest estimate) specified. There is currently no standardized procedure of assessing uncertainty in economic evaluations (Briggs et al. 1994). For the purposes of the RCES, we considered an adequate sensitivity analysis to be one that identified the sensitive parameters and then meaningfully justified the range of values used. The most sensitive parameters in each study were also noted.

Presentation of study results

Finally, we recorded the study results, as reported in the published study. Typically, these were in the form of an incremental cost per life year, or quality-adjusted life year, gained, reported with various discount rates. We also noted fundamental miscalculations or deficiencies in the presentation of results, ways in which the presentation of cost-effectiveness ratios could potentially mislead the user and other points coming to the attention of the person reviewing the study.

Using the register

The RCES is currently available in hard copy form. This consists of a hierarchical series of tables (Figure 1) with an introduction and user guide. The (shaded) flow lines shown indicate how each table in the RCES can be cross-referenced. A full categorisation of the content of studies is found in Table E. However the user can consult Table A to clarify the meaning of data entries and codes or refer to Tables B-D which provide indexes to studies by disease, ICD code or intervention type. Table A is shown in abbreviated form in this discussion paper as Table 1 on page 4.

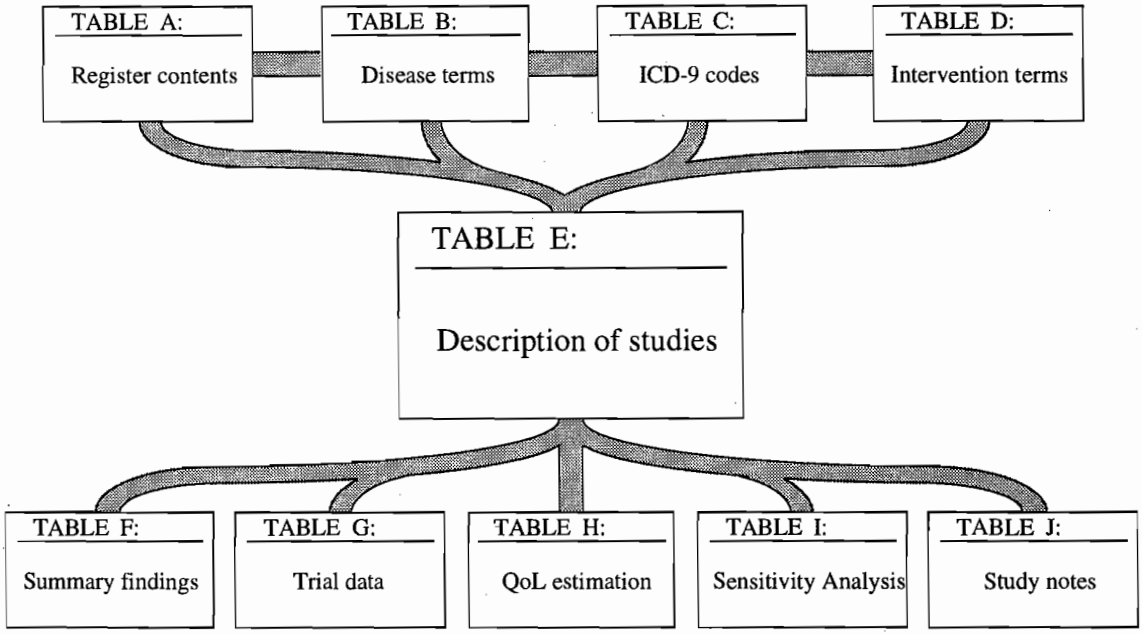

FIGURE 1: Searching with the Register Hard-Copy

Table E can be used to search rapidly for studies by author, by publication date, disease field, ICD-9 code, intervention type, outcome model, and outcome type (QALY, Life-Year, Lives-Saved). When studies are identified, the user records the item number and tables containing data entries. Entries are always found in Tables F and J (summary findings and notes), and sometimes found in Tables G-I depending on the study.

When extracting data from the register, it is important for users to be able to gauge the quality of information, particularly when the intention is to make comparisons between health technologies. The quality of medical evidence in studies varies widely, from a well-conducted RCT that used economic endpoints to undisguised clinical opinion; most evidence falls

somewhere in between. Most economic evaluations involve some form of modelling of disease and survival: if the methods and assumptions are reported then these will have been recorded. Users should also consider the dates relating to publication and cost data, the country of origin and costing methodology. Particular attention should be given to the precise details of the intervention and its comparator. These points are illustrated in a worked example, which makes reference to tables in the RCES: the relevant extracts are reproduced in Figure 2. Definitions for Table headings in Figure 2 , if not self explanatory, may be found on page 4.

