

Unlocking the value of observational research

5 things every researcher must know

The use of observational research is increasing, as regulators, payers, and patients require more long-term data on product safety and effectiveness, as well as demanding the product's demonstrated value in treating disease. PAREXEL® has the global, in-house, multidisciplinary experts in pharmacoepidemiology, pharmacovigilance, regulatory affairs, and research operations to optimize observational research on any scale – from highly specialized, local studies to comprehensive, global studies with thousands of sites and tens of thousands of patients.

Introduction

The use and scope of observational research studies within the pharmaceutical industry has increased over past decades to include clinical, patient-reported, economic, and other health outcomes endpoints, thereby giving value to multiple stakeholders for as many different purposes. Unlike randomized clinical trials, observational studies allow for the evaluation of the use and effects of healthcare products (including drugs, biologics, devices, vaccines) under conditions of usual care in a real world setting. This reference white paper will empower the reader to understand and apply the fundamental principles of observational research, and to take advantage of the value and potential of this approach.

This white paper gives an overview of the role of observational research in the pharmaceutical industry by exploring 5 basics:

1. The rationale for the conduct of observational research
2. A high level overview of the application of observational research in clinical development and life cycle management
3. Definitions of key observational research terms
4. Descriptions of the main types of observational research studies
5. A discussion of the governance of observational research studies and a review of the regulatory landscape in the EU and US with respect to regulation, legislation, and guidance documents that influence the role of observational research.

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When should I conduct an observational research study?

The driving forces to use observational research studies in the pharmaceutical industry are threefold:

1. When treatment information under conditions of usual care in a real-world setting is needed.
2. When the conduct of a clinical trial would be considered unethical.
3. When the conduct of an observational research study is methodologically superior to that of a clinical trial.

1. Even when there are published randomized clinical trials (RCT) results, there may be clinically or policy-important differences in treatment effectiveness in real-world use in comparison with the outcomes observed in RCTs.

Well-controlled randomized clinical trials are used to demonstrate a product's efficacy and safety before a product is approved, and are widely considered the gold standard of research methodology to assess treatment effects. However, even clinical trials have limitations that preclude or limit their usefulness in certain situations, especially for studies of safety and treatment effectiveness under conditions of usual care in a real world setting. Why? Because clinical trial populations rarely are representative of the post-market population to whom products are prescribed.

Limitations associated with clinical trials are commonly referred to as "The Three Toos."

Trials are considered 'too narrow' in that they have very restrictive inclusion and exclusion criteria, and these carefully selected patients may not reflect real life patients in whom the drug will be used. Patients in clinical trials may also receive better, more structured care than real life patients.

Trials are considered 'too few' in that they generally have substantially fewer patients than observational research studies, which (especially for retrospective database studies) can reach many thousands of patients and millions of patient-years¹ of exposure.

Trials are considered 'too short' with respect to the length of the clinical trial in contrast to the fact that some patients in the post-market setting may be prescribed a product over the remainder of their lifetime.

In summary, observational research studies typically have very broad inclusion criteria representative of real world exposure, sometimes including off-label use, can consist of hundreds to tens of thousands of patients (or, patient-years) and are often conducted over periods of years rather than months as are the majority of clinical trials.

3 driving forces to use observational research

Need for
real-world data

Ethical
considerations

Superior
methodology

¹ Patient-years is a measure of product exposure used in the denominator of incidence rates that is more informative than a count denominator comprised of patients who took a drug of interest, regardless of the length of exposure.

2. In the pharmaceutical industry, there are situations and circumstances where it would be unethical to conduct a clinical trial.

Consider the causal association between lung cancer and smoking, which was established through the conduct of observational research studies. Given that smoking is a known cause of lung cancer, it would now be unethical to conduct a randomized clinical trial where nonsmoking individuals would be randomized to a smoking arm and then asked to smoke for some period of time in order to determine the future risk of developing lung cancer. Therefore observational research can help uncover

the harmful effects when direct clinical research is not possible.

3. In many situations, the conduct of an observational research study can be methodologically superior to a clinical trial.

For example, a comparative effectiveness study of two approved products to evaluate the difference in treatment effects under conditions of usual care in a real world setting, or a natural burden of disease or treatment study. Only observational research methods are appropriate for these examples.

RCT or observational research study?

