

Postapproval Studies: More Critical and CHALLENGING THAN EVER



Phase IV data are in high demand by more stakeholders.

As the need for postapproval data reaches a critical point, the industry explores the multiple options and struggles to determine which methods are best for collecting and analyzing important data. There are as many ways to collect data with today's real-time technologies as there are data to collect, and not one single process can meet all of the needs of postapproval stakeholders.

Several of our experts point to patient registries as a viable approach and add that both prospective and retrospective techniques will remain important. Therefore, the best method is not a particular approach but rather a careful evaluation of the fundamental questions to be addressed by each research effort, and an understanding of how the information will be employed. In other words, our experts say, start with the end in mind.

Finding the Right Approach

In summary:

1. Registries provide opportunity for flexibility and adaptability.
2. Registries have real-world focus.
3. A single approach will not meet every postapproval study requirement.

DR. EMMA JAMES. SYNAGEVA BIOPHARMA. What would be considered best really depends on the question that's being asked, the degree of certainty required, in what population, and what the budget is. The different methods all have validity for certain questions, with associated strengths and weaknesses. Without clarity on this, it is extremely hard to get the study design right or be confident that the data will have utility to a range of decision-makers. In clinical practice, EHRs are viewed as important for collecting data, improving patient care, and reducing costs, and they may provide a powerful means to collect large amounts of postapproval

data in the future as data mining techniques become more sophisticated. EHRs and prescription databases are relatively quick and cheap to analyze, especially if retrospective data from individuals are sufficient. Prescription databases and pharmacovigilance databases are useful for signal detection, but they suffer from lack of comprehensive data entry. This means that results should be interpreted with caution — although this is a common theme in the observational research setting. Similarly, as we are far from a systemwide implementation of standardized EHRs, their utility is currently limited in terms of the wide variety of data that need to be collected across different healthcare systems, and despite advances, the growing diversity of clinic EHRs lack integration and interoperability with Internet-based biomedical databases. For population-based studies, Phase IV trials or registries may be more appropriate. Pragmatic clinical trials are often considered the gold standard for effectiveness research. They generally include a broader population than clinical trials designed to obtain regulatory approval, and so are more generalizable to the population being treated in the real world, providing answers about the risks, benefits, and costs of an intervention as they would occur in routine clinical practice; these should, of course, be run with due scientific rigor — i.e., randomized, blinded, and multicenter studies are best. However, they

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are complex to analyze, expensive to undertake, and there may be challenges in recruitment as the drug under study is available to be prescribed by clinicians; prospective observational studies such as registries are often conducted instead. Patient registries have predefined objectives and can be designed to maximize the available information by collecting both retrospective and prospective observational data on a variety of different parameters. They attempt to standardize longitudinal collection of data from physician records and those collected by other means, including prescription information, socioeconomic data, and patient-reported outcomes, and have the capability to evolve as more is learned about a given topic. Especially in the rare disease space, a registry may be designed to capture a wide variety of data over many years to learn about the disease itself, management practices, and barriers to treatment access regionally and globally, as well as to help develop meaningful relationships with physicians involved in patients' care, and to generate evidence to support treatment licensing and reimbursement. The PROs, which are generally subjective and considered to be softer endpoints, can be collected alongside harder clinical data to provide complementary evidence, and are useful for inclusion in cost-effectiveness models. Registries, however, are generally voluntary on the part of the physician and the patient; therefore, there are inherent biases in the data that need to be considered, as well as challenges in ensuring data quality and complete-

ness that must be considered through the life cycle of the study.