Example: What is the evidence of the cost-effectiveness of lung cancer treatments?

Extract from **Table B**: Index to studies by narrow and broad disease terms

> lung cancer, 40, 143; see also: non-small cell, small cell
> non-small cell lung cancer, 52, 105
> small cell lung cancer, 77

Searching Table B, five possible studies are identified. Examining Table E (Figure 2) to find out more about these studies, all studies are from the USA or Canada. Examining the study titles and the Intervention type field it appears that two items are preventive (40, 143) and three involve treatment (52, 77, 105). It is useful to confirm this impression by examining the Economic description fields in Table F since study titles are sometimes vague or misleading. As mentioned previously, all items will have information recorded in Tables F and J (summary findings and notes). Examining the TABLE field in Table E, all items (unusually) in this search have entries for trial data (Table G), one study has quality-of-life data (Item 77, Table H), and three studies have a sensitivity analysis recorded (Table I). Some studies address more than one question and thus may have several entries in the RCES: only one entry is selected here from each study. The findings in each of the tables are examined in turn.

☞ Outcome model

Interestingly the two preventive studies both used a modelling approach based on a formal meta-analysis (statistical combining of trial evidence), whereas the studies involving treatment are all based on RCTs. Since trial data is potentially available for all five studies, each has an entry in Table G. An examination of Table G shows that very little is known about the trials entering the meta-analyses in the preventive studies other than that both studies (GP advice and nicotine gum) performed a thorough review of the medical literature and extracted one-year cessation from smoking data. The three treatment studies provide more information and it is possible to assess the size and methodology of the trials. It is noteworthy that all three studies feature truncated survival

measurement and it is interesting to see if these survival findings are used directly in the economic analyses or extrapolated in some manner. None of the treatment studies recorded whether their analyses were conducted on an intention-to-treat or treatment completers basis. This is clearly a concern since considerable bias may be introduced with an analysis of treatment completers.

☞ QALY, Life-Years gained, Life-Years saved.

All five studies reported outcome as life-years saved; one study (Item 77, Goodwin et al) estimated quality-of-life. Table H shows that the authors used 7 descriptive health states and obtained a valuation of quality of life from a sample of seven patients and fourteen health service staff. The study authors do not record when in the progression of disease the patient measurements were taken or if health worker and patient valuations differed.

☞ Summary Findings.

All five studies reported findings in terms of a cost per life-year saved ratio; one study reported a cost per QALY (Table F). For illustration, note that Cummings et al (Item 40) have incorporated the cessation rate achievable from smoking, at one year, into a disease model: the health effects have been modelled over the life-expectancy of those treated (Outcome duration). Only the direct costs of intervention up to 1 year have been included (cost duration, cost boundary); the study is recent as is the cost data. Goodwin et al (Item 77, entry 1) have extrapolated the trial survival data since outcome duration in the economic model is life-long (LL); their costing model includes direct health service and patient costs as well as costs falling on other agencies. Register users should note the different modelling assumptions that are involved and consider their potential impact on the cost-effectiveness ratios reproduced in these tables. Both the preventive studies feature discounting of future costs and benefits at 5%. When either costs or benefits are measured over a duration of more than several years then it is usually only appropriate to compare results from different studies which use the same discount rate. The exception is for studies where costs and benefits are measured over only a few years. Then, the effect of discounting is relatively unimportant and such studies can be compared, on an individual basis, with any other study using any discount rate.

☞ Sensitivity Analysis.

Two of the entries selected (77 and 143) featured a sensitivity analysis adjudged to be 'adequate' for the purposes of the register. The study by Cummings et al (40) also conducted a sensitivity analysis but not for the entry selected. The range reported in the study by Goodwin et al reflects different assumptions about hospitalization rates necessary for treatment. Where sensitivity analyses are conducted adequately in studies these give a useful feel for the confidence readers should place in the result. It is difficult to advise register users as to how they should place studies without a (complete) sensitivity analysis alongside those with one.

☞ Notes (Table J, not reproduced here)

Considering the study by Cummings et al, the notes in Table J indicate that the analysis of disease progression is based upon extrapolations from observational data: the possibilities are that intervention will not achieve all of the differences seen to naturally occur between different groups of people, and that intervention may have unwarranted side-effects. The therapeutic treatments have the common feature that they involve the comparison of one treatment with another. Goodwin et al (Item 77) actually state that the relative survival of a cohort with supportive care only is unknown but that such an 'intervention' would be unacceptable to society! It is important to consider the treatment options presented in the register and where possible to assess if any intervention is appropriate.