How would you assess the abuse deterrent qualities of a putative abuse deterrent opioid formulation among high-risk opioid abusers?

An abuse deterrent formulation embeds an opioid antagonist into the product, such that when a patient attempts to tamper (e.g. crush and swallow, inject, or snort) with the product it releases the opioid antagonist which blunts the euphoric effect of the opioid.

- Patients at high-risk of abuse are *a priori* likely to attempt to tamper with the product. Thus, the more ethical approach is to conduct an observational research study, the inherent design of which allows for the study of patients prescribed an opioid, as well as individuals who obtain an opioid through diversion (e.g. theft, provided by a family member, bought illegally). (FDA Advisory Committee Meeting, October 2010).

2

General applications of observational research

Observational research within the pharmaceutical industry has evolved to be an integral part of clinical development, life cycle management, and drug safety surveillance evaluations. Observational research is not a scientific discipline in itself, but a methodology central to a number of scientific disciplines. Epidemiologists and pharmaceutical outcomes staff are now being routinely integrated into clinical

development and brand teams at most mid-size and large companies across the industry to fill the extensive need for observational research methods in epidemiology, pharmacoepidemiology, pharmacoconomics and outcomes research, each of which has unique and complimentary roles within the pharmaceutical industry.

On the drug development and life cycle management continuum, companies frequently use observational research studies to:

- Define the natural history of a disease and patients' responses to treatment
- Estimate target population size
- Define patient populations suitable for clinical trials
- Standardize outcome measurements
- Estimate event rates to help determine a clinical trial's sample size and duration
- Improve patient-reported outcome measures for clinical trials
- Provide help in the design of long-term clinical outcome trials, to increase opportunities for patient follow-up
- Contribute to drug safety evaluations, including risk management strategies and effectiveness evaluations of risk minimization activities
- Conduct drug and vaccine safety and outcomes studies after marketing
- Evaluate the comparative effectiveness between approved products under conditions of usual care
- Identify health care resources and costs associated with treatment
- Identify drug utilization patterns for approved pharmaceuticals

The examples cited above are common within the pharmaceutical industry and are often championed by different groups and individuals within a company that may include drug safety and pharmacovigilance, epidemiology, medical affairs, health outcomes, marketing and commercial, and clinical development. PAREXEL has responded by aligning itself organizationally, hiring seasoned subject matter experts in observational research, and establishing a dedicated observational research leadership and operational delivery teams to provide strategic direction and oversight for all observational research studies.

Because of the current global economic climate and the need for sponsors to more efficiently apply resources, there is a growing trend for sponsors to ask CROs to conduct observational research studies that include a range of objectives.

It has become common to see studies with both clinical (effectiveness and safety) and value proposition endpoints. Additionally, post-approval safety studies required by regulatory agencies are increasingly being leveraged by sponsors to include additional endpoints in order to maximize the value of the study data at minimal extra costs. The goal is to be as cost-effective as possible in data collection efforts while maximizing the additional information gained, and to ensure that the study remains scientifically useful to participating investigators. This is accomplished, in part, by assessing the feasibility of additional data collection efforts, determining the scope of data collection needed to address additional secondary study objectives, and evaluating whether there are any regulatory or ethical considerations.

Start with the end in mind

The operational approach for the observational research examples listed above have in common one major theme that is reflected in nearly all relevant recommendations, which is to 'start with the end in mind.' That is, to first identify the scientific and commercial objectives of the observational research study, to determine how the study results will be used, and to define the target audiences. These factors greatly influence both the study design and the operational considerations related to the conduct of observational research studies.

Start with the end in mind



3

Key definitions and nomenclature

Observational research methods are employed within a number of different scientific disciplines used in the pharmaceutical industry, for example, epidemiology, pharmacoepidemiology, statistics, economics, pharmaceutical outcomes research and survey research. However, methodologies and terminology differences exist across those disciplines. It is common to hear the terms epidemiology, pharmacoepidemiology, observational, outcomes, noninterventional, nonexperimental, real-world, and registry used interchangeably in association with observational research in the pharmaceutical industry. While it is not factually correct to do so, the intended message is clearly understood to be “not a clinical trial.”

Noninterventional versus interventional

All observational research studies are non-interventional and are based on real-world data, which is defined loosely as data “not from a clinical trial.” Instead, real-world data are obtained under conditions of usual care between a health care provider and patient. In contrast, RCT by design are interventional and carefully specify treatment interaction between the health care provider and patient.