LEE KING. ICON. EHR databases, administrative claims data, physician records, or patient self-reports all have varying degrees of purpose and effectiveness in the capture of postapproval data. However, in my opinion, patient registries are generally the best way in which to gather or collate postapproval data. Registries, if properly designed, are flexible in nature, provide a great opportunity to not only bring together any number of data capture methodologies and systems in an efficient, and more importantly, an adaptable manner, but are also able to adapt to the ever-changing landscape of real-world medicine. In some cases, the prospective data collection method can be made more efficient by combining it with existing data sources. On the other hand, studies using retrospective data from administrative claims databases allow for a quick and inexpensive assessment of real-world treatment patterns, measurement of clinical outcomes, and evaluation of healthcare use. Retrospective database analyses are used to quantify the burden and cost of a disease, evaluate patterns of care, compare the performance of marketed products, and explore market opportunities for targeting a new product. They have limitations that can be mitigated if they are combined with prospective data collection. The required patients are identified through review of the database and then either



“ Use of robust medical informatics can be extremely successful in identifying potential sites with a high-volume target audience. ”

MARIA HARRISON / PRA

EXPERTS ►



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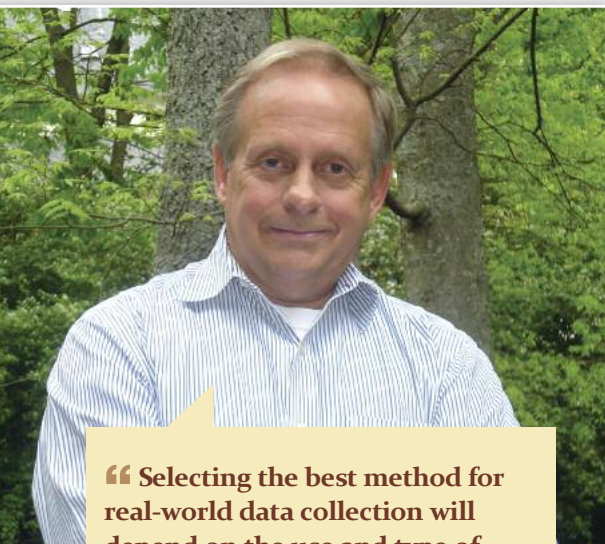
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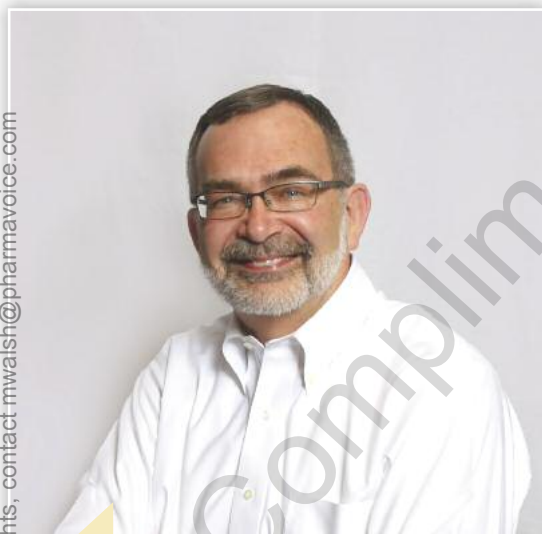
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“Selecting the best method for real-world data collection will depend on the use and type of data required.”

STEVE ALBRECHT / Chiltern International



“Despite advances in the electronic collection of data, the gathering of prospective information will continue to take greater importance in postapproval studies.”

DR. RON WEISHAAR / PharmaNet/i3

additional information is obtained from chart review — or perhaps examination of free-form notes from the EHR — or they are enrolled in a registry. In some cases, retrospective approaches are the only feasible way of addressing a question. For example, when assessing outcomes where there are multiple potential causes, it might not be feasible to prospectively collect all relevant information, and pre-collected information becomes the most efficient option for measuring strength of the association.

STEVE ALBRECHT. CHILTERN. In selecting the best method for real-world data collection, the method will depend on the use and type of data required. Registries provide a population-based real-world look at product use, effectiveness, safety, etc. If designed and initiated properly, registries can serve as a forum where stakeholders put their ongoing product knowledge base to the test in the real world. Registries are an excellent platform to combine varied data sources such as site, database sources, and PRO into one well-designed research application to study a disease or product. Registries are also adaptable while they are in progress, allowing for the incorporation of new ideas or information being generated by an event or trend. Registries provide design flexibility to the stakeholders facilitating focus on primary and secondary objectives, while using varied data sources and collection methods. Although randomized controlled trials (RCTs) have their place, these study designs lack real-world focus — populations for whom the product is prescribed but weren't studied in the RCT — and as a result, registries provide an excellent, versatile Phase IV choice.

