The Value of Observational Data in Health Care Decisions

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KEY POINTS . . .

Has the pace of scientific discovery outstripped the ability of the RCT to meet the needs of patients?

How can a Quality Adjusted Life Year have meaning without a Patient Adjusted Product Year?

How, on the date of FDA or EMA approval, can a product tested in 2 to 300 ideal patients in a controlled setting be assumed safe and effective for all patients in all circumstances?

The following article was based on a presentation given during the Second Plenary Session, "What Are the Advantages and Disadvantages of Using Observational Data as the Basis of Decision Making in Health Care? How Could This Affect the Future of Randomized Controlled Trials?" at the ISPOR 19th Annual International Meeting, May 31- June 4, 2014, Montreal, QC, Canada

Diagnosis related groups (DRGs) had not yet been implemented, solo practice was the norm, and Actifed was a prescription drug when I began practice in 1976. Much has changed since then, driven primarily by the rapid and ever-accelerating pace of discovery. But alas, much has not changed. Let us reflect on the issues or, perhaps looming crises that happens when progress meets stasis.

Data are not knowledge; data are numbers. In health care, knowledge is gained by the application of data to patients. Wisdom results from the proper application of knowledge to the right patient at the right time. How do we obtain the data, apply the results to the right patient, and know value has been added?

Since the mid-20th century, the Randomized Clinical Trial (RCT) has been considered the gold standard for evidence development. At the conclusion of a typical RCT that achieves statistical significance, we only know that, for a group of 200 ideal patients with no comorbidities, concurrent medications or behavioral problems, FDA requirements were met. The assumption then follows that: "...At the moment of licensing, an experimental therapy is presumptively transformed into a fully vetted, safe, efficacious therapy for all to use, with the expectation that it will work for everyone and be safe for all." In the real world, obtaining these results are doubtful, hence the notion of statistical significance as an intermediate outcome.

How do we get more accurate data? Clinical innovations must be followed throughout their life cycles with indications evolving along with experience. It is through this process that knowledge and wisdom can emerge. The domain of cancer research defines the current dilemma and opportunity. It is rapidly transforming itself from one which, since its inception, systematically administered chemotherapy to patients with cancers defined by a subjective pathologic description of microscopic appearance, to one which is defined by the unique characteristics of tumor genomes. Targeted genetic therapies are following closely behind. The implications of such a transformation to our understanding of cancers are profound. If, for example, rather than four or five pathologist-defined variants of breast cancer, there are hundreds of gene-specific mutations or translocations, the very nature of our understanding of the disease(s) breast cancer must be re-imagined. Randomized controlled trials are unimaginable considering the genetic diversity of the populations impacted by these diseases. Yet the need to develop evermore powerful and targeted intervention will be met.

What might the path forward look like? Observational studies, which the rules (guidelines) are now fairly well defined and accepted, must inevitably replace RCTs in many clinical settings. Observational studies would require close collaboration between innovators and payors who have the unique ability to track patients over extended periods of time. The opportunity to get promising products to the market earlier in their development for the potential benefit of those patients, and only those patients, most likely to benefit is clear. Progressive clinical indications would be linked to demonstrations of clinical efficacy. Older indications could be dropped if after-market experience proved the treatment to be less effective than anticipated.

What are the benefits of such collaboration? Even if there were no change to the research infrastructure as we know it today, consider how the addition of continual, longitudinal evidence (data) and experience might alter clinical research and its results. We would learn about domains that are unknown and largely unknowable today:

1. What happens to trial participants following the conclusion of a clinical trial?
2. What are the cumulative costs of care during and following a trial?

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3. Are benefits truly generalizable or do response rates vary based on ethnicity, sex, age, comorbidities, or other demographic factors?
4. Are harms similarly defined?
5. Can untreated patients be identified and offered therapy if trial results are affirmed by "real world" data?
6. Is a treatment failure really a treatment failure, or did the patient fail to comply or fail to fill a prescription?
7. For ultra-rare and rare diseases, can the identification of impacted potential patients help in accelerating accrual to clinical trials?"

That we could have arrived at the 14th year of the 21st century without consideration of these domains while amassing data, assessing and valuing clinical innovation defies logic, ethics, and business sense. New thinking, relationships, and infrastructure are called for. Elsewhere, this is known as adaptive licensing.