Registry

A registry is an organized system that uses observational research study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy

purposes (AHRQ 2010). For example, the Epidemiology, and End Results (SEER) Program of the U.S. National Cancer Institute is a national cancer registry designed to collect and provide information on cancer statistics in an effort to reduce the burden of cancer among the U.S. Population. It is used to drive US healthcare policy related to cancer prevention and control.

Although a registry is not an actual observational research study design, the term has evolved within the pharmaceutical industry as an umbrella term that covers all epidemiologic observational research studies. In fact, the Agency for Healthcare Research and Quality (AHRQ), along with industry sponsorship and collaboration, published a handbook in 2010 entitled *Registries for Evaluating Patient Outcomes: A User’s Guide*, 2nd edition. Chapter 3 of the handbook is called “Registry Design” and lists the most common epidemiologic observational research study designs as cohort, case-control, and case-cohort. These research study designs are discussed in the next section.

Therefore, when the term registry is used, it can be used as the umbrella term to represent the conduct of an observational research study; it can refer to one or more specific study designs used in epidemiologic observational research, such as the cohort study, case-control study or cross-sectional study; or, it can refer to an actual registry, similar to the SEER Cancer Registry. In the pharmaceutical industry, registries are often classified on the basis of disease or exposure. The most commonly used terms are disease (or, condition) registry and product (or, exposure) registry.

Scientific disciplines

Epidemiology is the scientific discipline dedicated to the study of the distribution and determinants of health and disease in human populations, and has broad applications within and outside of the pharmaceutical industry.

Pharmacoepidemiology is a sub-discipline of epidemiology that is primarily focused on studying the relationship between the use of pharmaceuticals (term is inclusive of drugs, devices, and biologics) and treatment-related outcomes, typically safety, under conditions of usual care in a real-world setting.

Pharmaceutical outcomes research focuses on the evaluation of health care interventions and their economic, clinical, and humanistic outcomes.

Outcomes research tends to focus on pharmacoconomics, pharmacoepidemiology, health services research, or drug policy and uses observational research methods to evaluate treatment and patient-reported outcomes, resource utilization, and costs associated with both disease and treatment.

The need to study real-world safety in the post-market setting was the driving force for the subsequent development of pharmacoepidemiology as a scientific discipline. Likewise, the need to evaluate health outcomes and economics led to the development of pharmaceutical outcomes field of study. These disciplines use observational research methods, but differ in their goals and objectives within the pharmaceutical industry, and their use of observational research terms and nomenclature. However, they are united in the goal to obtain real-world data under conditions of usual care and to conduct observational research studies with scientific rigor and integrity.

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Epidemiology study designs, data sources, and directionality

The three key, and most common, epidemiologic observational research study designs, found in virtually all epidemiology and pharmacoepidemiology reference text books are 1) the cohort study, 2) case-control study, 3) the cross-sectional study, and 4) case-cohort study. This section briefly describes each of these study designs; however, it is important to note that there are a number of other related study designs not discussed here.

Epidemiology study designs

Cohort study

Cohort studies follow a group of people who possess a characteristic over time to see if they develop a particular endpoint or outcome. Cohort studies are used for descriptive studies, as well as for studies seeking to evaluate comparative effectiveness and safety or quality of care. Cohort studies may include only people with exposures

(such as to a particular drug or class of drugs) or disease of interest. Cohort studies may also include one or more comparison groups for which data are collected using the same methods during the same period. A single cohort study may in fact include multiple cohorts, each defined by a common disease or exposure. Cohorts may be small, such as those focused on rare diseases, but often they target large groups of people (e.g., in safety studies), such as all users of a particular drug or device. Some limitations of registry-based cohort studies may include limited availability of treatment data and under-reporting of outcomes if a patient leaves the registry or is not adequately followed up. These limitations are typically considered and addressed when planning, conducting, analyzing, and interpreting a cohort study. Cohort studies of prospectively enrolled patients are referred to as “prospective cohort studies,” whereas cohort studies conducted within secondary data sources, such as a health care provider database, are referred to as a “retrospective cohort studies.” In the absence of the words prospective or retrospective, a cohort study is presumed to be prospective. See the section below on Sources of Data and Study Directionality for more discussion of the terms ‘retrospective’ and ‘prospective’.