NEAL MANTICK. PAREXEL. There is not one study design that is able to achieve the needs of every study objective and of every stakeholder. It is important to begin with the end in mind to understand the strategic, scientific, and commercial messages that are required to support the product in its current life cycle stage, the target audiences for those messages, and the desired timing of delivering the messages to those audiences. For example, understanding the results of a new product's pivotal study data relative to the current standards of care for a disease may be best served by a retrospective analysis of electronic health record databases. The retrospective data could be collected, analyzed, and presented to the target audiences in a relatively short amount of time. On the other hand, using a postmarketing study to better document emerging adverse events to supplement the

findings of the pivotal study in support of a new product approval may best be achieved by a prospective registry-like program. In general, prospective studies take a longer time to start up, to collect a sufficient amount of data, to analyze, and to publish the results compared with a retrospective study.

MARIA HARRISON. PRA. In today's world, there are many stakeholders who are interested in real-world data, such as regulatory authorities, reimbursement payers, physicians, patients, caregivers, and advocacy groups. Each group has a different perspective and goals, thus requiring different data sources. Secondary data sources, such as EMR, prescription databases, and chart-review, are good for high-level characteristic analyses, but lack some of the value provided by primary data sources. These include patient registries and safety-surveillance studies, where data such as quality of life, healthcare use, and patient reported outcomes can be captured directly from the patient through various methods specific to the population. There are various user-friendly technologies that capture patient data, such as Web-based ePRO, SMS, patient interviews, and portals.

DR. RON WEISHAAR. PHARMANET/i3. It is tempting to predict that the day is near when postapproval research will involve nothing more than accessing information from de-identified electronic medical records. Electronic analysis of prescribing records, claims databases, and medical records are being employed more frequently than ever before to provide a window through which the real world of medical care can be glimpsed. This view can offer particularly useful insights into evolving patterns of care for various conditions, such as the degree to which subtyping of cancer patients is being employed to guide various therapeutic regimens. However, the requirements for postapproval research are simply too varied to assume that a single approach can be employed to meet every need. Despite advances in the electronic collection of data, the gathering of prospective information will continue to take greater importance, since the core requirements for postapproval studies — determining risk and benefit — are difficult to achieve using retrospective approaches or surrogate markers. As countries around the globe become increasingly concerned with the escalating costs of new medications, reimbursement agencies and payers will require that postapproval studies include information collected directly from patients regarding the impact of such medications on their daily activities and their

overall reliance on the healthcare system. Likewise, governments charged with the welfare of their citizens will almost certainly mandate more registries and other types of observational studies to carefully examine the long-term safety of patients treated with newly approved products in real-world clinical settings. The best method for gathering postapproval data is not any particular approach, but rather a careful evaluation of the fundamental questions to be addressed by each research effort, and an understanding of the use for which the information will be employed. Once those considerations have been addressed, the appropriate method to employ for obtaining the necessary information is generally obvious.

Meeting the Challenges of Postapproval Patient Recruitment

To be successful, patient recruitment methods for postapproval registries must be conducted differently from the techniques used for other study phases. For the study to be effective,



“ Since no one study design is able to achieve the needs of every study stakeholder, it is important to begin with the end in mind. ”

NEAL MANTICK / Parexel International



“ A hybrid approach to gathering data is quite efficient, especially with the integrated technologies available today. ”

LEE KING / ICON Clinical Research

the sponsor must secure commitment from both the physician and patient, and both

parties must realize the value of the study and their continued support of it. Another impor-

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Critical Path Initiates ePRO Consortium

