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Access with Evidence Development
The US Experience

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Abstract

The concept of access with evidence development (AED), also known as 'coverage with evidence development' in the Medicare programme, has long been discussed as a policy option for ensuring more appropriate use of new technologies in the US. This article provides a comprehensive overview of more than 10 years of US experience with AED, both in the public and private healthcare sectors. Beginning with a discussion of the successes of private plans' conditional coverage for high-density chemotherapy for autologous bone marrow transplants for metastatic breast cancer and Medicare's conditional coverage of lung-volume-reduction surgery in the 1990s, the article moves on to describe how Medicare worked to codify AED as one of its coverage policy options in the early part of this decade. More recent private and public sector initiatives are also discussed, including an overview of barriers to implementing AED. Despite the complexity of political, financial and ethical issues faced in implementation, AED is now a permanent fixture of US coverage policy. Future initiatives within the Medicare programme and with private payers in the US are much more likely to succeed by relying upon the simple but consequential principles laid out at a Summit convened in Banff, Alberta, Canada in 2009 and presented in another article in this issue.

The concept of 'access with evidence development' (AED) – previously called conditional coverage – has long been discussed as a policy option for ensuring more appropriate use of new technologies. Health plans in the US have more than a decade of experience in such schemes, although there are just a score of examples, largely because of the complexity of political, financial and ethical issues faced in implementation.

AED is a way to reconcile the tension between strict evidence-based standards and being responsive to rapid innovation of emerging technologies. AED provides health plans with a more proactive policy option than the traditional coverage/non-coverage dichotomy. This mechanism enables health plans to keep pace with rapidly developing medical innovation, while generating valid evidence on the relative benefits and risks of the emerging treatments. Patients gain early access to new technologies under the controlled setting of an organized research study, while the plans ensure that the research is designed to address their questions.[1]

While there have been other articles summarizing Medicare's experience with AED,[2] and individual case studies of private experience,[3-7] this article provides a more comprehensive overview of the US experience. It was an outgrowth of a meeting of a special interest group of the professional association Health Technology Assessment International (HTAi) convened in Banff (Alberta, Canada) in 2009 with the aim of sharing

perspectives among colleagues from several different countries involved in implementing AED.

1. A Brief History

1.1 Early Experience

During the 1990s, there were several examples in the US that showed AED could dramatically change practice patterns, improve patient care and provide payers with a positive return on investment. These early case histories were tantalizing to policy makers because of their success, but they also highlighted the challenges that private and public health plans would face if AED was to become part of the fabric of coverage decision making. Although these cases have been widely written about in the literature, the lessons they offer merit repeating and synthesizing.

1.1.1 High-Dose Chemotherapy with Autologous Bone Marrow Transplant for Metastatic Breast Cancer

Health plans at the early part of this decade faced tremendous legal pressure to cover high-dose chemotherapy with autologous bone marrow transplant (HDC-ABMT) – a surgical procedure where bone marrow is extracted prior to a patient undergoing high doses of chemotherapy and is then replaced after treatment to restore a patient's ability to fight infections. Despite a paucity of evidence that the procedure worked, plans ceded to the pressure and covered it for several terminal cancers. When an evidence review solicited by the Blue Cross Blue Shield Technology Evaluation Center (BCBS TEC) suggested that the potential harm of HDC-ABMT might outweigh its benefits for use in metastatic breast cancer,[8] BCBS plans representing employees enrolled in the Federal Employees Health Benefits Program (FEHBP), the National Cancer Institute (NCI) and the Bone Marrow Transplant groups embarked on a collaborative demonstration project evaluating its effectiveness relative to standard chemotherapy. The metastatic breast cancer study was part of a package of AED studies (including studies of epithelial ovarian carcinoma and multiple myeloma) supported by BCBS plans. All of these conditions had NCI randomized controlled trials (RCTs) underway that were available for enrolment. Initially, coverage was provided only to beneficiaries who agreed to participate in these trials. At the time, there were about 4 million federal employees in the plans administered by BCBS.[5]

