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SPECIAL ISSUE Real-World Evidence Gathering

Increasing Demands for Real-World Evidence: A View Through the Looking Glass

By Sean Hart, MBA, General Manager, Product Approval and Commercialization



Introduction

You are responsible for the development of a new pharmaceutical product...you are under tremendous pressure. You must think about the demands of the market for your product, including risk management, post-marketing commitments, comparative effectiveness, pricing and market access, publication strategy, regulatory hurdles, distribution needs, and so on and so on. How do you begin to prepare for the multitude of needs surrounding the development of your product and the generation of real-world data to support uptake in the marketplace? The task ahead can seem daunting. Late phase programs are specialized and critical to gathering the evidence for new products; they are not commodity services and

there are new studies and requirements being added every day. It is crucial to understand the options before you – what is required and what is “nice to have” – and how to plan accordingly to ensure, from design through implementation, that patients are kept safe and that the true value of a new product is obtained by measurement of real-world data.

To help our clients understand the invaluable nature of the late stage business and the potential for positive impact on their products, UBC has assembled this special edition of *EvidenceMatters* to report on the expertise required to conduct registries and large-streamlined studies. These programs are not “simple” or “cookie cutter” and creative approaches are needed to solve your complex challenges and provide evidence of best practices that drive patient safety and commercial performance.

Catalysts for Change

Increasing demands on the pharmaceutical industry include portfolio innovation, new emerging global markets, personalized medicine, a broken “blockbuster model,” continued profitability, and increased pressure of proving “real-world effectiveness.” Pharmaceutical companies must also appropriately respond to regulators, payors, practitioners and patients. They must respond with complete and accurate evidence that allow decisions to be made around the value of a product, safer use and better patient care.

A growing trend in the industry is that products must demonstrate real-world effectiveness or comparative effectiveness through 1) assessment of drug benefits, relative benefits and costs and 2) appraisal of evidence to inform on coverage and sometimes pricing considerations.¹ Data collected and analyzed by country-level bodies ultimately will power the success and use of many new drugs.

Countries (governing bodies) all conduct ongoing assessments of products once they are on the market to ensure the benefits in “actual use” correspond to fair reimbursement and continued payment support. If products do not demonstrate real-world benefit, the likelihood of their continued success is nearly non-existent. A few (but not all) of such countries include those listed in Table 1.

The need to generate authoritative, real-world evidence that demonstrates effectiveness, safety and value requires careful planning. The mandate for increased evidence beyond that of the product label requires

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the need for scientific and epidemiologic expertise. Companies must be forward thinking with their product life cycle planning and strategically identify and define the evidence that must be collected and analyzed to make an impact on product success. Evidence needs include:

- Safety & Risk Management
- Real-World Effectiveness
- Pricing & Reimbursement
- Product Value
- Patient & Physician Outcomes
- Patient Adherence & Compliance

As things begin to take shape for the post-approval evidence needs of a product, important tactical questions begin to surface. Can an outcomes measure be included in a post-marketing, required global registry to address evidence needs beyond safety? Can direct patient outreach be used in order to meet the specific needs of a post-approval program? Should a comparative effectiveness study be considered earlier in the planning process in order to address payor questions or requirements? How do we collect and analyze trends in patient compliance and adherence within an observational study?

Collecting information on real-world effectiveness in post-approval programs has become necessary to show the true value and safety of a product. No longer is the approval of the product the final hurdle; instead it is the beginning of a new set of challenges that require solutions that are provided in post-approval research and analysis.

Stakeholder-Driven Evidence Development

The health care industry continues to have increasing pressures to deliver more robust information to key stakeholders, including regulatory agencies, payors, and most importantly, patients. Biopharmaceutical and medical device companies are continually navigating the evidence waters to not only understand these increasing demands, but also to evaluate what solutions exist to meet these challenges.

This all comes at a time when pharmaceutical companies are managing the scale of their own business to improve efficiency, limit expense, increase strategic outsourcing, and focus the value development planning for their new products. The attention to patient safety and minimizing risk is not changing and remains paramount; however, the attention to the question of the value of a product is increasing on a global basis.

We at UBC recognize that the success for products relies on strong evidence development from as early as Phase II, where the focus is on risk management planning, outcomes assessments, and value development planning, all the way through to the development of wrap-around support services for post-approval product access.

We hope you find this special edition of *EvidenceMatters* focusing on evidence needs within the peri- and post-approval stages informative.

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Reference

¹ Sorenson C. Use of Comparative Effectiveness Research in Drug Coverage and Pricing Decisions: A Six-Country Comparison. *The Commonwealth Fund — Issues in International Health Policy*. 2010 July; 1420(91):1-14.

Table 1

COUNTRY	GOVERNING BODY
France	Economic Committee of Health Products (Comité Economique des Produits de Santé — CEPS) / French National Authority for Health (Haute Autorité de Santé — HAS)
Germany	Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen — IQWiG)
United Kingdom	National Institute for Clinical Excellence (NICE)
Denmark	Danish Medicines Agency (Lægemiddelstyrelsen — DKMA)
Netherlands	Pharmaceutical Care Committee (Commissie Farmaceutische Hulp — CHF)
Sweden	Dental and Pharmaceutical Benefits Board (Tandvårds- och läkemedelsförmånsverket — TLV)

Strategic Importance of Phase IV Studies: Compiling Evidence to Enhance Product Uptake

By John E. Linnehan, MPH, MBA, Research Associate and Teresa K. Wilcox, PhD, Senior Research Scientist

The need for drug and medical device makers to show additional evidence for their currently marketed products is growing, while the evidence itself is often not available. In these situations, Phase IV prospective studies are of utmost strategic importance.

