

The Association of Health Care Journalists  
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Panel Discussion: Medical effectiveness: Is there a NICE in U.S. future?  
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## **Historical Background of the U.S. Efforts to Deal with Clinical Effectiveness, Comparative Effectiveness, and the Politics Surrounding Those Efforts**

### **BACKGROUND**

**Definitions:** Comparative effectiveness research compares clinical outcomes, or the “clinical effectiveness,” of alternative therapies for the same condition. Technology assessments encompass studies of the safety, efficacy, effectiveness, cost-effectiveness, and the social and ethical implications of technologies.

#### **Brief Review of Current Major Public Healthcare Technology Assessment (HTA) Activities:**

*The Food and Drug Administration (FDA)* predecessor started in the Department of Agriculture in 1862 and remained there until June 1940. Subsequently, as FDA, it moved to the Department of Health, Education, and Welfare (HEW), now called the Department of Health and Human Services; FDA focuses on the safety and efficacy of medical products.

*The National Institutes of Health (NIH)* traces its roots back to the Marine Hospital Service (MHS) in 1862. It has grown from just over \$4 million in 1947 to more than \$29 billion today. Of particular HTA importance, NIH holds Consensus Development Conferences (CDC) for investigators and physicians to appraise new modes of therapy or evaluate existing therapies. Since 1977, NIH has produced more than 100 CDC statements that have rapidly dispersed research findings to practicing physicians regarding devices, drugs, and medical or surgical procedures.

With the introduction of the Medicare and Medicaid programs (1965), the Social Security Administration began to look at items and services for which these programs paid. In 1977, the Health Care Financing Administration, now called the *Centers for Medicare & Medicaid Services (CMS)*, was established to administer Medicare and Medicaid programs. In 1999, CMS opened to the public its internal procedures (HTA process) for developing national coverage determinations.

With enactment of Medicare and Medicaid, the PHS also established the *Office of Health Practice Assessment* in 1965. It performed HTA to aid Medicare coverage decisions and was replaced by NCHCT in 1978.

*The Agency for Healthcare Research and Quality (AHRQ)* started out as the National Center for Health Services Research and Development, Health Services and Mental Health Administration (1968-73). It conducts and supports research, demonstration projects, evaluations, development of guidelines, and dissemination of information on health care services and delivery systems.

The Medical Technology and Practice Patterns Institute is an independent non-profit institute whose mission is to provide research services related to safety, clinical effectiveness, patient outcome, cost, and cost effectiveness of new and emerging medical technologies. MTPPI has not received public or private funding for work related to this analysis.

## Discontinued HTA Programs

***The Office of Technology Assessment (OTA, 1972-1995)*** was the key resource for Congress when confronting technological issues in crafting public policy. It brought a healthy balance to the analytical resources available to the executive and legislative branches of government.

Politics Surrounding OTA's Demise - "Aside from budgetary considerations, other reasons to abolish OTA that were alleged during the congressional debate were that it was duplicative of existing or potential private sector work, that it had contradicted or might contradict important views of congressional leaders, for example, its negative assessment of the "star wars" program, that it tended to governmental and regulatory, rather than private sector, solutions to problems, and in general was a captive of the Democrats." (Herdman R, Jensen J. *The OTA Story: The Agency Perspective*. 1997. *Technol Forecast. Social Change* 54(2 and 3):131-44).

***The National Center for Health Care Technology (NCHCT, 1979-82)***, whose charge was to assess the usefulness of established and new medical technologies. The center fulfilled two main functions:

1. *Multifaceted assessments* of technologies (e.g., safety, efficacy, effectiveness, and cost effectiveness, social, ethical and economic impacts), and
2. *Scientific and medical evaluations* for use in making Medicare coverage decisions (i.e., determining whether specific procedures are "reasonable and necessary" and, thus, appropriate for reimbursement by Medicare).

***Importance:*** Multifaceted assessments comprised a series of questions that best examine the major impacts that a specific technology might have on the health care system, including impact on alternative technologies; this was the first organized attempt to formalize comparative effectiveness research. Such analysis could address the possibility of expanding, limiting, or eliminating a service or specific application of a service under review.

Scientific and medical evaluations were viewed as gate-keeping functions, because they were a necessary step to gain access to the market place.