Extract from **TABLE E:** Description of studies in the Register (see Table 1, page 4, for heading definitions)

Item	Author	Item title	Journal	Date	Vol/No/Page	Nation-ality	Disease field	ICD-9	Intervention type	Funding sources	Outcome model	QALY, LY, LS	Sens a.? OK?	TABLE
40	Cummings SR, Rubin SM, Oster G	The cost-effectiveness of counselling smokers to quit	Journal of the American Medical Association	6/1/89	261; 1: 75-9	USA	lung cancer, neoplasm	162	smoking education	F	EF	L	My	FGIJ
52	Dillman RO, Seagre SL, Propert KJ et al	A randomized trial of induction chemotherapy plus high-dose radiation in stage III non-small-cell lung cancer	New England Journal of Medicine	4/10/90	323; 14: 940-5	CAN, USA	non small cell lung cancer, neoplasm	162	drug, radiotherapy	u	X	L	N	FGJ
77	Goodwin PJ, Feld R, Evans WK, Pater J	Cost-effectiveness of cancer chemotherapy: an economic evaluation of a randomized trial in small cell lung cancer	Journal of Clinical Oncology	u/10/88	6; 10: 1537-47	CAN	small cell lung cancer, neoplasm	162	drug	u	X	QL	Sy	FGHIJ
105	Jaakkimainen L, Goodwin PJ, Pater J et al	Counting the costs of chemotherapy in a National Cancer Institute of Canada randomized trial in non small-cell lung cancer	Journal of Clinical Oncology	u/8/90	8; 8: 1301-9	CAN	non small cell lung cancer, neoplasm	162	drug	u	X	L	Sn	FGJ
143	Oster G, Huse DM, Delea TE, Colditz GA	Cost-effectiveness of nicotine gum as an adjunct to physician's advice against cigarette smoking	Journal of the American Medical Association	12/9/86	256; 10: 1315-1318	USA	Lung cancer, neoplasm	162	education, drug	CG	EF	L	N	FGIJ

Extract from **TABLE F:** Summary findings

Item	Entry	Author	Economic intervention description	Economic comparison description	Publication Date	Outcome model	Outcome duration	Cost duration	Cost boundary	Δcost Y/N?	Currency	Pub. cost date	ΔCost/LS £, 1991 [rc]	ΔCost/LY £ 1991 [rc,rb]	ΔCost/QALY £ 1991 [rc,rb]
40	2/2*	Cummings SR, Rubin SM, Oster G	Opportunistic brief advice and booklet from a physician to quit smoking, follow-up visit two week after cessation:: male, age 45-50	Advice by a physician to quit smoking	6/1/89	O	LL	1y	H	Y	US $	1984		4609 [5,5]	
52	1	Dillman RO, Seagre SL, Propert KJ et al	Induction chemotherapy plus high-dose radiation for stage III non-small-cell lung cancer patients without distant metastases. Chemotherapy: cisplatin and vinblastine, radiation: 60 GY over a 6-week period	High dose radiation alone	4/10/90	X	LL	LL	H	Y	US$	1987?		7960 [0,0]	
77	1	Goodwin PJ, Feld R, Evans WK, Pater J	Chemotherapy for (terminal) advanced small-cell lung cancer. Cyclophosphamide, doxorubicin (Adriamycin) and vincristine (CAV) alternating with etoposide and cisplatin	CAV alone	u/10/88	X	LL	LL	HPA	Y	CAN $	1984		2365 [0,0]	3155 [0,0]
105	1/2*	Jaakkimainen L, Goodwin PJ, Pater J et al	Chemotherapy for (terminal) advanced non small-cell lung cancer. Vindesine and cisplatin (VP)	Best supportive care (without chemotherapy)	u/8/90	X	LL	LL	H	Y	CAN $	1984		10372 [0,0]	
143	3/12*	Oster G, Huse DM, Delea TE, Colditz GA	Addition of Nicotine gum, to physician advice against cigarette smoking, in primary care. Male, age 45-49	Physician advice to quit smoking	12/9/86	EF	LL	<1y	H	Y	US $	1986?		3408 [5,5]	

* One study entry selected from a number found in the RCES.