Increasing Demand for Evidence

In today's health care environment, pharmaceutical companies and medical device makers are facing increasing pressure to demonstrate evidence of product value, be it in terms of cost, effectiveness, or both. Both public and private health care payors increasingly require evidence of effectiveness to cover or reimburse for the use of drugs and medical devices. Even drugs and devices that are FDA-approved and covered in certain indications face coverage restrictions for indications in which evidence is not deemed sufficiently robust.

From a health policy perspective, recent legislation and policy in the U.S. — while still taking form — promise to further increase the evidence burden on manufacturers. The 2009 American Recovery and Reinvestment Act earmarked \$1.1 billion for comparative effectiveness research (CER).¹ This commitment to CER suggests that manufacturers may eventually be required to provide evidence for their products compared to a wider array of competitors. Furthermore, in President Obama's 2010 health care reform bill, the Patient Protection and Affordable Care Act, accountable care organizations (ACOs) were prioritized as an alternative method of Medicare physician payment to begin in 2012.² The mandate of ACOs is to improve patient care by cutting costs, suggesting an increased demand for cost and effectiveness evidence in the coming years.

An Evidence Base that is Often Limited

In the face of increasing demand for evidence of product value, many manufacturers are finding that the evidence base in support of their products is limited. This is especially true with products already established within the marketplace. In many situations, existing evidence is simply too old and fails to be relevant to evolving clinical practice. Furthermore, existing evidence may not be specific to the indication or population of interest for a given policy, or a given product may be compared to a placebo rather than other relevant products. In the unique case of medical devices, the current 510(k) product approval process allows a device to be marketed solely on the basis of demonstrating "substantial equivalence" to a predicate device,³ with just minimal new evidence of safety and efficacy.

Case Study: A Phase IV Trial to Remove Barriers to Patient Access

United BioSource Corporation (UBC) was recently approached by a prominent medical device manufacturer facing very similar challenges to those outlined above. The manufacturer's field-based sales force was reporting that physicians were hesitant to prescribe the use of their simple, portable, non-invasive devices because payors were restricting coverage to a very specific indication. At the same time, these payors were providing significantly less restrictive coverage for a competing device on the basis of better efficacy evidence. In this situation, the manufacturer was losing access to patients on the basis of a poor evidence base. The technology around this class of devices had existed for 30 years; when initial FDA approvals were given, less stringent evidence was required, and future iterations of the device were approved on the basis of "substantial equivalence."

In collaboration with this manufacturer, a *Value Development Plan* was assembled for their product that would remove barriers to reimbursement. In the initial fact-gathering stage of this process, a team of pricing and reimbursement experts assessed the reimbursement landscape and highlighted reasons for and against coverage in payor policies. To identify needs for specific evidence, experts in this type of strategy highlighted key stakeholders, defined value propositions for the client's products, assessed the existing evidence base, and identified critical gaps. The value development team then collaborated with internal thought leaders across numerous practice areas to outline five short and long term strategies for evidence generation.

While many strategies enabled the client to catch up to the field in terms of available evidence, a Phase IV large streamlined observational trial was proposed to catapult the client ahead of the field in the area of comparative efficacy data. In designing the Phase IV prospective study, the value development team took advantage of the expertise of multiple practice areas to create a thoughtful, methods-driven approach under the direction of an experienced principal investigator. The study conceptualization team included experts in health economics, biostatistics, clinical trial operations, safety and risk management, and clinical data management. In addition to study design, a communication and dissemination plan was developed to provide both yearly interim and final updates of trial results to keep payors and clinicians informed of the developing evidence base. Refer to Figure 1 for a summary of the value development process pertaining to this case study.

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Strategic Importance of Phase IV Studies

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Support was provided, based on previous experience, in conveying the concept of the Phase IV trial to senior management within the client's organization. Ultimately, senior management was convinced that the proposed study design would meet the company's near and long term evidence

needs for optimizing market access and thus enhancing company revenue. The prospect of generating best-in-class evidence and lifting the restrictions on access to patients who would benefit from their products was paramount, and the budget-conscious client ultimately made a significant financial commitment to conduct this trial.

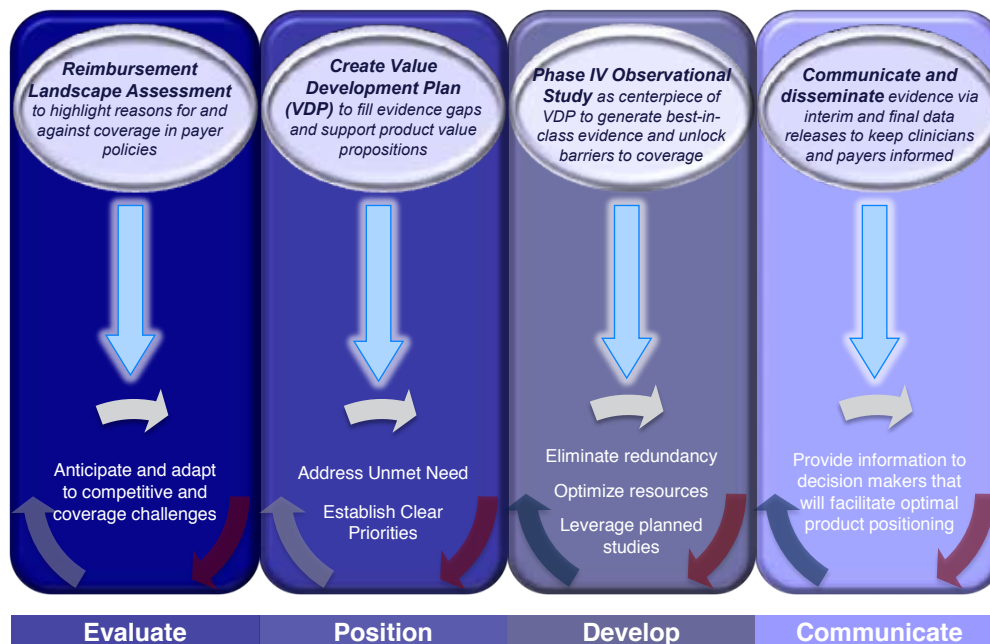
Conclusion

The health care landscape is continuously evolving. Requirements for evidence on the part of manufacturers' products are increasing, yet actual evidence is often lacking for a variety of reasons. While numerous methods exist to build an

improved evidence base for marketing products, Phase IV prospective studies provide manufacturers with the highest quality evidence possible. Armed with this evidence, manufacturers can unlock barriers to patient access and enhance product uptake.