In response to the need for better measures of patient experience in clinical trials, particularly late-phase safety monitoring, Critical Path Institute (C-Path) established the Electronic Patient Reported Outcome (ePRO) Consortium comprising five founding firms — CRF Health, ERT, ICON, invivodata, and PHT — that provide innovative electronic data collection technologies for capturing patient reported outcome (PRO) endpoints in clinical trials. C-Path's role in the ePRO Consortium is to serve as a recognized and respected neutral third party that provides overall administrative support and oversight. The mission of the ePRO Consortium is to advance the quality, practicality, and acceptability of electronic data capture (EDC) methods used in clinical trials for PRO endpoint assessment. To accomplish this mission, they provide a noncompetitive, neutral environment to test the measurement equivalence of PRO measures migrated to or among alternative administration methods. The ePRO Consortium will work with the PRO Consortium, a group of 25 pharmaceutical companies working to develop novel PRO measures, to migrate the PRO instruments developed within the PRO Consortium to all relevant EDC platforms.

Source: Critical Path Initiative. For more information, visit c-path.org.

tant element to successful recruitment for observational studies is a well-managed scientific advisory board, our thought leaders suggest. Advisory boards provide valuable assistance with developing an effective study design and publishing the results of the research conducted, and can also encourage colleagues to join as sites through letters, small group discussions, and responses to frequently asked questions.

In summary:

1. Secure commitment and engagement from physicians and patients.
2. Foster feeling of patient community; emphasize patient benefits.

3. Create study design with minimal burden on participation.

DR. WILLIAM CROWN. OPTUMINSIGHT. Regulatory agencies in the United States and European Union have new increased authority to require postmarketing studies to assess known signals of, or potential for, serious risk. This will mean an increase in postmarketing, multicountry studies with large numbers of patients and sites. But, as is common in postmarketing trials, many may be run by less-than-fully experienced investigators. Despite the challenges, real-world or nonrandomized data will be essential, including careful identification of safety endpoints and experience in epidemiological methods for the analysis of observational data, including ensuring patient safety, data integrity, and cost-effectiveness.

DR. RON WEISHAAR. PHARMANET/13. Recruiting patients for Phase IV studies, particularly registries and other types of observational projects, is much different from recruiting for pre-approval clinical trials. The latter efforts often focus on identifying investigators with years of research experience — clinical trialists — who frequently have several study coordinators and other staff focused on an assortment of trials, and whose practices often do not reflect the manner by which clinical care is provided in a real-world setting. Patient recruitment for registries requires a much different approach. Indeed, reliance on clinical trialists and heavy use of media campaigns generally run contrary to the fundamental underpinnings of observational research, which seek to understand how patients respond in a naturalistic setting. While employing traditional approaches could stimulate the rate of patient enrollment, the risk is that any such increase would damage the integrity of the study by producing skewed results that had little relevance to the real-world clinical environment. Given that the goal of a registry is generally to look over the shoulder of physicians and to observe how they routinely care for their patients and how their patients respond to the care provided, the best approach for ensuring effective recruitment is to employ a study design that imposes minimal burden on participation. For physicians, this means that case report forms should be short and simple, and if possible should resemble the approaches to data collection routinely employed in a standard practice. For patients, imposing a minimal burden means that no exceptional demands will be made in terms of mandated visits or additional blood draws,

and that any required questionnaires can be answered while they wait to see their physician, or at their own convenience via the Internet or in response to a text message.