The public reaction against health plans participating in these trials was swift and powerful, with charges that health plans were using the trials as means of avoiding paying for beneficial treatment because of its high costs.[9] In the mid 1990s, under political pressure from Congress, the Office of Personnel Management mandated that FEHBP plans could not require coverage in the context of clinical trials. In other words, patients could seek and obtain coverage without being randomized for HDC for any of these three diseases.[5] This undermined AED and reduced rates of participation in the clinical trials. Despite slowed enrolment, the trials for metastatic breast cancer eventually showed that HDC-ABMT increased the risk for death.[10-12] As a result, many BCBS plans made a decision to no longer cover it for that condition. The case of HDC-ABMT for metastatic breast cancer is a classic tale of the dangers of premature coverage. During that decade, more than 20 000 patients with breast cancer were treated with HDC-ABMT at a cost of about $US2 billion, resulting in an estimated 600 premature deaths.[5] Without these collaborative trials, HDC-ABMT for metastatic breast cancer would likely have become standard of care.

1.1.2 NETT

Another AED success story in the US was the NETT (National Emphysema Treatment Trial). This was a collaboration among the Centers for Medicare and Medicaid Services (CMS), the National Heart, Lung, and Blood Institute (NHLBI) and the Agency for Health Care Research and Quality (AHRQ) to fund an RCT comparing lung-volume-reduction surgery (LVRS) to standard medical therapy for patients with severe emphysema. Early favourable reports from uncontrolled case series for LVRS led to its rapid adoption, and the procedure was reimbursed

under previously existing billing codes.[6] After CMS noted a large increase in these procedures and a review of the medical evidence showed a potentially high associated mortality rate, CMS agreed to pay for treatment only in the context of enrolment in a trial to gather further evidence on the safety and efficacy of LVRS. On the basis of this trial, a high-risk subgroup was identified where quality of life could potentially improve, but no overall survival benefit was found. Although Medicare agreed to cover the procedure for a wider population than the high-risk subgroup, rates of use dropped sharply. During the 2-year period after the study findings were published in 2003[13] approximately 500 surgeries were billed to Medicare in contrast to the 3000 surgeries billed per year immediately prior to the trial.[2] As a result of these changed practice patterns, net Medicare spending was reduced by an estimated $US125 million annually.[2]

For both examples, supported trials were lengthy and costly. For example, the NETT trial took 8 years to complete and cost an estimated $US135 million.[3] Once evidence became available from the ABMT trials,[10-12] advocates discounted the results as not reflective of current practice.[14] In the face of rapidly evolving medical technology, the timeliness of these studies to ensure continued political support is crucial. A major lesson from these early years was that future AED endeavours would need to consider ways to gather evidence in a less costly and more rapid fashion.[2]

1.1.3 Coverage for 'Promising Therapies'

Many managed care plans adopted policies in the latter part of the decade to pay for usual care costs for 'promising' investigational or experimental therapies used for cancer or other terminal illnesses if the patient was enrolled in a clinical trial.[15] Some of these policies look and feel very similar to AED. This coverage category of 'promising' therapies has been in place at Aetna plans since 1991,[9] enabling them to cover investigational technologies with a high probability of substantially improving patient outcomes. Under these policies, the plan will pay for the cost of experimental care, but there is no requirement for enrolment in a specific trial (R. McDonough, personal communication). Consequently, Aetna has little control over the design of the trials. A collaborative agreement between the Coalition of National Cancer Cooperative Groups and United HealthCare Group established in the late 1990s allows United HealthCare plans to support patient care costs for patients enrolled in designated Cancer Cooperative Group Clinical Trials (most of which are NIH sponsored) within the United HealthCare network.[15] United HealthCare has developed criteria for qualifying trials and review of data from these trials feeds into final coverage determinations.

