

## Making the ‘MOST’ of Prospective Observational Studies

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Real-world evidence from scientifically valid and innovative observational studies is being required, increasingly, by governmental and commercial payers globally. The findings of these studies are also important input into the decisions of regulators and health system managers responsible for protecting population health, as well as the decisions of physicians managing the health of individual patients. In parallel with the intense attention being paid to the safety of medical interventions has come an equally vigorous scrutiny of their financial cost and value. Data from randomized controlled clinical trials (RCTs) remain the gold standard of evidence for assessing treatment efficacy as a result of their high internal validity.<sup>1,2</sup> However, the lack of external generalizability of RCTs makes them less appropriate for the measurement of the real-world *effectiveness* of interventions—such as outcomes like medication adherence and health care resource utilization.<sup>3-5</sup>

Observational studies have thus become a critical means to describe clinical practice and to measure its safety and value, the latter encompassing aspects of clinical, economic, and patient-reported outcomes. Growing interest in both comparative effectiveness research (CER),<sup>6-8</sup> and health economics and outcomes research (HEOR) patient registries<sup>9</sup> is evidence of this demand and the steady maturation of observational research methods. The evidence generation aspects of CER focus on whether, and to what extent, therapies work in typical practice settings. The outputs of CER research are useful for clinical guideline development, evidence-based medicine, and the broad social and economic assessment of health technologies. Prospective, observational, parallel cohort studies are commonly employed to examine the comparative effectiveness of alternative therapeutic strategies.<sup>10</sup> In the current environment, market access can depend on positive comparative data from the real-world setting.

Alongside the increasing importance of CER, pre- and post-market patient registries are also examples of a new emphasis placed on the inclusion of HEOR variables such as resource utilization, treatment satisfaction, and health-related quality of life (HRQoL). A registry could be considered the ultimate outcomes research project, with the opportunity to prospectively collect real-world data on effectiveness, safety, HRQoL, satisfaction, resource utilization, costs, work loss, productivity, and other outcomes that are relevant to the overall assessment of the value of health care products and services.<sup>11</sup>

Observational HEOR registries can offer some important advantages over randomized clinical trials.<sup>5</sup> Contributing to their value, for example, is their relatively longer duration and their broader and less restrictive patient selection criteria, which permit the enrollment of real-world patients who are typically excluded from RCTs as a result of either comorbid clinical characteristics or demographics.

To achieve the **MOST** appropriate prospective observational study design for the intended purpose, multi-disciplinary research teams that offer expertise in the product’s market landscape, streamlined, global clinical operations, study design and methodology, and technological innovation are warranted. All of these capabilities are critical for the successful design and execution of the study.

- **Market Landscape** An in-depth understanding of a product’s market and competitive landscape is imperative. For example, knowledge of usual care treatment comparators, per product label target patient populations and sub-populations of interest; product uptake patterns; physician and regulatory perspectives on medical need; and the benefits of study participation can impact the ultimate design employed. Preliminary efforts aimed at achieving a better understanding of the views and perspectives of various marketplace stakeholders may

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be a worthwhile investment early in the design and conceptualization phase of the observational study under consideration. Similarly, it can be advantageous to build strategic opportunities to collect survey or interview data from physicians or payers at the study sites directly into the observational study launch process, outside of the study protocol. The convenience of utilizing the study framework as a “Trojan Horse” can permit efficient supplementary data collection in relation to stakeholder perceptions of unmet need, clinical and economic benefits, site characteristics, and even local treatment guidelines, which can aid in the interpretation of study results by putting the data into context.

- **Operations** Understanding the operational feasibility of a proposed observational design is key to study success. As these types of studies are designed to better understand the real-world outcomes of a patient population, minimizing protocol-mandated visits and extraneous data collection in an effort to streamline the study and decrease overall investigator burden are necessary. In short, observational studies are less burdensome on investigators, clinical sites, and patients than typical Phase II/III clinical trials. Once implemented, the ability to respond operationally to challenges typical of late phase research, such as the frequent need for non-academic, routine medical care investigators and study sites, slow or highly variable rates of patient enrollment, and investigator and/or patient sub-optimal or non-compliance to study processes, is also an important determinant of success. Operational leadership must be proactive, innovative, and remain flexible enough to anticipate the most formidable of challenges before they arise.
- **Science and Strategy** An optimal prospective observational study design requires scientific leadership and methodological expertise in various and diverse disciplines—epidemiology, biostatistics, health economics, patient-reported outcomes, as well as pricing and reimbursement. Moreover, expertise in

strategic evidence generation that can inform the identification and prioritization of specific data requirements for key stakeholders, and minimize or streamline data collection burden to sites or patients, is also highly beneficial. The process by which each study design parameter is considered to achieve a final refined set of study design specifications can be an arduous and time-consuming process for a project team but is well worth the investment.

- **Technology** Technology should most certainly not drive study design, but it is an important tool to be used to improve the operational efficiency of studies. Innovative data collection technologies that fit seamlessly into site practice, or even a patient’s daily routine at home or work, can do much to support an observational research study. Additionally, regardless of how data are collected, whether via electronic data capture (EDC), interactive voice/web response system (IVRS/IWRS), live call center support, etc., technologies can support the need to access data practically in real time, permitting rapid interim and data analyses and dissemination.

In summary, real-world observational data can constitute key evidence of the value of health care technologies and services. Observational data including HRQoL, resource utilization, medication compliance, lost productivity due to illness, or even caregiver time spent providing informal care can contribute to a comprehensive empirical evidence base, which can be drawn upon to better understand unmet clinical need and to support the optimal use of medical technologies. Faced with a myriad of prospective observational study design possibilities, multi-disciplinary and collaborative teams must aim for the right level of real-world evidence for the right purpose. Moreover, in the all too common context of research time and funding constraints, scientific credibility and validity in relation to targeted data gathering must be balanced with market place knowledge, practicality, and efficiency. Randomized controlled clinical trials are not ideal for the gathering of effectiveness data, and well-designed practical trials are often cost

prohibitive. However, important and useful data can be gathered using well designed and executed prospective observational studies. As one author asserts, “the popular belief that only randomized, controlled, clinical trials produce trustworthy results and that all observational studies are misleading does a disservice to patient care, clinical investigation, and the education of health care professionals.”<sup>12</sup>

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