DR. EMMA JAMES. SYNAGEVA BIOPHARMA. There seems to be relatively little consideration given to strategies for Phase IV studies compared with those in Phase I-III. A critical barrier to research in the postmarketing setting is that the drug is already available to be prescribed by clinicians, which acts as a disincentive for patients to participate in further research. Successful recruitment relies on obtaining and maintaining physicians' interest as well as patients' involvement. In an era of increasing evidence demands, patients and physicians are being asked to provide growing amounts of data, which will continue to pose a burden. Companies need to find cost-effective ways to incentivize people to participate in postmarketing studies in ways that are not considered inducements to prescribe. From the patient perspective, flexibility to limit their time at the physician's office may help, for example, provide PROs via the Internet rather than on paper copy, provide them with regular informational updates recognizing how their data are contributing, and find non-intrusive ways to remind them about any data collection needs. Tools using social media or smartphone technology should be considered. Companies need to recognize that, especially in the Phase IV setting, patients are people and not research subjects, and it is important that they are engaged and motivated. From the physician and site perspective, this includes reasonable budgets to reimburse the time taken to consent the patient and collect and report the relevant data; providing translated documents in other languages for their use; and non-fiscal incentives, such as authorship on publications, roundtable meetings with other investigators to network and hear about advances in the area, and the ability to use analyses for their own research. There is the mistaken tendency for sponsors to think that Phase IV studies can answer every possible question for every potential stakeholder, but in reality, this results in incomplete or low-quality data. This is especially true for sites that are generally less experienced in the research world, which may be the case for some Phase IV investigators. Sponsors may need to spend more time training sites and forming strong relationships to encourage prioritization of data entry and to help resolve queries to ensure high-quality data.

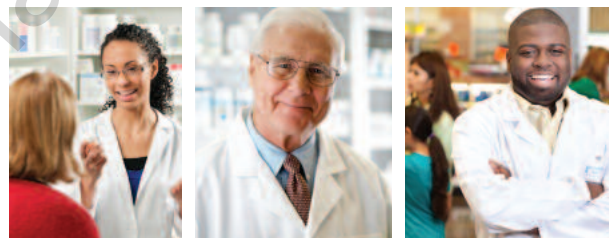
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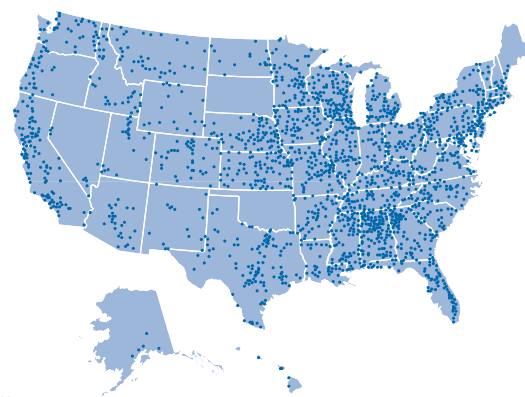
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cruitment and patient retention. Much of the incentive for patients may revolve around drug availability or specialty care. Site payments are almost always lower in Phase IV, postmarket studies, reflecting the less-intensive workload required, which can impact on site motivation unless this is addressed specifically through motivational activities. In today's environment we need to look to some of the more patient-focused benefits. Patients like to feel engaged. Allowing patients to be a part of a community that is tasked with helping to study a disease — their disease — gives them a real sense of accomplishment. This feeling of community can be fostered around their condition through the use of information delivery both through the physician and externally such as focused Web portal information delivery or the use of social media designed for this purpose. In addition, we can aid physicians in demonstrating patient progress through the use of patient profiles showing a patient's personal improvement, such as a QOL scale. These patient profiles demonstrated through the recruitment process can add visible value to the physician/patient relationship. These benefits are something that a patient would not normally receive in most earlier-phase trials. Patient-reported outcomes followed over time are an example of how profiles can be used effectively in visualizing global ePRO assessments. Sometimes merely using a patient call center can help in recruiting, if patients know they have a place to call to ask questions. Patient recruitment involves a combination of techniques and a tailored recruitment strategy, with every action having a purpose that brings results. Therefore, we need to be innovative in our approaches to recruiting patients to show them they bring significant value and they are part of a larger population. So in short, we must present a value to patients outside of the norm.

NEAL MANTICK. PAREXEL. The key to optimizing patient recruitment efforts is to ensure that the participating physicians understand two things. One, they have to recognize the clinical value and that they are scientifically engaged in the proposed study. Prioritizing the must-haves for information, given the product's current life-cycle stage is critical in order to focus participating physicians, he says. And two, they anticipate minimal site burden associated with their participation. From the sponsor's point of view, it is important to understand that postmarketing study commitments imposed by a regulatory authority on a sponsor do not necessarily extend to a commitment on physicians to participate.

