

Peter Pitts – 23rd February (Stockholm, Sweden)

Recently, I attended a conference of French pharmaceutical executives, legislators, and regulatory officials that focused on the theme “Economics and Ethics.” While the consensus was that ethics are foremost, economics came in a very close second.

This was particularly true when it came to a robust debate on “ethical standards based on resources.” In other words, ethics in the reality-based world.

During the conference, one leading consultant suggested that pharmaceutical development programs should not proceed beyond mid-stage clinical trials until the company developing a given molecule meets with reimbursement agencies to gauge the likelihood of a positive coverage decision based on clinical endpoints.

I found this not only frightening but wrongheaded. How could such a highly-paid consultant so completely miss the point? Healthcare systems exist to serve their citizens, not to act primarily as actuarial bean counters. Is financial prudence important? Certainly, but not at the expense of the right medicine for the right patient at the right time. That’s a medical decision. That’s ethics.

But when a healthcare system is a government-pay model, cost-based often trump patient-centric ethics. Consider the remarks of Thomas Lonngren, executive director of the European Medicines Agency, who warned that cost-benefit analysis could become a barrier to patients getting certain safe and effective medicines. “It could come to a situation where we are approving a product based on efficacy, safety and quality,” he said, “...but the patient can't get it because the health technology institute says it is not cost-effective.”

Today, health technology assessment is a short-term, shortsighted, politically-driven policy that results in one-size-fits-all medicine. While it may provide transitory savings in the short-term, current strategies result in a lower quality of care that result in higher healthcare costs over time.

Restrictive formularies and health care systems that deny patients access to the right medicine at the right time but pay for more invasive and expensive procedures later on have their priorities upside down.

So why is the current health technology assessment model enjoying such wide support? I believe it is because HTA drapes a veil of pseudo-science around the blunt instrument of one-size-fits-all price controls.

In the United Kingdom, Sir Michael Rawlins, chairman of United Kingdom’s National Institute for Health and Clinical Excellence or NICE, told the British House of Commons that comparative effectiveness, a means of health technology assessment, is not based on empirical research. “There is no empirical research anywhere in the

world, it is really based on the collective judgment of the health economists we have approached across the country,” he said. “It is elusive.”

The problem is that health technology assessment, as it is currently designed, places into conflict the short-term budgeting dilemmas of governments elected for relatively short periods of time with the ever-lengthening life spans of their electorates.

According to Professor Frank Lichtenberg of Columbia University, for health technology assessment to yield valid patient-centric and cost-wise decisions, it is necessary to have reliable estimates of not only cost and QALY, but of other inputs as well, such as VSLY, the value of a statistical life year.

Professor Lichtenberg believes that incorrect estimates of some or all of these key inputs are often used, and due to these estimation biases health technologies that are truly cost-effective may often be rejected as cost-ineffective. For the patient, these mistakes can be deadly.

Consider the QALY equation. It is an out-dated and blunt tool when you consider that, at \$50,000 per individual (at the high end), it is not even close to the most modest VSLY projection.

One study, by Kip Viscusi and Joseph Aldy, argues that the value of a statistical life for prime-aged workers has a median value of about \$7 million in the United States. A second study, by Kevin Murphy and Robert Topel, puts the VSLY at \$373,000.

Attention must be paid. If the devil is in the details (and it is), it’s time for a deep dive beyond simplistic and self-serving HTA perspectives on “comparative effectiveness.” But where will new evidence models come from?

So, where does HTA data come from?

Christian Behles, director and professor of drug regulatory affairs at the University of Bonn and an advisor to the German government, points out that while Germany’s Institute for Quality and Efficiency in Healthcare or IQWiG casts a suspicious eye on industry-designed pharmaco-economic studies, they use industry-sponsored randomized controlled trials as the basis of their comparative effectiveness findings.

He also notes that these randomized controlled trials were not designed for head-to-head comparisons. In other words, IQWiG embraces industry-sponsored data that was not designed to be used comparatively, while rejecting industry-sponsored data that was specifically designed to show the value of a new innovative medicine.