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Figure 1. The UBC Value Development Process Pertaining to Phase IV Trials

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Strategic Registry Designs and Operational Infrastructures as a Foundation for Efficient Evidence Gathering Across the Product Life Cycle

By Krista A. Payne, MEd, Senior Director & Senior Research Scientist and Sallyanne Williams, MBA, Clinical Program Director, Peri- and Post-Approval Services

Delineate Evidence Requirements

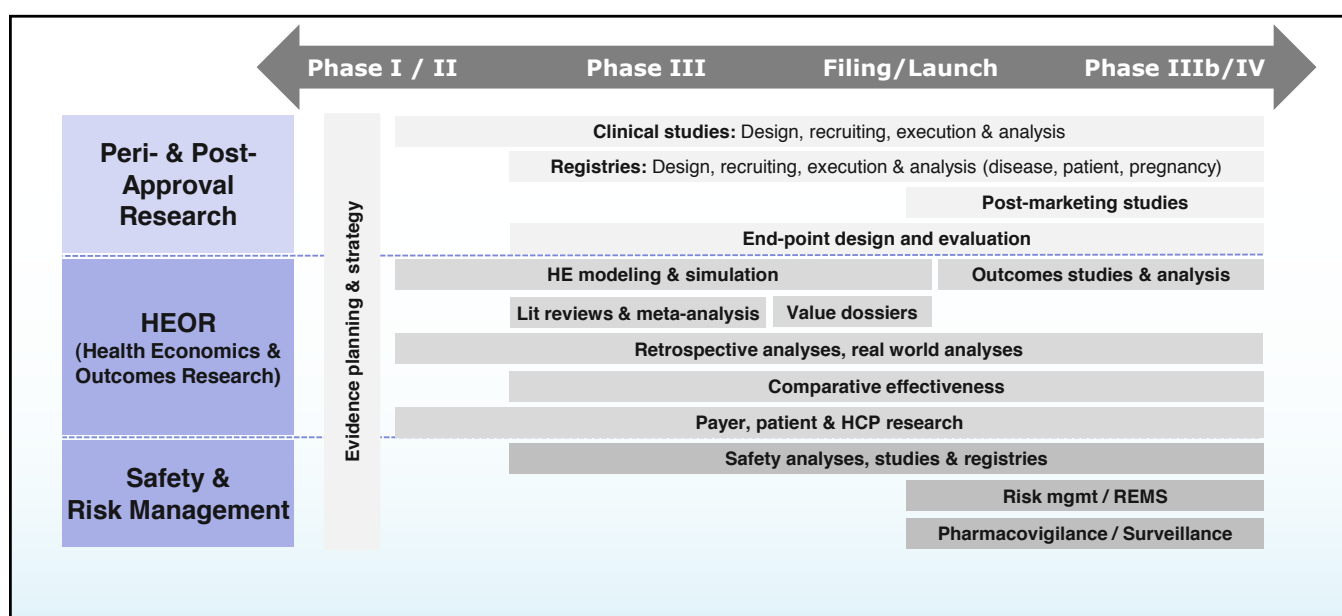
Real-world evidence requirements across all phases of drug commercialization are increasing. So too is the level of scientific rigor that stakeholders, including regulators, payors, physicians and patients, are seeking. Optimal product positioning and market uptake requires a thoughtful multi-year, multidimensional strategy that culminates in an evidence base which will facilitate product coverage, reimbursement and adoption. Value demonstration planning and strategic

evidence gathering should ensure that available data are fully integrated and new research projects are designed to build on a unified body of evidence that will effectively communicate value.¹

In alignment with a comprehensive value development plan, a scientifically diverse array of national and international studies must be conceptualized, designed and implemented within a relatively short period of time — typically no more

than five to seven years (See Figure 1). Research and development costs associated with even the simplest of protocol-driven data collection studies can be significant. When compounded over multiple studies and years to support a full range of product safety, value and effectiveness messages, funding and timeline implications can be prohibitive.² In the context of increasing evidence requirements and fewer research dollars to fulfill stakeholder-driven evidence needs, cost and time efficient, real-world evidence gathering in support of product commercialization should be prioritized.

Figure 1.
Evidence Gathering Across the Product Life Cycle



Designs employed to gather real-world evidence vary markedly in terms of study parameters and scope, thus opportunities to incorporate efficiencies within a program of studies may not be immediately obvious.

- Often considered retrospective registries, multinational retrospective chart review studies can be used to gather comprehensive patient-level repositories of international clinical and resource utilization data. These data can inform current patterns of treatment, including off-label prescribing, populate burden of illness and other more traditional health economic evaluations, and inform trial or registry designs.

Conceptualize Strategic Designs

A main benefit of a robust evidence generation strategy is that data needs over the product life cycle can be anticipated. The “right” design at the “right” time for the “right” audience can be delineated and planned for appropriately. More importantly, stepwise, strategic real-world study designs can be conceptualized and implemented sequentially and synergistically with the aim of optimizing cost and timeline efficiencies over a multi-year program of studies. Unfortunately, given the sheer volume and diversity of data that are required (See Figure 1), as well as competing evidence priorities, information silos, and organizational complexities within pharmaceutical and device companies, peri- and post-approval studies are typically designed and executed as separate stand-alone initiatives. These explanatory factors, as well as others, contribute from the outset to an inherent evidence gathering inefficiency that may require a paradigm shift in study planning if significant time and research dollars are to be saved.

