Stimulus Funds Force Hard Look at Comparative Effectiveness Research

By Rabiya S. Tuma

Two much-anticipated national reports on comparative effectiveness research appeared at the end of June, a first step toward spending the economic stimulus funds intended to compare different medical interventions, improve medical care, and ultimately help contain health care costs. Of the $1.1 billion in the American Recovery and Reinvestment Act allocated to comparative effectiveness research, the Office of the Secretary of Health and Human Services receives $400 million, the Agency for Healthcare Research and Quality (AHRQ) receives $300 million, and $400 million will go to the National Institutes of Health. The National Cancer Institute and other institutes at NIH hope to fund grants from the shared pot of money. But before that can happen, policy leaders need to decide just what constitutes comparative effectiveness research.

Even with the new reports—one from the Institute of Medicine (IOM) and one from the Federal Coordinating Council for Comparative Effectiveness Research—that remains a surprisingly open question.

“Comparative effectiveness research are three words that people have put together and decided sound great,” said Otis Brawley, M.D., chief medical officer of the American Cancer Society. “It is the trend right now. The general concept is that we frequently have more than one treatment and we don’t know which one is better. We need to compare them so we can use what is, first, the most effective and, second, the cheapest. Beyond that, the definition gets muddied because people take it to mean much more specific things that are incredibly different.”

The definition that has emerged from the two groups are broad and do not include cost effectiveness as a necessary component. They do emphasize, however, head to head comparisons of interventions and strategies—not necessarily treatments—and studies conducted in real-world populations, typical of physicians’ practice. The IOM also selected 100 current priorities for comparative effectiveness research, including seven that relate to cancer (see sidebar, p. 1039).

At a press conference, Harold Sox, M.D., editor of the *Annals of Internal Medicine*, and co-chair of the IOM committee, said the criteria for selecting priorities included three key elements: a focus on comparing active interventions; evaluating effectiveness in typical practice settings; and identifying what patient characteristics would predict benefit.

With general definitions and priorities supplied by the two reports, the momentum now moves to the Office of the Secretary of Health and Human Services, which must create a detailed plan of how to spend all the $1.1 billion; grants must be awarded by September 30, 2010. “This is where the rubber really meets the road,” said Robert Croyle, Ph.D., director of the Division of Cancer Control and Population Sciences at the National Cancer Institute. That plan, mandated by Congress, is due July 30th.

However, with such a large pot of money available, discussions on how to spend it are already underway in the cancer community at large. In May, the Friends of Cancer Research, a non-profit organization that promotes collaboration between oncology stakeholders, sponsored its own report on the role of comparative effectiveness research in cancer. Twenty-six medical associations and advocacy groups have endorsed the white paper, including the American Cancer Society, the American Association for Cancer Research, and the American Society of Clinical Oncology.

“The purpose of the white paper is to begin to define some common language so that we can begin to debate the merits of various forms of comparative effectiveness research that go on,” said Kim Lyerly, M.D., director of the Duke Comprehensive Cancer Center in Durham, N.C., who co-chaired the Friends of Cancer Research committee. For a starting point, the report distinguishes between efficacy, which is a measure of how something works in an idealized trial setting, and effectiveness, which is a measure of how something works in regular clinical practice—in the real world.

The cancer advocacy group’s report also lays out what should be included in the comparative effectiveness research umbrella, including database analyses and clinical trials. “Some purists would say that comparative effectiveness research would have to analyze database information [and] that is all it is,” Lyerly said. “We think that in oncology, comparative effectiveness research should include clinical research and the generation of data—not just the analysis of existing data.”

