Coverage with Evidence Development: An examination of conceptual and policy issues

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The application of conditionality to coverage decisions for healthcare technologies is increasing. Coverage with Evidence Development (CED) represents a specific approach to coverage for promising technologies for which the evidence remains uncertain. CED demands that additional evidence is generated to address the sources of uncertainty and secure ongoing coverage. This study explores the conceptual and policy issues relating to CED and discusses issues involved in operationalizing CED in practice, including presenting criteria for which technologies may be most suitable for CED. This study is intended to further the debate on the use of CED as well as highlight areas that warrant further research.

Keywords: Coverage, Evidence development, Health technology assessment

With continued pressures on healthcare budgets, innovative technologies are subject to increasing scrutiny before healthcare decision makers agree to provide coverage for their use. Health services throughout the world have adopted a range of approaches to evaluate new technologies before their widespread adoption. Whereas the majority of activities have focused on pharmaceuticals and medical devices, other healthcare interventions, including diagnostics, imaging technologies, and surgical procedures, are increasingly being evaluated before widespread adoption.

Health technology assessment (HTA) is one technique that has been widely adopted to help to manage the introduction and appropriate use of new technologies (1). HTA involves the medical, social, ethical, and economic implications of the development, diffusion and use of a health technology. HTA has been positioned as a “bridge between scientific evidence and the needs of policymakers” (2). HTA emerged partly in response to the uncontrolled diffusion of health technologies that occurred in the past (8) and is now frequently used to inform decisions on the coverage and reimbursement of new technologies.

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but it still does not overcome the problems related to the short duration and controlled environment of many trials.

As with the patient health outcomes, healthcare resource use can be monitored in regulatory trials, providing a direct comparison between the new treatment and the control. The same issues arise over the relevance of the comparator arm and the duration of observation. There is also the issue of protocol-driven costs that may not occur in routine practice.

Although uncertainty around the cost and effectiveness data is important, it is not the only source of material uncertainty. Coverage decisions usually have to be made at a time when data on all the relevant variables and comparisons are not available from high-quality studies. Many qualitative judgments and assumptions can come into play in structuring a model to address the relevant questions. Formal analytical techniques can be used to measure the “value of information” (3,4), but ultimately a judgment must be made as to whether the benefit of more evidence is greater than the cost of delaying the decision until it is available.

Making decisions under uncertainty for technologies early in their life cycle may result in the coverage of technologies that are subsequently shown to be clinically or cost-ineffective. Conversely, coverage may be restricted for technologies that later prove to be clinically and cost-effective. In both cases, there are opportunity costs in terms of healthcare expenditure and/or health benefits associated with these inappropriate decisions.

Coverage with Evidence Development (CED) is one of several policy options that have been posited to overcome the problems associated with making coverage decisions under uncertainty. The application of conditionality to coverage decisions has been widely discussed (9,14). Conditionality allows a technology to be made available under specific conditions, usually for a defined period, after which the benefits of the technology are reviewed. Where conditionality is dependent upon the generation of further evidence through formal studies to support the value of a technology, this approach has been labeled as CED (17). The application of CED to date has tended to consider promising but unproven technologies in indications characterized by limited alternative treatment options (e.g., treatments for advanced colorectal cancer), suggesting that decision makers are more cognizant of uncertainty in areas of high unmet need. CED ensures that patient access to promising new technologies is not prevented but is managed in a coordinated way, while also generating additional evidence to reduce any uncertainty about the value of the technology. CED differs from traditional postmarketing evidence generation in that the objective of the additional evidence generation is to reduce uncertainty around a specific aspect of the evidence base and, thus, help to inform further decisions about ongoing coverage, often at predetermined points in the future. The role of the decision maker in determining the nature of the research is also expected to be greater than in traditional postmarketing studies.

An example of the use of CED is that of the Centers for Medicare and Medicaid Services (CMS) in the United States. CMS issued guidance in 2005 (5), with further revisions in 2006 (13), to describe when CED should be applied and how it should operate. The guidance was issued following the organic development of CED within CMS. CMS has now made some promising technologies with an equivocal evidence base available on the grounds that the technologies are only used in clinical trials or as part of a registry to help provide further evidence on their effectiveness. The introduction of CED offered a formal option for CMS to make promising technologies available that would otherwise fail to meet their criteria of “reasonable and necessary” and thus, be ineligible for coverage within their system. In Australia, the Medical Services Advisory Committee (MSAC), which determines the coverage of medical devices, has the ability to “provide interim funding to enable data collection, within an agreed research framework, in order to establish the evidence base” (12). Other countries to have piloted the use of CED include Canada and England, where the process has been driven by the findings of HTA reviews of technologies, and the Netherlands, where CED is being increasingly applied to pharmaceuticals for use in hospital settings. Similarly, the Catalan Agency for Health Technology Assessment in Spain has made recommendations on the funding of further research to support coverage decisions (6).