1.2 Medicare's Coverage with Evidence Development

In the following decade, Medicare was becoming increasingly frustrated that systematic reviews constantly turned up poor-quality studies or those that did not meet their needs for coverage determination. In particular, the elderly and disabled, who constitute the patients covered by the Medicare programme, were often underrepresented in clinical trials. In addition, most trials failed to compare treatments with currently covered alternatives, and the outcomes reported in trials were typically short-term, physiological outcomes that were of limited importance to patients or their clinicians. In response to the need to generate more relevant evidence for coverage decisions, as well as for other health policy decisions, CMS concluded that it would need to actively use its payment authority to promote the development of evidence that was adapted to meet its needs.[2]

Since the NETT, CMS has supported ten initiatives that required participation in approved studies as a condition of payment (table I). As the use of what the Medicare programme calls CED became more visible, particularly when applied to Medicare coverage of implantable cardioverter-defibrillators, more attention was focused on the legal authority that had been offered as its foundation. The NETT had implemented CED under the Social Security Act (Medicare's original statutory coverage authority), which allows

Table I. Medicare initiatives using coverage with evidence development (CED)

Topic	Study type	Start year	Authority[a]	Mandatory participation for coverage
Lung-volume-reduction	RCT	1995	42 USC 1395y(A)(1)(a) 'Reasonable and necessary'	Yes
Carotid stenting vs carotid endarterectomy	RCT	2001	Category B Investigational Device Exemption (42 CFR 405.211)	Yes
Frequent haemodialysis	RCT	2002	42 USC 1395b-1 'Demonstration authority'	Yes
FDG-PET for suspected dementia[b]	RCT	2005	42 USC 1395y(A)(1)(a) 'Reasonable and necessary'	Yes
Implantable cardiac defibrillators[b]	Registry	2005	42 USC 1395y(A)(1)(a) 'Reasonable and necessary'	Yes
PET for cancer[b]	Registry	2005	42 USC 1395y(A)(1)(a) 'Reasonable and necessary'	No
Off-label uses of colorectal cancer drugs[b]	RCT	2005	42 USC 1395y(A)(1)(a) 'Reasonable and necessary'	No
Cochlear implantation[b]	RCT	2005	42 USC 1395y(A)(1)(a) 'Reasonable and necessary'	Yes
Long-term oxygen therapy trials[b]	RCT	2006	42 USC 1395y(A)(1)(a) 'Reasonable and necessary', 42 USC 1395y(a)(1)(E) and 42 USC 1320b-12 'AHRQ Research Authority'	Yes
Artificial heart	RCT	2008	Category B Investigational Device Exemption (42 CFR 405.211)	Yes
Sleep apnoea	Approved clinical study; type not defined	2008	42 USC 1395y(A)(1)(a) 'Reasonable and necessary', 42 USC 1395y(a)(1)(E) and 42 USC 1320b-12 'AHRQ Research Authority'	Yes

a The CFR is a compilation of all regulations issued by the executive branch and its agencies. The USC is a compilation of all Federal laws. The Social Security Act was passed in 1935, but demonstration authority was allowed under a provision known as the Social Security Act Amendments of 1967, which authorized the Medicare programme to conduct demonstration programmes.

b Listed as a formal CED coverage policy at the Medicare website.[16]

AHRQ = Agency for Healthcare Research and Quality; **CFR** = Code of Federal Regulations; **FDG** = fluoro-2-deoxyglucose; **PET** = positron emission tomography; **RCT** = randomized controlled trial; **USC** = US code.

Medicare to pay for services considered to be 'reasonable and necessary' for the diagnosis and treatment of illness or injury.[17] Because that legislative language had never before been used as a basis for limiting coverage to services provided in clinical trials, there was pressure for the agency to be more explicit about when it had the authority to require additional research as a condition of coverage, and why the application of CED was now considered to fit within the legal framework of 'reasonable and necessary' services.

