IHE Brief

Comparative Effectiveness: An Overview

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COMPARATIVE EFFECTIVENESS: AN OVERVIEW

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1. COMPARATIVE EFFECTIVENESS AND UNITED STATES HEALTH CARE

The use of the term "comparative effectiveness" (CE) has attracted considerable attention, particularly in the United States. This booklet examines the concept of CE and its relationship to other assessment frameworks.

Definitions and Scope of Comparative Effectiveness

The Basics

When describing how well a health technology works, "effectiveness" refers to how well the technology performs under routine or average conditions of use. In contrast, "efficacy" refers to its performance under optimal conditions of use, for example in some types of clinical trial or in a centre of excellence.

Comparative effectiveness (CE) therefore refers to how well a health technology works under routine ("real world") conditions as compared with one or more different technologies that are used for the same purpose.

Definitions and scope

Beyond these basics, views on the definition and scope of CE have varied. Buckley (5) points out that there is currently no standard definition of comparative effectiveness. Definitions include:

- Center for Medical Technology Policy (24): "…a set of analytic tools that allows for the comparison of one treatment – drug, device, or procedure to another treatment on the basis of risks, benefits, and potentially, cost."
- Institute of Medicine (16): Primary comparative effectiveness research involves the direct generation of clinical information on the relative merits or outcomes of one intervention in comparison to one or more others. Secondary comparative effectiveness research involves the synthesis of primary studies (usually multiple) to allow conclusions to be drawn.
- US Congressional Budget Office (7): "…simply a comparison of the impact of different options that are available for treating a given medical condition for a particular set of patients."
- American College of Physicians (4) : …the evaluation of the relative (clinical) effectiveness, safety, and cost of two or more medical services, drugs, devices, therapies, or procedures used to treat the same condition.
- Neumann (9): Comparative effectiveness generally means an analysis based on clinical, not economic grounds. That is, it addresses whether drug A offers more clinical benefit than drug B, not whether its extra health benefits are worth its extra costs. At its heart, it is still about obtaining better value; not paying for care that does not work. However, it says nothing about whether drug A's added clinical benefits are worthwhile.

The definitions differ on inclusion of economic analysis in the comparison and some of them appear to embrace efficacy as well as effectiveness. They do not clearly indicate the nature of the information that is being sought, though this is sometimes dealt with in supporting material. For example, Tunis indicates that "effectiveness" implies a focus on "real world" outcomes, and that methods of comparison can include prospective clinical studies, observational studies with electronic medical records or administrative data, systematic reviews and modelling. (24)

Reasons for Promoting Comparative Effectiveness

Clinical and economic assessment is not new in the US health care sector, and CE might be regarded as the latest in a series of attempts to introduce evidence into policy. In the past 40 years there have been several attempts to integrate economic evaluation into policy in the US. In the 1960's, the Johnson administration introduced the Programming, Planning and Budgeting system (PPB) into the policy arena. In the 1980s, the Office of Technology Assessment (OTA) developed a health technology assessment (HTA) program. More recently, the Agency for Healthcare Research and Quality (AHRQ) was set up as the lead federal agency in the area of clinical and economic assessment. However, none of these entities succeeded in integrating cost effectiveness into the policy environment. Although rising costs have plagued the US health care environment for years, more attention has been paid to financial and market reforms than on how to integrate evidence into practice.

Reasons suggested for adoption of CE include:

- *Congressional Budget Office*: "…there are opportunities to constrain health care costs without incurring adverse health consequences. One approach that could reduce total health care spending involves generating more information about the relative effectiveness of medical treatments and enhancing the incentives for providers to supply, and consumers to demand, effective care." (20)
- *American College of Physicians*: "The absence of readily available comparative effectiveness information interferes with the ability of physicians and their patients to make effective, informed treatment choices that meet the unique needs and preferences of the patient and facilitate the ability of payers to optimize the value of their health care expenditures." (4)
- *Advanced Medical Technology Association*: "Sound comparative effectiveness research can be used to assist patients and physicians in medical decision-making by identifying the relative advantages and disadvantages of alternative means to prevent, diagnose and treat disease, including non-treatment as a potential option. Armed with the knowledge of which conclusions can and cannot be drawn from a given study or systematic review, patients and physicians will be able to use the research findings appropriately for individual diagnosis and treatment situations." (3)

The United States Context for Comparative Effectiveness

Several factors contribute to the context of proposals and expectations for CE in the US:

- The US health care system is complex, with involvement of many jurisdictions, payers, professional groups and other associations.
- "…..disillusionment with traditional cost-containment approaches, deepening anxiety about the safety and effectiveness of drugs and medical care, recognition that little is known about the optimal use of existing diagnostic procedures and treatments, and the explosion in health care expenditures anticipated as Baby Boomers age." (8)
- Federal government support for technology assessment has been variable and limited. The abolition of the Office of Technology Assessment and attacks on the Agency for Healthcare Policy and Research, resulting in a large decrease in funding, are referred to by several commentators. (4, 8,13, 27) Efforts by other federal agencies are fragmented and underfunded. (8)
- Promotion of CE by the AHRQ, which uses this term to describe some of its assessment reports. Current related AHRQ activities include its support of 13 Evidence-based Practice Centers (EPCs), and its Effective Healthcare Program, a network of 13 research centers to generate evidence of clinical effectiveness.[1]
- US policy makers have tended to resist using cost effectiveness analysis. "Notably, the US Medicare program's policy does not consider costs and cost-effectiveness when deciding whether to cover a new technology. Other payers have a similar policy: they consider new technologies on the basis of clinical evidence not economic evidence." (19)
- Concerns at growth in the costs of health care. "If costs per enrollee in Medicare and Medicaid continue to grow at the same rate as they have over the past four decades, federal spending on the two programs would increase from about 5% of GDP to about 20% by 2050 - roughly the share of the economy now accounted for by the entire federal budget." (20)
- Overall, there seems little appreciation of the extensive assessment information that is available internationally from HTA programs and other sources. Some commentaries make reference to assessments undertaken in other countries, most often considering the work of NICE. (4,7,17,18) There is some recognition that assessment experience from other countries can be helpful to the US. (7,12)

1 The network contracted with AHRQ to address these priorities and complement the work of the EPCs is called DEcIDE (Developing Evidence to Inform Decisions about Effectiveness).

Proposals for a National United States Agency

There have been various suggestions on creation of a national organization to sponsor, undertake and coordinate CE assessments and research. (3, 4, 8, 14, 19) This system would serve the role of honest broker in qualifying evidence-based medicine. (18)

Essential features of such a body include administrative independence; dedicated funding; production of objective and timely research; use of reliable methods; widespread dissemination; and a governance and organizational structure that lends it legitimacy. (8) Openness and transparency in all aspects of research have also been emphasized. (3)

Funding requirements would depend on the extent to which CE research involved synthesizing existing evidence rather than conducting new clinical trials. Funding requirements for new trials would be much higher than those for synthesis activities. (19)

Options for location of a national centre include: AHRQ; within another agency in the Department of Health and Human Services; as part of a quasi-governmental entity such as the Institute of Medicine (IOM); within a public foundation or the private sector; as a freestanding nonprofit institution; or one affiliated with a university. The centre could also be created as a federally funded research and development organization. Placement within a quasi-governmental entity was considered the most attractive option. (27)

Recommendations in a report from the Institute of Medicine envisage a single national entity with responsibility for production of information on CE. The activities of the entity would focus on systematic reviews of CE and generation of clinical guidelines. (14)

A bill introduced into the US House of Representatives in May 2008 specified funding over five years to support CE studies conducted by AHRQ on drugs, medical devices and treatments. (6) Items in the bill included establishment of a Comparative Effectiveness Advisory Board (including the Director of AHRQ) which would provide input on research priorities, and recommend how to organize research, how findings should be disseminated, and on the establishment of one or more federally-funded research and development centers.

The American Recovery and Reinvestment Act of 2009 allocates $1.1 billion for comparative effectiveness research. Of the total, $300 million is for AHRQ to build on its existing Effective Health Care program. This program allows for input from all perspectives into the development of the research and implementation of the findings. Of the remaining funds, $400 million each will go to NIH and the Office of the Secretary, Department of Health and Human Services. The legislation calls on the Institute of Medicine to recommend research priorities for these funds and gather stakeholder input.

A report is due June 30, 2009. In addition, the Federal Coordinating Council for Comparative Effectiveness Research will be created to offer guidance and coordination on the use of these funds. (1)

Coverage and Priority Setting

While some of the pressure for use of CE has come from experience with evaluation of pharmaceuticals, a broader scope for types of technologies to be covered is suggested by several commentators:

- The technologies being evaluated should be commonly used, of high individual or aggregate cost, subject to rapid change, or for which there are many alternatives and substantial uncertainty about which intervention should be used for which patient population. (8)
- To be most useful, CE research needs to focus on the full range of new and existing medical therapies that have come on the market over the past several decades. (27)
- CE research should include research involving health system changes that affect the management and delivery of health care items, services, and procedures. These include innovations in insurance benefit designs, adoption of electronic medical records, greater use of information technology tools to reduce medical errors, improved discharge planning to allow patients to return to their home or a less intensive setting, when medically appropriate. (3)

Setting priorities

Determination of priority for research and practices reviewed is a key concern.