The following sections of this study discuss the key conceptual and policy issues associated with CED, attempt to further develop thinking on the practical applicability of CED, and identify further issues to be addressed. The study reflects discussion between and correspondence with those attending a meeting of the Health Technology Assessment International (HTAi) Policy Forum in February 2007, although not all those individuals, nor the organizations they come from, necessarily agree with all the opinions expressed in this study, for which the authors take full responsibility. (Names of those participating in the meeting of the Health Technology Assessment International Policy Forum in February 2007.)

POSITIONING OF CED
This section addresses the following two questions: (i) What factors should be considered in deciding whether to develop a CED system to help overcome uncertainty in coverage decisions? (ii) If a CED system is developed, what criteria should be applied to identify technologies suitable for CED?

Considerations in Developing CED as an Option
CED attempts to balance the wishes of patients, manufacturers, and healthcare decision makers, all of whom want to make promising technologies available to patients while also ensuring the efficient use of scarce healthcare resources. This strategy has similarities with ongoing debate about the regulation of new medicines and how the approval of new
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Table 1. Potential Advantages and Disadvantages Associated with CED

<table>
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<tr>
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<th>Potential advantages</th>
<th>Potential disadvantages</th>
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<tr>
<td>Decision makers</td>
<td>Allows patient demand to be met through managed entry of promising technologies with significant uncertainties. Influence over evidence generation to ensure it meets decision-makers’ needs.</td>
<td>Potential for investing in technologies that prove not to be cost-effective. Extra burden of monitoring and review in the light of further evidence (and possible costs of data collection if not fully borne by manufacturer). Difficulty in withdrawing technologies that prove not to be cost-effective.</td>
</tr>
<tr>
<td>Healthcare providers</td>
<td>Access to promising technologies earlier in their life cycle. Increases treatment options available to patients.</td>
<td>Risks involved in using technologies that are not fully evaluated or recommended by guidance.  May increase exposure to litigation.</td>
</tr>
<tr>
<td>Manufacturers</td>
<td>Adoption (initially limited, but with potential to expand) of technologies with equivocal evidence that otherwise might be rejected</td>
<td>Delays to market access for effective technologies. Additional burden of data collection/analysis. Restrictions on pricing decisions.</td>
</tr>
<tr>
<td>Patients</td>
<td>Access to promising technologies that may otherwise not be available.</td>
<td>Access to technologies that may prove to be ineffective or for which disbenefits may outweigh benefits.</td>
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CED, Coverage with Evidence Development.

medicines can be expedited without detriment to patient safety. The pressure to expedite both regulatory and coverage decisions is driven at least in part by more informed patients demanding access to promising technologies.

Whereas CED appears to offer a potentially attractive solution to this issue, it is a complex system to implement, with impacts on patients, healthcare decision makers, and technology manufacturers and needs to be carefully considered before adoption. Table 1 summarizes some of the advantages and disadvantages of CED for each of the major stakeholder groups.

For healthcare decision makers, CED introduces an option that allows the product to be made available in a controlled manner while also allowing the decision maker to define what evidence is required to support further use of the technology. Potential disadvantages for decision makers are the extra demands of agreeing the study design and monitoring and reviewing the data collected, and the challenge of withdrawing coverage if this is the conclusion reached. (There is a general consensus that it is politically more difficult for decision makers to withdraw coverage—even if formally temporary—than to refuse coverage in the first place, in situations where the case against coverage is of similar weight [15]). Decision makers—or closely related bodies—may also be expected to contribute to the costs of collecting the data in CED, as has been the case in Spain (7). A further important consideration is whether the existence of a CED option will reduce the incentives for manufacturers to undertake appropriate research both before and after the licensing of a product.

For manufacturers, the introduction of a CED system allows promising technologies to be made available that might otherwise be rejected. However, the burden of proof often rests with the manufacturer, and adoption of a CED system may therefore increase costs for manufacturers. Moreover, there are concerns that the existence of a CED option may make decision makers more likely to demand further evidence for technologies on which they would otherwise make decisions. Depending on how the CED process operates, it may also lead to the manufacturer being forced to reconsider the pricing of the technology, although this may not always be feasible.