One relevant precedent was a 1995 Interagency Agreement between the US FDA and CMS, which established a mechanism for Medicare coverage of devices under clinical investigation if they were refinements over already covered predicate devices (Category B devices receiving an Investigational Device Exemption [IDE]). Under this agreement, selected investigational devices may be eligible for Medicare coverage, but coverage is not required. CMS saw this agreement as a way to ensure the covered trials met their evidentiary requirements for 'reasonable and necessary'. In a decision memo for one IDE-qualifying device – balloon angioplasty used to treat patients with carotid artery disease at high risk for stroke – CMS required beneficiaries be enrolled in an ongoing NIH clinical trial to be eligible for payment.[2] The decision memo also laid out the agency's preliminary thinking about when a technology would warrant CED. A limitation of this agreement was that it applied only to a select category of devices, and did not encompass the wide range of emerging technologies that might warrant this approach to reimbursement.

CMS also explored its demonstration authority as a basis for imposing conditions for additional data collection. Since 1967, CMS has had the authority to conduct demonstration projects to determine whether changes in payment, service coverage, or delivery systems could provide ''incentives for economy while maintaining or improving quality in the health care system.''[18] Payments for demonstration projects are generally derived from the Medicare trust fund. As such, the Office of Management and Budget (OMB), which scrutinizes how trust fund dollars are spent, usually requires such programmes to be 'budget neutral'. Under a 2002 agreement between CMS and the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK), Medicare would pay for the additional costs associated with more frequent haemodialysis, as long as a patient was enrolled in an NIDDK-sponsored trial. The aim of these trials was to evaluate the impact of daily versus thrice-weekly haemodialysis on patient well-being and the cost of delivering therapy. As these trials required changing Medicare *payments* for an already approved procedure, and increased payments were expected to be offset by reduced hospitalizations (thus fitting OMB requirements), it could be considered to be a demonstration, but it was also clear that the restrictions tied to this authority meant it was not the best vehicle for CED. Payments under this CMS/NIDDK agreement were not linked to coverage determinations. Demonstration authority was also considered as a basis to support the development of the positron emission tomography (PET) registry for oncology, but was denied because that policy did not focus on the frequency or payment level for the technology.

After a cluster of pilot CED projects were issued in 2005, again citing Medicare's coverage authority, the pressure from industry to clarify the circumstances under which CED could be recommended and the basis for Medicare's legal authority to conduct CED grew more intense. In July 2006, CMS issued a guidance document on CED.[19] The guidance document described a statutory provision of the Social Security Act §1862(a)(1)(E)[20] that is tied to §1142[21] (authority for AHRQ), which allows CMS to work jointly with AHRQ to gather data to evaluate the medical evidence and pay for the clinical costs of research when the evidence does not meet the agency's criteria for 'reasonable and necessary'. The guidance document further distinguished cases when the evidence was considered inadequate for making a coverage determination and further data collection was required (Coverage under Study Protocol) from cases where a technology met the criteria for 'reasonable and necessary', but there were outstanding questions about its safety and efficacy for its use in broader populations or clinical settings, or there were continuing concerns about whether its introduction would significantly change the way patients were managed (Coverage with Appropriateness Determinations). CMS further codified the use of CED by amending its clinical trials policy in 2007 to explicitly allow for this option.[22]

As noted in table I, not all CED initiatives in Medicare have required participation as a condition of coverage and approved studies have used both observational study designs and RCTs. The case history and lessons learned from these early pilots have been well documented elsewhere,[2] but in general, the Medicare approach to date has been *ad hoc*. Without formal arrangements among industry, the clinical research community and patient organizations for pursuing this research in a timely manner, it has been hard to finance CED efforts, and the rigour of the supporting study designs has also suffered. Although CED has only been used twice since the CED guidance policy was issued, the importance of Medicare's experimentation in the early part of this decade is that the precedent for formal use of CED within CMS coverage policy has been established. However, Medicare's use of CED continues to be limited by the lack of specific statutory language providing Medicare with the explicit authority to limit coverage of certain technologies to patients who are enrolled in clinical studies. That situation is likely to continue to limit Medicare's ability to implement the policy effectively. While this may remain unresolved in the near term, it is still possible to focus on how to refine the CED process under existing authorities.