Politics Surrounding NCHCT's Demise - The principal opponents of the NCHCT's continuation — namely the Health Industry Manufacturers Association (now the Advanced Medical Technology Association) and the American Medical Association - took issue with NCHCT's *multifaceted assessment authority*. They argued that (1) physicians conduct their own technology assessments, so the NCHCT was redundant; (2) the NCHCT was a cost-control scheme in disguise; and (3) the NCHCT served as a health care industry regulator without codification of rules for decision making, a powerful charge in light of the anti-regulatory sentiments that swept into Washington in the early 1980s. When the Reagan administration eliminated the NCHCT by zeroing its budget for fiscal year 1982, its scientific and medical evaluation functions were transferred to the Office of Health Technology Assessment (OHTA) within AHRQ.

## **Challenges In Conducting Healthcare Technology Assessment**

Once a new medical technology is approved, there is tremendous pressure from investors to expand the market size (sales), both within the approved indication(s) and elsewhere (off-label applications). The HTA analysts find themselves under immense pressure to approve a wide diffusion of new technologies. The following is a short list of the main challenges they face in limiting technologies to those that are, in fact, both efficacious and cost-effective.

Experts agree that there is a dearth of data and studies, making assessment of healthcare technologies a difficult task. “[I]n...almost 80% of the [126] assessments conducted at NIH [between 1981-87], the reviewers had to rely on expert opinion because no controlled research evidence was available for their assessment. Also, because OHTA adopted NIH conclusions in 93% of the cases, it appears that a significant proportion of coverage decisions at the national level relies on expert opinion rather than on scientific evidence.” (Dubinsky et.al. Analysis of the National Institutes of Health Medicare coverage assessment. *Int J Technol Assess Health Care*. 1990;6(3):480-8).

NCHCT’s medical technology evaluation functions were based on FDA approval, NIH recommendations, published literature of early limited application, and professional opinion. In many cases, FDA approval hinged on whether use of the product could achieve a surrogate endpoint target (i.e., a lab value or other intermediate measure); the presumption was that the surrogate endpoint target was related to improvement in a clinical endpoint (improved survival, less cardiovascular events, etc.). Other than these requisite FDA clinical trials, there was a severe shortage of studies to demonstrate real-world clinical effectiveness, a deficiency that compromised the ability of professional groups to comment on the usefulness of a product or procedure.

*Expanded and off-label indications* - Technologies that were covered by Medicare only for a limited use, quickly were applied by care-givers to the treatment of patients with complications/comorbidities, patients who had been excluded from the requisite FDA clinical trials; for these patients, the benefits of the new technologies were unknown. Application of these technologies also moved to other indications (off-label use), again without the support of valid scientific evidence. Citing the findings of a RAND study, the Congressional Budget Office said recently, “Overuse occurs when a service is provided even though its risk of harm exceeds its likely benefit — that is, when it is not warranted on medical grounds....”

## **Practical Problems of Comparing Treatments**

Richard Smith, editor of the *British Medical Journal* points out that "only about 15% of medical interventions are supported by solid scientific evidence...85% are not." (*BMJ* Vol 303 Oct 1991) As long ago as 1985, the Institute of Medicine (IOM) report on *Assessing Medical Technologies* raised similar concerns, “Two factors make it intrinsically difficult to compare different treatments. First, the subjects receiving the treatments usually are different people, so difference found between the treatments could be due to differences among the subjects in the groups. If the groups differ in any systematic way (whether recognized or not), the treatment comparison may be biased; bias can exaggerate, nullify or reverse true differences. Second, even if the treatments could be compared in the same patients (as sometimes happens), the contrast between the treatments will vary from one patient to another, producing uncertainty in the overall assessment. This is the problem of variability. Large samples can reduce the disturbance of variability but does not help with bias.”

