The Role of Registries in Nutrition Health Economics and Outcomes Research

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The true value of any medical technology is rarely described exclusively by its price tag. To truly understand value (a product's cost relative to its benefit, ie, its cost-effectiveness), it is necessary to consider a product's immediate and beneath-the-surface impact in terms of both costs and outcomes.

An improved clinical outcome associated with a particular drug or device may entirely offset a seemingly expensive acquisition cost. The modest cost of a product may truly become the tip of a dangerous iceberg if a less effective or less efficient product, for example, leads to higher rates of admission for expensive hospitalizations, extensions of hospital stays, or readmissions. Hence, to be truly comprehensive, assessments of value must consider a variety of direct and indirect factors, including the product's price, physical properties, and ability to impact clinical outcomes (Figure).

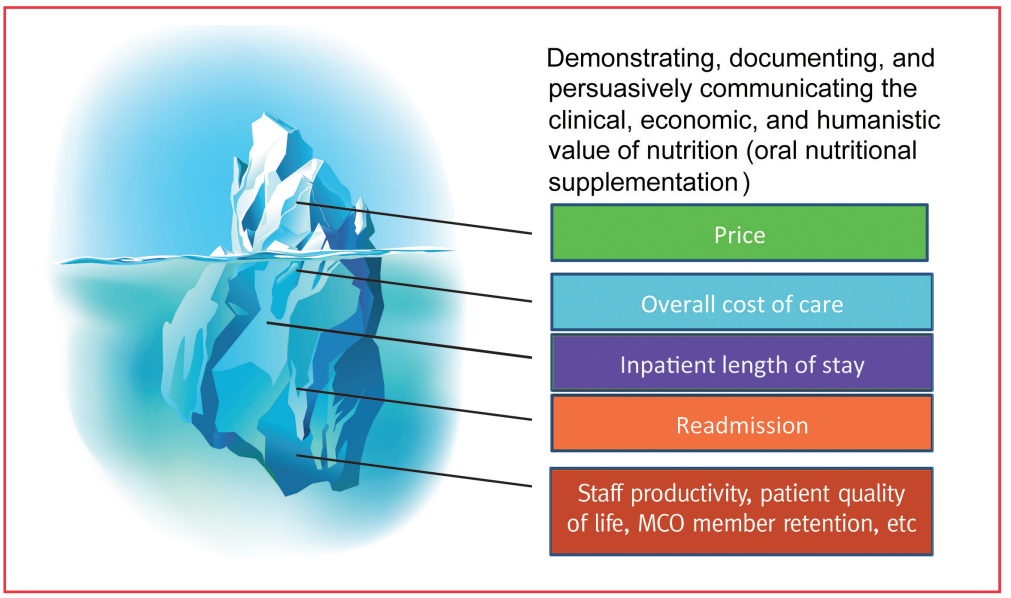

Figure. Nutrition health economics and outcomes research. Humanistic value is measured by patient-reported outcomes, such as patient satisfaction and health-related quality of life.

MCO=managed care organization

At the same time, however, one must weigh the quality of the evidence supporting each of these factors to better appreciate whether an opportunity to achieve improved cost-effectiveness is realistic or essentially theoretical. While findings from controlled research may indicate great promise for a product's value position, use in actual practice settings may reveal that the promise is less attainable.

Regrettably, the assessment of value is often more of an art than a science, inasmuch as it must rely on information obtained from situations that range from "highly controlled but artificial" to "uncontrolled but more reflective of the real world." Fundamentally, a solid understanding of the sources of data and their varying levels of quality can serve as an extremely useful foundation for making conclusions relating to any product's value.

Consider the case of automobile mileage, generally established through rigorous testing under controlled conditions on a test track. The reality is, however, that "your mileage may vary," considering a wide variety of real-world conditions that the average automobile encounters—different driving styles, different weather, and of course, actual traffic. Evaluating the value of a product used in medical care—the far more important consequences notwithstanding—sometimes is fraught with similar caveats, considering the sources and veracity of the evidence that is presented.

Well accepted as the gold standard underlying clinical research, randomized controlled trials (RCTs) strive to control for as much variation as possible in order to prove or disprove—within statistical tolerances—a hypothesis that typically asserts a product's effectiveness. Homogeneity is sought through careful site and patient selection, robust inclusion and exclusion criteria, and adherence to a rigid protocol, dictating the nature of the intervention for testing. As a result, users of such data can have greater reliance on the quality of the conclusions. Accordingly, such clinical trials merit independent monitoring and other quality assurance steps to maximize the reliability of their findings. As RCTs are generally the basis for regulatory approval of a product's release to the marketplace, our high expectations for the rigor of this form of research are appropriate.