Healthcare providers may welcome the introduction of CED if it allows for earlier access to promising technologies, thus increasing treatment options available for their patients. However, they may also exercise some degree of caution about the use of technologies that are not fully evaluated or recommended by guidance. Given the increasing trends for litigation, some providers may remain reluctant to use a technology that remains under evaluation, particularly if the uncertainty relates to the clinical aspects of the technology.

The main benefit of CED to patients is access to technologies that have apparent benefits but remain unproven by conventional evidentiary standards. There are many examples of patients lobbying for access to developmental or unproven technologies in recent times, most notably in cancer and HIV indications. CED can allow patients access to such technologies and to participate in further research to generate evidence that will inform their own and other patients’ subsequent treatment. The main risk for patients is that they will be exposed to a technology which subsequently proves to be ineffective. In the case of pharmaceuticals, in non–life-threatening diseases, this finding may not have a significant impact on long-term outcomes, other than causing the patient to miss-out on optimal treatment for a period of time. In the case of medical devices, this may result in the need for re-operation or removal of a device if it fails to deliver expected health benefits (e.g., in the case of hip prostheses).

The degree of uncertainty that affects a technology at the time of launch is linked, at least in part, to the regulatory...
framework that applies to the technology. The requirements for approval of new pharmaceuticals are relatively stringent, specifying the need for well-designed, robust, randomized controlled trials on safety and efficacy endpoints. Medical devices can be approved on a more limited evidence base that shows that the product is capable of meeting a stated need and many are approved for use with no evidence from randomized controlled trials (depending on the class of product). The regulation of medical diagnostics requires evidence on their sensitivity and specificity to predefined clinical markers but takes no account of the impact of the diagnostic on treatment decisions or health outcomes. Surgical procedures meanwhile, remain largely unregulated with the exception of professional peer-review and clinical audit.

As the level of evidence required for approval for each of these classes of technology becomes less robust, the likelihood of uncertainty occurring increases. It could be argued that surgical procedures, diagnostics, and medical devices are more appropriate candidates for CED, although other factors may also influence whether CED is appropriate (for example, the budgetary impact of a technology). However, most systems that have developed a CED option seem to consider each technology on an individual basis to determine whether CED is a feasible solution to overcoming uncertainty, rather than restricting CED to certain classes of technology. Suggested criteria for identifying suitable technologies for CED are developed below.

**Identifying Technologies Suitable for CED**

Whereas all coverage decisions involve some degree of uncertainty, many can be resolved without resorting to CED. Even where CED exists as a policy option, it can be costly and complex and decision makers should give careful consideration to other ways of proceeding in the face uncertainty before choosing to go down that route.

Where there is uncertainty over the cost-effectiveness of the technology, it may be possible to bring the upper estimate of cost-effectiveness below an acceptable threshold by reducing the price of the technology. Although this can potentially lead to a rapid resolution, it requires a degree of flexibility from the manufacturer and assumes that margins on technology development are sufficient to allow prices to be readily reduced. Equally, it may be possible for the decision maker to exercise some flexibility on their threshold for cost-effectiveness to accommodate the uncertainty. Previous studies have discussed the appropriateness of accepting higher cost-effectiveness ratios for specific drugs (e.g., orphan drugs) or conditions (10).

Where uncertainty relates to the clinical effectiveness of a technology, further analysis of the available data with some degree of modeling or extrapolation may help to reduce, or at least quantify, the degree of uncertainty. Value of information analysis (VOI) may then show that additional evidence generation is not worthwhile.

Increased contact between manufacturers and decision makers during the development of a product may also help to overcome uncertainty by agreeing on what evidence is required to support coverage and defining the acceptable degree of uncertainty. Such discussions would follow the model increasingly being adopted by regulators but would require decision makers to be adequately resourced to engage in a timely and informed dialogue. There might also be scope for decision makers and regulators to work together more closely with one another in agreeing expectations with manufacturers.

When, then, should CED be used? As a general rule, it is suggested that CED is best suited to the following circumstances: where there are reasonable grounds for believing that a technology will offer significant benefits but there is uncertainty around the clinical or cost-effectiveness of the technology that can be overcome through evidence that can be generated in an appropriate time frame, and is the main source of equivocality in a coverage decision.

Figure 1 attempts to illustrate which technologies are suitable for CED. The diagram is a schematic representation of the selection of technologies suitable for CED. The horizontal axis represents the likely extent of net positive or negative performance in relation to current alternative treatment options (that is the origin represents a point where the technology is equivalent to current treatment), and the vertical axis indicates the degree of uncertainty.

