



Optimizing Information Under Coverage With Evidence Development

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Conference Report

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Key Themes

Overview

As manufacturers work to bring new products to market and as payers wrestle with coverage decisions on these new products (as well as for new procedures), both parties desire ways to produce evidence that helps inform these decisions. To date the gold standard for evidence has been randomized controlled trials (RCTs), but RCTs are time consuming, expensive, and impractical in answering all of the questions that exist.

Use of observational data, and in particular prospective registries, has significant value in aiding such decisions, although they be inadequate for making coverage decisions alone. In addition, registries can be used for quality improvement purposes, to detect signals about adverse events, and to identify questions to be answered in future RCTs. The key unresolved questions regarding registries include funding, design, transparency, and methods.

Context

On October 24, 2007, the Health Industry Forum hosted a conference that brought together leading researchers, industry executives, payers, public officials, and health care practitioners to assess practical considerations for Coverage with Evidence Development (CED).

The purpose of the meeting was to begin to assess whether CED can generate sufficient evidence through observational research—in particular through prospective clinical registries—for payers to refine coverage policies. Case studies were presented on: the Medicare ICD Registry; the National Emphysema Treatment Trial (NETT); autologous bone-marrow transplantation (ABMT) for breast cancer; and drug-eluting stents.

Participants evaluated these case studies and discussed: 1) How well can prospective registries support coverage policy? 2) How should registries be designed to provide optimal information? 3) Who should fund their development and ongoing maintenance? Key themes from this event are summarized below; summaries of each case study and discussion follow.

Key Themes

- **Payers face coverage challenges with new medical technologies.**

When new medical treatments are introduced, the evidence supporting their safety, clinical effectiveness, and cost effectiveness is often limited. Clear processes exist for drug and device manufacturers to establish the safety and efficacy of their products through randomized controlled trials (RCTs) in order to gain regulatory approval. But these trials have many limitations and may be insufficient to demonstrate effectiveness in real-world settings. Of further importance, medical procedures are

not FDA regulated and have no requirement for evidence of effectiveness prior to use. As a result, complex, risky, and expensive procedures like ABMT for breast cancer and LVRS (lung volume reduction surgery) were widely used despite extremely limited clinical evidence. These two procedures were essentially discontinued once RCTs demonstrated low (or no) benefits relative to risk. Still, a wide range of medical procedures remain in use with very limited supporting evidence.

Payers and policymakers face difficult choices. Should they deny coverage and restrict access to promising new technologies or allow coverage for treatments of unproven effectiveness and safety? Payers are particularly concerned about covering expensive treatments that are only marginally effective (at best), because scaling back coverage after a technology becomes widely used is virtually impossible unless the therapy is shown to cause substantial harm. In addition, once coverage is established, it is difficult to monitor off-label usage.

While RCTs are the evidentiary gold standard, it is impractical to demand RCT evidence for the broad range of indications or patient subgroups in which effectiveness may vary. Payers and manufacturers are searching for other ways to determine whether use of a therapy should be narrowed or expanded.

- **CED provides an approach that aims to let payers move beyond blunt yes/no coverage decisions by covering new therapies in concert with systematic evaluation.**

On July 12, 2006, the Centers for Medicare and Medicaid Services (CMS) issued a guidance document describing Coverage with Evidence Development (CED), a form of national coverage determination (NCD) requiring data collection as a condition of Medicare reimbursement. CED can help support multiple objectives of Medicare coverage policy by increasing patients' access to promising technologies while requiring an expanded evidence base to support health care decision making and future refinements in coverage policy. (The principles of the CMS guidance are summarized on page 5.)

Importantly, CMS's CED policy only applies to therapies that would not otherwise be covered; the default decision in the absence of CED is non-coverage. This creates an incentive for providers and manufacturers to work with CMS on designing data collection strategies. CMS can require patients to enroll in an RCT as a condition of coverage or require providers to submit data to a prospective registry. The goal is to use this evidence to refine coverage decisions.

- **Registries have value as a complement to RCTs in refining coverage policy, and have other benefits as well.**

The principal question posed to conference participants was whether observational data collected from prospective registries would yield sufficient evidence for designing coverage policy.

One participant observed that “for some questions there is no substitute for an RCT.” Conference participants agreed that registry data alone is insufficient for making coverage decisions. But they also generally agreed that registry data, in combination with RCTs, could be used to refine coverage policy by identifying variation in risk or benefit by patient demographics, clinical subgroups, site of care, and physician experience. However, to date this assertion has not been tested in the marketplace. In general it would be easier for payers to modify coverage policy based on safety risks identified in registry data than on clinical effectiveness information.

Aside from the coverage question, participants identified a number of benefits of registries:

1. *Real-world perspective.* Registries document how technologies are used in actual practice. As a practical matter, CMS and private payers have few effective ways of tracking how new technologies are utilized. Registries can help evaluate off-label use as well as potential inappropriate practices.
2. *Post-marketing surveillance.* Registries can provide post-marketing surveillance by identifying adverse and rare events in large patient populations.
3. *Influence clinical practices.* Research based on registry data may significantly influence practice. For example, a 2007 study showing increased risk of death or heart attack for patients with drug-eluting stents (DES) versus bare metal stents contributed to a significant reduction in DES use.
4. *Quality improvement.* Registries can help benchmark provider performance and inform quality improvement. Registries may also help policymakers identify and intervene with poor performers.
5. *Guide future research.* In situations where registry data is not considered sufficient to revise coverage policy, it can be used in generating hypotheses to inform future RCTs.