However, even the most rigorous RCT is not without flaw in its structure, design, execution, and/or replicability. Indeed, the very controls that enhance the validity of findings from RCTs may cause a study to vary importantly from the conditions of actual medical practice. Therefore, a different form of research is required to understand treatment regimens and support processes employed in the real world—settings in which patients present for treatment with characteristics

and/or under conditions that were perhaps specifically excluded from RCTs, but that are truly reflective of medical reality. In addition, it is vital to understand the medical outcomes attainable from the use of products in the relatively uncontrolled conditions of actual medical practice.

Observational (noninterventional) patient registries can complement RCTs by focusing on the processes used and outcomes achieved in the real world. When designed carefully, registries can provide important insights into the best practices that can achieve the best outcomes, while examining further the impact of critical variation that occurs in actual medical practice. Rarely based on an *a priori* hypothesis and intentionally not structured to include the controls that improve the definitiveness of an RCT, patient registries are not without limitation, making it necessary to interpret their findings carefully. However, a prospective patient registry may nonetheless represent the best opportunity to understand a product's clinical, economic, and humanistic performance in the real world—information that is of increasing value to patients, providers, payers, regulators, and policy makers (Table).

Table. Patient Registries: Defining Characteristics

- Observational, naturalistic, real world
- Not driven by protocol *(per se)* nor randomization
- Not driven by hypothesis *(usually)*, but not purely exploratory and, therefore, not definitive
- Large, multicenter, long term *(typically)* to benefit from geographic and patient variability, and sheer numbers
- Scientific Advisory Panel *(recommended)*
- Active practitioner participants *(generally),* with clear participant benefits
- Institutional Review Board/Ethics Committee approval, informed consent, privacy protected *(always)*
- Ongoing analysis, reporting, publication, but finite time line *(typically)*
- Requires customized operational approach—data collection, monitoring, site management, project management, program management

The value of nutritional enhancement products provides a useful case in point. While controlled studies[1] have consistently demonstrated the clinical benefit of maintaining acceptable levels of nutrition in both hospital and ambulatory patient settings, systematic use of oral nutritional supplements is highly dependent on

both institutional policy and patient compliance, with the latter of even greater importance outside of the hospital setting. Accordingly, a patient registry may serve as the most appropriate mechanism for understanding the relationship between actual use of oral nutritional supplements and clinical outcomes, taking into account the considerable variability that exists in the real world in terms of actual patient consumption.

Without striving to prove what already is established in controlled clinical research, a registry can potentially establish a correlation between increased use and better outcomes, and may help explain the factors that improve the strength of the correlation (eg, relating to patient demography, hospital policy, and physician encouragement). Taken together, the data from controlled clinical trials and information derived from a more open observational registry may serve as a more robust "portfolio" of data upon which to base a decision.

Patient registries are employed to provide a view into real-world processes and outcomes in a wide variety of therapeutic areas, and are increasingly mandated by regulatory authorities as a condition of product approval (or as a requirement for maintaining marketing authorization). Indeed, while regulatory authorities fully expect findings from RCTs as the basis for approval decisions, increasingly they recognize that these controlled studies do not paint the entire picture, inasmuch as the homogeneous context is rarely reflective of actual product use. Many regulatory authorities appropriately view their authority as extending to the post-approval setting, as a product's safety profile is not truly informed until it accommodates real-world conditions.

In many countries, health authorities also are charged with stewardship over product value—clinical performance and cost-effectiveness—and, hence, are increasingly demanding data from observational research initiatives to better understand the extent to which the promise from RCTs is achievable in the real world.

Registries are characterized by the "wide net," which typically is cast in order to embrace the broadest possible continuum of patients, physicians, processes, and other variables that reflect a real-world scenario. Many registries include far larger numbers of patients and physician sites than were included in pre-approval studies. The benefit of such large numbers often merits advanced statistical techniques in developing matched cohorts to support more homogeneous between-group comparisons. However, some registries are designed only to focus on the

real-world performance of a single product. In these registries, it is possible to undertake pre-approval and post-approval (product exposure) comparisons in a manner in which patients serve as their own controls for comparison purposes.

A common expectation of a registry is a better understanding of how a product actually is used in the real world and what outcomes are attainable. Accordingly, rather than the clinical trialists who are more typically involved in controlled pre-approval research, a post-approval initiative would more likely seek to enroll actual medical practitioners (eg, primary care physicians who may rarely participate in clinical research). This is representative of an even broader spectrum of operational realities, which are necessary to consider carefully in the design and implementation of a registry.

Primary care physicians, for example, must receive appropriate training in regard to their role in patient enrollment and data collection, as well as in even more basic study components, such as patient privacy and external ethical approvals. These same physicians must have appropriate levels of support to maintain their enthusiasm in the registry, but not so much so that the very practices and outcomes under observation are themselves impacted. Indeed, while data quality is always an important issue, and a registry is no exception, site and data monitoring are not undertaken in the traditional sense. The protocol underlying an observational registry will not mandate a particular intervention, so monitoring and remedies for protocol violations generally are not required.