- It is reasonable to consider new or emerging interventional procedures as an appropriate starting place, or existing practices where the evidence is particularly strong and unlikely to be contested. As the credibility of the center grows, its reach could expand to a variety of medical areas. (18)
- The CE research agenda must be prioritized and designed with pre-stated objectives, research questions, and stakeholder input…to ensure relevance to real world clinical decision-making. (3)

Criteria proposed by Teustsch et al are:

- What is the value of gaining additional information?
- What do we really need to know to make a good policy decision regarding the use of one technology or another in the treatment of a particular health condition?
- How certain do we need to be about what we know?

How these questions are answered can permit researchers to decide upon the appropriate methods to assess CE. (22)

Types of Information to be Used in Comparative Effectiveness Studies

Pressures for use of CE come from wishes to:

- obtain evidence on technology performance more quickly than is possible using conventional approaches (randomized control trials)
- move beyond placebo–controlled approaches that have often been used in regulatory studies
- obtain findings that reflect "real world" use of technologies
- obtain better information on performance of technologies in sub-groups of the overall patient population

Some of the commentaries appear to envisage abandonment of rigorous evidence-based approaches in favour of "rapid and relevant" methods. More realistic overviews note the need for a range of methodologies, depending on the questions that are to be addressed and policy context.

"Other approaches to gathering evidence, including observational clinical studies, use of administrative databases and modelling approaches offer benefits but also have risks and disadvantages. The appropriate methodology will depend on the policy or other type of question that is being addressed, and time considerations will usually be an important consideration.

There is no single 'right' answer on which approach along the continuum from observational data to strict evidence-based decisions is correct, but rigid adherence to one approach or another will clearly lead to suboptimal decision making. The proper choice of method requires that stakeholders clearly assess the purposes, harms, and benefits of alternative approaches and establish criteria against which different technologies should be evaluated." (22)

"A wealth of useful information does exist in observational studies and other sources. It can be assembled through rigorous literature synthesis, including meta-analysis. The full spectrum of information can then be incorporated into a formal analytic framework, such as a decision tree or Markov model, which can be used to assess the benefits, harms, and costs of alternative interventions… analysts can extrapolate from one population, time frame, or technology to another…take advantage of expert opinion and make reasonable assumptions to link diverse information…The risks associated with this approach arise from assumptions that are not well founded and from combining information that turns out to be inaccurate or inappropriate." (22)

Medicare claims data collected by Centers for Medicare and Medicaid Services (CMS) for payment purposes are now available for use in CE and other types of study. Suggested future approaches in the US include use of large electronic health record databases to advance the evidence base for clinical care (9), and development of a management information system for patient reported outcomes. (18) Use of practice-based evidence for clinical practice improvement has been suggested. (12)

Updating information

"Whether more evidence should be obtained at any stage ought to depend on whether the value of the information obtained…outweighs the cost and time of conducting the necessary studies. When decisions are made on imperfect information, processes need to be in place to reevaluate those decisions as new information becomes available, and decision makers need to consider the costs and benefits of changing those policies once adopted." (22)

"It is essential to the public good and the advancement of medical practice and well being of patients to maintain a review process that considers improvements or declines in clinical outcomes as essential data in the modification of treatment protocols. Review panels would be comprised of national and international experts with special topical expertise for the intervention or practice under review." (18)

Attitudes to Economic Analysis

Attitudes on inclusion of economic analysis in CE range from support for this to be undertaken by a national body, to suggestions that economic analysis not be linked to CE at all.

Clear support for economic analysis by a national CE body comes in the proposals from the American College of Physicians. The College recommends that a national CE entity should be charged with systematically developing both comparative clinical and cost-effectiveness evidence for competing clinical management strategies. (4)

In background to its recommendation, the ACP comments that "patients and their advocates are concerned that use of any cost data, including formal CEAs, will inappropriately limit access, be used primarily for cost containment, and be a substantial step toward rationing of care. These fears are particularly strong in the US, where the belief that the richest nation in the world should not consider cost in decisions about access to tests and treatment seems to persist. This opposition often focuses on cost-effectiveness data rather than cost data alone. Many insurers use information about cost because they must manage finite budgets."