2. New Developments

As the Medicare programme paved the way for legitimizing CED as a coverage policy option, interest in this option has continued to grow in other sectors. Recently, the BCBSA TEC began an investigation into the contractual and legal framework to support AED, an option that they call the 'Third Path', and are seeking to strengthen their partnerships with organizations such as the NIH and the Veterans Administration to facilitate a pathway for evidence generation for a highly select group of investigational technologies.[23] Washington state has used AED to support coverage decisions for its worker's compensation programme. The Washington State Department of Labor and Industries funded an AED study on spinal cord stimulation for chronic back and leg pain, agreeing to pay for the treatment for injured workers only for those who participated in the study.[24] Based on results from this 3.5-year prospective observational study,[25] the Industrial Insurance Medical Advisory Committee recommended the Department of Labor and Industries maintain its existing non-coverage policy for spinal cord stimulators. Findings will also be reviewed by the State of Washington Health Technology Assessment committee in the near future to make coverage recommendations regarding other state insurance programmes, including their Medicaid programme (J. Turner, personal communication).

There is widespread interest in AED as an option for generating better evidence on genetic tests. AED has been recommended for the development of biomarkers by the Institute of Medicine (IOM),[26] the Secretary's Advisory Committee for Genetics in Health and Society (SACGHS),[27] and committee members of the Evaluation of Genomic Applications in Practice and Policy (eGAPP) Working Group.[28] In 2007, United HealthCare entered into a performance-based risk-sharing scheme (a variant of AED) with the manufacturer of Oncotype Dx, a genetic test used to determine whether women with early-stage breast cancer would benefit from chemotherapy.[29] Under this agreement, temporary coverage was provided while data were collected about the effects of the testing on changing practice patterns. United HealthCare reserved the right to lower the price paid for the test if substantial numbers of women for whom the test showed no benefit still received chemotherapy. Medicare's continued support for AED is evidenced by a recent proposed coverage determination for pharmacogenetic testing for warfarin response, calling for the use of AED to gather better evidence on the effects of the test on hard patient outcomes, such as myocardial infarction and death.[30] The authors are also aware of another pilot AED project being conducted by United HealthCare. In this project, United is collaborating with General Electric to study the benefits of magnetic resonance guided focused ultrasound for the treatment of uterine fibroids. The details of this pilot have not yet been publicly released.

Despite these recent experiments, AED is still rarely used in the US. In a California Health Care Foundation (CHCF)-funded project, the Center for Medical Technology Policy (CMTP), where both authors work, interviewed a wide range of stakeholders to better understand the perceived barriers to implementing AED and to develop a policy framework for facilitating its use among private health plans.[1] Some of the concerns voiced by stakeholders are listed below.

- *Changing the threshold for coverage*. Stakeholders have differing views about the direction of change for the evidentiary threshold for coverage that would result from AED. Members of health plans express concern that AED could lower the evidentiary threshold for coverage without ever producing the robust information needed to make a coverage determination. By contrast, representatives from industry express concern that by involving health plans in the study design, evidentiary standards may be raised, and may thereby slow innovation and increase their costs of product development.
- *Increase patient care costs*. Consistent with the concern that AED lowers the evidentiary threshold, payers are often skeptical that AED will reduce costs in the long run.

- *Conflict of interest*. Patients and consumers may distrust the motives of payers in their efforts to support evidence development through coverage, and may assume that the primary objective is cost containment, and not a genuine effort to support early access to innovations and clinical research.
- *Coercion/therapeutic misconception issues*. As with any clinical trial, patients may choose to participate because they see the research study as a way to attain healthcare that they would otherwise not get. There has been a healthy discussion of whether or not this is coercion.[31]
- *Data security/patient confidentiality issues*. Members may be skeptical of health plans' motives for additional data collection, particularly if the AED study involves genetic testing, given that despite legislation to the contrary, patients are usually afraid of genetic discrimination by health plans.
- *Anti-trust laws*. As AED studies may require large populations in order to recruit adequate numbers of participants, more than one health plan may need to participate. Active collaboration in a research study among health plans could be perceived as a violation of anti-trust laws unless great care is taken to avoid discussion of topics such as provider reimbursement.
- *Use of patient premiums to support research costs*. Patients may resist the notion of using some of their healthcare premiums to support research, if that is the mechanism by which research is funded.
- *Investment in expensive, lengthy trials*. If health plan funds cannot be used to support research, this raises the question of where funding will come from to support these complex trials.

