

# An Algorithmic Approach to Optimal Study Design for HEOR and Real-World Evidence

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**The algorithm presented in this paper attempts to strike a practical balance between simplicity and comprehensiveness in helping steer researchers and their colleagues to appropriate research designs for outcomes research and value demonstration.**

## INTRODUCTION

Real-world data (RWD) and real-world evidence (RWE) are commonplace terms among health economics outcomes research (HEOR) and pharmacoepidemiology professionals, but these are now the subject of broadened interest within biopharma, medical device, and clinical research organizations. This has been fueled by a number of factors, with the December 2018 release of FDA's Real-World Evidence Program Framework likely being the most prominent reason for non-HEOR staff to hop on board the RWE bandwagon.<sup>1</sup>

This phenomenon presents a variety of challenges, including the need to establish agreed-upon terminology and common understanding of the available methodologic approaches for RWE generation. Most everyone within biopharma understands the tools of clinical research and the randomized controlled trial (RCT) design, but far fewer are familiar with RWD sources, methods of analyses of these, prospective approaches to RWD collection, and pragmatic clinical trials. The wider array of research methodologies can be daunting and make it difficult to find a path forward.

Health economists have faced this challenge before on a variety of fronts, including deciding on the appropriate choice of modeling approach in cost-effectiveness analysis. In these instances, algorithms have proven useful as a guide to optimal model design given the nature of the patient population, disease of interest, and treatments under consideration.<sup>2-4</sup>

An algorithmic approach might also be useful to provide high-level guidance on optimal study design in outcomes research and value demonstration—to date, however, no such algorithm has been provided. The purpose of this paper is to address this gap and provide a framework to facilitate discussions of real-world research design involving colleagues of varying degrees of technical expertise.

## AN OVERVIEW OF THE ALGORITHM

The most frequently utilized study designs for outcomes research and value demonstration include:

- Retrospective analyses of computerized health records (administrative claims and/or electronic health records [EHRs])
- Manual chart review
- Prospective observational studies and registries
- Pragmatic trials
- Phase IV clinical trials
- Economic modeling

**Confusion abounds over terminology and the wide range of research designs available for outcomes research and value demonstration.**

The algorithm depicted in the figure begins at the top and systematically leads the user to one of the research designs along the bottom. It consists of a series of structured questions, most involving yes/no responses, as follows:

- 1) Is the study focused on an intervention?
- 2) If so, is the intervention on the market?
- 3) Are data needed for the study available from existing sources?
- 4) If so, are those existing sources accessible in computerized form (i.e., in administrative claims or electronic medical records [EMRs])?
- 5) Is the study intended to be comparative?
- 6) If so, is the scientific rigor of randomization needed?
- 7) If so, is the study setting real world?
- 8) If the intervention is not on the market, is the study intended to assess product value?

Responding to each of these questions within the structure of the algorithm successfully guides the researcher to 1 of 6 different research designs identified above and depicted at the bottom of the figure.

## STEPPING THROUGH THE ALGORITHM

Question #1 asks whether or not the study is focused on a product. In nearly all instances, what we mean by “product” is a drug, a biologic, or a medical device. However, in some instances, the focus might be on a medical procedure, such as a surgical intervention or diagnostic test. Studies that are not product-focused will typically be disease-focused, emphasizing the following kinds of measures:

- Epidemiologic: incidence, prevalence, morbidity, mortality
- Economic: healthcare utilization, costs of care, treatment patterns
- Humanistic: disease burden, patient-reported outcomes (PROs), health-related quality of life, utilities

If the study is not product-focused, Question #3 asks whether or not data

on study measures are available from existing sources. It may be that all, some, or none of the data are available from existing sources. If all or some are available from existing sources, there is potential for conducting the study as a “hybrid” retro-to-prospective data collection effort that combines different data sources, as shown in the algorithm.

Question #4 asks whether or not the data are available in computerized form. In almost all instances, computerized data will be in the form of administrative billing claims or EMRs. If the answer is yes, then a retrospective database analysis could be performed. If the answer is no, then a manual chart review would be in order.