▪ **Policy development for registry-based CED should focus on solving funding, design, transparency, and methods issues.**

The key issues to be dealt with are:

1. *Funding.* Payers cover the cost of therapies being studied under CED; however, finding funding for research costs may be challenging. CMS does not fund clinical research and individual payers may be reluctant to provide funding if they don't see a likely return on the investment. As a result, to date there has been no agreement on who should cover these expenses—manufacturers who realize increased revenue from newly allowed product sales, or payers (and society), who stand to benefit from more appropriate utilization based on the evidence generated. Some participants believe that funding should come from specialty societies who can use registry data for quality improvement purposes.
2. *Registry design.* Clinical registries are most valuable if they include long-term, follow-up data. But long-term follow-up increases both the cost and time required to reach a decision. If manufacturers are required to fund registries, there is certain to be significant debate over how much data is “enough.”
3. *Transparency.* Participants see transparency as essential for the credibility of registry data, regardless of the research sponsor. They believe that the greatest credibility and impact would come from central participation of medical specialty societies.
4. *Methods improvement.* While most participants believe RCTs are the research gold standard, few industries other than medicine require RCTs to support their decision making. With the high cost of RCTs there is considerable interest in finding other methods that can produce credible data for decision making. In particular, participants are interested in best practices for analyzing observational data and expressed interest in a “methods summit” to find ways to use observational methods with greater confidence.

Framework for Effective Use of CED to Inform Decision Making

Presenter: Alan Garber, MD, PhD, Stanford University

Quick Summary

- In July 2006, the Centers for Medicare and Medicaid Services (CMS) issued guidance for Coverage with Evidence Development (CED), establishing principles and evidentiary priorities for its use.
- CED will improve access to novel medical therapies by providing treatment to patients while systematically studying its effects.
- CED proponents believe that evidence can be gathered through observational means such as registries, which complement RCTs and answer important questions about treatments.
- Criticisms about the validity of observational studies remain, fueled by lack of consistent methods and practices.
- Despite questions about whether observational data is good enough for decision-making, there appear to be situations where observational data used for CED can add value.

Context

Dr. Garber summarized how CMS is approaching CED and raised the question of whether causal inferences about treatments and other health interventions can be drawn from observational data, particularly patient registries. Participants debated this question, identifying the benefits and shortcomings of observational data and discussing situations where it can be used.

Key Points

▪ CMS has issued guidelines and stated principles for CED.

In July of 2006, CMS put forth its rationale for coverage with evidence development with the following guidance: The purpose of CED is to generate data on the utilization and impact of the item or service evaluated in the NCD (National Coverage Determination) so that Medicare can:

- a) Document the appropriateness of use of that item or service in Medicare beneficiaries under current coverage;
- b) Consider future changes in coverage for the item or service;
- c) Generate clinical information that will improve the evidence on which providers base their recommendations to Medicare beneficiaries regarding the item or service.

One participant indicated that CMS is breaking CED into two categories: 1) coverage for appropriateness determination (CAD) where a treatment is covered but evidence must be gathered on appropriateness of the treatment among different subpopulations

of patients and by different providers; and 2) coverage under study participation, which is less utilized.

Eight principles were stated governing Medicare's application of CED. These are:

1. *Transparency.* NCDs requiring CED will occur within the NCD processes, which is transparent and open to public comment.
2. *Provide needed evidence.* CED will not be used when other forms of coverage are justified by the available evidence. This means that CED will not be used if a treatment is already covered; it will only be used when a treatment is not yet covered and more evidence is desired to inform coverage. The intent of CED is to develop evidence only when evidence is not available by other means.
3. *Increase access.* CED in general will expand access to treatments and technologies because it will provide coverage in areas which would not otherwise be covered.

"CED will be used in situations where a technology wouldn't otherwise qualify for coverage."

— Alan Garber, MD, PhD

4. *Use seldom.* CMS expects to use CED infrequently.
5. *Information complementary.* The intent is that the evidence produced by CED will not be duplicative but will be complementary to existing medical evidence.
6. *Complement FDA.* CED will not duplicate or replace FDA's authority in assuring the safety, efficacy, and security of drugs, biological products, and devices.
7. *Complement NIH.* CED will not assume NIH's role in fostering, managing, or prioritizing clinical trials.
8. *Compliant with law.* Any application of CED will be consistent with all laws.

In deciding on their evidentiary priorities in applying CED, CMS's focus will be based on:

— *Disease burden.* Which diseases represent the greatest burden to Medicare beneficiaries?

— *Economic burden.* Which diseases and their treatments are the costliest to Medicare?

— *Value of incremental knowledge.* Where are there the most significant deficits in knowledge?

Priority areas for CED will be where there is uncertainty and where incremental information has value in reducing that uncertainty and making a difference in improving treatment decisions.

- **The key question regarding CED is whether causal inferences about treatments and other health interventions can be drawn from observational data.**

There are multiple options for CED-generated data. Among them are RCTs, registries (special purpose data collection efforts), routinely collected clinical data, claims files, and other administrative databases.

Of these options RCTs, which are protocol driven, are viewed as the gold standard. (Or, as one participant pointed out, multiple RCTs that provide validation of a set of conclusions are the true gold standard.) But conducting an RCT (or multiple RCTs) to answer all questions is unrealistic.

CED can help generate evidence which may otherwise never have been developed. CED can add value in complementing RCTs through larger sample sizes and in providing evidence regarding the effectiveness of a treatment in subgroups, in excluded populations, and in “real-world” treatment settings. Potentially, CED could be used to evaluate off-label uses of approved drugs, and be utilized in situations where RCTs are too difficult to conduct. CED led by Medicare may even be more efficient compared to multiple, privately sponsored RCTs.

But concerns remain regarding the ability to use observational data, especially registries, to draw causal inferences. But there are many criticisms of using observational data. Among them:

- An intervention may not be standardized.
- There may be no blinding.
- Tests of statistical significance can be misleading
- Selection effects can mean those included in observational studies aren’t included randomly but receive a treatment based on the bias of the provider.

In considering the potential uses of CED, insurers and manufacturers must consider: Can efficacy and effectiveness of a treatment be determined from CED data? And will CED data ultimately be good enough to be used in making coverage decisions?