Therefore, the goals of engaging the physicians clinically and minimizing the burden on site staff are crucial.

MARIA HARRISON. PRA. Patient enrollment challenges differ depending on the Phase IV study design. For example, if a Phase IV interventional study includes a placebo arm, will patients consent to participate if they have access to an available treatment? In contrast, noninterventional studies are limited to the patient population at a particular practice and standard of care. Use of robust medical informatics has been extremely successful for many studies to identify potential sites with a high volume of the target population. Ultimately, both the physician and patient must recognize the value of the study and they need to not only participate, but to remain engaged in the study over the duration.

LEE KING. ICON. The best way for companies to improve their patient recruitment efforts for Phase IV studies and trials is through the modification of expectations. There seems, in my view, to be a misconception that a Phase IV study will automatically enroll at double or even triple the enrollment rate experienced by the company during the clinical development of the product. This is typically not the case. While enrollment rates might be somewhat higher, it is very indication-specific and will greatly depend on the market penetration of the product. To successfully conduct a Phase IV study, one must go through many of the same steps as with an early-phase study, including activities such as surveying the competitive landscape and conducting comprehensive feasibility analysis. Feasibility may be the single most overlooked component in the Phase IV space as companies begin to rely on physicians identified through their own internal marketing groups versus in a more traditional manner. So, in this regard, companies must understand and prioritize. If sites are being solicited for participation based on some criteria other than their ability to enroll patients at the desired rate, then the expectation of the enrollment period must be modified. Another area for consideration is the enhancement of both physician and patient engagement in the Phase IV study by providing high-quality medical information describing the current understanding of the patient's conditions and therapy alternatives. It is important to highlight the product benefits, while maintaining transparency on any associated risks and establishing clear treatment expectations. Successful enrollment is inherently linked to patients' confidence in their

StudyLink Program Unlocks the Pharmacy Channel for Clinical Trial Patient Recruitment

McKesson's StudyLink Program, a new solution designed to educate and recruit clinical study participants through its network of community-based pharmacies, pairs robust patient prescription claims data and strong pharmacist-patient relationships common in the community pharmacy to efficiently identify, engage, and prescreen potential participants for investigational, postmarketing, and observational studies. Investigators benefit from high-quality referrals from pharmacists, while study sponsors benefit from access to a large, untapped pool of potential study participants.

The StudyLink Program uses three layers of screening to prequalify community-based pharmacy customers for clinical studies:

- » Prescription claims and demographic data
- » Pharmacist vetting of the prospective participants, and
- » Patient outreach on behalf of the pharmacist.

The Center for Information and Study on Clinical Research Participation (CISCRP) recently conducted market research to examine the viability of the pharmacy as a channel for education about clinical trial participation. Key findings include:

- » Individuals reporting some understanding of clinical research are more inclined to participate in a trial.
- » Study respondents wanted their pharmacists to tell them about clinical trials, yet were unlikely to request that information and, as such, were unlikely to receive it.
- » Respondents with better relationships with their pharmacist were more willing to accept information about clinical trials

Source: McKesson StudyLink Program.

For more information, visit mckesson.com/studylink.

physician and perceptions around the industry as a provider of effective and safe medicines. Increased access to information will serve to both elevate that physician confidence and improve perceptions. **PV**



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As the pressure for more postapproval data is made available to a wider variety of stakeholders, designing a postapproval study to meet these needs can get tricky. Sponsors need to first have a thorough understanding of each stakeholder's goals and be able to cull the most pertinent data from the study. Since not every stakeholder need can be met with one study design, the goal is to meet the needs of the most urgent by prioritizing according to relevance, purpose, and timelines, our experts say. This will require a rethinking of how postapproval studies are conducted, including embracing a more collaborative approach and a study design that reflects the standard of care under which newly approved treatments are routinely administered, with few restrictions on patient or site participation.

