Evaluating the Optimal Approach to Address the Research Question: What are the Trade-Offs Among Observational Study Designs?

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Observational data are often required to meet complex mandates by regulators and payers to demonstrate real-world product value, safety, and effectiveness. Guidelines on using real-world evidence exist[1], as well as questionnaires to assess the relevance (extent to which findings, if accurate, apply to the setting of interest to the decision maker) and credibility (extent to which the study findings accurately answer the study question) of observational studies.[2] These documents, as well as numerous Good Practice Task Force findings[3-6], set an expectation of scientific rigor and relevance. However, choices still exist in selecting the optimal approach to addressing the research question(s).

So many possibilities ... selecting the optimal approach

A number of study types can be executed that result in tailored, fit for purpose data to demonstrate real-world value of biopharmaceutical products and medical devices. These data may be used to demonstrate unmet need, populate and validate economic models, and aid in the development and implementation of PRO instruments. These can include literature-based meta-research techniques, database analytics, medical chart reviews, surveys, and prospective studies.

The selection process should be grounded in good research practices and consider the following:

- What are the key research questions?
- Who is the target audience for the findings?

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- Who are the patients of interest and how best can you identify them?
- What are the design considerations associated with the research questions?
- What are the timeline and resource constraints?

What are the key research questions?

Often, researchers have a number of questions they are interested in addressing with an observational study and the list tends to grow as the excitement for the project expands among internal stakeholders. Teams are very interested in understanding the target population, unmet need, patient journey, treatment outcomes, and the potential role or impact for a product or disease area. It is important to agree which research questions take priority if trade-offs are to be made in the study design. Additionally, it is important to have well formulated questions to inform study design; ambiguous questions lead to a high risk of useless findings. Study design choice is highly influenced by the breadth and granularity of the essential elements of the research questions.

Cohort characterization

Characterizing the cohort of interest can have a number of components. One might be interested in the incidence and/or prevalence of the disease of interest, which can heighten the importance for understanding the underlying general population (i.e., the equation denominator) and new cases of the disease. Also, the target cohort may be such that it is important to describe their sociodemographic and clinical characteristics so that decision makers can readily identify the patients in routine clinical practice and/or within their health system. Lastly, identification of key risk factors for disease

progression, treatment failure, or an adverse outcome may be critical in supporting a value proposition for early intervention or use of an alternative treatment option.

Unmet need

Central to most product value propositions is residual unmet need in the target population – either to the patient, caregiver, and/or health system. The research questions relate to the impact of the disease on the patient's underlying physiology, severity of signs and symptoms, clinical sequelae, functional status, and health-related quality of life. Depending on the perspective of the target audience, these questions can extend to assessing the associated impact on the caregiver, health system, or society. Often, this incorporates evaluating the effect, lack of effect, or risks of current standard of care.

Patient journey

Understanding the patient journey provides insight into the diagnostic and care pathway, timing of disease progression, and current treatment patterns. While sponsors may have an initial map of the journey from advisory boards or market research, data from observational studies may be vital for quantifying or monetizing the journey for burden of disease messages or to inform and provide data for economic models. Findings can be used to evaluate opportunities for improving patient care by changing the evaluation process or offering new and/or early intervention into the course of the disease. Design considerations include the breadth and heterogeneity of sites of care, providers, diagnostic and treatment options, and health system differences.

Treatment outcomes

Assessment of treatment outcomes via observational research frequently includes evaluation of current treatment options. This might include clinical effectiveness, safety, and/or treatment adherence as it is well recognized that while randomized clinical trials (RCTs) provide strong internal validity, they are limited by their generalizability to the "real world." Thus "real-world" evaluation of treatment outcomes may focus on diversity of the patient population, indications for use, long-term outcomes (both effectiveness and safety), and the influence of provider and patient behavior. In some instances, the essential purpose is to bridge between clinical trials of the new intervention and clinical practice; either because comparative assessment requires data for a particular measure that was not collected in the RCTs for the current standard of care, or because an essential study measure is not routinely assessed in clinical practice.

Economic impact

For any of the above elements (cohort characterization, unmet need, patient journey, treatment outcomes), description of the impact on the patient, health system or societal resources can be important. This can be reported as units of use (days lost from work, emergency

Case Study 1: Evaluating an established cohort from the payer perspective

Situation: *The sponsor is interested in four research questions in descending priority.*

1) What are the treatment patterns following diagnosis (well-defined by ICD-10 codes) for the subsequent year?