- **In order to withstand the scrutiny from stakeholders, accepted methods for collecting and analyzing observational data must be established.**

In addition to the basic criticisms of observational data, Forum participants were in general agreement that unlike RCTs, there are not established and widely used best practices for observational data. As one participant said, “There is a crying need for good research practices for observational data.” (Dr. Steve Goodman pointed out that the recently published *STROBE* guidelines provide structured practices for observational data.)

There are cases where observational studies have accurately predicted the results of RCTs, yet other examples where properly conducted RCTs refuted multiple observational studies.

“Sometimes observational studies predict results of RCTs, especially when there are multiple studies of both types.”

— Alan Garber, MD PhD

Participants were unable to provide any information about the general confidence level in using observational data for decision making in the absence of an RCT, but one participant said there is data showing that observational studies are about twice as likely to be overturned as RCTs. (Other participants cautioned not to put too much validity in that data.)

It was suggested that observational data can facilitate formal modeling to extend the results of RCTs, and that observational data can be used to help go beyond yes/no coverage decisions to help quantify the effect size.

- **Despite the criticisms of observational data, there are good candidates for using observational data for CED.**

Dr. Gerber identified what he sees as the best candidates for CED. These are:

- As a complement to RCT rather than a substitute.
- When the effects observed in RCTs are unlikely to be representative of real-world effects obtained in a community.
- When sources of natural variation in use of a procedure are uncorrelated with outcomes.
- When there are predictable outcomes (with low unexplained variance).

Medicare ICD Registry

Presenter: **Stephen Hammill, MD**, Mayo Clinic

Chair: **Barbara McNeil, MD**, Harvard Medical School

Quick Summary

- In 2005, CMS further developed the CED process by authorizing the expanded coverage for Implantable Cardiac Defibrillators (ICDs) and requiring the systematic collection of implant data via an ICD registry.
- There are more than 200,000 ICD implants in the registry and more than 1,400 hospitals provide data; most hospitals provide data for all patients receiving ICDs, not just Medicare patients.
- The registry has set a precedent in collecting enormous amounts of data to be used for research; the collection process itself may provide significant benefits because it benchmarks performance of hospitals and providers.
- While the goal is to use this data to refine coverage decisions, the existing registry does not answer some key questions regarding long-term health outcomes, requiring a longitudinal study that will take considerable time and money.
- Funding to support a second, longitudinal registry is uncertain as many industry manufacturers, providers, and insurers debate its merits and priority.

Context

Dr. Hammill provided background on the creation of the ICD Registry, described the results to date, and outlined future plans for this registry. Forum participants raised questions and shared their perspectives on this registry.

Key Points (Hammill's Presentation)

- **CMS saw the ICD Registry as an opportunity for proof of concept on CED.**

When CMS published its final national coverage decision (NCD) for implantable cardioverter defibrillators (ICDs) on 1/27/05, CMS expanded the indications for ICD but did so based on the premise of CED—Coverage with Evidence Development. The intent was to collect evidence to refine the coverage decision over time and determine if the technology was more or less beneficial for certain subpopulations. The registry was conceived through a working group, led by the Heart Rhythm Society and comprised of members from industry (e.g., Medtronic and St. Jude) and professional organizations (e.g., ACC and HFSA), with observers from FDA, CMS and other at-large experts.

"Science tells us what we can do; guidelines are what we should do; and registries are what we are actually doing."

— Stephen Hammill, quoting Lukas Kappenberger, MD, HRS ICD Policy Conference, 9/16/2005

Dr. Sean Tunis, a former CMS administrator who was instrumental in the decision to establish a registry during CMS's ICD coverage decision, explained that CMS viewed this registry as a step in proving the concept of CED. Before this decision, CED had rarely been done. While CMS hoped the registry would produce scientifically and clinically important data, there was no certainty about the usefulness of the data that would be produced. However, CMS thought that even if the data wasn't useful, the creation of this registry would still help validate the notion of systematically gathering evidence about a technology while covering it.

Dr. Hammill quoted then-CMS Administrator, Mark McClellan, who commented on CED in February of 2005 that CMS sees as the goal of CED to "Develop evidence on what works best in clinical practice...explicit, rapid evidence based on a process that is predictable with transparency...to improve the knowledge base by which patients and providers can make better treatment decisions." Writing specifically about the ICD Registry in *Heart-Rhythm* in 2006, CMS's Steve Phurrough (with Hammill and Brindis) said that "CMS's goal is to determine whether primary prevention ICDs are appropriate for the Medicare beneficiaries who meet the clinical conditions identified in the agency's NCD of 1/27/05."

- **The ICD Registry has been successful in collecting a tremendous amount of data, and is evolving into an important research tool.**

As of July 2007, the ICD registry has collected data from more than 1,400 hospitals on more than 200,000 implants. Extensive amounts of clinical data are collected on a host of measures related to the implant procedure. Hospitals are encouraged to submit data not just on CMS patients, but for all patients receiving an ICD. Of the 108,000 implants entered into the registry in 2006, 70% had Medicare as their primary insurer and 30% had another payer. (A selling point to encourage hospitals to participate is that quarterly benchmarking reports are provided to all participating hospitals, which enable a hospital to compare its performance with other hospitals of similar size.)

The ICD Registry is going through an evolution, redefining the registry's purpose, goals, and target audience. The purpose will be expanded to follow up on leads. The data collection forms will be improved, and the registry will evolve to become more of a

performance reporting tool that measures provider performance on procedural outcomes and complications.

The key next steps for the registry are to develop version 2.0 to support the extensive number of research projects that desire to use data from the registry (more than 25 research requests for registry data have been received to date), and to change the source of payment from industry and payers to hospitals. Next year participation will cost a hospital \$1,800 and the following year it will go to \$3,000, which is anticipated to be the long-term price. (Some payers are mandating that hospitals participate in the ICD Registry as a way to collect data and measure results.)