Wilensky opposes the ACP's recommendation that the new entity should prioritize, sponsor, and produce cost-effectiveness information. (26) She argues that the use of cost-effectiveness information is more politically contentious and its modelling more technically controversial than comparative clinical effectiveness and suggests payers should do cost-effectiveness analyses, not the national entity.

An industry organization paper draws attention to the need to consider different perspectives in CE work, including cost-related studies, and notes that inclusion of economic analysis in a study will increase complexity. (2) Another industry view is that only clinical effectiveness should be studied. "Patients should have access to the interventions that are best for them. Consequently, any government-funded comparative effectiveness research initiative should study clinical effectiveness only… By focusing government resources on well-designed clinical effectiveness research, quality of care should improve and ultimately should have a favorable impact on overall efficiency in the health care system." (3)

There appears to be little in the commentaries relating to methodological aspects of economic analysis in the context of CE research. The ACP refers to some general issues on CEA in its position paper (4) and a paper commissioned for the Medicare Payment Advisory Commission (MedPAC) includes comments on economic analysis and some of its potential problems in an appendix on evidence-based measures. (18)

An earlier paper from the National Health Policy Forum provides information on the approach taken in the UK by NICE, though there is only limited detail on economic analysis aspects. (17) Overall, there is little consideration in the commentaries on use of economic analysis in assessments undertaken by agencies in other countries or reference to guidelines that have been developed, not least in Canada.

Dissemination of Findings

The importance of effective dissemination of CE findings is recognized in various commentaries. Most consideration is given to preparation and format of different types of assessment/dissemination products rather than mechanisms for interacting with organizations and individuals.

- "The initiative must integrate diverse evaluations and communicate well with professional stakeholders, industry, physicians, and the general public. This requires the development of a standard reporting format for effectiveness evaluations, and the implementation of a formal review process before the final release of official reports. The review should include both internal evaluations and external commentaries." (8)
- "The panel should develop recommendations for educating both the general public and the medical profession and for promoting discussion on the use of comparative clinical and cost-effectiveness information to meet the needs of the individual and to help ensure the equitable distribution of finite health care resources throughout society." (4)
- "Information developed from the reviews…must be able to reach multiple audiences of varying levels of sophistication, in culturally appropriate and consumer friendly ways. Such comparative information may include intervention protocols, procedure fact sheets, web-based guidelines and expected clinical outcomes. The involvement of professional associations, schools of medicine, payers and other key stakeholders as avenues of dissemination is critical to widespread voluntary practice adoption." (18)
- "The challenge is to accurately convey the results in plain language and be viewed by stakeholders as valuable sources of information. Changes in information technology such as electronic records, could serve as a timely way to link dissemination of best practices to provide real time information to providers treating patients." (18)
- "The new center could help training and technical assistance for users of CE by developing standards, possibly utilizing the existing network of AHRQ's EPCs to serve hubs that could facilitate train-the-trainer programs and provide feedback to the center on issues that may influence clinical outcomes." (18)

Use of Information from Comparative Effectiveness

An article from the Congressional Budget Office notes that to affect medical treatment and reduce health care spending, the results of CE research would have to change the behaviour of doctors and patients - that is, get them to use fewer services or less intensive and less expensive services than they would otherwise choose. (20)

Mechanisms suggested by CBO for achieving such change include:

- public and private insurers to modify their coverage or payment policies… For example, insurers could choose not to cover drugs, devices, or procedures that were found to be less effective or less cost-effective
- adjust doctor and hospital payments to encourage the use of more effective services.
- require enrollees to pay at least a portion of the additional costs of more expensive treatments that are shown to be less effective or less cost-effective (in which case enrollees would have to decide whether the added benefits were worth the added costs).

  "…the new approach, sometimes called a value-based insurance design, would be tailored to the patient's condition and treatment."

Others point out that information alone will not be sufficient.

- "Information must be tied to appropriate infrastructure and financial incentives to affect medical practice." (8)
- "Voluntary adoption of highly rated practices is contingent on credibility of the entity conducting reviews, stakeholder involvement and support and viable economic incentives." (18)

Several sources comment on the issue of population versus sub-group or individual data and analysis:

- "The panel should consider how physicians should use cost-effectiveness in the context of the physician-patient relationship to reflect the need for patient care to be patient-centered, considering the individual's characteristics and preferences, and should take into account the opinions of the treating physician as the patient's advocate. (4)
- When one approaches CE research, it is important not to regard the patient population as homogeneous…Each patient has his/her own preferences that need to be taken into account by the clinician when prescribing a course of treatment… What might be appropriate for one patient may not be appropriate for another. If a clinician or agency relied upon the results of a CE study which was based upon population averages, a clinician or agency could decide on a treatment that is inappropriate… (5)