To address some of these risks, CMTP's framework for AED recommends that a number of protections should be put in place:

- Health plans need to ensure that technologies subject to AED are selected in a transparent manner using clearly defined, pre-specified criteria.
- Rigorous study designs need to be developed and patient protection measures need to be put in place, including a robust informed consent process.
- Health plans supporting the same study need to maintain their own reimbursement policies for study technologies and use their own policy language to support AED in order to operate within the formal constraints and spirit of anti-trust legislation.
- Health plans need to develop good policy and programme or contractual language to support AED. CMTP has identified three options for this language, including adding language to the experimental and investigational exclusion, allowing for AED as extra-contractual payments (such as a demonstration programme), or writing AED into policy as a supplement to clinical trial language.
- An independent third party could be used to act as the coordinating entity for AED, building a firewall between a research coordinating centre collecting the data and AED sponsors to ensure patient privacy.
- Health plans may decide to support patient care costs, but research funding would need to be obtained from product developers or public research grants. A public/private partnership is most likely essential to support this research.

CMTP is testing this framework in a CHCF-funded project, which has produced formal criteria to select topics for AED,[32] and identified three potential high-priority topics in the area of cardiology for consideration by a multi-stakeholder working group. These are (i) genetic testing for warfarin dosing, (ii) catheter-based ablation for treatment of atrial fibrillation and (iii) percutaneous aortic valve replacement. As noted above, CMS has recommended AED for genetic testing for warfarin dosing and the Scottish Health Authority[33] and a hospital health technology assessment unit in London, Ontario, Canada (J. Martin, personal communication) are pursuing an AED project in aortic valve replacement, confirming that these topics may be compelling enough to warrant AED. The multi-stakeholder working group recently selected genetic testing for warfarin dosing for the AED pilot, with the hope that CMS and private health

plans could align their efforts to obtain better evidence about this technology. Seven private health plans are participating. One goal of the pilot is to work through the details of this framework with each of the participating plans. The lessons learned will be widely disseminated to aid other private plans interested in participating in AED.

3. The Banff Summit: Opportunities and Challenges

Although the history of AED has been uneven, and the challenges substantial, AED has become a credible policy option for both public and private health plans in the US. An affirmation of AED was recently issued in conjunction with the release of a Medicare National Coverage Determination for PET. According to Charlene Frizzera, Acting Administrator of CMS, ''This expansion in coverage for PET scans shows that the CED program is a success. CED allowed us to cover an emerging technology, learn more about its usage in clinical practice, and adjust our coverage policies accordingly. Thanks to CED, Medicare beneficiaries have greater access to cutting edge medical technologies and treatments.''[34] With the increased funding available for comparative-effectiveness research, health plans face a window of opportunity over the next few years to develop collaborations to produce evidence that will meet their needs.

The recent summit of policy makers and researchers from several countries held in Banff further reinforced the broad enthusiasm for AED as a policy tool. One striking aspect of each of the presentations at this meeting was the consistency and familiarity of many of the challenges encountered – most experiences with AED in many different settings had independently encountered a very similar set of motivations, challenges and implementation mistakes. One of the key recurring themes for many of these initiatives was that the evidence development part of AED rarely worked well when the policy was applied simply as a means of avoiding or delaying a difficult decision. From this shared experience, it became clear that one critical success factor for AED was the need to clearly define the decision problem prompting consideration of AED, articulating a study objective that was directly targeted to the decision problem, and ensuring that the AED study was designed in a way that could feasibly address that objective. All of the Medicare experience with CED to date, both positive and negative, can be predicted entirely by the degree to which these conditions were met. Future initiatives within the Medicare programme and with private payers in the US are much more likely to succeed by relying upon these simple but consequential principles.[35]

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