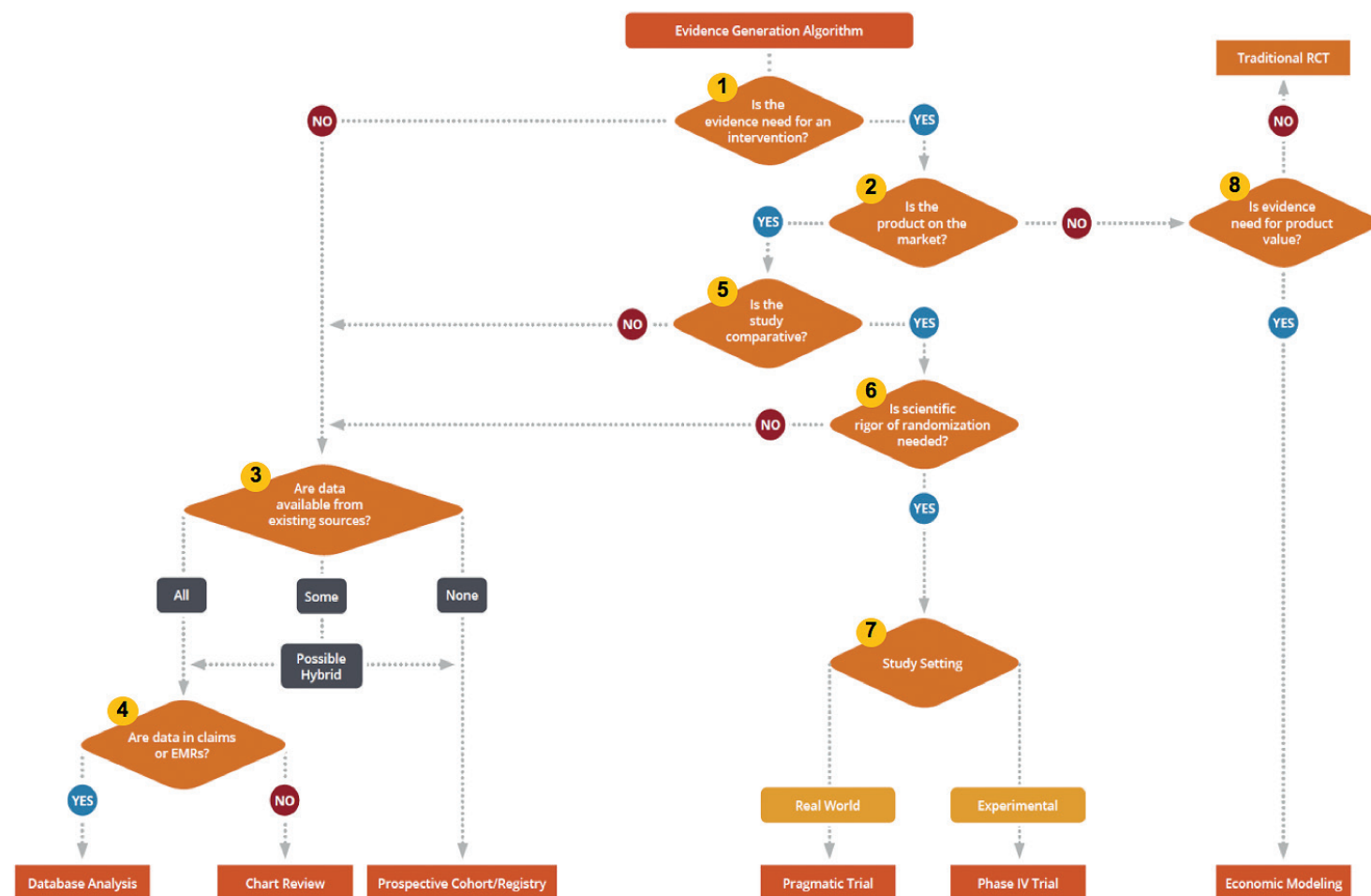
If none of the data are available from existing sources, or if a hybrid approach is being used, then the study would be classified as prospective observational

or disease registry. From a methodologic perspective, each of these study types would be considered noninterventive, because the research does not impact the treatment decisions or care processes being observed. Regulatory classifications might differ, however.

Going back to Question #1, if the study is indeed product-focused, then Question #2 asks whether or not the product is currently on the market. This is usually a rather straightforward question to discern based on dates of regulatory approval and market launch in relation to the timing of the study.

If the product is on the market, Question #5 asks whether or not the study is comparative in nature, involving head-to-head generation of results for 2 or more interventions. In those instances where this is not obvious, a comparative analysis might be indicated by reference

Figure. An Algorithm to Select Optimal Study Design for Outcomes Research & Value Demonstration



to such terms as:

- Comparative effectiveness analysis
- Relative effectiveness analysis
- Usual care (eg, drug A versus usual care)
- Standard care (eg, drug A versus standard care)

If the study is not comparative, the algorithm takes us back to the availability of existing data sources, Questions #3 and #4. Potential study types would then include database analyses, manual chart reviews, prospective observational, or registry. In this instance, though, it would be a product registry rather than a disease registry. Even though product-focused, all of these study types would still be considered noninterventional by methodologists. However, here too, regulatory classifications might differ.

If the study is comparative, Question #6 asks whether or not the scientific rigor of randomized treatment allocation is desired. If the answer is no, the algorithm takes us back over to the noninterventional study types and Questions #3 and #4 about suitability of existing data sources. If the answer is yes, it is necessary to assess the intended study setting to classify the study, which is the subject of Question #7.

The study setting may be experimental or real world. If real world, then the study would usually be classified as a pragmatic clinical trial, although this is somewhat of a gross simplification as there are multiple dimensions associated with the degree of trial “pragmatism.”<sup>5-6</sup> Pragmatic trials would have more-relaxed patient eligibility criteria and a less-intrusive study protocol, usually with active comparators. If experimental, then the study would usually be classified as a phase IV clinical trial. The methodologic classification for both study types is interventional.

If the product is not on the market, the study is more likely to be a phase II to III clinical trial and therefore, not in the real-world research realm. An exception occurs if the project is aimed at demonstrating product value, the possibility of which is raised by Question #8. If yes, it would be done most likely via economic modeling.

## CONCLUSIONS

Current trends in the health sector have fueled broader interest in RWE generation on the part of personnel within the biopharma, medical device, and contract research industries outside of the departments of HEOR and pharmacoepidemiology. Confusion abounds over terminology and the wide range of research designs available for outcomes research and value demonstration. While algorithms are widely used to provide guidance in economic modeling and clinical decision making, no such solution exists for selecting the most appropriate real-world research design. The above-described algorithm attempts to address this gap. Based on structured responses to a series of fairly simple questions regarding study focus and objectives, we have found through repeated use that this decision-making approach can facilitate the selection of optimal real-world research design. This algorithm may be useful to researchers, sponsors, stakeholders, and others interested in assessing alternative study designs for outcomes research and value demonstration. •

## REFERENCES

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## ADDITIONAL INFORMATION

*The preceding article was based on a poster presented at ISPOR 2018. To view released presentations from this conference, visit the ISPOR Scientific Presentation Database at [https://tools.ispor.org/RESEARCH\\_STUDY\\_DIGEST/research\\_index.asp](https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp).*