Case-control study

A case-control study identifies patients on the basis of an outcome of interest, using either incident or prevalent cases, and is generally considered to be a retrospective study design. Cases are defined as patients who have experienced the outcome of interest, for example, a disease under study (e.g. atrial fibrillation), or an adverse event of interest (e.g. veno-occlusive disease). Controls are selected on the basis of being free of the outcome of interest and representative of the source population from which the cases arise. Exposures are then assessed by looking backwards in time at patients’ medical records or patient interviews. The case-control design is often used to identify and characterize the etiology of rare diseases because of its efficiency in terms of its ability to inform with respect to cost and time. In studies where extensive data collection is required, the case-control design is more

efficient and cost-effective than a cohort study because a case-control design collects information only from cases and a sample of controls (i.e., not from all possible controls), whereas a cohort study collects information on all subjects. A properly designed, conducted, analyzed and interpreted case-control study should usually yield study results similar to those expected from a cohort study of the population from which the cases were derived.

Matched case-control study design

One observational research methodological technique utilized in case-control studies is to make cases and controls more like each other, similar to the concept of randomization in clinical trials. This can be accomplished through a matched case-control study design, where controls are matched to cases on the basis of a number of a priori factors such as age, gender and race.

Incidence density sampling

Another important methodological technique is to utilize a special form of sampling of controls, referred to as incidence density sampling, to select controls from the source population. If this type of sampling is used, then the epidemiologic parameter (i.e., the odds ratio - a statistical measure of association between an outcome under study and an exposure of interest) being estimated from the case-control study is an unbiased estimator of the incidence rate ratio, which is the statistical parameter typically obtained from comparative prospective cohort studies. This is an important design and analytic feature of case-control studies, but is difficult to incorporate into study design considerations for pharmaceutical investigations. In fact, if the study design is being applied to existing registry data, the use of the cohort design may in fact be preferable since it avoids the challenge of selecting controls, which may introduce bias.

Cross-sectional study

In observational research investigations, the cohort and case-control studies are the two main study types most commonly employed, as they both can be used to assess causal associations – a fact not largely appreciated or widely accepted within the pharmaceutical

industry. The third, and much less common, epidemiologic study design is that of the cross-sectional study. Individuals are assessed at a single point in time with respect to an exposure of interest and outcome under study. The distinguishing feature of a cross-sectional study is the inability to establish a time sequence of events between exposure and outcome; therefore, cross-sectional studies cannot be used for causal assessments. However, they are useful in the effectiveness evaluations of risk management strategies and associated risk minimization activities. The cross-sectional study design is also useful for survey research, and in knowledge, attitudes and practices (KAP) studies of patients and or health care providers.

Case-cohort study

In contrast to the three studies described above (i.e., cohort, case-control and cross-sectional studies), the AHRQ handbook on Registries for Evaluating Patient Outcomes lists the three most common observational research study designs as the 1) cohort study, 2) case-control study and, 3) the case-cohort study. The latter study design, the case-cohort study, is simply a variant of the case-control study and utilizes a methodologically different type of sampling scheme for the selection of controls from the source population from which cases arise. Like cohort and case-control studies, the case-cohort study design can be used to establish causal associations.

Source of data

Data sources in observational research are classified as primary and secondary data. Primary data is simply any information collected in real time for a specific need, and secondary data refers to data that has already been collected for another purpose and is available for subsequent additional analyses. For example, randomized clinical trial data is considered to be primary data for the purposes of establishing safety and efficacy. However, if that data is later used for ad hoc analyses unrelated to the original purpose of the study, it is considered to be secondary data. The US SEER Cancer Registry collects primary data related to

policy-making purposes yet it is made publicly available for researchers and in this capacity it is referred to as secondary data, because the researchers did not collect the data themselves. There is an increasing need within the pharmaceutical industry for companies to request observational research studies using secondary data, which includes, for example, electronic health records, claims and administrative databases, prescription databases, national disease or exposure registries and a host of others. PAREXEL is meeting this need by establishing collaborations with several large health care provider institutions to obtain access to these valuable secondary data sources.

