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Optimizing Information Under Coverage With Evidence Development

When new medical treatments are introduced, evidence supporting their effectiveness is frequently limited. Drug and device manufacturers must establish the safety and efficacy of their products through randomized controlled trials (RCTs) to gain regulatory approval. But these RCTs have many limitations and may be insufficient to demonstrate effectiveness in real world settings. In contrast, medical procedures are not FDA regulated and have no formal requirement for evidence of effectiveness prior to use. Complex, risky and expensive procedures like autologous bone-marrow transplantation (ABMT) for breast cancer and lung volume reduction surgery (LVRS) have been widely used despite extremely limited clinical evidence. Those two procedures were discontinued once RCTs demonstrated low benefits relative to risk. A wide range of medical procedures remain in use despite important uncertainties about their real world benefits, risks and costs.

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 expensive treatments that are marginally effective, because scaling back coverage after a technology becomes widely used is virtually impossible unless the therapy is shown to cause substantial harm. It is impractical to demand RCT evidence for the broad range of indications or patient subgroups in which effectiveness may vary. Payers, providers, and manufacturers are searching for other ways to determine whether use of a therapy should be narrowed or expanded.

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 by clinicians and patients and future refinements in coverage policy. Principals of the CMS guidance are summarized below.

Principles Governing the Application of Coverage With Evidence Development

1. NCDs requiring CED will occur within the NCD processes, which is transparent and open to public comment.
2. CED will not be used when other forms of coverage are justified by the available evidence.
3. CED will in general expand access to technologies and treatments for Medicare beneficiaries.
4. CMS expects to use CED infrequently.
5. CED will lead to the production of evidence complementary to existing medical evidence.
6. CED will not duplicate or replace the FDA's authority in assuring the safety, efficacy, and security of drugs, biological products, and devices.
7. CED will not assume the NIH's role in fostering, managing, or prioritizing clinical trials.
8. Any application of CED will be consistent with federal laws, regulations, and patient protections

Source: Adapted from CMS Guidance Document.

On October 24th 2007, The Health Industry Forum hosted a conference of leading researchers, industry executives, public officials and healthcare practitioners to discuss practical considerations for CED policy. In particular, the meeting focused on whether observational data collected through prospective clinical registries under CED would be sufficient to support payers in refining coverage policy. Participants examined case studies to evaluate the following questions: 1) how well can prospective registries support coverage policy; 2) how should registries be designed to provide optimal information; and 3) who should fund registry development and ongoing maintenance? Key themes from the meeting are summarized below.

CED lets payers move beyond blunt “yes/no” coverage decisions by allowing new therapies into practice in concert with systematic evaluation.

Medicare’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.

- In 1995, Medicare required patients to enroll in an NIH-sponsored RCT of lung volume reduction surgery as a condition of coverage. Under this arrangement Medicare patients could only access LVRS through one of seventeen designated centers. The trial ultimately enrolled 1,200 patients, cost \$37 million (excluding actual treatment costs), and was completed in 2003. Although Medicare covered LVRS in 2004 based on RCT results, most pulmonologists stopped referring patients because of high surgical mortality documented during the trial. Despite a successful outcome this experience also illustrates challenges of an RCT approach to CED.
 1. Substantial political opposition from surgeons
 2. Significant funding requirement.
 3. Long time required before results support a final coverage decision,
 4. Limited access for patients located far from designated centers.

- Medicare’s first registry under the new CED policy was for expanded coverage of implantable cardioverter defibrillators (ICDs). Findings from the first year of data collection - the baseline registry - were published in September 2007 with information from more than 108,000 ICD implants. Importantly, the baseline registry contains no data on whether patients’ ICDs fired (i.e., whether it was actually used to address a life threatening heart rhythm). It also did not collect long term data on patient survival. Therefore, this registry is unable to answer CMS’s primary question - whether patient outcomes differ for key patient subgroups (i.e., patients with “ejection fractions” above and below 30 percent). The American College of Cardiology, Heart Rhythm Society, Medtronic, CMS and others are currently designing a longitudinal registry that will collect firing and survival data over a five year period. Funding for this registry, however, remains unresolved. This example illustrates a variety of challenges for registry-based CED.
 1. Uncertainty about the extent to which evidence generated using observational data (without control groups or randomization) will be considered sufficient (scientifically or politically) to support revisions in CMS coverage policy or informing clinical decisions.
 2. Expanding the requirement for collecting long term follow up data through prospective registries increases the cost and time to decision.
 3. Registry data requirements necessitate difficult negotiation between the payer, health care provider, and product manufacturer.
 4. Without federal support, a mandate or other reliable and bias-free source of funding, registries may suffer from inadequate funding.

Prospective registries can complement RCTs in developing coverage policy.

The principal questions posed to conference participants was whether observational data collected from prospective registries would be 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 are insufficient for making coverage decisions. 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, this assertion has not been tested in the marketplace. Concerns were also raised about the fact that different stent registries reached conflicting conclusions on the same questions, raising concerns about the reliability of this data. In general it would be easier for payers to modify coverage policy based on risks identified in registry data than on effectiveness information. Aside from the coverage question, participants identified a number of benefits of registries.

1. Registries document how technologies are used in actual practice. 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. Registries can provide a post-marketing surveillance by identifying adverse events in large patient populations.
3. Research based on registry data may significantly influence practice. A 2007 study showing increased risk of death or heart attack for patients with drug eluting stents (DES) may have contributed to significant reduction in DES use seen later that year.
4. Registries can help providers benchmark performance and inform quality improvement. Registries may also help policy makers identify and intervene with poor performers.
5. In situations where registry data are not be considered sufficient to revise coverage policy, they will frequently generate useful hypotheses to inform future RCTs

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

- **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 costs and individual payers face a classic free rider problem. 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.
- **Registry design.** Clinical registries are most valuable if they include long-term, follow-up data. Doing so increases both the cost and time required to reach a decision. If manufactures are required to fund registries, there is certain to be significant debate over how much data is “enough.”
- **Transparency.** Transparency is essential for the credibility of registry data regardless of the research sponsor. Participants believed that the greatest credibility and impact would come from central participation of medical specialty societies.
- **Methods improvement.** While most participants believe RCTs are the gold standard, very few industries other than medicine require RCTs to support decision making. With the high cost of RCTs and the capabilities to collect and analyze observational data, participants called for a “methods summit” to find ways to use observational methods with greater confidence. Other participants voiced the need for increased efforts to reduce the complexity and cost of randomized trials.

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Conference presentations and a more detailed proceedings document are available at www.healthindustryforum.org*

The Health Industry Forum is based at Brandeis University and chaired by Professor Stuart Altman. The Forum brings together public policy experts and senior executives from leading healthcare organizations to address challenging health policy issues. The Forum conducts independent, objective policy analysis and provides neutral venues where stakeholders work together to develop practical, actionable strategies to improve the quality and value of the US healthcare system.

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