Health care is dangerous. Transparency and an understanding of the impact of innovations and discoveries on real patients in their own "real worlds" will make it safer. Much safer.

With respect to value, most of the world has accepted the Quality Adjusted Life Year (QALY) as the benchmark for coverage wherever a fixed-budget is allocated for health care. Although imperfect, a value of about $50-60,000 is considered the threshold to be crossed. If we can assign a value to a human life, why, then, can we not also do so for a product? Can we develop a parallel calculation to truly enable the calculation of value? I will call it the PAPY - the Patient Adjusted Product Year.

PAPY = **P**atient-**A**djusted **P**roduct **Y**ear

A product would be evaluated against patient-centered criteria such as:

- lack of other therapeutic options,
- survivability enhancement,
- lowered morbidity,
- similar outcomes for less money,
- better outcomes for the same money, etc.

One reason is that Industry indicates that such a scheme would discourage innovators and stifle research. Nonsense; this is looking into the wrong end of the telescope. Turn it around. If we get the formula right and could prove, for example, that a single week or two of therapy might really be worth $85,000, $100,000 or $125,000, would our research pipelines not once again fill with potential antibiotics to treat such global threats as methicillin-resistant staph and antibiotic resistant tuberculosis, gonococcus, and other emerging microbial threats to world health? Had we agreed on a reasonable definition of a PAPY (akin to the QALY) colchisine would still be priced at 3 cents per pill.

Unfortunately, when discussing value, price must be considered. The cost of health insurance and the overall cost of health care is the singular result of the cumulative prices of the products and services consumed by patients. Gleevic, for instance, is a truly remarkable product which, when introduced, transformed chronic myelomonocytic leukemia (CMML) from a fatal to a chronic disease (with virtually no side effects) literally overnight. The pills are priced at about $80,000 per year. So it is a rare disease, you might say. But based on the above on genomics and, say, breast cancer, is it not conceivable that all diseases will, someday, be considered rare? Could anyone afford that? Can value ever be determined by half-equations accounting only for clinical data and the value of a QALY? No -- price matters. So, as we evolve a new and better system for the creation and analysis of data relating to drug and device development and performance, with all players at the table, we must also rethink the definition of value. But getting better products to the market sooner begs the issue of improper or inappropriate utilization. This, too, must be addressed as we reconsider the pipeline for new products. Truth, honesty, and transparency must be the watchwords of those who would apply such technologies to patients.

Consider off-label drug and device use as another example of the loss of the potential contributions of any drug or device discovery process, old or new. "Korn's Definition" of an off-label drug prescription is a clinical trial with an "n" of 1, with no patient protections and no data collection. In a demonstrably unsafe delivery system, how can such practices be tolerated? Harmful and ineffective treatments will be given thousands of times over due to the lack of evidence (recorded data) related to the outcomes of such therapeutic adventures. A simple registry could solve the problem. Yet, such registries do not exist. Patients are often unaware of the harms and limited likelihood of benefits that are likely to accrue from such prescribing practices. After all, if an indication does not appear on a drug label, it probably means that the developer did not test it or, if it did, that it failed to meet FDA thresholds. Hence, the needs for cumulative information (data) about experiences from off label usage.

We have briefly explored gaps in knowledge where data meets stasis. Where gaps occur, harms accrue. When this is known, willful continuation of the status quo cannot be considered reasonable or ethical. Not in the practice of medicine. Not in the drug or device development industry. Not in accrediting agencies or boards. A model has been developed in Ontario that is worthy of international consideration, adaptation, and beta testing. Behaviors and activities by all participants in the health care enterprise must be examined and reexamined.

Health care is dangerous. Transparency and an understanding of the impact of innovations and discoveries on real patients in their own "real worlds" will make it safer. Much safer.

The creation of significantly significant data changes nothing. The safe, measured, and thoughtful introduction of data into clinical practice by competent, compassionate clinicians does. It leads us to wisdom. The nature of evidence (data), its clinical and monetary value in the arc of care, and the truthfulness with which we deal with what is known must all be reconsidered – soon. Clinicians and institutions that embrace these concepts and, more importantly, live by them in each of their clinical areas of expertise, must be those who choose to lead or who are asked to lead. Only then will we see the emergence of a safer, more ethical patient-centered delivery system. ■