When is an industry study not an industry study? It seems that, for IQWiG, the answer is “when it’s convenient.”

What we need is new perspective and a new model – and they must both begin by explicitly acknowledging that the core philosophy must be a patient-centric proposition.

A health technology assessment model for the 21st Century should reflect and measure individual response to treatment based on the combination of genetic, clinical, and demographic factors that indicate what keep people healthy, improve their health, and prevent disease.

Our rapidly aging society demands a new healthcare paradigm capable of providing for its needs in the 21st century. Equality of care must be matched with quality of care.

Comparative effectiveness strives to show which medicines are most effective for any given disease state. Is there a “more effective” statin? A “more effective” treatment for depression?

But how do you compare two molecules (or three or more) that have different mechanisms of action or patients who respond differently to different medicine based on their personal genetic make-up?

Comparative effectiveness in its current form leads to a “one-size-fits-all” approach to healthcare, which means that it doesn’t fit anyone all that well.

The concept is good, but the tools are wrong. And the results are unacceptable. This is why it is so important for physicians to maintain the ability to combine study findings with their own experience, expertise and knowledge of the patient in order to make optimal treatment decisions.

Government sponsored studies that conduct head-to-head comparisons of drugs in “real world” clinical settings are regarded as a valuable source of information for such coverage and reimbursement decisions—if not necessarily for making clinical decisions.

Two such studies, the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE), study and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study, were two such “practice-based” clinical trials, sponsored in part by the National Institutes of Health, to determine whether older (cheaper) medicines were as effective in achieving certain clinical outcomes as newer (more expensive) ones.

The findings of both CATIE and ALLHAT were highly controversial, but one thing is crystal clear: even well-funded comparative effectiveness trials are swiftly superseded by trial designs based on better mechanistic understanding of disease pathways and pharmacogenomics. And, since most comparative effectiveness studies are underpowered, they don’t capture the genetic variations that explain differences in response to medicines by different patients.

When you use the same 20th century tools for clinical trial design – you get the same 20th century data. Not acceptable.

Those in favor of comparative effectiveness favor large scale randomized trials to compare drugs. The problem is that randomized trials tend to ignore differences in clinical outcomes due to side effects or genetic variations. The result is that researchers will most always find no difference in the effect of medicines, a result that is biased in favor of older, cheaper drugs.

But it's important to move beyond criticizing comparative effectiveness in its current form, and instead focus on creating a policy roadmap for integrating technologies and science that is more patient-centric.

We need a new model. We need to develop proposals that modernize the information used in the evaluation of new treatments. Just as the key scientific insights guiding the U.S. Food and Drug Administration's Critical Path program are genetic variations and biomedical informatics that predict and inform individual responses to treatment, we must establish a science-based process that incorporates the knowledge and tools of personalized medicine into HTA decision-making.

For example, the FDA, in cooperation with many interested parties, has developed a Critical Path opportunities list that provides 76 concrete examples of how new scientific discoveries in fields such as genomics and proteomics, imaging, and bioinformatics can be applied to predict the safety and efficacy of investigational medical products.

What we need is a Critical Path for Comparative Effectiveness to begin the process of developing a similar list of ways new discoveries and tools (such as electronic patient records) can be used to improve the predictive and prospective nature of healthcare technology assessment.

It's a complicated proposition, but an essential goal. Cost must never be allowed to trump care, and short-term savings must not be allowed to trump long-term outcomes. Just as we need new and better tools for drug development, so too do we need them for comparative effectiveness measurements.

Where you stand often depends on where you sit. If you're a payer (either public or private), saving money can often mean denying expensive care. If you're a patient, you might have another view.

In an era of personalized medicine, one-size-fits-all treatments and reimbursement strategies are dangerously outdated. We may not all agree on the answers – or even on the path to the answers -- but at least we can all agree that this is not, and must not be exclusively, a debate about saving money. It must be about patient care.