Researchers Consider Value-of-Information Theory for Selecting Trials

By Charlie Schmidt

Oncology faces a dilemma with newer cancer drugs that are both too expensive and not effective enough, according to critics. Now some researchers and economists say that there’s a way to address that problem while drugs are still in the pipeline. Called value-of-information (VOI) theory, it can be used when deciding which clinical trials to fund, according to Larry Baker, D.O., a professor of internal medicine at the University of Michigan Medical School, Ann Arbor.

Baker chairs the Southwest Oncology Group (SWOG), one of the large National Cancer Institute–sponsored clinical trial cooperative groups. Rather than basing funding selections on expert opinion, gathered during roundtable reviewer discussions, Baker hopes to use what he says is a more rigorous process grounded in VOI theory. VOI, he said, will ideally force those designing trials to aim for wider effect differences between treatment and control groups. At the same time, it will make the selection process less vulnerable to visceral reviewer reactions, poor communication, and a tendency to define minor treatment gains as acceptable, he said.

“We’re looking for more significant clinical payoffs,” he said.

The VOI approach was presented at the last meeting of SWOG’s advisory board, with a supportive response, according to Baker. “We’ll be holding a retreat with our leadership in February, with an aim to get their endorsement,” he added. And an R01 grant application to develop the approach has been submitted to the NCI, he said, with Scott Ramsey, M.D., Ph.D., of the Fred Hutchinson Cancer Research Center in Seattle, as principal investigator.

New Approach to Uncertainty

Developed for environmental and engineering applications during the 1950s, VOI was later adapted for health care by Karl Claxton, Ph.D., and Mark Sculpher, Ph.D., both economists at the University of York in the UK. The technique puts a value on reducing uncertainty. It does this by calculating how the costs and consequences of decisions made with current evidence differ from those made with future evidence that resolves key unknowns. Should the future evidence prove more valuable than the current evidence, then undertaking research to obtain it makes sense, especially if the associated costs can be justified.

This approach is, of course, challenging, because it’s impossible to know in advance how a particular study will turn out. But that doesn’t mean that researchers can’t make educated guesses about what the data could look like. They can infer outcomes on the basis of preliminary studies in animals or people, for instance, or on more indirect information, such as knowledge of the drug’s mechanism of action.

A VOI analysis explicitly describes these predictions, along with downstream consequences for affected patient populations. “VOI leads you to ask, ‘How uncertain are we about a given issue in health care?’ ‘How much do we lose as a consequence of that uncertainty?’ and ‘How much do we gain by resolving it?’” Claxton explained.

To illustrate how SWOG might use VOI in its funding decisions, Fred Hutchinson’s Ramsey offered this example: Consider a drug that looks promising in phase II for pancreas cancer—which is rare, deadly, and resistant to therapy—versus a phase II trial for a drug in breast cancer with positive lymph nodes, which is common, not so deadly, and for which many, albeit imperfect, treatments are available. The VOI approach, he explained, would model trial costs, number of future patients likely to be affected by either disease, potential clinical benefits from treatment, and drug costs to payers, with each parameter contributing to an overall estimate of the treatment’s clinical value. If the quality of the science behind those parameters was similar, he said, SWOG might want to go with the trial that offers information with the most value, i.e., the best VOI.

VOI ordinarily presents options in financial terms so that researchers can compare how medical value, measured in quality-adjusted life-years (QALYs), for instance, varies among competing clinical trials. QALYs assign monetary value to 1 year of life saved by treatment, adjusted for the loss in quality from drug side effects and other symptoms of being sick. Countries with national health care use QALYs to compare expected societal benefits from one treatment versus another. The UK’s Health Technology Assessment Program, for example, which selects clinical trials for funding, bases those decisions in part on a QALY-based VOI system.

But in the United States, where the medical economy is more diffuse, and where cost controls in health care are politically vulnerable, a monetized VOI system could be problematic. Neither Baker nor anyone else with a role in health care delivery wants to be seen as denying opportunities for medical improvement on the basis of cost.

“For us, monetizing VOI is the wrong approach,” he said flatly. “Sure, if two trials offer the same clinical benefits for different prices, then obviously you choose the one that’s less expensive. But things are rarely so simple.” And ideally, Baker added, clinical benefits expressed by VOI will not be limited to overall survival. “We would propose to choose the endpoint that would demonstrate the most clinical benefit,” he said. “If the endpoint is progression-free survival versus overall survival, then that’s fine. If the endpoint is volume decrease in tumor burden associated with increase in performance—this would need to be developed—then so be it.”
SWOG’s consideration of VOI is in partnership with Ramsey, who is both an oncologist and a health economist. Ramsey said that VOI could help SWOG lessen its chances of making two types of errors: giving treatments that don’t work and withholding treatments that would otherwise be effective.