- Multi-faceted disease registries are another important source of “benchmarking” data that also reflect natural history of disease and standards of care, but also include patient-reported outcomes (PROs) and other effectiveness outcomes. Pregnancy and product exposure registries are implemented to better understand real-world product safety and conditions of safe use.
- Pragmatic trials, which are observational in nature but with the added benefits of randomization, evaluate comparative effectiveness — increasingly important in the context of current trends in product commercialization and spending.³

Despite such differences in study aims, objectives and specifications, important cost and timeline efficiencies can be realized by systematically seeking out and building upon methodological and operational synergies. By design, all of these study types aim to collect data that reflect real-world patterns of care, and clinical, safety and effectiveness

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Strategic Registry Designs

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outcomes. Because each of these studies would be executed as part of the same product's commercialization process, key design elements — including patient selection criteria, sub-groups of interest, clinical and patterns of care variables of interest, and other patient outcomes — are likely to overlap significantly. These synergies can be exploited both by “recycling” selected content from study documents, such as protocols, case report forms (CRFs), informed consent forms, statistical analysis plans and even statistical programming, and also by strategically integrating even markedly different designs within a single protocol. If the number of study protocols can be reduced, so can the number of site contracts and ethics and other mandatory approvals, as well as the number of months of study start-up. While the efficient use and repurposing of study materials from one project to another over time is primarily a documentation, communication, and knowledge transfer exercise, combining study protocols to achieve hybrid, longitudinal designs requires a bold, strategic vision and multi-year commitment of resources. Those willing to make this level

As an example, a schematic representation of a stepwise approach to the integration of multiple real-world studies, including a chart review, and disease and product registries over multiple years, is shown in Figure 2. Preliminary, foundational chart review activities provide important information about variability in patterns of care and clinical outcomes, but they can also serve as the means to identify prevalent cases of interest for enrollment in a prospective component of a hybrid design⁴ such as a disease registry. Once implemented, disease registries, within which a wealth of clinical, health economic and PRO endpoints can be collected, can also be a highly efficient framework to evaluate the real-world safety profiles of new and emerging products once they enter the market. A detailed view of a hypothetical integration of a disease and safety registry is shown in Figure 3.

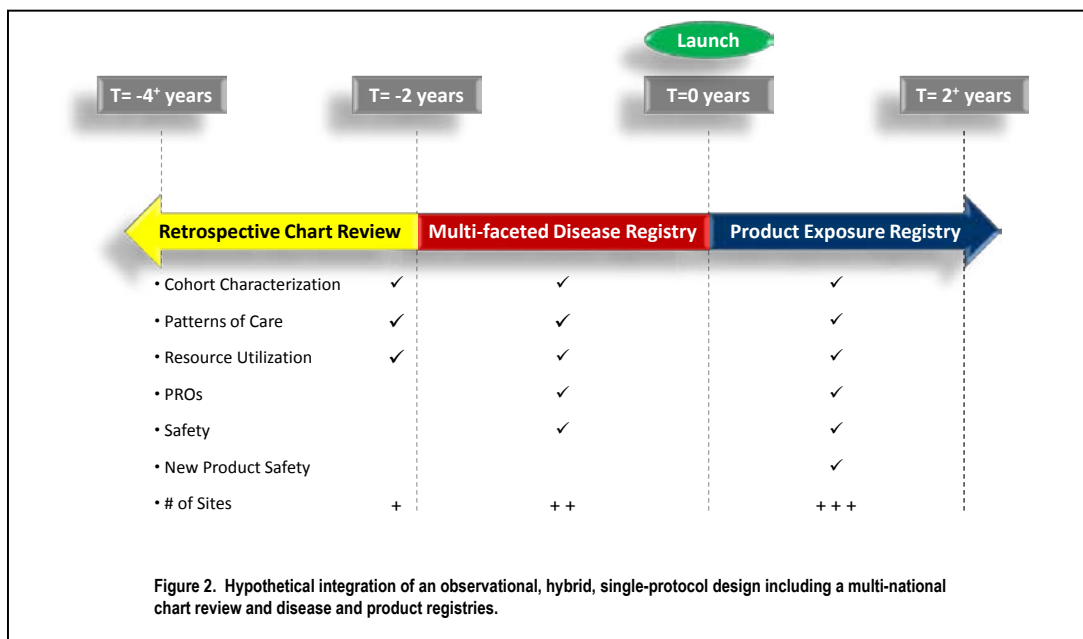
Build Synergistic Infrastructures

Establish Networks

Study start-up activities, including site recruitment, contracting, regulatory document collection and training, are key drivers of total study cost regardless of the type of study executed. Therefore, strategies such as the early identification and implementation of a network of investigators who agree to a mandate to support a program of studies