Extract from **TABLE G:** Trial data

Item	Entry	Author	Treatment description	Control description	Date	Nation-ality	Funding Source	Trial type	S/M Centre	Duration	Selec-tion	Power calcul.	Refusal, %	Random-ization	Trial size	Drop out rates, %	Blind-ing	Hypo-thesis	Anal-ysis	Group comp.	Primary outcome	p-value	QLS
40	All	Cummings SR, Rubin SM, Oster G	Advice by a physician to quit smoking	No intervention	6/1/89	USA	F	EF			u						u				1 year cessation rate	<0.05	L
52	1	Dillman RO, Seagre SL, Propert KJ et al	Induction chemotherapy (cisplatin and vinblastine) plus high-dose radiation (60 GY over a 6-week period) for stage III non-small-cell lung cancer	High dose radiation alone	4/10/90	CAN, USA	u	X	M	3y	Y	Y	u	M	155, 78, 77	14%	N	H	u	N	Survival	0.01	L
77	1	Goodwin PJ, Feld R, Evans WK, Pater J	Chemotherapy for (terminal) advanced small-cell lung cancer, CAV alternating with etoposide and cisplatin [3 courses]. Prophylactic cranial radiation for responders	Cyclophosphamide, doxorubicon and vincristine (CAV) [3 courses] alone. Prophylactic cranial radiation for responders	u/10/88	CAN	u	X	M	median <1y	N	u	u	M	289, 145, 144	u	u	H	u	N	Mean survival	0.03	QL
105	1	Jaakkimainen L, Goodwin PJ, Pater J et al	Vindestine and cisplatin for (terminal) advanced non small-cell lung cancer, National Cancer Institute of Canada study BR-5	Best supportive care (without chemotherapy)	u/8/90	CAN	u	X	M	median <1y	N	u		M	94, 44, 50			H	u	N	Mean survival	≤.01	L
143	All	Oster G, Huse DM, Delea TE, Colditz GA	Nicotine gum, to facilitate smoking cessation.	placebo gum	12/9/86	USA	CG	EF													1 year cessation rate		L

Extract from **TABLE H:** QoL estimation

Item	Entry	Author	Date	Disease field	Outcome model	Nation-ality	Description of health states	Health state evaluation	When valued?	Where valued?	Valuation tool	Health utility valuation	Intervention QALYs [rb]	Comparison QALYs [rb]	Δ QALYs [rb]	Scale	Benefit duration	Health omissions	S-E included
77	1	Goodwin PJ, Feld R, Evans WK, Pater J	u/10/88	small cell lung cancer, neoplasm	X	CAN	7 descriptive states	P=7, H=14			CR, SG		0.392 [0]	0.292 [0]	0.100 [0]	/patient	LL	N	Y

Extract from **TABLE I:** Sensitivity analysis

Item	Entry	Author	Funding sources	Study type	Intervention cost duration	Comparison cost duration	Cost boundary	Currency	Published cost date	Type of sens a.?	Range Δ C/LS £, 1991 [rc]	Range Δ C/LY £, 1991 [rc,rb]	Range Δ C/QALY £, 1991 [rc,rb]	Sensitive parameters
77	1	Goodwin PJ, Feld R, Evans WK, Pater J	u	X	LL	LL	HPA	CAN $	1984	S		2365, [0,0], cost -ve benefit +ve, 24243		Rate of hospitalization
143	3	Oster G, Huse DM, Delea TE, Colditz GA	CG	EF	<1y	LL	H	US $	1986?	S		3408, [5,5], 1692, 18225		Effectiveness of gum

FIGURE 2: Sample extracts from RCES tables

Register content

Two hundred and two studies were obtained and subjected to methodological review. It was found that 100 of these reported a cost-effectiveness ratio, in cost per life saved, cost per life-year gained, or cost per quality-adjusted life-year (QALY) gained. All 100 studies are included in the RCES discussed here.

Another 47 of the 202 studies were also included since they provided useful information for health care decision makers. These consisted of:

- studies where benefits were not aggregated (e.g. to a QALY), but which represented best useful economic evidence;
- studies that required a simple costing exercise in order to interpret the results in a cost-effectiveness framework; and
- studies that could be interpreted as a cost-minimization analysis.

A list of the 147 studies included in the RCES is listed in the Appendix, in alphabetical order. Fifty-five studies were excluded from the main RCES because they were irretrievably flawed, constituted a review or duplicate of another study, or contained information too partial to be useful. A table, listing these studies, together with reasons for exclusion, was not included in the published version of the RCES.

Since some studies addressed more than one technology or stratified findings by age or gender, the 100 studies reporting summary cost-effectiveness ratios gave rise to 407 entries in the register. The content of the RCES in terms of outcome measure used is shown in Table 3. Although the register does not currently contain an exhaustive list of all available studies it nevertheless provides useful evidence of the kinds of studies that have been conducted in the last two decades.