Technologies that fall under the shaded area (beneath OA) are those that are deemed suitable for coverage. That is, the balance between the expected net benefit and the degree of uncertainty is acceptable to the healthcare decision maker.

Those technologies that fall in the shaded area (between OA and OB), that is those with a potential net benefit but some degree of uncertainty, may be deemed suitable for CED. These should be reviewed for the presence of “material uncertainty,” in the evidence base. That is uncertainty to such a degree that it prevents a clear-cut decision, but whose resolution will enable a definite decision to be made. For example, the point estimate of the cost-effectiveness of a technology may be within an accepted threshold (e.g., £20,000 per quality-adjusted life-year in the United Kingdom), but the variability in the cost and effectiveness data means that there is a high probability that the technology may not be cost-effective. Collection of further data may reduce that variability and increase confidence in the validity of the point estimate as a basis for the decision.

Technologies that fall above OB are less likely to be considered suitable for CED on the grounds that the expected net benefit is relatively small and the uncertainty relatively high. However, there may be cases where technologies in this sector may be considered suitable for CED on other grounds (for example, the limited availability of alternative treatment options).

The diagram is intended to be a simple schematic and does not take into account the intricacies of CED in practice.
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Figure 1. Identifying technologies suitable for Coverage with Evidence Development (CED). Illustrative representation of when to consider CED.

For example, there may be cases where a technology that has a small but negative effect may be considered suitable for CED if the degree of uncertainty means that the effect could actually be positive. It is also worth considering whether healthcare decision makers have a tolerance for uncertainty, even under CED. In which case, there may be technologies that, despite having an expected net benefit, are simply subject to too much uncertainty to be suitable for CED and may require the manufacturer to generate additional data before discussing a CED arrangement. This would take into account the potential perverse incentives for manufacturers to disinvest in research before launch on the grounds that a CED approach to coverage will always be available. These are issues that warrant further consideration.

A checklist of particular questions that need to be considered before entering into a CED process for a technology is given below.

- Does the technology offer a potentially significant advance on current treatments (e.g., in severe conditions with a high unmet need) but with material uncertainty as a result of equivocal evidence?
- Will collection of additional data reduce the uncertainty?
- Will collection of that data within a CED process, that is, in a routine care situation, increase the relevance of the data to the coverage decision?
- Can CED provide information to help reduce uncertainty within an appropriate period (for example, the patent life of the technology or before the technology is likely to be superseded)?
- Will granting of conditional reimbursement prevent the use of optimal study designs in the additional data collection, for example, by reducing incentives for patients to participate in trials?
- Is the benefit of an improved decision sufficient to justify the costs of a CED process?

PRACTICAL ISSUES

Agreement on Data Requirements and Study Design

Once the variables on which new data are needed have been identified, agreement must be reached on the evidentiary standards to which data should be collected to reduce the level of uncertainty around the decision to acceptable levels. From the cost-effectiveness analysis, it will be possible to identify the range within which the value of a variable must fall to give reasonable confidence that an appropriate level of clinical benefit and/or cost-effectiveness will be achieved. The new data collection should be designed to show more robustly whether the variable falls within the required range. All stakeholders should agree in advance to the design of the study, and to accept its results.

Time Horizon

For each application, the CED process should have a target date by which the revised decision will be made. The completion time for any new data collection will be determined with this in mind. In view of the pace of technical change in health care, a CED process lasting more than 3 years risks becoming of limited relevance in the face of changing clinical practice. This risk may be greater for
surgical procedures and devices, where continual incremental improvements to the technology take place. Difficulties can arise, for example, if patient recruitment rates in studies are lower than expected. If CED becomes indefinite, without the benefit of new evidence, it is no different from coverage with inadequate evidence. On the other hand, if CED is stopped because the new data are not available in a timely manner, then patients and manufacturers may believe they have legitimate objections. Decision makers must be sure that collection of relevant new data is feasible within a relatively short period before embarking on a CED process.

Finance and Management of Studies
The funding of any further data collection is a potentially contentious issue. Whereas the general expectation is that manufacturers and sponsors of technologies will finance the extra data collection in CED, there are examples of government funding (e.g., MSAC in Australia, Catalan Agency for Health Technology Assessment [CAHTA] in Spain). For surgical procedures, there may be no manufacturer involved, so public sector or health system support may be needed. However, many procedures now use specific equipment that requires the involvement of a manufacturer.

The overall management of studies will generally be best undertaken by, or on behalf of, the decision-making body. A steering group representing all stakeholders may be helpful in maintaining support for the process.