▪ **Longitudinal data is needed to answer coverage decisions.**

While one of the underlying reasons for establishing this registry was to make more precise coverage determinations, the data collected to date has not been able to answer this question. The current registry contains no ICD firing data or long-term survival data. Getting the information necessary to answer this question—and others—requires following patients over multiple years. Because prior RCTs have shown that ICDs tend to provide little benefit in their first 18 to 24 months, the data that could impact coverage decisions will take at least three to five years to collect.

With this in mind, in March of 2006 HRS was asked to reconvene the (now expanded) working group to develop a longitudinal registry that could refine the CED questions. The task force defined several important coverage decisions to be addressed by a second, longitudinal registry.

The plan for this longitudinal registry was to have 350 randomly selected implanting MDs and to enroll and follow 3,500 patients for three years for events and five years for survival. Funding of \$3.5 million was needed to support the desired study design. However, to date just \$2 million has been received, forcing a reduction in the study size to 2,000. Fewer patients in the study leads to a decrease in the confidence intervals.

Key Points (Participants' Discussion)

- **Ability to answer coverage questions.** Since one of the primary reasons for the ICD Registry was to help refine coverage decisions, the question was raised about when evidence will exist to be able to answer coverage questions for specific populations. Dr. Hammill suggested that it will take at least four or five years for the evidence generated to be able to help inform coverage decisions. However, some were skeptical whether data from this registry would ever be useful in refining coverage decisions; with little/no history of using observational data to affect coverage and with no control group, some view using such data to change coverage as unlikely, especially after nearly a half-decade of established use.
- **Quality improvement.** While uncertainty existed around the ability of the ICD Registry to impact coverage, Dr. Robert Califf suggested that just the data collection process has been valuable in that participating hospitals and providers know they are being watched. He suggested that the registry has “paid for itself in spades” because overall quality has improved and some poor providers have stopped performing implants. Use of this registry as a performance-reporting tool is seen as one of the key uses going forward. However, some concerns were expressed that using data for quality-improvement purposes is fundamentally different from using it for research purposes.
- **Combining data.** Several participants argued that the evidence in the ICD Registry would be far more valuable if combined with other sources of data, such as claims data and data collected by device manufacturers about when an ICD fires. However combining the various sources of data faces technical challenges (for example, integrating multiple software platforms) and political barriers in that the parties who have the data may not want to share it.
- **Who pays?** A key issue of debate regarded who should pay for the longitudinal study. Despite the fact that ICDs comprise a \$1.0 to \$1.5 billion per year industry representing significant outlays from insurers and significant revenue for industry, raising \$3.5 million for the longitudinal registry has been a struggle. From industry's perspective, they already spent \$4 million into the initial registry and have committed \$1.5 million for the longitudinal registry. AHIP, the national association of health insurance companies, has pledged another \$1.0 million. Amidst “competing priorities” there is reluctance among these parties to contribute additional funds.

National Emphysema Treatment Trial

Presenter: **Scott Ramsey, PhD**, Fred Hutchinson

Chair: **Barbara McNeil, MD**, Harvard Medical School

Quick Summary

- The National Emphysema Treatment Trial (NETT) was conducted following the national coverage decision by HCFA to only cover lung volume reduction surgery (LVRS) in the context of a randomized clinical trial.
- The NETT, which took eight years and cost almost \$60 million, found LVRS not to improve mortality or morbidity except in one small subgroup.
- Despite the negative outcomes, NETT is seen as a success where CED yielded clear results that affected coverage and medical practice.
- While CMS approved coverage after the RCT for the subgroup, use of this procedure in practice has been rare, suggesting that the true impact of CED may be in affecting provider treatment decisions rather than insurer coverage policy.

Context

Dr. Ramsey described National Emphysema Treatment Trial (NETT) and Dr. McNeil led a discussion of participants' observations and learnings from NETT.

Key Points (Ramsey)

- **NETT is an early example of coverage with evidence development in the context of an RCT.**

At the time of the trial, emphysema was responsible for 18,000 deaths a year and affected two million people. From CMS's perspective, it was an especially important disease with a large number of patients (32.4 cases per 1,000 people over 65), unsatisfactory clinical management, and large geographic and racial disparities in care.

In the mid-1990s, a small observational study of Lung Volume Reduction Surgery (LVRS) had generated tremendous buzz around the potential of this procedure to deliver improved outcomes for patients with emphysema. Within 18 months following the presentation of the study's results, CMS noticed thousands of LVRS procedures being performed. However, CMS also noticed that 30-day mortality rates were 17% to 20%.

After reviewing a summary of the evidence on LVRS, a NHLBI workshop in September of 1995 called for a controlled trial of LVRS. National Emphysema Treatment Trial was a multi-center randomized clinical trial comparing medical treatment with lung volume reduction surgery (LVRS) to medical treatment alone in patients with severe emphysema.

In December of 2005, HCFA (the predecessor to CMS) issued a national coverage decision for LVRS which failed to provide reimbursement for the procedure based on inadequacy of evidence and potential for extensive morbidity and mortality. But recognizing the importance of generating additional evidence, the agency created a code for LVRS and agreed to cover the procedure only in the context of a clinical trial and if performed at one of seventeen participating medical centers.

- **Results of the trial yielded strong evidence, which formed the basis for providers and insurers to make treatment and coverage decisions.**

Three years into the trial an article from the trial was published in the *New England Journal of Medicine* showing that mortality of the high-risk subgroup in the study that received LVRS had increased. Publication of these results followed by articles in the mainstream press led to trepidation for the procedure and hurt further recruiting and enrollment efforts.

The final results of the study showed no impact of LVRS on survival, no difference in quality of life, and higher surgical morbidity rates for individuals who received the LVRS procedure, compared to those receiving only medical treatment. Exercise capacity of those receiving LVRS increased, but questions lingered about the meaningfulness and repeatability of that measure.