2) How often do patients switch treatments and what are the reasons for switching?

3) What is the time-to-disease progression as measured by a change in radiography?

4) What is the current prevalence of this cohort?

Topic	Administrative Database	Chart Review	Patient Survey	Longitudinal Observational
Treatment Pattern	***	**	*	***
Switching/Reason	*	**	**	***
Time-to-Disease Progression	*	**	*	***
Prevalence	***	*	**	**

* fair ** good *** excellent

Design consideration: *Bearing in mind the target audience being a payer, one might consider a chart review or longitudinal observational study design. However, mitigating circumstances such as the timeline until data are required or available budget might alter this choice.*

department visits, etc.) or as monetary costs. This is one area where it is particularly important to understand the granularity of detail required. For example, is it sufficient to report that an adverse event occurred, or is it critical to describe the specific procedures and associated resources for that event?

Who is the target audience for the findings?

Understanding the level of precision and robustness for the findings required by the target audience offers guidance on the design, endpoint selection, and cohort source. For example, in selecting a source cohort, if the study's target audience is a clinical development team that is finalizing a comparator arm for a randomized trial, broad representation of clinical practice is critical, while if the goal is to gain a detailed understanding of caregiver impact for a particular subgroup, a more targeted approach might be taken to identify the source cohort.

Internal intelligence

Questions asked by internal stakeholders such as portfolio planning, clinical development, and pricing might include 1) characterization of target populations; 2) description of the current treatment patterns, including order of treatment progression and use of combinations; 3) benchmarks of concurrent comorbidities, complications, and outcomes of care; and, 4) residual unmet need where a new option might be positioned.

External decision maker

Study design and source cohorts can vary widely among research for external decision makers (patients, providers, regulators, and payers) as each applies unique decision making criteria on availability, selection, and use of an intervention. For example, while payers and patients are interested in quality and cost, the measures of quality and the source of costs differ for each group. U.S. payers assess quality of chronic obstructive pulmonary disease (COPD) care by the presence of a spirometry assessment, while patients are interested in relief of symptoms and the ability to perform daily activities.

Who are the patients of interest and how best can you identify them?

Identification of the source cohort (or sampling framework) for a study is critical not only to the structure of study operations but also to the precision and robustness of the findings. Research questions which impact the selection of the sampling frame might include:

- What are the clinical characteristics of the target population? If, for example, the condition is rare or a product has a low market share, one might consider site based design (chart review, prospective observation) where one could gather granular data on the target population.
- How large are specific subgroups? One would need to consider a design which allows collection of data across a broader cohort where the subgroups exist. Challenges could exist if histological examinations or laboratory test results are needed that might not be available in an administrative database.
- Who are the treating clinicians? The source cohort for the study must include these prescribers. For example, using a general practitioner data source would not allow one to track chemotherapy patterns that must be followed by an oncologist.

What are the design considerations?

A number of additional challenges must be considered in designing a study.

Representativeness

If there is a priority to represent the target population, one must consider the approach to sample ascertainment. Consideration should be given to a source cohort that is similar to the population it represents, or in some cases consideration should be given to conducting the study in multiple source cohorts. For example, when it is known that there are differences in care and potentially outcomes based on health system/country differences.

Need for long-term follow-up

If long-term follow-up is critical, source cohorts either have the ability to track the participants continually over time, possibly independent of provider/payer, or have the ability to collect data intermittently without significant loss to follow-up.

Alignment to Clinical Trial Findings

While measurement of clinical practice endpoints in a randomized clinical trial allows for easier interpretation of study findings, this is not always possible. A real-world study may be designed to provide a bridge between the clinical trial results and longer term clinical outcomes (e.g., bridging between QTc interval length and the risk of sudden cardiac death).

Precision of the Estimate

While one can estimate the precision of an estimate with a specific degree of confidence (e.g., 95% confidence interval), there are a number of factors which can affect this. For example, there can be systematic bias in missing data, measurement error, specification error, etc.

To address these challenges, a hybrid design as Case Study 2 may be necessary.