Data Collection and Analysis
This should be undertaken by a body independent of the decision maker and the manufacturer, such as a contract research organization or research institute. If the new data are from an extension of an ongoing clinical trial, then the existing arrangements can be extended. Subject to the normal rules regarding confidentiality of patient data, and issues of commercial confidentiality, the final data set as well as the analysis should be available to all stakeholders on request.

Decision with Further Evidence
The new data should be incorporated into an analysis that the decision maker can use to underpin the Decision with Further Evidence (DFE). How this is done will vary depending on the decision-making system in each country, for example, with regard to the degree of public consultation on the new analysis. Any appeal of the DFE should follow the standard process of that system. It should be acknowledged that, even after additional evidence generation, there will continue to be some degree of uncertainty and it may be that the level of evidence remains suboptimal. In that situation, the decision maker will nonetheless need to be prepared to decide whether to agree coverage (with or without conditions) or withhold coverage. A decision to embark on a further round of CED would only be reached in exceptional circumstances, for example, where there had been significant changes in the decision context from when the time scale and other conditions of the original CED were decided.

OPERATIONALISING A DECISION WITH FURTHER EVIDENCE (DFE)
Following consideration of the additional evidence generated, the outcomes of the DFE may range from no coverage, through restricted coverage, to unconditional coverage of a technology. If the evidence generated is sufficient to overcome all the pre-defined aspects of uncertainty, then it may be appropriate for the technology to be made freely available for use (within the licensed indication). Conversely, if the additional evidence fails to reduce the uncertainty then there may be a rationale for suggesting that use of the technology should stop. However, these outcomes should be regarded as the two ends of a spectrum, and the more likely outcome is that some form of restricted access is indicated, (e.g., use in patient sub-groups). The issues discussed above, relating to the adequacy of the outcomes and the limits on evidence generation are critical to ensuring a resolution can be reached.

The means of ensuring appropriate use of a technology after a DFE will vary depending on the remit of the body involved in establishing the CED process. Where the CED process is managed by a body with direct control of coverage, then disinvestment in a technology is relatively simple. The removal of coverage is usually a sufficient incentive mechanism to contain any further use, at least on a widespread basis. Similarly, removing restrictions on coverage or increasing coverage levels should also allow for expanded uptake.

Where CED is managed by a body that does not directly control healthcare budgets (e.g., National Institute of Clinical Excellence [NICE] in England and Wales), then changing investment may be more challenging. As noted earlier, the removal of health technologies that subsequently prove to provide inadequate benefit compared to existing technologies is more difficult than restricting access to and diffusion of technologies at their launch. Similarly, there may be reluctance to increase use of a technology where patients and clinicians have become accustomed to restrictions based on earlier assumptions of limited effectiveness.

Whatever the source of uncertainty, it will affect confidence in the cost-effectiveness of the technology. As stated above, where technologies prove to be less effective than originally thought, it may be appropriate to reduce the price of the technology to maintain cost-effectiveness. Conversely, where the technology proves to be more effective than initially thought, the manufacturer may also want the freedom to increase price to such a level that the price reflects the value of the benefits (e.g., the cost-effectiveness moves to the limit of any accepted threshold). These processes are, of course, dependent on the agreement of the pricing authorities and manufacturers and may be more applicable to some systems than in others.
DISCUSSION

The previous sections have addressed the main considerations in the design and operation of a decision-making system using CED. It can be seen that the details of implementation are dependent on the specific context in which reimbursement decisions are made in individual healthcare systems. Discussion at the HTAi Policy Forum meeting covered several issues relating to this, for which there is insufficient space in this study for full discussion. The most important of these issues are links with the regulatory approval system and patient involvement in the CED process.

If decisions regarding coverage of technologies are to be made close to launch, the main source of data to inform such decisions will be from the regulatory process. These processes vary in their evidentiary standards for different types of technology, but generally focus on clinical benefits and patient safety issues. Other data relevant to coverage decisions, such as patient quality of life outcomes and healthcare resource use can be collected in trials designed to meet the needs of regulators, and this is increasingly done in the pharmaceutical sector. Use of such data in coverage decisions introduces uncertainty over the relation between behavior (of both clinicians and patients) observed in a controlled clinical trial environment and behavior in a routine care situation. If the 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 these variables without delaying access to treatments with clinical benefits demonstrated in trials. If the uncertainty over the cost-effectiveness results from the lack of strong clinical evidence, then 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 randomized studies were needed, as partial coverage through CED may reduce incentives for patients to take part in such studies. It can be argued that, if the clinical evidence is inadequate, then a product will not be licensed, especially a pharmaceutical. However, the comparators and outcomes used in regulatory studies may not match those required for coverage decisions; what is adequate for licensing may not be sufficient for a reliable coverage decision. Any coverage decision maker contemplating the use of a CED process should fully explore the potential benefits of closer collaboration with regulators in generating the most relevant, reliable, and timely data.