Because of extreme pressure to show positive results of LVRS for some segment of the population, a great deal of intense post hoc analysis took place to find a group where LVRS was beneficial. This analysis showed that LVRS had no effect or a negative effect for most subgroups, but one subgroup termed "upper lobe, low exercise" did show better mortality. Based on the positive results for this small subgroup CMS agreed to cover LVRS if it was preceded and followed by pulmonary rehabilitation (which CMS doesn't cover) and if the LVRS procedure was performed at a NHLBI-certified NETT facility.

Even after coverage was granted, the number of LVRS procedures diminished substantially; just 324 procedures were performed over the next two years. In the end, the medical community recognized the results of the NETT as showing no benefit or even negative effects for most patients.

- **Economically, NETT was expensive research but the value of the information produced was significant.**

When looking at the value of conducting this trial, Dr. Ramsey assessed the economic value of the information gained from NETT. The Value of Information Theory holds that gathering information via clinical trials is costly, but making the wrong clinical decisions is also costly. In other words, did the economic investment that supported NETT yield information that saved

money or improved health? In calculating these costs, one must also estimate the ramifications of not sponsoring an evidence-generating trial. It is costly to adopt a treatment which causes harm, but it is also costly to not adopt a treatment that would yield positive results.

The total cost of NETT was estimated to be over \$59 million, with only \$18 million of that amount spent on trial-related treatment costs. For a payer willing to pay for a modestly-beneficial therapy (e.g., one with a cost-effectiveness of \$50,000/QALY), the expected net benefit of sampling is calculated at \$3.41 billion. Even if a payer was willing to pay for a marginally-beneficial therapy (\$100,000 QALY), the expected net benefit is \$7.32 billion. Thus the investment in this research was significant but the economic value of the information was far higher.

Key Points (Participants' Discussion)

- **Emphasizing success.** Despite the negative results from the trial, several participants commented that NETT was a great success. It answered the key clinical questions it was designed to answer, kept thousands of patients from unnecessarily getting surgery, saved lives, and saved Medicare millions of dollars.
- **Why aren't there more NETTs?** Based on the success of this specific trial and of the model of covering a procedure only as part of a clinical trial, several participants asked, "Why aren't there other trials such as NETT?" Several participants suggested that NETT was an expensive, time-intensive, politically challenging battle, and CMS simply lacked the appetite to engage in another such confrontation. It was also suggested that the producers of medical technology oppose such research, health plans don't actively support it, and there are concerns among some groups about having payers drive the research agenda.
- **RCTs versus registries.** At the time of the coverage decision there was debate regarding whether to create a registry or to conduct a randomized controlled trial. Now that the research has been completed, Dr. Ramsey feels strongly that in this instance, observational data would not have yielded the same answer as the RCT. Due to the buzz and momentum surrounding LVRS, a RCT was essential to answer the clinical questions with certainty and credibility.

"Would we have gotten the same answer without an RCT? No. I can't think of another methodology to answer this question."

— Scott Ramsey, PhD

Dr. Ramsey suggested an RCT was demanded when: there is a very expensive procedure with high morbidity and mortality; the procedure would potentially be used broadly with thousands of patients; and the existing data is inadequate.

- **Using registries for appropriateness.** If a coverage decision is purely yes/no, where either everyone or no one receives coverage, then registries may have limited value. But registries can recruit a substantially larger number of patients and identify sub-group effects which can be used to determine appropriateness and effectiveness for certain people and in certain situations. (Dr. Donald Berry commented that both RCTs and registries are useless for screening purposes.) While an RCT seemed to make sense in this situation, it was pointed out that this RCT with just 1,200 enrollees took eight years to complete and cost almost \$60 million to conduct. CED won't work if every clinical question takes this long and this much money to answer.
 - **Issues with covering only in a study.** The point was raised that advocacy groups will inevitably object to situations where the only way that patients can receive a certain treatment is if they consent to be part of a clinical trial. Others responded that for an unproven, experimental therapy to be paid for, it is appropriate for it to be part of a research program. Individuals can elect not to participate in a trial or pay for the procedure elsewhere out-of-pocket. Professor Altman believes that there will be a vigorous debate on this subject but feels the trend for CMS to put restrictions on coverage is only going to increase due to the agency's economic pressures.
- NETT also emphasized the difficulties of generating evidence in practice. Dr. Ramsey commented on the difficulties of getting study volunteers to agree to participate. Recruiting efforts were significant, with millions of dollars spent on media. More than 31,000 individuals inquired about the trial, about 3,800 went through screening, and 1,200 were randomized, far below the initial goal of 2,500 patients.
- **Risks of new medical technologies.** Dr. Steve Goodman commented that this case study illustrates the ability of a producer to sell a new medical technology without good evidence. Others commented on a key difference between technologies (drugs and device) and procedures: bringing new product to market involves far greater testing and regulation while new procedures require much less scrutiny.

ABMT for Breast Cancer

Presenter: **Wade Aubry, MD**, UCSF

Chair: **Marc Berger, MD**, Eli Lilly

Quick Summary

- The history of Autologous Bone Marrow Transplants (ABMT) demonstrates how public fervor can affect coverage decisions, where physician advocacy and strong public demand led to widespread use, even without solid evidence
- When payers refused coverage, litigation ensued and federal and state insurance coverage was mandated.
- After as many as 40,000 individuals received treatment costing approximately \$2 billion, multiple RCTs ultimately showed no benefit from ABMT.
- The case study also shows the need to weigh conflicting values, such as speed versus evaluation; the needs of one patient versus the benefits to a patient population; and the need for integrity in the evaluation process, with a safety valve for individual cases.
- The processes for evaluating drugs and procedures differ dramatically. Dr. Aubry recommends a public-private partnership to evaluate procedures.

Context

Drawing from *False Hope: Bone Marrow Transplantation for Breast Cancer*, the book he co-authored chronicling the saga of Autologous Bone Marrow Transplants (ABMT), Dr. Aubry described the history of High Dose Chemotherapy (HDC) and ABMT, drew conclusions, and offered a recommendation for the evaluation of procedures. Participants then shared their thoughts on this case study.