	No. of studies	No. of entries	Entries with Cost/QALY	Entries with Cost/Life Year	Entries with Cost/Life Saved
Studies reporting a cost-effectiveness ratio	100	407	207	227	46
Other studies included in the register	47	84			
Studies excluded	55	-			

TABLE 3: Summary of cost-effectiveness data in the RCES

A summary of entries, by ICD-9 coding, contributing cost-effectiveness ratios to the Register is shown in Figure 3. Some diseases could legitimately be classified under more than one code thus 407 entries contributed 434 entries by ICD-9 code. Most evaluations were concerned with neoplasms, or circulatory, genito-urinary and digestive disorders. Approximately half of the circulatory disorder entries (ICD-9 codes 390-459) related to serum cholesterol modification evaluations: these often generated results stratified by age, sex and risk factors. More than half of the genito-urinary disorder entries related to the management of renal failure.

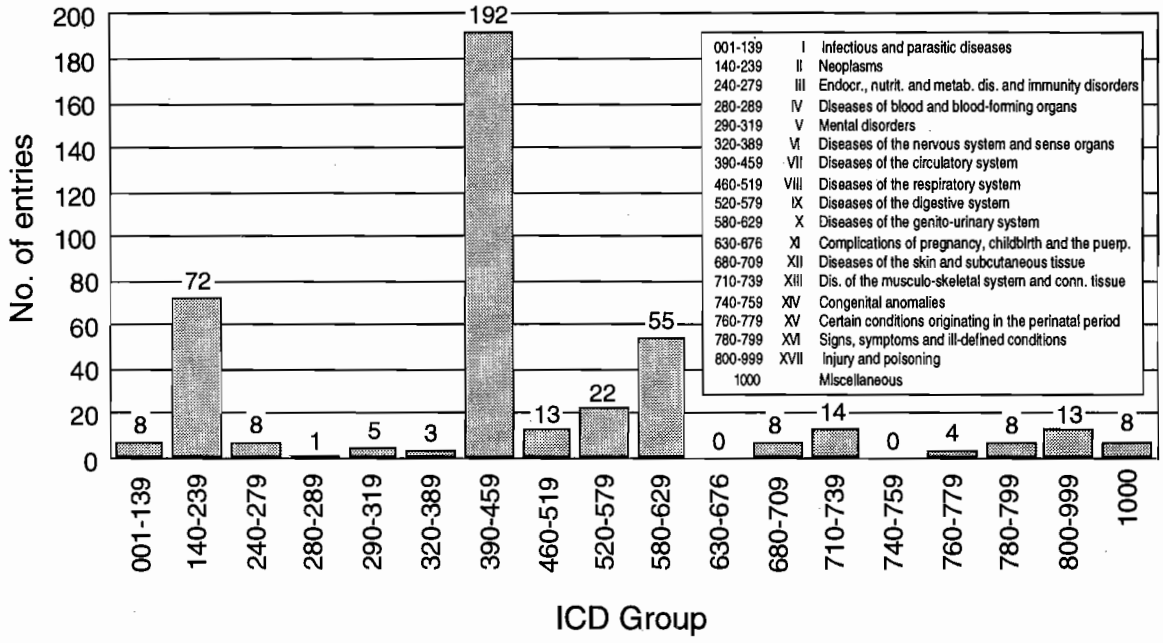

FIGURE 3: Entries in the Register by ICD-9 code.

A summary of the kind of outcome models used is illustrated in Figure 4. Very few analyses have been based directly on the findings of RCTs, often considered the gold standard in clinical reporting. However, the preponderance of entries based on epidemiological cohort models or 'other' evidence is noteworthy. 'Other' studies include those that use, as their primary source of clinical data, uncontrolled patient case series or clinical opinion. Suitable RCT data is frequently unavailable to assess health care technologies, particularly at the time when implementation decisions are made. Consequently analysts often attempt to model the impact of health care services and procedures by drawing together the evidence available. Epidemiological cohort models indicate or suggest the impact on a patient cohort over time attributable to some risk factor modification. Evidence used may be drawn from observational studies or derived from trials using intermediate clinical endpoints. In Figure 4 this is seen as by far the most common form of evaluation found in the RCES.