Patients are involved in the use and evaluation of technologies in multiple ways. They are the beneficiaries of successful new treatments; they bear the risk of adverse events (and in some countries the cost of using products); they are the participants in trials to test new products; and they may be part of the coverage decision-making process through membership of committees such as the NICE Appraisal Committee and the Scottish Medicines Consortium. How patients become involved in coverage decision making currently varies between countries, but the whole issue is worthy of further study. Data from patients is a vital part of the analysis to support decisions. For example, the outcome measures used in cost-effectiveness studies increasingly reflect patient and societal preferences. There is no consensus on how far the views of patients should directly influence coverage decisions, especially in CED. For example, patients do not want ineffective treatments, but they might be willing to accept a higher level of risk and uncertainty around the benefits of treatment than clinicians or health system decision makers.

In attempting to cover the whole range of issues pertinent to CED, the discussion at the HTAi Policy Forum inevitably raised more questions than answers. This study is an attempt to capture the flavor of those discussions and to draw attention to the most important factors to be considered before using CED. In so doing, it is hoped that this approach contributes to identifying those specific circumstances in which CED might provide a better way forward than current procedures in securing the most benefit from existing and emerging health technologies.

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The study by Hutton, Trueman, and Henshall provides a thoughtful and helpful set of observations about the potential benefits of linking reimbursement to requirements for further clinical research (coverage with evidence development—CED), as well as the likely challenges and obstacles to implementation. In this commentary, we will expand upon several of the key points made in their study and offer some additional suggestions for moving this policy discussion forward.

CED AS AN EVIDENCE-BASED MEDICINE TOOL

An important motivation for CED, in addition to the desire to make promising technologies rapidly available, is that the traditional hierarchy of evidence-based medicine (EBM), which has been widely adopted in health technology assessment (HTA) and coverage decision making, can impose expensive, lengthy evidence requirements to demonstrate clinical effectiveness. These rules of evidence, while fully defensible from a methodological perspective, may in some cases be inconsistent with the pace at which technologies are developed, modified, and abandoned. For example, a prospective validation of the clinical utility of cancer biomarkers might require years of follow-up, and such studies are unlikely to be affordable or feasible for small venture-backed companies developing these diagnostic tests. This temporal mismatch between the pace of technological evolution and the pace of evidence development creates a potential niche for CED.

In effect, CED can be seen as a means of implementing EBM in a real-world setting. Policy makers are often expected to make coverage decisions based on the “best available” evidence, which can, at times, be inadequate. By having a “yes” or “no” decision as the only options, promising technologies may be rejected or ineffective (or unsafe) ones adopted, depending more on political and other pressures than evidence. This finding can perpetuate the problems of scientific uncertainty, underuse and overuse of services, and failure to resolve uncertainty through further evidence generation.

POSITIONING CED IN A TECHNOLOGY’S LIFE CYCLE

CED might best be viewed as a policy mechanism that can help in those circumstances where generating reliable evidence faces various types of predictable challenges. For emerging and newly approved technologies, the challenge is that the standards of conventional EBM may require substantial additional time and expense to meet, even in circumstances where the initial evidence suggests potentially important advantages over existing technologies. The most efficient approach to evaluating such technologies without undesirable delay, from the patients and health system perspective, may be through CED.

The CED approach may also be useful for existing technologies, in at least two different contexts. First, in the case of those technologies that have been adopted with some enthusiasm, but for which reliable evidence on risks and benefits has never been generated, particularly when evidence begins to accumulate that raises questions about their net health impact. High-dose chemotherapy with bone marrow transplant for metastatic breast cancer is an example of this use of CED. Randomized trials of this technology were conducted through a CED approach as a result of increasing doubts about the benefits and risks of the procedure. Second, certain technologies may be available but underused, because there is limited market incentive to conduct the necessary studies. This may be true for preventive, health maintenance, or public health interventions that have no natural commercial sponsor, and these technologies may also be good candidates for CED. We believe CED can be a powerful tool for reducing uncertainty and better targeting new and established technologies and clinical practices at different stages throughout their life cycle. Restricting it to experimental and new technologies may not be taking full advantage of this policy’s potential.