The reality is that one study design may not be able to satisfy the needs of all members of a very diverse healthcare delivery stakeholder audience, says Neal Mantick, senior director and global head of observational research, Parexel International.

Prioritizing the must-haves for information given the product's current life-cycle stage is critical in order to focus participating physicians, he says.

"By applying appropriate statistical methodologies, data from one study may be able to be analyzed and presented in several ways, based on the needs of several stakeholder audiences," Mr. Mantick adds. "However, this flexibility should be planned for during the initial study design and protocol development to achieve this objective."

This type of forward thinking will bring all stakeholders, even payers, into the planning early.

"It seems clear the changing climate around the increased demand for medical and economic added value along with the more stringent regulatory and access requirements

makes it imperative for companies to quickly master integrated strategic Phase IV planning," says Lee King, VP, late phase clinical trials research, ICON Clinical Research. "This approach proactively identifies the relevant stakeholders and their needs along with those of the regulator in a coordinated fashion."

Sponsors will have to especially take into account the new trend of purchasing decisions being made by committee instead of by individuals and start to include all members in the decision-making process when designing the study. Payers, for example, are likely to limit access based on relatively little data and most would like to be consulted ahead of time in the design of postmarketing studies, Mr. King says.

"This collaborative approach can serve to potentially help the price/reimbursement negotiations and value perception even in cases where the studies to support value are in the planning stages but not complete at the time of price and reimbursement discussions," he says.

According to Mr. King, physicians are also looking for evidence-based medicine that will enhance their understanding of patient safety to guide their decision-making. The data generated in these Phase IV studies should be developed to confirm or validate prior pivotal data allowing physicians to make evidence-based decisions while, at the same time, potentially meeting a requirement of patient stakeholders who are increasingly demanding early access to new interventions.

Steve Albrecht, global head of late phase, Chiltern International, suggests that all available evidence needs to be assessed through the perspective of all the stakeholders via a formal and validated analysis of the evidence gaps to ensure it is clearly adaptable to that purpose.

"Evidence needs to be viewed in its context



“Evidence needs to be viewed in its context of how fit for the purpose it is for the goals of the data use.”

STEVE ALBRECHT / Chiltern International

of how fit for the purpose it is for the goals of the data use," Mr. Albrecht says. "Subsequently, the ability to accommodate these prioritized data gaps should be discussed to inform stakeholders and to develop good study design and data collection."

Non-data gaps such as dissemination and relationship with various stakeholders — KOLs, physicians, purchasers, regulators, reimbursement agencies, patients, and patient organizations — also must be considered in the effective utilization of the Phase IV study and its results.

Weighing the administrative burden that the different types of study designs, data collection methodologies, and documentation requirements place on the site is crucial in the postapproval setting, Mr. Mantick says.

"Research-naïve sites, which are often considered for observational studies, may find the requirements related to participating in a study overwhelming," he says. "Therefore, understanding the requirements of study participation from the site's perspective and intro-

“Disease registries can help collect valuable data that address the needs of several stakeholders.”

MARIA HARRISON / PRA

several years down the road as the demands of the healthcare community change,” he adds.

Understanding the Limitations of Postapproval Studies

Given that observational studies are designed to reflect the naturalistic environment of real-world clinical practice, which might include academic research centers, community clinics, and neighborhood on-call treatment centers, they have inherent limitations and possess considerably more noise than carefully controlled and highly restrictive clinical trials, says Ron Weishaar, Ph.D., VP, Phase IV development, PharmaNet/i3.

“Such caveats do not necessarily mean that observational study designs cannot be employed to address the needs of comparative effectiveness research; however, they do suggest caution must be employed when an observational study approach is employed for such efforts, and that statistical techniques routinely employed for standard clinical trials may not be appropriate,” Dr. Weishaar says.

The solution for conducting comparative

ducing simplified templates and study processes, as well as employing innovative technologies that facilitate site participation and patient recruitment, for example, Web-based communication platforms and the social media, is of critical importance.”