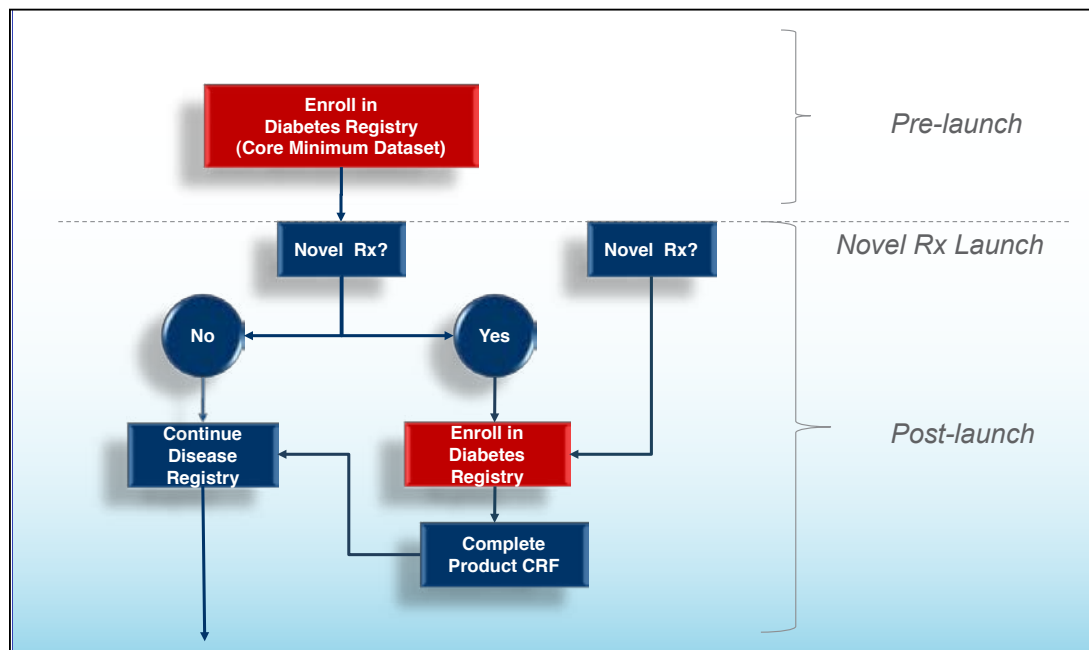
over time will result in measurable cost and timeline efficiencies. Once enrolled in a research network, pre-screened investigators amenable to participation in multiple studies and sub-studies will contribute to decreased start-up time and burden from one study to the next. While randomized controlled trials (RCTs typically require the involvement of academic or specialty care centers, observational studies generally draw upon the same mix of study sites that better reflect routine medical care. As an example of the growing awareness of the importance of investigator networks, a recent call has been made for new registries to be implemented where

Figure 2. Stepwise Approach to the Integration of Multiple Real-World Studies



of upfront strategic investment do so with an inherent belief that over the product commercialization period, the total cost and resource requirements of the program as a whole will be significantly less than if each study was conducted as a stand-alone initiative.

possible within already existing registries that have been sponsored by professional organizations.⁵ It is postulated that this approach would ensure broad unselected populations, avoid competition between RCTs and registries, and stimulate and encourage scientific and clinical input from academia.

Figure 3. Integration of a Disease and Product Registry

for enrollment. This quest for cost-efficiency through EDC has recently inspired one company to conduct a “virtual” clinical trial that relies solely upon electronic versus face to face encounters between researchers and participants.⁹

If a comprehensive EDC infrastructure is designed early, then opportunities for synergies within and across studies can be

Reliance upon pre-existing networks of patients is also an appealing strategy for recruitment and enrollment. Electronic medical record (EMR) or other health data including diagnostic and pharmacotherapy information can be analyzed to identify potentially eligible patients,^{4,6} or alternatively, populations of patients can be built expressly for the purpose of study participation. Researchers in Dundee and Edinburgh, for example, are establishing a national register of residents of Scotland who would be willing to be contacted about health care research.⁶ Additionally, numerous, online, high volume, international panels of pre-consented and screened populations of patients have been established that can support scientifically rigorous international burden of illness assessments.⁷ Popular patient support and advocacy organizations can also be utilized to access specific patient cohorts of interest.⁸

Prioritize Innovation and Technology

Designing and implementing an optimal electronic data capture (EDC) and communications infrastructure early in the product commercialization process can also result in significant efficiencies. Innovative, multimodal EDC systems far exceed basic data capture capabilities in terms of core functionality. A tailored, fit for purpose EDC system can serve as an epicenter of research activity, facilitating study recruitment and enrollment, data capture and management, and global study communications. Study Coordinating Centers can use such systems to manage multiple studies across multiple study sites simultaneously, as well as to enhance study and data quality in real time. Investigators can access these infrastructures to enter study data, download study reports and their own data reflecting their patients’ clinical and study outcomes, and learn about new studies opening

capitalized upon more readily. For example, though an EDC build contributes to fixed costs upfront, once the investment is made in a study protocol and an e-CRF, sites and patients from a second or third wave of countries can be enrolled at any time downstream from the initial implementation for only a modest incremental cost. This can be particularly advantageous for research sponsors who may want to fund fixed study start-up costs through global budgets but share market-specific variable costs with local affiliates who may be gathering evidence in support of reimbursement and market access on different timelines.

Synergies and efficiencies across a program of studies resulting from early investment in an EDC infrastructure can be realized, particularly in relation to common core data elements. There will be significant overlap in key variables such as patterns of care, resource utilization, and clinical outcomes of interest. By creating libraries of e-CRF formats, data dictionaries, statistical analysis plans and associated programming code and validation rules, and drawing upon these investments from one study to the next, research time and costs can be greatly reduced. This approach will also result in consistency across study datasets which will permit the pooling and cross-analysis of data from multiple studies, especially important in the context of increasing comparative effectiveness evidence requirements. The availability of electronic data in real time also permits the rapid analysis of data to support ongoing data dissemination and reporting, as well as to inform the design of subsequent downstream studies.

Successful electronic data capture must also incorporate research sponsor-driven data management, safety reporting

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Strategic Registry Designs

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specifications and standard operating procedures. These specifications are likely to be consistent across real-world study types, thus efficiencies may be gained by tailoring the EDC infrastructure to ensure adherence to all sponsor required data and safety monitoring processes. Once these specifications have been integrated, each subsequent study supported by the infrastructure will require little, if any, review prior to study launch.

Increase Your Return on Evidence Gathering Investments

Strategic and synergistic real-world evidence gathering across the product life cycle can and will contribute significantly to cost and timeline efficiencies. To this end, the following general recommendations may be useful.