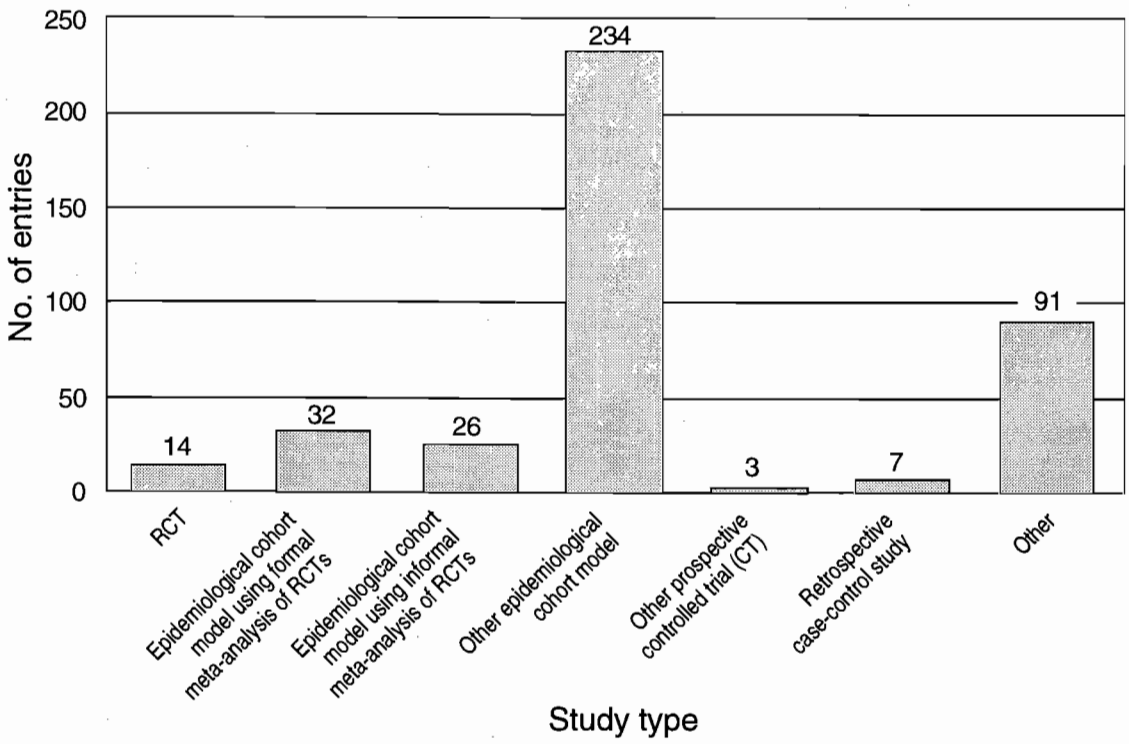

FIGURE 4: Prevalence of outcome models found in the Register

The RCES is currently less comprehensive in its coverage for recent years. Figure 5 gives the number of studies and entries in the Register by year of publication. It can be seen that coverage beyond 1991 is sparse. This can be contrasted with the exponential rise in the number of published studies in recent years (Elixhauser et al, 1993).