**Table 1: Parallels Between What Happened 30 Years Ago and the Current Situation**

THEN	NOW
<b>seminal event:</b> Medical Technology: The Culprit Behind Health Care Costs? Proceedings of the 1977 Sun Valley Forum on National Health led to the creation of NCHCT	<b>seminal event:</b> American Recovery and Reinvestment Act of 2009...comparative effectiveness of health care treatments and strategies...that compare the clinical outcomes...
<b>1977 U.S. population:</b> 220,239 M, life expectancy (years) at birth: WM = 70 WF = 77 BM = 64 BF = 72	<b>2004 U.S. population:</b> 294,088 M, Life expectancy (years) at birth: WM = 75 WF = 81 BM = 69 BF = 76
<b>use:</b> Explosion of medical device technology applications (~30% of healthcare costs <sup>1</sup> )	<b>use:</b> Internet (info explosion), Biotechnology + Outpatient Technology Increase
<b>evidence to support use:</b> 15% of medical interventions are supported by solid scientific evidence (an educated guess) <sup>2</sup>	<b>evidence to support use:</b> 15% of medical interventions are supported by solid scientific evidence (a guess), <b>but now it is possible to determine “real-world” clinical effectiveness</b>
<b>payment:</b> Medicare payment based on fee-for-service	<b>payment:</b> Medicare prospective payment (hospital DRG, etc.) and fee-for-service
<b>1977 healthcare cost:</b> ~8% of GDP <b>uninsured:</b> 27,089 M (12.3%)	<b>2007 health care cost:</b> 16.3% of GDP <b>uninsured:</b> 45,657 M (~15.5%)
<b>1977 Unemployment rate:</b> 6.4%	<b>2009 (March) Unemployment rate:</b> 8.5%

### A Case Study Of Today’s Challenge

**Importance:** Treatment of chronic conditions accounts for ~80% of health care costs (~\$2.3 trillion/yr). Chronic anemia is a common condition among end-stage renal disease (ESRD) patients; the Medicare ESRD program serves as a microcosm of what universal healthcare could be.

We use epoetin (EPOGEN) treatment of chronic anemia, a common complication of chronic kidney disease and end-stage renal disease (ESRD), as a case study to exemplify (1) attempts to expand the market size of a drug, (2) studies necessary to assess market expansion, and (3) the translation of scientific evidence into policy formation. Documentation of epoetin therapy is unique because Medicare requires providers to submit monthly epoetin dosages and hematocrits for payment of this service. Medicare’s epoetin reimbursement policy also created a perverse financial incentive to overuse this drug. These two phenomena make epoetin an excellent subject for a comparative effectiveness demonstration study that could be replicated.

<sup>1</sup>Medical Technology: The Culprit Behind Health Care Costs? Proceedings of the 1977 Sun Valley Forum

<sup>2</sup>Richard Smith Editor, British Medical Journal (Vol 303 Oct 1991)

Epoetin was introduced in 1989 to reduce the need for infusion of blood units for treatment of anemia among ESRD patients. Prior to availability of epoetin, blood units were frequently administered to approximately 10% of the ESRD patients (another 6% received an occasional blood unit for mild anemia). The remaining 84% of patients did not receive blood unit infusion for treatment of anemia. By 2005, however, 99% of in-center hemodialysis patients received epoetin treatment. How did this therapy diffuse to near-universal use among the dialysis population? Was this diffusion supported by sound scientific evidence (see Tables 2A & 2B below)? How can it be that a comprehensive technology assessment still has not been conducted more than two decades after epoetin has been widely marketed?

Epoetin dosing levels have changed dramatically since the substance's introduction into the U.S. market. The mean dose of epoetin has increased about fourfold in dialysis patients, and Medicare expenditures for epoetin rose to ~\$2 billion in 2004, constituting 11% of all Medicare ESRD costs. Unfortunately, other than studies documenting usefulness for a small group of patients who would otherwise be dependent on infusion of blood units, there are no other clinical trials to guide policymakers on how to cover and/or reimburse this costly treatment. Despite this deficiency of valid scientific evidence, Medicare has consistently covered/reimbursed for the expanded use of epoetin, at a cost to the Medicare program of over \$20 billion to date.

In an attempt to both increase sales for approved indications and to expand epoetin use to other indications, proponents commissioned clinical trials and highly flawed observational studies which ended with conflicting results that raised more concerns. Justification for this prodigious drug expenditure continues to rest on the presumption that a positive change in the surrogate endpoint (in this case, hematocrit) is related to an improvement in a clinical endpoint (improved survival, quality of life, etc.), despite the fact that this presumption has been disproved by clinical trials and disallowed by the FDA.