- Engage in rigorous early value development planning and strategic evidence generation. A plan which clearly delineates the “right” data for the “right” audience at the “right” time will ensure that data collection efforts are focused and coordinated and contribute to successful reimbursement and market access outcomes.
- Consider the appropriate use of secondary sources of health care data as a means to identify a focused cohort of potentially eligible investigators and patients for participation in studies.
- Build a network of investigators who are committed to a well-described, scientifically rigorous, multi-year program of complimentary studies.
- Initiate network study sites with a mandatory core study protocol designed to achieve a standardized, longitudinal core minimum dataset. Offer subsequent opportunities for new and existing sites to “opt in” to additional studies and sub-studies of interest through notifications communicated via the EDC infrastructure.
- Design studies in stepwise and strategic fashion, and strive to combine designs and research objectives into a common study protocol where possible. The integration of multinational chart review studies and disease and product registries are particularly well-suited to this synergistic approach.
- Establish a central repository of study documents and materials including protocols, e-CRFs, statistical analysis plans, data dictionaries, and coding to ensure optimal use and re-use of fixed cost investments.
- Implement an EDC infrastructure early in the product life cycle to support a standardized approach to the collection of key data elements, investigator communications and recruitment within and across studies.

- Offer participating investigators opportunities to access their own data electronically in real time. Benchmarking patient data within and across study sites through the use of customized reports and data visualization techniques can serve as an effective participation incentive by offering investigators important clinical information as well as opportunities to participate directly in study publications.

In summary, an early adoption and implementation of strategic study designs and operational infrastructures can provide important opportunities for significant savings in terms of commercialization timelines, costs and human resource requirements. Though this approach does demand a greater investment earlier in the product life cycle in relation to the planning and execution of real-world studies, the return is likely to exceed expectations. As research dollars decrease and evidence requirements increase, new and sustainable research strategies and methodologies that contribute to a high quality, on-time delivery of an evidence base that meets stakeholder requirements are clearly warranted.

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Multi-Faceted Registries: Not Your Typical Safety or Pregnancy Exposure Registry

By Chris Pashos, PhD, Vice President

Patient registries play a critical role in assessing the safety of medical interventions and quantifying the effects of pregnancy exposure. Safety and pregnancy exposure registries typically are designed to fulfill a single objective and feature similar research designs based on guidance from the Food and Drug Administration (FDA).^{1,2} On the other hand, many, if not most, prospective, observational patient registries are best described as “multi-faceted.” Multi-faceted registries typically are designed to achieve several important, yet varied, scientific objectives that meet the diverse information needs of physicians, providers, payors and patients. To meet those objectives, these registries obtain various types of information from clinicians and patients using an array of integrated data collection modalities.

Registries can be designed to better understand a disease, its treatment, and its outcomes as they exist in the real world, and increasingly are focusing broadly across these three aspects. Accordingly, the objectives of multi-faceted patient registries include, for example, more than one of the following:

- Understanding disease presentation, including its heterogeneity and course over time
- Documenting actual medical practice, including variations by health system, clinician and/or provider characteristics
- Understanding barriers to and facilitators of appropriate care and positive outcomes. These barriers and facilitators can involve society, health system, clinician and patient characteristics.
- Evaluating outcomes, such as
 - Clinical outcomes, short-term as well as long-term
 - Economic costs, as borne by different constituencies — patients, payors and providers
 - Patient (and caregiver) impact, including health-related quality of life (HRQOL), adherence to regimen, and satisfaction with care
- Documenting real-world value, effectiveness and safety associated with different health care interventions, be they medicines, biologics, medical devices, surgical procedures or other services

With diverse objectives, however, comes the need to be as efficient as possible in research design and data collection. For the multi-faceted registry to successfully meet its objectives, data collection must be focused on the most important data elements needed to fulfill the agreed-upon objectives and be accepted as feasible and appropriate by those who

are providing the data, including academic or community clinicians, specialists or primary care practitioners, patients or family caregivers.

These objectives and characteristics of multi-faceted patient registries in the abstract are demonstrated by a limited set of four actual examples sponsored by biopharmaceutical companies and patient advocacy organizations.

Example 1

The first example is NORA — the National Osteoporosis Risk Assessment study, which enrolled more than 207,000 U.S. women over the age of 50 through more than 4,000 physicians. The registry involved multi-year follow-up surveys (of up to seven years post-baseline) to assess practice patterns, patient health-related behavior, clinical outcomes, and health-related quality of life outcomes. The multi-modal data collection approach, comprised of computer-assisted telephone plus mail, ensured a response rate at year one of nearly 90%, and rates over 80% across consecutive data collection waves over many years overall and in clinically- and demographically-defined subgroups. Findings released in both scientific journals and venues, and through the lay media, quantified clinical risks of falls and fractures among postmenopausal women overall. Significantly, NORA quantified the risk in various ways — by patient demographic and clinical characteristics and by therapeutic or preventive regimens. Findings identified risk based on such factors as patient intake of calcium and vitamin D, timing and duration of postmenopausal hormone therapy, and estrogen cessation. These data helped the medical community to better identify those at greatest short-term and overall risk of severe negative clinical outcomes.^{3,4} As well, NORA quantified the health-related quality of life associated with fracture. Significantly, it created greater clinician and population-wide awareness of osteoporosis, and support for effective preventive measures. A notable contribution of NORA to the clinical community was the quantification of outcomes and risk levels among both racially white populations and in ethnic and racial minorities who had not previously been well studied.