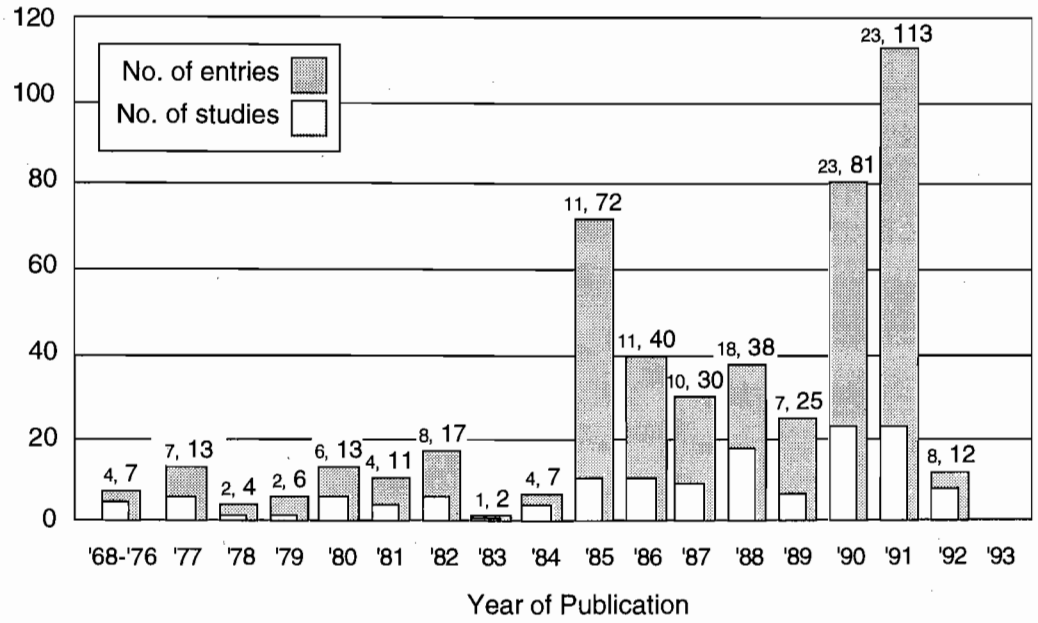

FIGURE 5: Studies and entries in the Register, by year of publication.

Quality Issues

A number of points arise from the process of assessing the studies in the RCES. These reflect the content and reporting of studies.

1 Studies often had undefined or inappropriate objectives, hence the template used in the RCES examined what each analysis actually contained and addressed in its data and methods. It is essential for analysts at the outset to have a clear objective for their work. This may take the form of a question posed (e.g. how should we treat hypertension?), involve a certain viewpoint or perspective (e.g. taking the viewpoint of society, the patient, a drug company), but may be limited by available data (e.g. what is the relative value-for-money of two drugs which achieve reductions in blood pressure in elderly men in an English community care setting). Together these facets define the achievable objective of the analysis, guiding appropriate methodolology, boundaries for inclusion of costs and benefits, findings and conclusions. A clear description of the treatment evaluated (who got what, where, how and when), the alternatives analysed and the setting of the study permits decision makers in other contexts to assess the relevance of consequent findings.

2 Considerable variation was found in the basic standard of reporting of analyses found in the RCES. For example, the year to which 'published' cost data related was ambiguous in about 25% of entries in the register. Potentially there are three dates relating to cost data in an economic study: these are:

   I the date (or period) of resource measurement;

   II the date (or period) of costing of resources; and

   III the date to which costs are reflated to arrive at a common year for internal consistency and publication purposes (the 'published cost').

   The funding source was undeclared for more than half of entries: there was no improvement in this rate in the studies reported since the beginning of 1990. Where an economic analysis was based on trial data (or a meta-analysis of trial data) the information given about the trial(s) conduct was seldom sufficient to assess its value.

For the 65 entries in the RCES using trial evidence, only

- 30% demonstrated that the patient sample was relevant to the economic study question being posed,
- 10% demonstrated that power calculations had been performed to determine sample size,
- 30% reported the rate of refusal to participate at the invitation stage of the trial,
- 30% reported the method, if any, of randomisation,
- 30% reported drop out rates,
- 33% demonstrated, at analysis, whether cohorts were comparable in important prognostic variables such as age and sex.

and most worrying, only

- 38% reported whether the analysis was on an intention-to-treat or treatment-completer basis.

3 The impact of health care technologies, in terms of resources and health outcome, has often been modelled since complete intervention data has seldom been available. Such modelling is likely to continue for the foreseeable future although it is likely that economic evaluations will be more commonly conducted alongside clinical trials (Drummond and Davies, 1991). However constructed, models involve assumptions and their use emphasises the need for transparent reporting of data methods and analysis. For example, the date of origin of epidemiological and outcome data entering into models is seldom presented. Sometimes data can relate to studies and populations 20 or 30 years old: the implications of this upon study findings needs to be discussed. For example, many evaluations of heart disease interventions draw on data from the Framingham Heart Study (Abbott et al 1987). Models can only be suggestive, they do not prove the value of health care interventions. Five studies in the RCES model the influence of cholesterol lowering on subsequent coronary disease in populations at risk. The studies suggest that through modelling the impact upon risk factors, obtained from observational studies, drug therapy will increase survival. However accumulation of trial evidence (Davey Smith et al 1993) has suggested that the effect of cholesterol lowering drugs in reducing mortality is not always beneficial and casts doubt on the validity of the findings of these studies. Future studies should clearly indicate

the technological date, or period, from which evidence of treatment effectiveness is drawn.

4 Quality-of-life data in the RCES were generally of illustrative quality, rather than reflecting precise estimates of health-related utility or preference. Forty-eight studies in the register, giving rise to 207 entries, reported cost/QALY data. There are broadly 3 aspects of quality-of-life estimation:

I The description used of the different levels of health status during and after treatment (e.g. a study may use the Rosser classification [Kind et al 1982] or define it's own health states).

II The assignment of patients under the various alternative treatments to health states during and after treatment. For example, is this achieved by clinical or patient opinion or some independent assessment?