- "Comparative effectiveness research should not be used by Medicare, insurance companies, or other public or private payers to deny coverage. Comparative effectiveness research typically analyzes which medical intervention, on average, is usually more effective across a population...CE research findings should be used as a reference, not a mandate, for individual treatment decisions..." (3)
- "Research findings should be communicated in a fashion that clearly acknowledges any limitations of the research and underlying data. Armed with the knowledge of which conclusions can and cannot be drawn from a given study or systematic review, patients and physicians will be able to use the research findings appropriately for individual diagnosis and treatment situations." (3)

Reservations about Quality and Possible Impact of Comparative Effectiveness Information

Quality of information

"Studies of…CE entail unique methodologic challenges…may be susceptible to systematic error, including selection bias, exposure misclassification, and outcome misclassification. They may also be vulnerable to random error, or confounding by a variable such as another drug, a disease, or the drug indication itself." (21)

Use of information by decision-makers

"…changing practice patterns can be difficult. For instance…thought must be given as to how findings from CE studies will be used by providers and patients when currently there is information that is not being incorporated into clinical practice." (5)

"CE won't remove the hard choices. CE and cost-effectiveness analysis can illuminate choices and tradeoffs inherent in many health care decisions, but they do not remove them." (19)

"CE will raise additional questions. CE research rarely "solves" a clinical question under investigation. The point is not that CE is not worth pursuing but that expectations should be tempered." (19)

Budget savings

"Promised savings of 10-25% from uncovering and cutting "waste" in the system are probably wild overstatements. Attempting to find and remove pure waste in the system is always a fool's errand, in part because CE research will uncover interventions that cost money but offer good value as well as those that do not work. Moreover, strong pressure from patients and physicians will remain to pay for care that offers uncertain benefit or questionable value." (19)

"… the likely impact of evidence based research is often oversold. Indeed, it would be difficult for any new organization simultaneously to raise the quality of evidence-based research, alter the way in which care is delivered, reduce variability around the country, and reduce costs at the same time. Yet such are the gains sometimes claimed…" (18)

"…evaluating the precise effect of new research is difficult because it is hard to know which studies will be undertaken and what they will find, but CBO estimates that such research would probably reduce spending for health care somewhat." (7)

Effects of the health care system

"Don't forget incentives. Inserting CE research into a system plagued by perverse incentives will only go so far. The information can help deliver better value, but only alongside intelligently designed systems and benefit packages that involve sharing risk at multiple levels." (19)

Interests of stakeholders

"Technology evaluations in health care can provoke controversy, anger, and hostility. A suggestion that a popular or expensive treatment is minimally effective or lacks data on long-term risks could be inimical to the interests of manufacturers, advocacy organizations, physician groups, or other groups, and will be received accordingly." (8)

Impact on innovation

Potential adverse effects of CE studies on health technology innovation have been raised by industry sources:

- Medical device technologies (both therapeutic and diagnostic products) pose a difficult challenge for producing timely and accurate CE information. (3)
- "Might the use of CEAs in coverage decision processes slow down or inhibit innovation…Denial of coverage would have a large adverse financial effect on a company and might make it more averse to the risk of investing in potential technical advances." (4)
- "CE generally focuses on a static world – that is, evaluation of a current therapy in the current state of the world in the short term. Evaluations by foreign agencies have led to decisions where an innovative therapy is not covered by a country's health service. However, these evaluations…do not take into account future patients and whether the decisions implemented now will have deleterious effects on the availability of future therapies." (5)

Strong counter-arguments include:

- "Innovation depends on multiple factors, including incentives offered by payers, society's overall willingness to spend money on health care, the available supply of venture capital funds… and the rigidity with which cost effectiveness thresholds are applied in policymaking decisions…use of cost-effectiveness data does not necessarily inhibit innovation but instead may actually stimulate the development of more cost-effective interventions." (4)
- "… concerns often find expression in rhetoric that conflates new with innovative and latest with best. However, novelty cannot be equated with benefit. An intervention's value resides in its ability to reduce mortality, morbidity, or save money, not in its unique mechanism of action...New interventions that offer substantial value will be rewarded with high demand and prices commensurate with their benefits - providing strong incentives for research and development." (8)
- "Great Britain's more systematic approach to assessing new health care interventions has prompted the more rapid introduction of effective new interventions throughout the NHS, particularly within local health authorities, or "trusts," that had been slow to introduce them." (17)

Further thoughts

It is difficult to see how suggestions regarding CE influencing decisions on individual patients are much different to what physicians do routinely during their consultations.