Example 2

A second multi-faceted registry enrolled more than 3,200 patients eligible for an innovative orthopedic biological process in North America, Europe and Asia. Regular surgeon-specific reports compared outcomes of all patients to those of the surgeon's patients to help individual surgeons to better understand their patients' outcomes and put them within a broader context. The registry was originally

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Multi-Faceted Registries: Not Your Typical Safety or Pregnancy Exposure Registry

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Example 2 (continued)

designed as a post-approval study to support greater understanding of clinical outcomes and patient functional status over the longer term, compared to the short term outcomes evaluated in earlier clinical trials. However, registry data were requested by the FDA and became part of the final Biologic License Application (BLA) submission. Thus registry safety and clinical effectiveness data contributed to regulatory approval, while those data along with longer term registry patient functioning data and clinical outcomes were used to support appropriate physician decision-making.

Example 3

The third example, the Sonya Slifka multiple sclerosis study, has been designed and implemented by the National Multiple Sclerosis Society (NMSS) since 2001. Two waves of multiple sclerosis (MS) patients have been enrolled over time to better understand care and outcomes of patients, most notably to understand barriers to care as well as facilitators of effective care. Findings have made clear the different roles played by different physician specialties and the value of integrated care that employs the expertise of the different specialties. Clinical and patient-centric outcomes have been evaluated with respect to disease-modifying agents as well as to other aspects of supportive treatment.⁵

Example 4

One more example is the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE). The ECLIPSE study followed more than 2,000 patients with chronic obstructive pulmonary disease (COPD) for three years, and involved the collection of diverse clinician-reported and patient-reported data. Along with obtaining data on critically important exacerbations and other clinical outcomes, data were collected on patient functioning and other patient-centric outcomes and on various biomarkers from serum and plasma samples. Peer-reviewed publications from ECLIPSE have documented the heterogeneity of COPD, biomarkers associated with that heterogeneity, determinants of comorbidities (including depression), and determinants of patient functioning. Most notably from this

study, ECLIPSE researchers have quantified the frequency, determinants and effects of exacerbations, and noted the implications of these findings on exacerbation-prevention strategies across the observed range of COPD severity.⁶

This limited set of examples of multi-faceted registries illustrates the flexibility they offer to investigate a diverse set of issues to better understand disease, its treatment and its outcomes. Critical types of data have been collected to meet various, and even very different, objectives. However, it is important to note that those various objectives have been met because the sponsors and research partners were attentive to design and implementation details. Specifically, although it may sound paradoxical, they avoided the temptation to try to do too much, thereby overburdening physicians or patients, and collecting little of value. As well, they focused on how best to collect the different types of data and endpoints, sometimes using different data collection modalities if that contributed to improving data quality.

Overall, multi-faceted registries are increasingly being added to companies' research armamentaria. Increasingly, sponsors recognize the value of multi-faceted registries, motivated by demand from clinicians, health care providers, and public and private payors who are expecting more information. With investments in multi-faceted registries increasing, it becomes even more imperative that registry design activities and operations be done appropriately. Then, a single, multi-faceted registry can be a cost-effective and timely way to meet multiple critical organizational objectives.

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Understanding the Natural History of Disease — A Fundamental Strategy During Drug Development and Beyond

By Annette Stemhagen, DrPH, FISPE, Senior Vice President, Safety, Epidemiology, Registries & Risk Management

Having an in-depth understanding of the disease or condition for which a drug or biologic is being developed seems fundamental, yet it is often surprising that Sponsors do not always fully understand disease natural history prior to or during drug development. In the overall scheme of product development, gaining this knowledge is a small investment that can pay large dividends.

A natural history study is an observational, epidemiologic cohort study designed to evaluate patients who have been diagnosed with a specific condition or disease. Ideally, patients are identified at the time of diagnosis, and risk factors, treatments, and outcomes are documented over the course of the disease. A natural history study is a way to estimate disease incidence or prevalence; describe the demographic characteristics of the patients with the disease; and to document changes in severity over time, occurrence of concomitant conditions, usual treatment patterns, and survival. Information can be compiled from a literature review or by conducting a study using a large automated database, a cross-sectional survey, a retrospective chart review, or an ad hoc prospective longitudinal cohort or registry. Some Sponsors have considered the placebo groups of randomized clinical trials as one source of natural history data.

Selection of the best design (or designs — in some instances, a portfolio of studies may provide the best insight) depends on several factors. Literature reviews are only feasible if historic cohorts exist. Often, however, if using the literature to estimate disease incidence or prevalence, estimates can vary widely depending on the methods used to collect the data, and the literature may lack sufficient detail to understand the reasons for the variation. If there are conflicting studies that show the frequency of a condition varying from 0.1% to 25% in the same population, then decisions on market size cannot reliably be made. Cross-sectional surveys can be used to estimate the prevalence of a condition. If the surveys are assembled to cover a heterogeneous, broad population, with patients at various levels of severity and at various time points in the spectrum of their disease, then some profile of disease characteristics and changes over time might be constructed. A carefully selected sample of medical charts may provide valuable insights into natural history, as long as the information required to understand the risk factors, historic and current treatments, and disease severity has been reliably documented in a similar fashion in medical charts across multiple practices in varied settings. Similar caveats apply to natural history studies conducted using electronic health records or medical claims databases. Prospective cohort studies or registries, while more costly than studies of existing data, can be the most efficient and

effective design for capturing a sufficient level of detail to inform decision making.

Regardless of the design, the information to be documented on disease natural history serves many purposes during the drug development process and beyond. In the early stages of drug development, as indications for use are being evaluated for study, an understanding of disease incidence or prevalence is important in estimating the potential market size for the product. This can assist in prioritizing the indications for development. Designation of an orphan condition depends on estimating the prevalence of a disease. Similarly, if it is determined that available treatments are limited, characterization of an unmet medical need can also help direct the development process.