“Both these errors have real consequences,” Ramsey said. “You’re either wasting money on unnecessary treatments, or you have patients suffering some preventable consequences of their illness or treatment. That raises the cost of care and imposes all sorts of additional burdens on society from lost productivity.”

Veil of Science
But VOI comes with important hurdles, not least of which is the challenge of explaining VOI to nonexperts. “The first response is confusion,” Ramsey said. “People have a hard time grasping what it means to quantify uncertainty. VOI requires that you build decision models that can seem abstract.”

Sculpher added that VOI perplexes even some economists, with its grounding in Bayesian rather than classical statistics. Whereas classical statistics deals in familiar constructs such as $P$ values and null hypotheses, Bayesian statistics deals in probabilities and distributions of potential outcomes. Indeed, model outputs from VOI are obtained from automated processes such as Monte Carlo analyses, which run simulated outcomes against each other thousands of times in various combinations.

Joshua Benner, Sc.D., a health economist at the Brookings Institution in Washington, D.C., worries that some might view VOI as an incomprehensible black box. “We need to do a better job at making VOI more accessible, so that folks understand what goes into it and what comes out,” he said. Benner is investigating whether VOI can prioritize comparative-effectiveness research in the United States, to which $1.1$ billion was allocated under the Obama administration’s economic stimulus plan.

That approach has some influential advocates, among them Mark McClellan, M.D., former commissioner of the U.S. Food and Drug Administration and director of the Centers for Medicare and Medicaid Services, now at the Brookings Institution. McClellan said in an e-mail that “some exciting work is under way to streamline the methods of VOI analysis so it can be used to assess a large number of potential research investments in a timely way.”

Peter Neumann, Sc.D., a professor at Tufts University School of Medicine in Boston, warns that VOI-enabled decision making could face a backlash from those who object to making funding choices so disputatiously. “Funding committees could face a perception that they’re hiding behind a veil of science and calculation,” he said. “And people who don’t like their conclusions might push back on those grounds.”

Defining Benefits
Another challenge, Neumann said, is that VOI originated from cost–benefit analysis, and most applications to date have used QALYs to compare how research alternatives match up around a shared financial metric. “They serve a very useful function in that regard, and it could be difficult to compare diverse treatments with a non-QALY-based system,” he said. “You need some sort of common currency, and that’s what QALYs offer—they can be applied to any disease, treatment, or intervention. So, it’s not clear what other metric you might use, although if you’re just comparing endpoints in oncology, this might not be so problematic.”

Still, although experts here tread carefully on the cost issue, drug prices are a constant concern. “We need to figure out costs in relation to effectiveness, and VOI will force that issue,” Ramsey said. “But this isn’t so much about cost control as it is about prioritizing research on both clinical and economic grounds,” he said. He pointed to trials now looking at long-term uses of drugs that cost thousands of dollars per month and may have little benefit. “If the expected benefit is just a few weeks of life, then that’s a terrible value proposition, and not one I would want to fund.”

Finally, some experts worry that VOI-based prioritization could undermine investments into rare diseases. VOI expresses benefits in population terms; that means that investments into highly prevalent diseases such as lung, breast, and colon cancer could be seen as more clinically valuable than investments into less common illnesses. McClellan cautioned that VOI could be helpful in setting research priorities only if it were used in conjunction with “other important considerations, such as the needs of vulnerable populations and patients with rare illnesses.”

Sculpher acknowledged that “by definition” VOI would ascribe less value to trials that benefit fewer patients. But he added that it’s not necessarily true that trials for rare diseases would lose out. That’s both because smaller trials cost less than large trials geared toward more common illnesses and because rare diseases typically have more associated uncertainties, he said. And under a VOI framework, the value of resolving uncertainty increases with the magnitude of the uncertainty.

But he added that decision makers here still need to determine how to define
treatment benefits. And modeling those benefits, as occurs with VOI, depends on a range of assumptions about the expected payback from research investments.

“That’s the reality in all this,” he said. “It’s a lot like trying to predict the weather—there’s a lot of uncertainty in those models, but we still use them and they help us make decisions in albeit imperfect ways.”

Sculpher sums up VOI as a way to ponder what we think we know and what we think we’re going to learn from additional information. “This is a conversation we need to have when our resources are limited and we have to make choices. And I think people fundamentally understand that.”

© Oxford University Press 2010. DOI: 10.1093/jnci/djq015