Key Points (Aubry)

- **Despite receiving unprecedented attention, it took time for RCTs on ABMT.**

ABMT emerged in the 1980s and was rapidly disseminated. What followed were two pathways:

- *The rational system of evaluation* emphasized systematic evaluation of evidence through technology assessments, practice guidelines, and clinical trials.
- *The “default” system of clinical use* reflected uncoordinated action driven by multiple Phase 2 studies, patients, physicians, lawyers, media entrepreneurs, and state and federal government mandates.

Among the multiple activities that took place over the next twenty or so years were:

- *The “face of the patient” emerged.* While only about 1,000 patients received treatment “on protocol” as part of a clinical evaluation path, between 23,000 and 40,000 patients received treatment off protocol. (There were about 600 premature deaths.) The median age of patients was 44 to 47; median length of stay was about 45 days; median charges were from \$71,000 to almost \$104,000, and over ten years the estimated total cost was about \$2 billion. About 54% of the patients receiving ABMT were covered by PPO/FFS and 23% by HMOs.
- *A set of basic issues emerged.* These issues focused on weighing the claims of individuals who wanted this treatment versus the needs of society to evaluate new treatments. Regarding evaluation, the key question was what type of research was needed? An additional issue was the role of payers in paying for evidence and in paying for experimental therapies.
- *Demand for the treatment intensified.* Patients demanded this treatment and physicians acted as forceful advocates for it. Some of them argued for coverage as “the best available therapy.” Among supporters were prominent physicians including a “dream team” of transplanters who created a document in 1990 arguing for coverage. The print and broadcast media participated in driving up demand and entrepreneurial oncology businesses emerged and grew rapidly to address this demand.
- *Some payers refused to pay, leading to litigation.* Tension developed between physicians who advocated for this therapy and insurers who followed their normal processes and methods and denied coverage due to lack of evidence. Litigation followed as patients sued insurers to have ABMT covered. Prior to the *Fox v. HealthNet* case in 1993 (which resulted in an \$89 million verdict for the plaintiff) insurers and patients each prevailed in court about 50% of the time. But after the *Fox* case, settlements strongly favored the plaintiffs. Even in the absence of evidence, some insurers started to cover ABMT just to avoid litigation. (The oncology centers registered trials with the FDA but didn’t conduct any RCTs.)
- *Governments mandated coverage.* The U.S. House of Representatives held hearings on this therapy in 1994 where they derided clinical research as “coin-flip trials” and mandated coverage for federal employees. By 1996, 16 states had also mandated coverage of HDC/ABMT for breast cancer.
- *Fraudulent studies.* During this time a researcher in South Africa conducted trials and published peer-reviewed results reporting benefits. These trials were ultimately shown to be fraudulent.

Finally during the 1990s insurers responded by funding several trials outside of coverage (an early form of CED). The NCI also

conducted several high-priority clinical trials. (One difficulty was recruiting patients for randomized trials. Since the therapy is available outside of trials and is often covered, few patients would want to be part of the control group.)

With high anticipation, results from multiple trials were presented at the ASCO meeting in May of 1999. With the exception of the fraudulent South African study, the trials all reported no benefit.

As could be expected, immediately following the presentation of this evidence, the number of patients receiving HDC and ABMT fell off dramatically as did the number of oncology centers.

- **Multiple lessons emerged from this experience.**

Dr. Aubry formed the following conclusions:

- *Initial conditions dominated the story.* The environment made it difficult to gain consensus that Phase 3 trials were necessary. Phase 2 studies proliferated and showed real promise; media reports highlighted positive patient stories; litigation ensued when payers refused coverage; MDs legitimized this experimental treatment as “standard of care” and some felt that randomizing patients (and therefore denying some this treatment) would be unethical; entrepreneurs jumped into the market; and it wasn’t clear who would own and pay for Phase 3 trials.
- *In situations like this, conflicting values are all pervasive.* Among the conflicts that have to be wrestled with are: early access to new treatments versus adequate evaluation of treatments; the potential individual benefit now versus potential collective benefit later; weighing the use of experimental procedures versus standard of care; engaging in policy discussions to improve the rational system without disabling the default system; and providing both integrity of the evaluation process and a safety valve for individual cases.
- *An institutional deficit exists for evaluating procedures.* When evaluating drugs, there is a clear evaluation process that is required by FDA and financed by sponsors. But there is no equivalent for procedures. Further, the financing to evaluate procedures is problematic.

- **Dr. Aubry recommends a public-private partnership to evaluate procedures.**

To address the deficit in evaluating procedures, Dr. Aubry recommends a public-private partnership to evaluate procedures through RCTs. This partnership would be housed in the NIH or the NCI. It would describe Phase 2 promise and articulate Phase 3 rationale, would limit access to new procedures to RCTs, and would provide for review of individual cases.

Such a partnership would have multiple benefits which would include: timely data on clinical effectiveness; some litigation protection for insurers in coverage decisions; and financing for researchers (from insurers) for RCTs.

Key Points (Participants’ Discussion)

- **Need RCTs to take anything away.** Dr. Berger remarked that people tend to overvalue things that they have and that might be taken away, but undervalue things that they don’t yet have. Due to the difficulty of taking something away, he suggested that to do so, an RCT may always be necessary.
- **Using data for multiple purposes.** Ms. Buto sees CED as intersecting in some ways with the FDA/regulatory approval process and with the conversations taking place about the need for post-market surveillance to detect safety signals. While the data needed for CED and for regulatory approval may not be identical, perhaps there are opportunities to simultaneously collect data for multiple purposes.
- **Announcing early.** Dr. Berry argued that in many situations the evidence is so clear that it is possible to announce results early, instead of waiting for the research to be completed. Based on the data, doing so can benefit patients and medicine.
- **The need for Phase 2.** Questions were raised whether Phase 2 research is necessary or whether it can be cut back or expedited to get to Phase 3 more quickly. (It was also suggested to go back after Phase 3 to review Phase 2 to assess possible errors.) Others argued for the need for Phase 2 as these studies contain intermediate endpoints that are necessary for Phase 3.
- **Including patients.** In Dr. Goodman’s view patient advocates are a critical group that is not at the table which should be included in this conversation.