Study directionality

Study directionality refers to the terms retrospective and prospective. In epidemiology, these terms are used to explain the reference point between the investigator and the exposure of interest and the disease under study. If an investigator begins the conduct of an observational research study and both the exposure and outcome have already occurred, then the study is defined as retrospective. However, if both the exposure and outcome occur after the study begins, then the study is considered to be prospective. As you might imagine, there are hybrid study designs, and the most common one is where the exposure has already occurred (or is ongoing) and patients are enrolled into a registry (umbrella term) and outcomes are assessed prospectively during a follow-up period. Most retrospective studies are conducted using either patient medical records and chart abstraction techniques, or existing health records (e.g., medical, pharmacy, and laboratory) database.

It is important for CROs to demonstrate an understanding of sponsors' needs when responding to RFPs and to accurately identify the study design, study directionality, and sources of data, as it influences the strategic and operational considerations (and timelines / costs) associated with conducting observational research studies.

5 Governance

The governance of observational research from a regulatory perspective is not as fully developed in the pharmaceutical industry as it is for clinical trials. However, the past decade, has seen an explosion in the number of guidances, recommendations, legislation and activities related directly and indirectly to the use of observational research studies in the pharmaceutical industry.

Guidelines for Good Pharmacoeconomics and Epidemiology Practices (GPP)

ISPE

Most prominent are the International Society of Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP), originally published in 1996 with revisions in 2004 and 2007 that address the design, conduct, analysis, and reporting of pharmacoepidemiologic research. They are published in the peer-reviewed journal *Pharmacoepidemiology and Drug Safety*. It's important to note that GPP have the force of law in the European Union and are required by the EMA for the governance of the conduct of post-authorization safety studies (PASS), that is, instead of following the guideline for Good Clinical Practices (GCP). The US does not have corresponding legislation, but the Food and Drug Administration (FDA) Office of Surveillance and Epidemiology (OSE), along with the Office of New Drugs (OND), has the authority to mandate observational research studies as post-marketing requirements for newly approved or legacy pharmaceutical products, and there is an expectation by the FDA that such studies will comply with the GPP. Therefore, because of the highly regulated environment in which pharmaceutical products are developed, approved and studied after approval for various reasons, many companies and CROs have adopted the position that all pharmacoepidemiologic

research, regardless of the purpose, should be conducted under the governance of the GPP. The GPP, in turn, refers to other guidances, including GCP.

FDA

Complimentary to ISPE's GPP, there are a number of other guidances from regulatory agencies and professional societies specific to observational research studies. For example, in February 2011, the FDA published Draft Guidance for Industry and FDA Staff on Best Practices in the Conduct and Reporting of Pharmacoepidemiology Safety Studies using Electronic Healthcare Datasets. The following month, they also released the Guidance for Industry: Post-marketing Studies and Clinical Trials, where they define the terms 'studies' and 'trials' differently. FDA developed this guidance in response to the US Congress' legislation which defined these terms (studies and trials) in the Food and Drug Administration Amendments Act of 2007 (FDAAA). The FDA guidance cites examples for each of the two terms, and correctly classifies observational research under the term 'studies.' Thus, although the phrase 'epidemiology trial' is often used, it's not factually correct from either a scientific discipline or legislative perspective.

ISPOR

Another well-known and respected professional society which has contributed to recommendations for observational research is the International Society of Pharmacoecconomics and Outcomes Research (ISPOR). ISPOR is a scientific educational organization dedicated to the development and dissemination of good practices in health outcomes research. ISPOR has published a series of consensus documents on key outcomes research methods known as the ISPOR Good Outcomes Research Practices and are available online at their website (www.ispor.org).

These consensus documents cover a wide array of observational research methodology and include, for example, comparative effectiveness research methods; economic evaluation methods for measuring drug costs and the development of budget impact models; mathematical modeling methods for treatment outcomes and economic evaluations; observational research study methods for database studies and medication adherence; patient-reported outcomes methods; and quantitative risk-benefit methods.

European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP)

In May 2011, the EMA's European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) released a guide on Methodological Standards in Pharmacoepidemiology, which seeks to review existing methodological guidance for research in pharmacoepidemiology and pharmacovigilance. It provides a structured architecture for thinking and learning about observational research, with the aim to support high quality pharmacoepidemiological studies and to stimulate innovation that benefits patients and public health at large. The stated intention is not to duplicate text from existing guidelines and textbooks, but rather to offer the researcher a single overview document and web resource. For each topic covered in the ENCePP guide, readers are referred to specific existing guidance after a brief introduction or overview of the relevant text. It is an excellent, concise yet comprehensive, and up-to-date resource for anyone interested in observational research in the pharmaceutical industry.