INFORMATION GENERATED THROUGH CED

The study by Hutton et al. notes that regulatory trials will often provide information limited to intermediate outcomes and with short follow-up periods. There are other important gaps in evidence that commonly remain after the completion of regulatory trials, which might also be addressed by studies supported through CED. Such gaps include information about risks, benefits, and costs in real-world setting (in the hands of typical clinicians as applied to the broad range of patients encountered outside the usual investigational context). Furthermore, questions of comparative effectiveness and value are generally not addressed in regulatory trials, nor are the risks and benefits of combination therapy with existing technologies. CED studies may provide valuable information on risks in large populations, offering substantially more information on product safety, particularly in those circumstances when a safety signal of uncertain significance has been identified. Finally, CED 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.

The study by Hutton et al. seems to assume that CED will generally be used in conjunction with decision making that involves cost-effectiveness models. However, the CED approach may also be applied in decision-making processes that do not formally incorporate costs or formal decision analysis. Judgments about the value of information and the implications of making a coverage decision with insufficient evidence could be made in a qualitative manner.
TIMELY EVIDENCE DEVELOPMENT

The study by Hutton et al. suggests that CED may only be appropriate for studies that can be completed in 3 years or less, and it may be true that this policy approach will have the greatest initial value in those circumstances described in the study (i.e., experimental technologies). However, some of the earliest US experience with CED involved trials of considerably longer duration. The National Emphysema Treatment Trial in the United States was completed with funding from the National Institutes of Health under a CED arrangement with Medicare, and this study took approximately 7 years to complete. Once the results were published showing significant harms and limited benefits for most patients, the procedure was almost completely abandoned, even though the Medicare coverage policy would have allowed coverage for all patients shown to have any functional improvement from lung volume reduction surgery. As mentioned above, the first major US-based CED application was for studies of high-dose chemotherapy and bone marrow transplant in patients with metastatic breast cancer, again requiring a multiyear randomized clinical trial (RCT). This study clearly showed that the procedure was harmful to patients, and the practice, has since, been abandoned. When patient access is not restricted, for example, when quality of life or safety information is collected in the context of a registry or a prospective cohort study of all eligible patients, longer time lines may not necessarily be an obstacle to implementing CED.

DECISION-BASED EVIDENCE MAKING

A critically important effect of CED mentioned in the study by Hutton et al. is that it provides the decision makers—payers, clinicians, and patients—with an opportunity to determine clinical research priorities, and to ensure that trials are designed to answer their questions. Traditional clinical research is often not designed explicitly to inform a decision, which increases the chance that the results will not be helpful in decision making. CED allows payers to use their reimbursement authority to determine what questions are studied, and critical elements of study design, such as the nature of the study population, comparison groups, study setting, outcomes measures, and so on. Such studies are generally referred to as pragmatic research, which has the distinguishing features of being designed to inform a decision. It is contrasted with explanatory research, which is intended to provide a deeper understanding of a condition or treatment, but not necessarily to assist in learning how it would best be managed.

STUDY TYPES UNDER CED

Deciding on appropriate and adequate study methods and designs under CED will be challenging, as the policy is trying to balance rapid access to technology with creation of evidence, and different stakeholders have different views of how this balance should be handled for each technology. Observational methods, perhaps using data from claims or electronic health records, have the appeal of providing broader access more quickly, but are inherently less analytically valid. The Medicare registry of implantable cardioverter-defibrillators (ICD) still contains only baseline data, without any firing data, and, therefore, is only able to look at questions such as whether patients are appropriate ICD candidates, how similar they are to trial patients, and rates of clinical complications that can be assessed by linkage to claims data. Funding has recently been secured to include firing data in this registry, which should allow analysis of patient characteristics that might predict which patients are most in need of the device.

When the uncertainty is around the effectiveness of a technology, an RCT or a pragmatic (practical) clinical trial (PCT) may be the most appropriate design. PCTs in particular, can provide reliable evidence more relevant to real-world effectiveness and may be completed more quickly and cheaply than traditional RCTs. However, these studies can also raise more complex policy and operational issues. Medicare has approved coverage for positron emission tomography scanning in patients with suspected dementia in the context of a pragmatic PCT, but such a study has not yet been initiated after more than 3 years of effort, primarily because a funding source for the research costs has not yet been identified. Furthermore, when an RCT/PCT is required, patient access may be restricted by the payer, depending on the degree of reversibility of wider technology adoption and the feasibility of a trial in such circumstances. However, the deciding factor here should not be accessibility but suitability of a study design to answering the decision makers’ question.