MTPPI epoetin studies address the translation of epoetin research into practice (over 99% of dialysis patients today receive this drug continuously) and the role of government in requiring and applying scientific evidence for policy formation. The two existing clinical trials (Besarab, 1998, and Singh, 2006) were terminated due to higher mortality rates in the higher target hematocrit treatment arms. Unfortunately, there are no other clinical trials to guide policymakers on how to pay for this costly treatment. Our contention is that Medicare policymakers should base their decisions about future payment for these and other services on a reasonable demonstration of "real-world" clinical effectiveness (see Table 2B).

## **Conclusion**

Rapid diffusion of costly health care technologies with undocumented benefits is endemic to the soaring costs of the U.S. health care system. Our case study is unique because epoetin dose and physiological response (hematocrit) data are readily available to assess, on a continuous basis, the benefits and risks of chronic anemia epoetin treatment. This case study is offered as an example of the advantage of expanding information required on Medicare claims in order to obtain vital data with which to assess treatment risks and benefits. It also serves as a cautionary tale of the pitfalls — both fiscally and in terms of patient safety — of not conducting comprehensive technology assessments.

**Table 2A: Case Study Summary - Current status of what is known**

1 <b>Evaluation:</b> FDA epoetin (EPO, EPOGEN) approval in June 1989, AHRQ assessment August 2001 concluded a lack of data to make definitive recommendations beyond those indications approved by FDA
2 <b>Market Size:</b> Prior to EPO, a small group (~10% ) of anemic ESRD patients were treated with red blood cell transfusions (RBCT). EPO elevates hematocrit (Hct) to avoid the need for RBCT, but not much is known about EPO effects on the other 90% of ESRD patients who receive EPO therapy (20 yrs have passed and over \$20 billion in costs paid by Medicare since FDA approved EPO )
3 <b>Treatment Target:</b> EPO's first FDA treatment target hematocrit was 30-33% max 36%, changed in 1994 to 30-36% because of hematocrit variability, CMS eclipses FDA by allowing an upper Hct limit of 39%
4 <b>Clinically Appropriate Target:</b> No study has addressed an appropriate target hematocrit, but clinical trial attempts to expand EPO use resulted in higher mortality among those targeted to higher hematocrits
5 <b>Effect of Policy on EPO Diffusion:</b> Congress imposed a fee-for-dose policy that led to rapid increase in EPO use (well over 300% since 1991) because providers target hematocrit to 36%, aggressively treat EPO hypo-responsive patients and overshoot the target (Fall 2007 - 43% <i>exceed</i> the upper bound of FDA target hematocrit)
6 <b>Lack of Science Supporting Policy:</b> Medicare EPO policies are not based on science and provide perverse financial incentives to overuse EPO, and its policy is heavily weighted to accommodate hematocrit variability - <u>hematocrit variability is no justification</u> for picking an appropriate hematocrit target nor have there been any studies over the last 20 years to determine an appropriate target hematocrit
7 <b>Effect of Financial Incentives on EPO Diffusion:</b> Product discounts/rebates and Medicare payment policy are incentives for EPO overuse - providers use starting doses much higher than FDA's recommendations - over 56% of EPO is consumed by 24% of ESRD patients with EPO hypo-response
8 <b>Risks Related to EPO:</b> Based on recent causal " <i>EPO dose - composite CV<sup>3</sup>-mortality event modeling</i> " preliminary results indicate that higher doses (>40,000/wk) cause increased risk events (25% higher); <b>placing over 20% of ESRD patients at increased CV-mortality risk</b>

**Table 2B: Case Study summary - Opportunity today to make informed changes**

9 <b>Product Labeling:</b> Since there are no studies that address an appropriate target hematocrit, FDA should further restrict epoetin product labeling target hematocrit to 33% $\pm$ 3% (thus achieving 30-36%), and emphasize lower titrated dose levels
10 <b>Impact on Costs:</b> Based on MTPPI causal " <i>EPO dose - hematocrit response modeling</i> " there is approx. 50% EPO overuse (~\$1 billion/yr), therefore, if based on EPO's historical <u>overuse</u> (directed by Congress), bundling EPO into the ESRD composite rate payment will reward providers with a ~\$1 billion/yr <u>windfall</u>

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<sup>3</sup>CV events include: myocardial infarct, stroke, and congestive heart failure