There will be limits to the number of patient sub-groups that could be practically defined for any health technology. Small sub-groups imply limited relevant specific evidence.

It might in practice be challenging for patients to make informed decisions on complex clinical situations as a result of additional CE data. And possibly those most in need would be least able to make use of such information.

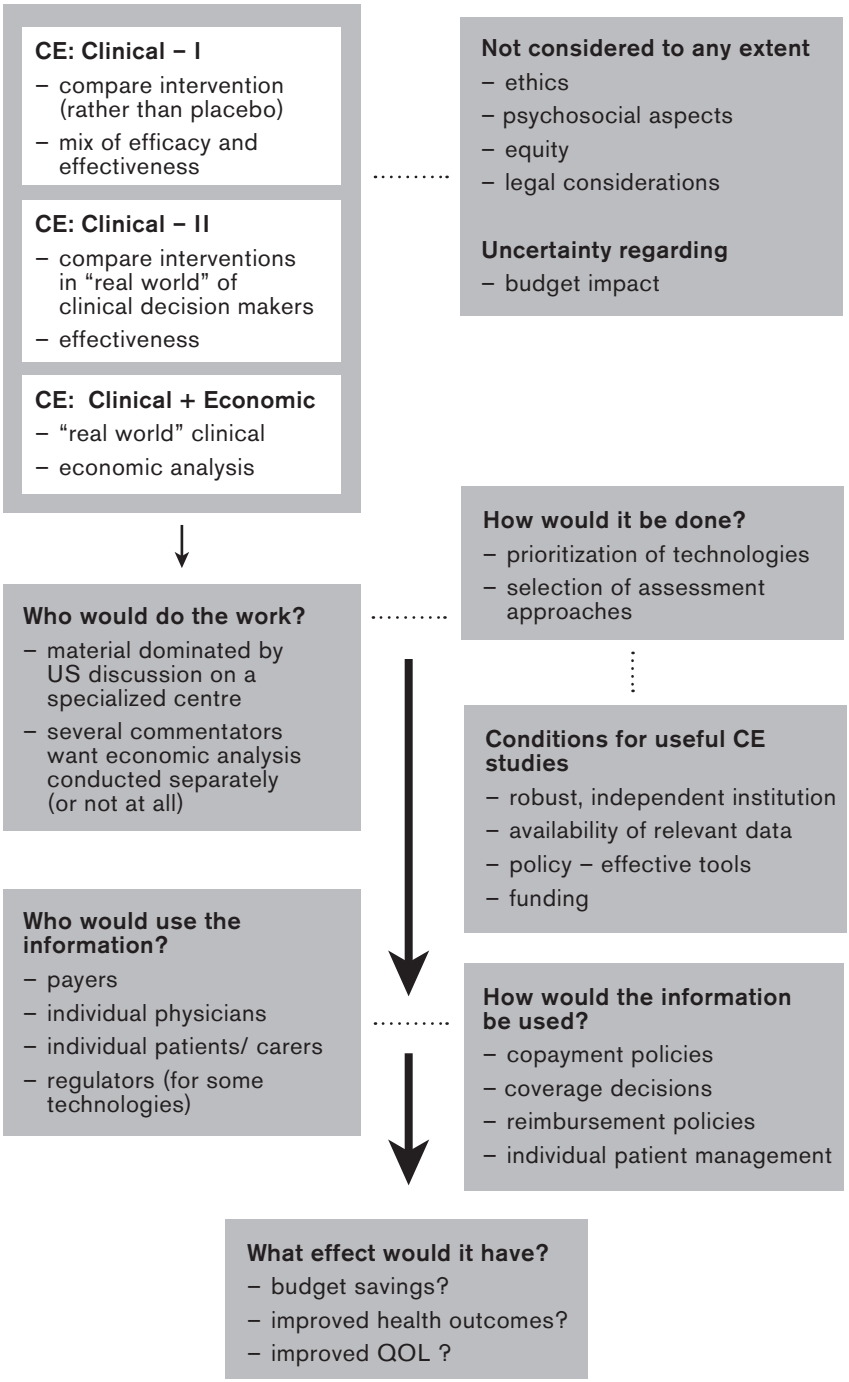
Some of the proposals for a national CE center specify use of expert panels and committees for advice, formulation of standards, etc. Details are lacking on how such bodies would be supported, how many topics they could cover, and how quickly they could provide responses.