**Research Infrastructure**

One reason that the oncology community expressed its views so soon after passage of the stimulus bill may be that cancer is ahead of other diseases in terms of comparative effectiveness research. Croyle and other experts said that oncologists are doing such studies now. “The cancer community has already been engaged in this domain and has substantial infrastructure...”
in place to answer a lot of questions in comparative effectiveness research that would be difficult to do in other disease domains in the near term,” Croyle said. Comparative effectiveness research has traditionally analyzed clinical outcomes using database reviews, and oncology already has extensive data sets, such as the NCI’s Surveillance, Epidemiology and End Results database and the Centers for Disease Control and Prevention cancer registries. Cancer outcome data are also available through the NCI-designated comprehensive cancer centers, the cooperative trials network, the Community Clinical Oncology Program, and the health maintenance organization cancer research network, which NCI has supported for several years and which covers more than 11 million individuals enrolled in managed-care plans across the country.

Croyle said he was pleased with the two new reports, including their emphasis on building the infrastructure needed to support comparative effectiveness research. “In cancer research, we are clearly positioned to be able to have complementary efforts that synergize with both reports and all three categories of money, the AHRQ piece, the NIH piece, and the Office of the Secretary piece. We certainly agree that building the data infrastructure is important, but we also have a lot to build on already. Some of the focus of both reports on dissemination is again a priority domain. For cancer research, the reports don’t require some radical realignment of NCI priorities; hopefully the cancer community will benefit from all categories of these funds.”
Despite having some infrastructure in place and experience with comparative effectiveness research, the cancer community has not always endorsed it enthusiastically. Diana Buist, Ph.D., associate investigator with Group Health Center for Health Studies in Seattle, said that Group Health has been doing this kind of research for about 20 years, including studies in cancer. She notes that because these studies are often observational in nature, the community has often undervalued them, but that they provide critical data about how health care is working in the real world. A recent report confirms that most CER studies to date have been observational (see Stat Bite).

For instance, Buist said, both tamoxifen and aromatase inhibitors have been shown to reduce breast cancer recurrence and mortality in clinical trials, but there are currently few data on whether patient adherence to the medications differs. If adherence does differ, then the long-term outcomes for the agents may differ as well. She acknowledges that problems of selection bias make interpreting this type of work more difficult (women with different characteristics may tend to choose one agent over the other). But statisticians are working on ways to compensate for these issues, she said, and the results of such studies can have important implications for cancer outcomes.

**Health Care Delivery**

Buist also argues that effectiveness research should not be limited to drugs or treatments. “If you limit comparative effectiveness research to treatment, it doesn’t answer a lot of questions we need [to answer] for the delivery of healthcare,” she said. Rather, effectiveness research should also examine what needs to be done to ensure good uptake and adherence to proven treatments or screening programs.

Buist’s view was echoed by the IOM report: approximately half of the priority items listed in the IOM report have to do, not with comparing interventions, but with delivery and translating research into practice. “There seems to be a really strong groundswell in both the community of nominators and in this committee to support this type of research. I think all of us recognize that this is something this country doesn’t do very well,” Sox said during the press conference.

One group that was relatively quiet was industry. Only 17 topic nominations came from device manufacturers and 11 from pharmaceutical or biologics manufacturers. When asked in interviews how they would like to see these monies spent, industry scientists said they want to see some of the federal funds used to better define patient populations and drug targets. “I would really like to see part of that money go toward the effort of understanding the heterogeneity of cancer and…selecting patients with specific mutations to define patient populations more carefully,” said Paolo Paoletti, M.D., senior vice president of research and development in the oncology unit at GlaxoSmithKline.

Murray Robinson, Ph.D., senior vice president of oncology at AVEO Pharmaceuticals in Boston, also argued for better patient selection and use of the money for biomarker research. He pointed to recent presentations at the annual meeting of the American Society of Clinical Oncology in which a traditional cytotoxic drug appeared to work better in an unselected patient population than a new targeted therapy. But when the targeted drug was used in a subset of patients who carried a specific genetic mutation, it provided enormous benefit, well beyond that of the cytotoxic agent.