Case Study 2: Hybrid design to address breadth of sample and granularity of endpoints

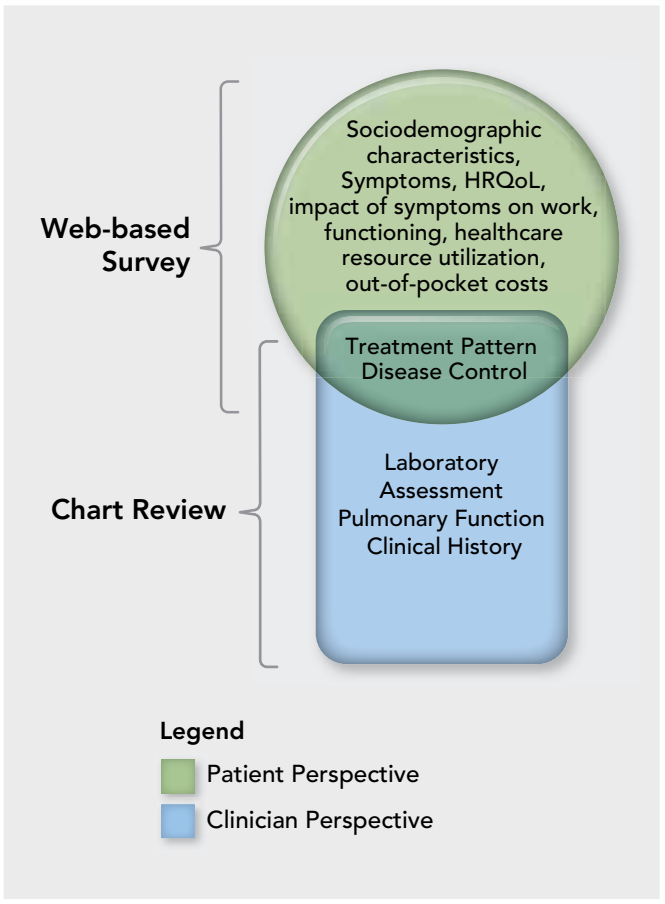
Situation: *The sponsor was interested in two key research questions with equal importance.*

1) What is the prevalence of the target population?

2) What is the disease burden and unmet need in the target population?

Measure of poorly controlled symptoms in the present maintenance treatment is indicative of a need to change therapy. However, among those with poorly controlled symptoms, the new product only treats those with an elevation of a specific serum marker and it is anticipated this is a small subgroup of the overall population. Furthermore, the primary endpoint in the clinical trial is measurement of pulmonary function.

Design Considerations: *As both detailed clinical characterization of those with poorly controlled disease and the presence of the biomarker and understanding the patient perspective of burden are important, a hybrid design chart review and a web-based patient survey was implemented. The chart review allowed the study team to capture the clinical detail associated with relevant biomarkers and clinical assessments, while the web-based patient survey provided the opportunity to describe the unmet need and impact of a breadth of patients with poorly controlled disease. A bridge using treatment patterns and measure of disease control was used to bridge between the data collection vehicles.*



Case Study 3. Same cohort, different design choice based on balance of data requirements and time constraints

Situation: *Two study teams considered a similar set of study parameters and concluded that different designs were the preferred choice. The decision between the two designs was driven by the requirement for longitudinal data, clinical confirmation of disease parameters, and timeline for data availability to decision makers.*

Topic	Study 1	Study 2
Cohort	Any treatment status	Naïve to prophylaxis
Geography	Global	U.S. (plan for global)
Need for clinician diagnosis	Not important	Important
Primary question(s)	Characterization of Unmet need healthcare resource use (HRU), non-traditional care, QoL	Treatment specific experience
Timelines	<12 months	18-24 months
Decision	Web-based patient survey	Longitudinal site-based with patient survey with clinical evaluation

What are the timeline and resource constraints for this project?

While in an ideal world all study design and implementation decisions are driven by scientific rigor balancing internal and external validity, this is not the reality for most study sponsors. The timeline for data generation and interpretation to meet decision maker requirements can be short or there are resource constraints within the sponsoring organization. Thus the selected study design is based on an assessment of the possible approaches to consider the trade-offs between the interpretation/bias of the findings and available time and resources. Even with similar research questions and similar target populations, different choices can be made, as seen in Case Study 3.

Conclusion

While to the untrained observer, collection of real-world evidence may seem "easier" than collecting data for a randomized clinical trial, I would suggest that the challenges are not easier; they are different. It is important to consider the breadth and importance of the research questions, the target audience for the findings, the target population being studied, as well as a number of other design challenges. Additionally, one must accept that there is rarely one perfect design which addresses all of these factors – let alone accounts for time and resource constraints. Regardless of the choice, good research practices for collecting and reporting real-world data are required. **The informed choice is yours!**

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