III The attachment of utilities or values to the health states: this may involve direct measurement, values taken from the literature, the author's opinion or use of a published value matrix (e.g. the Rosser matrix). Where valuation is by direct measurement, the number of clinicians, patients, relatives or others involved should be reported along with the measurement approach used (e.g. time trade-off or visual analogue scale). For patients and relatives giving values, also involved in treatment, when and where values are taken is also important.

For the 207 entries in the RCES the Rosser classification was the most common (38%). Another 30% of studies described their own health states. Valuation of health states in half of studies was by the authors themselves or from the published literature.

5 Conduct of sensitivity analyses was often unsatisfactory. For the RCES an adequate sensitivity analysis was defined to be one that demonstrated (rather than chose) the sensitive parameters and then meaningfully justified the range of values used for each parameter. Although 77 of the 147 studies in the register conducted some sort of sensitivity analysis, only in 27 studies were these considered adequate. Unfortunately, there is no standardized procedure of assessing uncertainty in economic evaluations (Briggs et al. 1994). Failure to conduct a comprehensive sensitivity analysis considerably reduces confidence in study findings. Udvarhelyi and colleagues state: 'Together, the inability to verify underlying assumptions and the inability to assess the robustness of conclusions based on them, lead to serious questions about the reliability of study findings'.

The RCES provides a useful starting point for conducting a sensitivity analysis.

I Demonstrate which are the sensitive parameters in an analysis and which are not.

II State sources for the values applied to each parameter stating their meaning.

In addition the following are helpful:

III Use threshold analysis, i.e. show under what circumstances an intervention may fail to meet certain criteria such as no net benefit, or an 'excessive' cost-effectiveness ratio, alternatively, plot how cost-effectiveness varies with each sensitive parameter.

IV Use multi-parameter variation to construct best and worse case scenarios, again justifying the values used.

V RCTs address uncertainty, in the context of a trial through use of measured variation and the subsequent confidence intervals. When available, these confidence intervals should be used to construct high and low boundary cost-effectiveness ratios. However, such studies may still need to conduct further sensitivity analysis to address the external validity (or transferability) of their findings. This is likely to be necessary for both costs and consequences.

6 Economic analyses, particularly those involving modelling, were often highly technical. Each intervention and its associated disease can present unique problems for analysts introducing a legitimate degree of 'art' into the process. Further, space considerations can limit the amount of detail that analysts can convey. It is perhaps unsurprising then that reviewers commonly acknowledge a degree of subjectivity when attempting to interpret or apply criteria to studies. However, when analytic processes are careful explained the credibility of the findings are enhanced.

Most economic evaluations involve modelling and assumptions in their conduct. Further analysis is required to assess generalizability of findings to other settings. In this light it is inappropriate to use the RCES to construct 'rigid' cost-effectiveness rankings of interventions. When the context of the data are understood, even then the RCES reflects orders-of-magnitudes of cost-effectiveness.

Discussion

Decisions in health care are made as a result of a complex interplay of social, political, cultural and economic factors. The data presented in the RCES are one relevant input to this process. However, concerns have been raised that health care decision makers might use cost-effectiveness data, particularly those presented in rankings or 'league tables', in an unthinking way. Certainly we do not consider it appropriate to use cost-effectiveness data in the way they appear to have been used in Oregon (USA), whereby health policy makers have decided that State funding under the Medicaid programme will only be available for procedures down to a given cut-off point in a ranking (Hadorn, 1991). Cost-effectiveness data are useful mainly as a way of stimulating debate and of guiding further analysis at the local level. This is why the RCES has been developed not as a league table, but as a database of studies.

For the RCES to be useful, decision makers need to be confident that it is both comprehensive and reliable. It was mentioned earlier that the coverage of studies published since 1991 is not extensive, so users should bear this in mind when interpreting data on the first version of the register.

It is also clear, from the quality assessment, that economic evaluation is an inexact science. In particular, studies not directly based on RCT data involve many assumptions and are vulnerable to many biases. Therefore, in order that the true value of study findings can be assessed, full and frank reporting of methods, data and assumptions is required. In many cases it is not possible to assess the quality of studies because of inadequate reporting. In the future it would be useful if authors considered the assessment scheme set out in Table 1 when reporting methods and results.

The Department of Health has commissioned the NHS Centre for Reviews and Dissemination at the University of York to develop the register, in the light of feedback from users of the current version. The intent is to provide cost-effectiveness data to the NHS using a user-friendly free text database

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