Along with understanding the information needs of the key stakeholders, sponsors must also consider the timeframe for reporting the results when designing the study.

The best study design that satisfies the more immediate needs may not be the best study design for future issues, Mr. Mantick says.

“Stakeholders’ information needs within the first six months of a product’s approval, for example, may be different from their needs

Phase IV Management Migrates Into Medical Affairs

An ever-more cautious regulatory environment, payers that require more and more data to justify formulary approval and reimbursement, and more crowded markets mean that Phase IV research is a requirement in practical terms for many products when they launch into the market, and only half of those companies surveyed by Cutting Edge completed their Phase IV studies on time.

To meet this challenge, many pharma, biotech, and medical devices companies are moving their Phase IV trial management out of clinical development groups and into medical affairs. A postmarketing research team with the full ability to plan and conduct trials unified within the medical affairs department has the advantage of sitting directly alongside those who both set Phase IV strategy and use the clinical and scientific information generated by postmarketing studies. After all, cross-functional communication in even small organizations can be extremely challenging.

Source: Cutting Edge Information.

For more information, visit cuttingedgeinfo.com/topic/phase-iv-clinical-trials/

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Postapproval Studies



“It is imperative for companies to quickly master integrated strategic Phase IV planning.”

LEE KING / ICON Clinical Research

effectiveness research that is relevant to the real-world clinical environment lies in examining each research opportunity on a case-by-case basis, Dr. Weishaar adds. Also, careful consideration must be given to determine whether the individual study objectives for CER can be accomplished in a manner that maintains an observational design, are affordable, and employ the advanced statistical techniques required to help make the most of data collected.

According to Maria Harrison, VP, late phase services, PRA, disease registries can help collect valuable data that address the needs of several stakeholders, as well as minimal IVD development to optimize targeted treatment selection, thus resulting in a patient-centric treatment approach.

“In many cases, a well-designed disease registry can collect real-world paradigms and effectiveness data to support various stakeholder needs,” Ms. Harrison says. “Collection of long-



“Stakeholders’ information needs within the first six months of a product’s approval, for example, may be different from their needs several years down the road as the healthcare setting changes.”

NEAL MANTICK / Parexel International

term follow-up data from not only the physician, but also from patients and caregivers, provides a wider definition of effectiveness and associated outcomes.”

Different Models Different Outcomes

Use of the RCT model to obtain comparative budgets for observational studies frequently leads to overengineered designs that not only fail to address the required research objectives, but are also generally too expensive to be funded, and as a result are often never conducted. When attempting to employ an observational study design for the collection of comparative effectiveness data, the most common mistake is to overcompensate by imposing operational constraints on the study that reduce variability, Dr. Weishaar says. Mandated visits, use of standardized patient assessment and laboratory analysis procedures, and frequent on-site monitoring are examples of common approaches to reducing variability.

“While achieving the goal of limiting the noise inherent in an observational study, these

procedures can also lead to inappropriate conclusions regarding study results, given that the imposed structure can limit the naturalistic underpinnings of the study, as well as reduce the willingness of patients and real-world physicians to participate,” he says. “Moreover, imposing significant constraints on an observational study almost always leads to a substantial increase in the cost of the research, frequently to the point where the study might be unfundable.”

The opposite approach, failing to appreciate the limitations of an observational study design, is equally flawed, since the results obtained will likely fail to provide the level of desired conclusiveness. To meet these challenges, sponsors need to think carefully about their approach to designing and funding registries and other observational studies. The trend to outsource the vast majority of clinical research efforts has led many sponsors to seek uniformity in the management of all clinical research projects, including the use of a common set of study specifications and bid grids for potential vendors. The model used to make such comparative assessments is generally the randomized clinical trial, which has limited applicability to the needs of a real-world observational study. Dr. Weishaar also suggests that sponsors should strive for more frequent interactions with regulatory agencies regarding observational studies, particularly mandated research efforts, to ensure that all stakeholders are considering the context, processes, realities, and limitations of such study designs. **PV**

EXPERTS ►



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