In fact, Croyle said the NCI has similar goals for comparative effectiveness research and that he had taken particular note of a section in the IOM report that sets defining patient populations and subgroups as a key goal. “I think there is appropriate concern in the cancer community that comparative effectiveness research not overgeneralize or ignore the important biological differences within disease subtypes,” Croyle said. “But the way we are looking at it analytically is as two different sources of variation, one at a population and healthcare clinical level and the other at the level of cells and tumors.”

To deal with this complexity, the NCI put out two “Grand Opportunity” grant announcements in the spring, one that covers traditional comparative effectiveness research and the other that tackles effectiveness research in the context of personalized medicine. “We were mindful of both the mandate to expand the infrastructure and methods for current strategies in comparative effectiveness research,” Croyle said. “But at the same time we wanted to be strategic and make sure that the comparative effectiveness research we are scaling up is informed by some of the special challenges that we have in cancer.”

Interestingly, biomarker studies in cancer were one of the topics nominated not through the web form and the general public, but by committee members. Sox said that after they initially winnowed the pool of nominations down they noticed that several key topics were not addressed at all, including biomarkers, treatment strategies for ductal carcinoma in situ of the breast, and hepatitis.

When asked if there is a downside to comparative effectiveness research from an industry point of view, Robinson acknowledged that there is some concern that such data will be used to deny payment for expensive new agents that have shown efficacy in trials. He points to National Institute for Health and Clinical Excellence (NICE) in the United Kingdom, which initially denied coverage of some targeted agents because they were deemed too expensive. “I think that’s what we all worry about,” he said. GlaxoSmithKline’s Paoletti agreed: “I don’t think in the U.S. we should go in this direction.”

IOM committee members stressed during the press conference that although cost is part of the research question posed in a few priority items and may have been used as a criteria for which topics should be highest priority, the goal of comparative effectiveness research is about helping patients and doctors make more informed decisions, “not about setting cost effectiveness standards or anything else that has to do with access to treatment based...
Defining and Prioritizing Comparative Effectiveness Research

Two new reports set the stage for the spending of $1.2 billion in stimulus funds allotted to comparative effectiveness research, including the $400 million that will go to the NIH.

The Federal Coordinating Council, whose primary role is to coordinate existing and future comparative effectiveness research and thus avoid redundant efforts by different agencies, defines it as the conduct and synthesis of research comparing the benefits and harms of different interventions of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in ‘real world’ settings.”

The Institute of Medicine (IOM), charged with establishing national priorities for comparative effectiveness research, states that it is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care.

The IOM identified 100 priorities, culled from 2,600 suggestions received through an online questionnaire and other channels. The final list, ranked by quartiles, includes seven related to cancer:

- Compare the effectiveness of management strategies for localized prostate cancer (e.g., active surveillance, radical prostatectomy [conventional, robotic, and laparoscopic], and radiotherapy [conformal, brachytherapy, proton-beam, and intensity-modulated radiotherapy]) on survival, recurrence, side effects, quality of life, and costs.
- Compare the effectiveness of management strategies for ductal carcinoma in situ (DCIS).
- Compare the effectiveness of imaging technologies in diagnosing, staging, and monitoring patients with cancer including positron emission tomography (PET), magnetic resonance imaging (MRI), and computed tomography (CT).
- Compare the effectiveness of interventions (e.g., community-based multi-level interventions, simple health education, usual care) to reduce health disparities in cardiovascular disease, diabetes, cancer, musculoskeletal diseases, and birth outcomes.
- Compare the effectiveness of film-screen or digital mammography alone and mammography plus magnetic resonance imaging (MRI) in community practice-based screening for breast cancer in high-risk women of different ages, risk factors, and race or ethnicity.
- Compare the effectiveness of new screening technologies (such as fecal immunochemical tests and computed tomography [CT] colonography) and usual care (fecal occult blood tests and colonoscopy) in preventing colorectal cancer.
- Compare the effectiveness of different benefit design, utilization management, and cost-sharing strategies in improving health care access and quality in patients with chronic diseases (e.g., cancer, diabetes, heart disease).

An interactive file of the list of priority topics is available at www.iom.edu/cerpriorities.