Drug-Eluting Stents

Presenter: **Mark Hlatky, MD**, Stanford University

Chair: **Marc Berger, MD**, Eli Lilly

Quick Summary

- Stents registries can provide information on questions that many RCTs cannot answer and can provide tremendous value in complementing RCTs.
- While numerous RCTs played a key role in showing the benefits of stents and helping secure their approval, these studies were limited in the generalizability due to few patients, a short time horizon, restrictive patient and provider selection, and lack of real-world data.
- Registries provide a real-world perspective that shows who is getting stents, how they are faring over time, and who is providing them, as well as the frequency of repeat procedures, rare complications, and other information.

Context

Dr. Hlatky provided background on stents, summarized the RCT research that has been conducted, and explained the role that registries have played.

Key Points (Hlatky)

- **RCTs were critical in the approval of stents, but their very design limits the ability to generalize their results.**

Balloon angioplasty, which was developed 30 years ago, proved effective at improving blood flow in coronary arteries, but registry data showed that restenosis occurred in about one-third of patients, necessitating a repeat procedure within six months.

Drug therapies were tried but were unsuccessful in resolving this problem. In 1986 stents (a simple mechanical scaffold) were developed. RCTs confirmed that they reduced but did not eliminate restenosis. Seeking to improve on the results of bare metal stents (BMS), drug-eluting stents (DES) were developed. These drug-coated stents went beyond the mechanical approach of BMS and were sophisticated devices that delivered drugs to prevent the tissue growth that caused restenosis. RCTs showed that DES resulted in lower rates of restenosis than BMS, though concerns were raised in 2006 about stent-related blood clots.

The RCTs that had been conducted and had played a key role in securing the approval of stents had focused on restenosis. However, these trials had left open the question of whether stents reduced death or MI. Meta-analysis was conducted of all trials to increase the statistical power for hard outcomes. A total of 29 RCTs with almost 10,000 patients compared outcomes for balloon vs. BMS; 11 RCTs with about 5,000 patients compared outcomes between BMS and DES. This analysis found that DES

resulted in fewer repeat procedures than BMS, and BMS had fewer repeat procedures than balloons. However the evidence also showed that there was no difference in rates of death and MI.

Yet despite the value of the many RCTs focused on balloons and stents, these RCTs had significant shortcomings. Among the limitations and issues with the RCTs were:

- *Few patients.* While more than 620,000 people in just the U.S. received stents in 2005, just 15,000 worldwide were enrolled in RCTs, a small percentage of the total patient base.
- *Patient selection.* Those patients selected to participate in the RCTs generally had less coronary artery disease and less comorbidity than the general stent population.
- *High volume centers.* Interventions included in the RCT were done in high-volume centers of excellence, which translates into better results.

“RCT research is often conducted among the best patients and the best centers.”

— Mark Hlatky, MD

- *Short follow-up.* Because the focus of the RCTs was on restenosis, the length of follow-up was short, typically between 6 to 16 months.
- *Routine angiograms.* In the research protocol of the RCTs, follow-up angiograms were routine, and they could detect problems requiring follow-up procedures. However, angiograms are not necessarily part of routine follow-up in the real world. Thus, the frequency of repeat procedures detected within RCTs may not correlate with that of the real, non-research world.

- **Multiple registries are complementing the stent RCTs.**

Multiple clinical registries collect data on stents. These registries provide real-world data on stents; they show how stents are being used in widespread practice and provide more data and data on longer-term outcomes.

“The value of registries is greatly increased by systematic, complete, long-term follow-up.”

— Mark Hlatky, MD

The specific benefits of these stent registries include:

- *Data on patient selection.* RCTs provide a limited picture of who receives stents, but registries show exactly who is getting them. It provides data on off-label use and on disparities by race or gender.

- *Risk data.* The registries are able to identify risk by patient (such as for young or old patients), and based on hospital and MD procedure volumes.
- *Repeat procedure data.* Registries provide the ability to see real-world repeat procedure rates, without distortion from the RCT protocols requiring routine angiograms.
- *Rare events.* Because the RCTs contain a relatively small number of patients, with fewer than 500 patients per research arm, it is difficult to see rare events. But the larger volume of patients in the registries makes it more likely to spot uncommon complications.
- *Data on longer-term events.* Registries supply evidence on late DES events, which were not possible to detect with the short-term follow-up in the RCTs. Analysis was shared from the Swedish Registry which showed over time a higher risk of death or MI from DES than from BMS.

"Large registries are complementary to RCTs and are helpful in monitoring use and outcomes in actual practice."

— Mark Hlatky, MD

Key Points (Participants' Discussion)

- **Clinical data needed.** For registries to have value they must have clinical data. Claims data and administrative data aren't viewed as good enough. Typically, important and necessary clinical data such as ejection fraction, lesion location, and disease comorbidities (like diabetes) isn't collected in claims data.
- **Standard definitions.** When multiple registries exist an issue is inconsistent infrastructure between registries and a lack of standard definitions and terminology. This lack of standards also complicates the use of clinical data in electronic medical records.
- **Safety signals.** A value of a registry is the ability to detect and identify safety signals. Ideally detection of such signals would involve a feedback process that reviewed and interpreted these signals. This feedback system could lead to further research and RCTs, using registries as a hypothesis-generating tool. However, typically no feedback system is in place to act on the signals that are detected and no funding is available to conduct research regarding the signals.
- **Stopping a registry.** There is no answer for when a registry should be stopped; it depends on the question that the registry was designed to answer. For example, a registry focused on answering questions about restenosis might exist for a year or two, but a registry designed to answer long-term safety questions would be expected to exist for many years. Some questioned whether stakeholders would ever decide there was enough data to stop a registry.
- **Adapt to change.** One participant pointed out that the nature of devices is evolving and constantly changing, but RCTs are rigid and don't adapt. Registries are able to capture the changes that occur.