Overall Concepts on Comparative Effectiveness in United States Health Care

Figure 1 summarizes some of the concepts on CE in the US context discussed previously:

A. Comparative effectiveness is defined or perceived in different ways
B. Some aspects relevant to assessment of health technology have received little attention so far
C. A national centre is seen as important for the conduct and coordination of CE studies, though there is scope for other organizations to be involved
D. Prioritization of technologies to be considered and selection of assessment approaches, depending on the questions to be addressed, will be key issues
E. For useful CE studies to be undertaken, several conditions – on independence, data availability and funding – will need to be assured.
F. There will be a variety of users of CE information, individuals as well as organizations
G. CE information will be used in association with various types of policy machinery
H. The hope is that CE studies will lead to cost savings and improvements in health outcomes.

Figure 1: Comparative effectiveness in US health care – components and concepts



2. COMPARATIVE EFFECTIVENESS AND OTHER ASSESSMENT FRAMEWORKS

Comparative Effectiveness and Health Technology Assessment

As discussed earlier, there are differing definitions and concepts of CE, but for all of them CE can be considered to be a major subset of HTA. From the HTA perspective, comparative effectiveness is not new to many of the agencies in the field, particularly those located in different countries of Europe.

In most formulations of CE, there is an emphasis on effectiveness rather than efficacy, attempting to address an issue that has long been seen as a limitation for HTA.

Some approaches to CE, such as a number of the reports published by AHRQ, seem no different to numerous HTA publications from agencies in many countries. For example, the AHRQ report on management of gastroesophageal reflux disorder (GERD), identified as its first comparative effectiveness review, is a good quality systematic review that essentially deals with the efficacy of treatments for GERD. It draws on evidence from high quality RCTs (which was preferred) with non-randomized and uncontrolled studies used to augment the evidence when there was a paucity of data or when RCTs were unavailable. (2)

Use of sources of evidence other than RCTs, including observational studies and administrative data bases, is common in HTA. Some of the work proposed for CE in the US could extend the scope of data base use in assessment in terms of broader linkages and more consistent, longer term follow up of health technologies after their introduction.

In the US there is support for incorporation of economic analysis in CE, though some parties advocate consideration only of clinical effectiveness. Views differ on how economic analysis linked to CE should be undertaken and applied. There appears to be little concrete on the practicalities of economic analysis with CE in the US context, whereas integration of economic analysis within HTA is well established in many countries. Luce et al. describe two pragmatic clinical trials of drugs which included HRQOL and cost outcomes to illustrate successful partnerships between managed care organizations and pharmaceutical manufacturers. (15)

CE using other types of evidence, as adopted for example by CMS in coverage with evidence development projects, also has parallels in the HTA experience. Examples of application of conditionality to coverage decisions have been given by the HTAi Policy Forum and in a review of Australian HTA projects. (11,13) The possibility of more rapid assessment using some CE approaches, with subsequent follow up as needed, has parallels in the widespread use of rapid assessments by HTA programs. (25)

General issues on dissemination of CE findings and the influence of these on decision makers are really identical to those that apply to HTA.

Implications of CE for methodology of cost effectiveness analyses

No publications were located that specifically addressed this topic; some of the commentaries include details on CEA and on its difficulties and limitations. There could be issues for CEA arising from use of poorer quality data (observational studies etc) or data that may not be fully relevant to the question that is being addressed. And there could be challenges for CEA for various patient sub-groups. But these would not be new issues for economic analysis.

Cautions in some of the commentaries are pertinent, but these are not new issues either:

"The risks associated with this approach arise from assumptions that are not well founded and from combining information that turns out to be inaccurate or inappropriate." (22)

"Cost-effectiveness analyses can and should report all of their assumptions and computations. In a properly conducted and reported analysis, this transparency could lead to more rational, consistent, and accountable choices than the behind-closed-door decisions of some current coverage policies." (3)

CE and Coverage with Evidence Development

Coverage with Evidence Development (CED) represents a specific approach to coverage for promising technologies for which the evidence remains uncertain. It requires that additional evidence is generated to address the sources of uncertainty and secure ongoing coverage. (13)

Potential advantages and disadvantages of CED have been summarized by Hutton et al. Advantages include managed entry of promising technologies that have significant uncertainties, with access to them earlier in their lifecycles. Disadvantages include the potential for investing in technologies that prove not to be cost-effective and an additional burden for decision makers of monitoring and review as further evidence is obtained. There are important gaps in evidence that commonly remain after completion of regulatory trials. (13)

The HTAi Health Policy Forum suggested that CED is best suited when there are reasonable grounds for believing that a technology will offer significant benefits but there is uncertainty on its clinical or cost effectiveness than can be overcome through evidence that can be generated in an appropriate time frame, and when the uncertainty is the main source of equivocality in a coverage decision.