Other sources

A partial list of other sources of recommendations related to observational research includes:

- International Association of Epidemiology (IEA) Good Epidemiology Practices, 2007. The IEA publishes the International Journal of Epidemiology. The GEP are IEA guidelines for proper conduct in epidemiologic research and can be found online at <http://www.ieaweb.org/>.

- Council for International Organizations of Medical Sciences (CIOMS) Guidelines for Ethical Review of Epidemiological Studies. These guidelines are referenced by the GPP and a summary can be found online at http://www.cioms.ch/frame_ethical_guidelines_2009.htm.
- Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): The STROBE Statement, 2007. The STROBE Statement was influenced by the work of the Consolidated Standards of Reporting Trials (CONSORT) Group and is indirectly referenced by the GPP. It can be found online at <http://www.strobe-statement.org/>.
- Meta-analysis of Observational Studies in Epidemiology (MOOSE), 2000
- ISPE Guidelines for Quality Conduct in Database Research in Pharmacoepidemiology, 2011
- Good Research for Comparative Effectiveness: GRACE Principles. These guidelines were developed for CER research in using observational research studies and were endorsed by ISPE in 2010. The GRACE Principles can be found online at <http://www.graceprinciples.org/prin.html>.
- EU EMA and US FDA Risk Management Guidances

Guidances

The International Society of Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) can be downloaded at: http://www.pharmacoepi.org/resources/ispe_guidelines_2008.pdf

FDA – Guidance for Industry: Post-marketing Studies and Clinical Trials: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080569.pdf>

FDA – Draft Guidance for Industry and FDA Staff on Best Practices in the Conduct and Reporting of Pharmacoepidemiology Safety Studies using Electronic Healthcare Datasets: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf>

ISPOR Good Outcomes Research Practices: http://www.ispor.org/workpaper/practices_index.asp

ENCePP Methodological Standards in Pharmacoepidemiology: http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE.pdf

Good Pharmacoepidemiology Practices (GPP)

Because of the regulatory and scientific importance attributed to the GPP, a few additional comments are warranted. The GPP defines pharmacoepidemiologic research as the study of the use and effects of health-care products, inclusive of pharmaceuticals, devices, and vaccines, and expanded its coverage in the 2007 version to include clinical, economic, and other health outcomes requiring study methods that were not covered in previous guidelines. Because pharmacoepidemiology is the scientific backbone of therapeutic risk management, inclusive of the process to assess a product's benefits and risks, and in the development, implementation, and evaluation of strategies to minimize the risk, the GPP also governs risk management evaluations (e.g., to quantitatively assess risk, and to evaluate risk minimization activities).

The GPP proposes minimum practices and procedures that should be considered to help ensure the quality and integrity of pharmacoepidemiologic research, and to provide adequate documentation of research methods and results. The GPP are not prescriptive for specific research methods, nor will adherence to guidelines guarantee valid research. The GPP state that scientific integrity (pharmacoepidemiologic studies conducted by a Clinical Research Organization (CRO) on behalf of a Sponsor) is a shared responsibility between the collaborating institutions. As an example, the GPP cite the following responsible entities: the Sponsor, the Principal Investigator (PI) who conducts the

study (who must be qualified in observational research methods), the organization who hires the PI, and the senior qualified epidemiology staff within the CRO. Thus, it is important in the outsourcing of observational research to ensure that a CRO has not only the operational expertise and GPP-compliant processes and procedures for study implementation, but also the ability to provide scientific oversight to ensure scientific integrity is maintained.

Continue exploring the value and potential of observational research

Subsequent white papers in this series will address critical operational aspects of observational research, contrast operational considerations between GCP and GPP studies, and will reveal when and how certain phase IV interventional trials studies can be operationalized using principles from observational research studies.

Visit the PAREXEL web site to learn more about our proven leadership in observational research and explore publications, podcasts and video. <http://www.parexel.com/services-and-capabilities/late-phase/observational-studies/>

Contact PAREXEL's PACE group for a customized executive briefing to see how observational research can add value to your clinical development and life cycle management activities.

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