Lessons Learned and Implications for Policy

Moderator: **Robert Mechanic**, Brandeis University

Panelists: **Troyen Brennan, MD**, Aetna, Inc.; **Kathy Buto**, Johnson & Johnson; **Robert Califf, MD**, Duke University; **Sharon Levine, MD**, The Permanente Medical Group; **Steve Phurrough, MD, MPA**, CMS; **David Steinhaus, MD**, Medtronic, Inc.

Quick Summary

- In general, participants support the idea of using CED and registries to collect data that informs and helps refine coverage decisions.
- Registries are seen as having other benefits which include quality monitoring, detection of safety issues, longitudinal monitoring, and detection of other signals.
- Participants were reluctant to conclude that decisions can be made solely using observational data. Observational data can inform decisions, help refine decisions, and help identify where further research is needed, but may not be enough to stand up to political pressures on its own strength.

Context

This panel of payers, industry members, a provider, and a researcher commented on whether data collected through CED can and should be used to refine coverage policy; who should pay for registries under CED; and whether reasonable decisions can be made based on observational data.

Key Learnings

- **In considering policy options around CED, it is important to keep the current less-than-ideal situation in mind.**

Participants were reminded of the context for this discussion: payers often lack adequate evidence to make coverage decisions for new treatments and medical technologies; providers often lack guidelines and/or quality measures for using new treatments; and once a treatment is approved there is often little evidence regarding the treatment's effectiveness. It is with this as the context that participants debated, "Isn't there a better way?"

- **In general, participants support the idea of more evidence for use in making and refining coverage decisions.**

There is consensus around the concept of gathering evidence prior to a treatment's approval and coverage, and recognition that today the process for gathering evidence about drugs is very different than for procedures.

There was general support for using CED for situations where a new treatment would not be covered due to inadequate evidence. Use of CED would allow new treatments to come to market, gain initial use, and have data collected about them. (While much of the conversation about evidence gathered

through CED focused on observational data and registries, it was also noted that CED was not limited to observational data and could also include RCTs.)

In particular, use of observational data can help define when treatments are appropriate and for whom, which in theory can help "refine" coverage decisions. However, several participants conceded that once a treatment is covered, changing or restricting the coverage can be very difficult.

Observational evidence can also have great value in monitoring provider quality and can be used to identify potential risks and safety issues and to detect other signals.

- **Amidst the support for evidence, the questions are which type of evidence to gather and who pays for it.**

The case studies and subsequent discussions made clear that there is no "one-size-fits-all" approach. The type of evidence to be gathered varies by the specific situation and the clinical and coverage questions to be answered.

There are clearly situations when an RCT (or even multiple RCTs) are necessary. The NETT and ABMT case studies are examples of situations where practices had gained widespread use and observational data would not have been adequate; RCTs were needed to show whether these controversial procedures had any benefit.

The value of observational data is seen in complementing RCTs to provide additional data and answers. This might include data in real-world situations, for particular subgroups, or in a longitudinal study that looks at effects over a longer period than an RCT. A registry can detect signals on use and safety, can be used for additional research purposes, and can be used to identify key unanswered questions requiring further RCTs.

However, while observational data, and particularly registries, are seen as having significant value in certain situations, it was not clear that this data provides the basis for making decisions or whether observational data could survive the political process. Without control groups or randomization, the methodology may be too fragile to provide actionable information that can withstand the pressures from affected stakeholders. It appears that for making decisions, especially important and high-dollar decisions, RCTs are needed.

There was not agreement regarding who should pay for the development of registries. Some participants felt that the burden of registries should be shared by all parties. Representatives from the medical products industry view it as appropriate that manufacturers fund registries in those situations where coverage would otherwise be denied due to lack of evidence.

Others felt that because payers have so much at stake, they should contribute to funding registries. However, among the payers present, CMS is legally constrained and can't pay the administrative costs of registries and Dr. Brennan from Aetna wasn't convinced of the value to Aetna of registries to the extent that he would be willing to pay. Before contributing to finance a registry he would need to believe that a registry was likely to produce information that would "make a difference" in a payer's coverage decision.

Some participants argued that evidence funded by payers would be questioned because the motives of payers (to not cover a treatment) would be suspect, and it would be difficult for payers to drive evidence into practice. In contrast, it was suggested that specialty societies should pay for registries to get evidence for quality improvement purposes. Specialty societies are best equipped to turn evidence into practice. The barrier is that specialty societies don't have an economic incentive to fund registries...

▪ **Despite the benefits of CED, it won't solve all problems.**

Some proponents of CED who view it as "temporary coverage" during which time evidence is gathered to enable a long-term coverage decision asked, "Why won't this [temporary coverage concept] work?" A few participants, though they support the concept of CED, provided practical barriers. These include:

- *CED can take too long.* A state of temporary coverage that lasted for two to three years (or longer) while evidence was being developed would be seen as too long and impractical to industry participants.
- *At times momentum for a procedure is unstoppable.* For certain treatments at certain points in time, it would be highly unlikely that CED could make a difference. For example, with IMRT (intensity-modulated radiation therapy), the cost is higher than for existing treatments and this treatment may offer no benefit versus existing treatments. However, providers are investing in facilities to provide IMRT and Dr. Brennan sees it as highly unlikely that any data produced through CED could make a difference at this time.

Other Interesting Points

- **Methods summit.** One participant mentioned the need for a "methods summit" to share best practices on designing observational trials using registries. It was mentioned that the IOM is having a meeting on methods.
- **Statisticians.** It was mentioned that statisticians are rarely included in discussions about research methodologies, but they should be.

Health Industry Forum Participants – October 24, 2007

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