CED may often make use of CE studies, including more rapid approaches to generating "real world" data. (13) CED studies may provide valuable information on risks in large populations and may provide an opportunity to explore subgroups of patients for whom benefits and risks are larger or smaller than the average effect identified in regulatory studies. (23) However, judgements will be needed regarding the type of methodology to be used, and the timing of the CED process, bearing in mind the need to provide practical advice for decision makers.

"If uncertainty over the cost-effectiveness of a technology at the time of launch results from concerns over what will happen in routine practice then CED offers a way of generating further evidence on those variables without delaying access to treatments with clinical benefits that have been demonstrated in trials. If the uncertainty over cost-effectiveness results from the lack of strong clinical evidence there may be more of an argument for delaying coverage until new clinical studies are carried out. This would be especially the case if more RCTs were needed as partial coverage through CED could reduce incentives for patients to take part in such studies." (13)

The Health Policy Forum noted that decision makers must be sure that collection of relevant new data is feasible within a relatively short period before they embark on a CED process. It also suggested that a CED process lasting more than 3 years risks becoming of limited relevance in the face of changing clinical practice, though Tunis and Chalkidou point out that early US experience with CED involved trials of considerably longer duration. (23) Examples include the national emphysema treatment trial which took 7 years

to complete and informed coverage decisions on lung volume reduction surgery, and a multiyear RCT on high-dose chemotherapy and BMT in patients with metastatic breast cancer (the procedure has since been abandoned).

In discussing the experiences of CMS in the use of CED for Medicare coverage policy Tunis & Chalkidou point to some of the practicalities that need to be borne in mind when contemplating a CE study. CED "may provide a mechanism to expedite access to promising technologies but the conditional limitations to those patients enrolled in a study may impose serious restrictions depending on the size of the study, how quickly if can be launched and how soon it can provide data that will inform a decision. The policy option has no meaningful impact if it takes a year or more to design, identify funding for and implements the study." Also, "Participation in clinical research has to become a routine, rather than an exceptional, management option for patients and clinicians under conditions of uncertainty."

Implications for Alberta, Canada and Other Jurisdictions

Health policy makers in Alberta, Canada are familiar with CE, which is similar to the concept of HTA. However, its use as a tool in health policy is different from what is being discussed in the United States.

Alberta's Ministry of Health has for years supported an HTA initiative, which is currently centered around the efforts of the Institute of Health Economics in Alberta, and the Canadian Agency for Drugs and Technologies in Health (CADTH) nationally, but its use in health policy is somewhat limited.

HTA in Alberta and Canada is a tool which provides information. Its widest use is in the listing of drugs in provincial formularies. CADTH's Common Drug Review provides information on CE to the provinces on specific drugs. The provincial formularies then use this information, along with other factors, to make a listing decision. Information on CE for other interventions is also available, both from CADTH and IHE.

Such information also has several potential uses, for example:

- It can be used by regional authorities in their budgeting exercises.
- It can be used by provincial medical societies in setting fees for services, increasing those for more desirable ones and reducing fees for less desirable services.
- It can be used by provincial bodies to determine which services will not be covered.
- It can be used to establish co-payments for drugs, having higher co-payments for those with a lower cost-effectiveness ratio.

Other issues that were discussed in the US literature are also relevant for Alberta. For example, conditionality was touched on in one of the Alberta Heritage Foundation for Medical Research reports:

"…conditional support may often be proposed for an "experimental" or "not adequately validated" technology. Options for future action by the funding authority might include:

- Introducing general financial support, for example through a schedule or through grants
- Denying support if there are strong indications that the technology is ineffective, or if there are adequate alternative technologies available
- Providing support in the context of a local primary study
- Providing limited support, conditional on collection of outcomes data or on restriction to a sub-population of potential clients
- Denying support for the time being, pending a future review of evidence reported in the literature

If conditional support is linked to requirements for collection of additional data, there will be a need for active management of future coverage for the technology by the funding body (for example a health authority) perhaps in association with an HTA program. Decision-makers will have to think beyond a basic 'gate keeping' response to the classification of a technology. Further developments in the technology and additional clinical findings should be taken into account. Also, the decision making organization will need to be prepared and able to rescind or modify the conditional approval if subsequent information on the technology does not confirm initial indications of efficacy, or if requested data collection is not implemented." (10)

As CE is introduced in the United States, decision-makers in Canada will become more aware of its uses. It is likely that the use of this information and that available from HTA sources will spread in Canada as well.

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Notes

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