The design of a registry's operational plan must reflect a critical balance that considers analytical goals, data granularity, site fatigue, budget, and a variety of other factors. It is necessary to consider nuances every step of the way (eg, a conventional agreement designed for an investigator participating in an RCT is rarely appropriate for a registry, inasmuch as the level of risk and legal liability is dramatically different). Particularly precise communication about the registry is required to assure that appropriate expectations are set among all critical internal and external stakeholders.

One can extend the previously used metaphor—a vehicle designed for the test track may not perform well under actual traffic conditions—another way. Comparing an RCT to an observational study is like contrasting an 18-wheel truck with a compact car—not only are the intended uses far different, but the processes for constructing the vehicles are dramatically different as well. True, both vehicles are constructed with the same principles and basic structure in mind—wheels, engines, etc. However, it is clear that an assembly line designed to produce trucks will not

prove particularly efficient in manufacturing a compact car. Similarly for clinical research, the operational processes underlying an RCT generally are not compatible with those designed to support an observational study. Although data are generated and sites and patients are enrolled, that is often where the similarities end.

Perhaps the greatest challenge facing sponsors of observational research and registries, and users of findings derived from them, is that this is a relatively new paradigm, a different animal so to speak. Many researchers and readers of research have relatively little experience with observational research. Therefore, they bring to these uncontrolled, real-world programs the same expectations they hold for RCTs and the data derived from them. This disconnect can lead to considerable discomfort and, more importantly, the inadvertent over-engineering of what in most cases is a relatively simple research initiative that seeks, for all intents and purposes, merely to "look over the shoulder" of the physician practicing medicine.

In the interest of improving the reliability and replicability of findings from an observational registry, inexperienced researchers often impose components and controls that affect the very processes and outcomes that are observed naturally and, in so doing, compromise the fundamental strategic intent of the study.

An ongoing survey on observational research[2] casts further light on these issues. Motivated by the often-contradictory specifications describing an observational study (eg, a request for a purely observational study containing a randomization scheme), this survey of more than 1500 multidisciplinary professionals involved in or funding observational research revealed a number of critical concerns:

- Many functional areas have involvement in observational research studies, increasing the chances for confusion in lexicon and perspective
- Many different purposes underlie these studies, although the survey authors found that the study's fundamental purpose often was unclear to those involved in the study and was assumed to be for simply registrational (ie, approval) purposes
- Observational research goes by many names, again reflecting different training and operational comfort zones
- Sponsors have varying levels of comfort with observational research, and the survey authors note that this sense of discomfort can cause a very tangible impediment to consistency in expectations for observational research
- Most sponsors do not have defined processes for observational studies, relying on conventional processes for seeking external support, design, and budgeting, which sometimes are designed for more conventional RCTs

- Sponsors have varying expectations for the conclusiveness of findings from observational studies, and the survey authors specifically sought to challenge the notion that "all studies are created equal"
- Sponsors are concerned that regulatory/health authorities increasingly are asking for observational studies, but are not necessarily appreciative of their limitations and are imposing RCT-like expectations
- Sponsors plan to become increasingly involved in observational research, a finding that the survey authors noted as an even more critical call to action for improved consistency, understanding, and education

Registry sponsors are well advised to consider these findings when designing and developing program specifications to assure that the strategic goals that the registry seeks to achieve are the foundation for its operational plan. The most successful registries are exemplified by the up-front involvement of a multidisciplinary working group, with its members lending their unique perspectives to the overall design. It is necessary that the perspectives and experience of members of such a multidisciplinary group are in agreement with the overall strategic goals of the registry; hence, registries are typified by compromise and balance.

The design of any and all research initiatives must serve a specific purpose, and that specific purpose must impact the underlying design and operational structure of the study. Fundamentally, findings from RCTs and from observational studies can complement each other and provide an enriched understanding of a product's performance and, therefore, its value. However, users of research findings must appreciate that the assertion of value, and the strength and replicability of that assertion, will become directly associated with the design of the study.

Observational studies are used increasingly to document real-world performance, but because of the natural variability of the real world, users must not place inappropriate reliance on these findings or consider them as definitive and conclusive. By contrast, while findings from RCTs are perhaps more conclusive, if the controls that improve their reliability are poorly representative of reality, they too provide an imperfect picture. However, observational studies and RCTs, when taken together, along with other studies and analyses, represent a nearly complete assembly of the pieces to an informative puzzle.

Note: *Registries for Evaluating Patient Outcomes: A User's Guide,*[3] available through the Agency for Healthcare Research and Quality, is a valuable resource for designing, monitoring, and evaluating successful registries to collect patient outcome data.

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