The practical challenge, maybe more marked with the RCT/PCT model, then becomes creating the operational infrastructure to support such studies being designed, approved by research ethics boards, funded, implemented, and analyzed in a more timely and efficient manner than is now true for traditional RCTs. Participation in clinical research has to become a routine, rather than exceptional, management option for patients and clinicians under conditions of uncertainty.

Arriving at the right study question and methodology will require a process and analytic methods with comparable sophistication to the current work of the appraisal committees that make judgments about coverage and guidance. As noted in the study by Hutton et al., this will require effective mechanisms to improve communication about priority setting, methods, and protocol development among experts and stakeholders, including patients, clinicians, payers, product developers, and researchers.

In the United States, the Center for Medical Technology Policy (www.cmtpnet.org) has convened several workgroups that include the full range of experts and stakeholders and is pilot testing a collaborative approach
to developing CED study protocols on selected emerging technologies (cardiac computed tomography angiography, radiation therapy for prostate cancer, and gene expression profiling tests for breast cancer). In Europe, EUnetHTA has a dedicated work stream on the assessment of new emerging technologies with the French partners actively exploring the concept of CED. Furthermore, in the United Kingdom, the recently published Cooksey Review of health research recommended the funding of “only in research” (the CED equivalent) recommendations made by the National Institute for Health and Clinical Excellence by the National Health Service R&D. Such recommendations have already been implemented in the UK context, including the MRC-funded CLASICC trial of laparoscopic surgery for colorectal cancer and the prospective cohort study of photodynamic therapy for age-related macular degeneration.

CRITERIA FOR CED

The stated criteria suggest that CED might best be used for technologies with potential significant improvements in health outcomes, and uncertainty about effectiveness or cost-effectiveness. This is similar to the criteria proposed in the CMS guidance documents of April 2005 and July 2006, which noted that the CED approach would generally be applied to potentially important technologies for which evidence is currently not adequate to determine impact on health outcomes.

Of interest, in a recent meeting, the NICE Citizens’ Council noted the potential of “only in research” as the ‘norm’ for providing new technologies until most uncertainty surrounding their effects is resolved. This strategy may be impractical in the current setting, however, one could imagine CED as being routinely applied to products once they have achieved regulatory approval, and show some evidence of clinical advantages to current technology. Perhaps all such technologies could be subjected to CED, once there was sufficient infrastructure in place to conduct additional studies affordably and efficiently. This highlights that the potential role of CED in coverage policy depends on building the conceptual and operational infrastructure for rapid and efficient practice-based research.

CRITICAL CHALLENGES

CED may in fact provide a mechanism to expedite access to promising technologies, but the conditional limitation to those patients enrolled in a study may impose serious restrictions, depending on the size of the study, how quickly it can be launched, and how soon the study can provide data that will inform a decision. Adequate resources to support high-priority CED studies will be essential so that necessary studies can be designed and implemented without delay. The policy option has no meaningful impact if it takes a year or more to design, identify funding for, and implement the study. Therefore, there would ideally be a funding pool maintained to support these studies, as suggested by Cooksey in the United Kingdom and in recent legislative proposals in the United States to provide funding for comparative effectiveness research. Rules to determine the contribution of product developers to clinical and research costs will need to be developed, as it does not seem reasonable that all costs for these studies should be borne by the healthcare system or public and private payers.

The study notes that CED studies should be managed by, or on behalf of, decision-making bodies. It would seem that the details of study design and management involve technical and operational expertise that may not always be sufficiently available within decision-making organizations. Therefore, one could imagine that much of the work of CED studies might be assigned to new or existing research organizations that would work collaboratively with the decision makers.

We strongly agree with Hutton et al. about the value of product developers and decision makers having greater dialogue and consensus on evidence standards for specific types of technologies. The need for CED could be substantially reduced if there were clear guidance documents that articulate the evidence requirements for coverage, and decision analysis can help formulate such rules.

An important implication of the study by Hutton et al. is the need for a concrete plan of action to address some of the critical scientific, policy, methodological, financing, operational infrastructure. We appreciate the excellent work of the HTAi policy forum inframing the critical issues and questions raised by CED. They have provided an extremely valuable framework for continuing discussions on this subject. With that in hand, we believe an important element to successful implementation will be moving quickly from theory to practice by working collaborative with all key stakeholders, including patients and the public, to design and implement CED studies. Launching pilots, ideally with multinational participation, will identify and help address key obstacles to implementing this option in different settings. Such initiatives can then serve as the platform for refining and improving the applicability and acceptability of CED as a viable policy option.

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