Understanding the disease for which a compound is being developed provides a great deal of important information that can be applied to effectively design the clinical development program. What safety risks are expected by virtue of the disease being treated? Does the disease itself put the patient at risk of liver toxicity? Or cardiac events? If so, then it is critical that such events be accurately captured during the clinical trials in a standardized

way, for both the active therapy arm and the placebo group, so that the risk due to the disease (which should be evident in the placebo group) can be understood in the context of the new therapy under study. Something as fundamental as design of case report forms can benefit from this information. The Food and Drug Administration (FDA), in its Premarketing Risk Assessment Guidance¹, acknowledged that “certain kinds of adverse events are not likely to be detected or readily reported by patients without special attention. When a drug has a potential for such effects, additional testing may be appropriate, e.g., CNS effects.” A similar philosophy should be adopted early in drug development in regard to adverse effects of the disease itself. The background morbidity or mortality due to the underlying condition must be factored into sample size calculations for the clinical trial program. In order to evaluate a drug with an adverse event

Understanding the disease for which a compound is being developed provides a great deal of important information that can be applied to effectively design the clinical development program. What safety risks are expected by virtue of the disease being treated? Does the disease itself put the patient at risk of liver toxicity? Or cardiac events?

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profile that may add to the background rate of specified adverse events, the clinical trial must be designed to have sufficient power to detect pre-specified increases over the background rates related to the disease itself.

How do you know that your clinical trial population represents the general population of patients with the disease without having an understanding of the patient profile? Are there demographic subsets of the intended population who may be at greatest risk? If so, how should these patients be included in the clinical trial program? Relying on clinical research sites only can distort the profile, making the clinical trial results less than optimally generalizable to the population to be treated in clinical practice after product approval. An added benefit from structuring the clinical trial to be more representative of the presumed population who will be treated with the marketed product is that a more generalizable clinical trial population might allow the product to be labeled for broader use.

A careful evaluation of patient profiles and current treatments for the disease can anticipate interactions of concern. What are the likely concomitant conditions that occur in patients with the disease? How are these conditions treated? This can alert researchers of possible drug-drug interactions that should be proactively assessed, which is important not only for concomitant biopharmaceutical therapies but also herbal products and dietary supplements. Understanding the progression of disease can identify critical milestones where the new therapy can have the most impact. Not only is this important from an efficacy standpoint, but also in relation to other outcome measures which may differentiate the new therapy, such as quality of life.

This philosophy is consistent with ICH E2E²: pharmacovigilance planning, in effect, requires understanding of disease natural history. In order to understand important potential risks, limitations of the human safety database, and populations potentially at risk or that have not been studied in the clinical trial program, one must understand the patient profile, the effects of the disease, the likely concurrent conditions, and other epidemiologic considerations about the indication for drug use.

Understanding the variability of the patient population is important in directing the types of patients who should be recruited for the clinical development program. While the inclusion and exclusion criteria of patients in the clinical trials must be restricted in some ways for practicality and

efficiency, it is important to understand which segments of the patient population are represented in the clinical program and which have been intentionally or inadvertently excluded. This information can be derived from the natural history study. The product's effectiveness and safety in the unstudied segments is a deficiency that should be remedied after product approval with enrollment of a heterogeneous patient population into the natural history study.

An effective approach is to institute a disease registry during the drug development period to gather natural history data, and then to extend the registry after product approval to understand how the new product fits into the treatment armamentarium. Switching patterns can be assessed; characteristics of patients initiated on therapy can be examined; and the safety profile of the new product under actual use conditions can be documented and compared with the data from patients with the same disease who have been treated with other therapies or not treated at all. Developing an exposure cohort within the natural history study extends the value of the initial study throughout the product's lifecycle.

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Using Simulation to Gauge the Likely Benefits of a Pragmatic Clinical Trial

By Jörgen Möller, MSc, Vice President, Modeling & Simulation; Ananth Kadambi, PhD, Director, Health Economics and J. Jaime Caro, MDCM, FRCPC, FACP, Senior Vice President, Research

What Makes a Clinical Trial Pragmatic?

Clinical trials are carefully designed to detect an effect of a particular intervention and minimize bias in doing so. This leads to features like randomization to achieve similar populations; blinding and the use of placebos to minimize the impact of patients and clinicians knowing which intervention has been given, and careful selection of patients and sites to increase the chances of showing an effect. Unfortunately, these features reduce the applicability of the results to routine clinical practice; and it is precisely this that payors and reimbursement authorities are looking for!

Loosening of these design constraints to make the trial results more relevant to clinical practice has led to the “pragmatic” clinical trial that targets the typical patients who will actually receive the interventions, a broader, less homogeneous group; compares multiple interventions, reflecting the standard practices; allows the treating physician to use expertise and knowledge of the patient to decide on treatment titration and switches as well as use of concomitant medications; and implements a much less strict protocol, with visits, alterations of therapeutic strategy and/or dose, types of biomarkers measured and the frequency of doing so, all determined according to real-world practices.

The move to a more pragmatic trial leads to several challenges, including:

- More difficulty in detecting an effect of the intervention
- More heterogeneity in response to the intervention
- More treatment switches
- Poorer adherence by the patient and even physicians

In short, in a pragmatic trial, the ramifications are less controlled and the results, therefore, less predictable. In planning these studies, it is very useful for all concerned parties to be able to forecast the results and examine the impact of putative changes in the trial design. Ultimately, decision makers would like to know the likelihood that a particular design will meet their criteria for success. This information can be provided by modeling the proposed trial using discrete event simulation (DES).

Discrete Event Simulation

DES is a modeling technique that conceptualizes the course of individuals in terms of the events they experience and the effect those events have on their health and other aspects, in continuous time, allowing chance to play a role.

It is particularly useful for simulating a pragmatic clinical trial because it allows for:

- Representing a population by modeling individual subjects, each with his or her own characteristics
- Applying admissibility criteria to select which subjects enter the trial; and at various times, not all at once
- Allocating treatment randomly or via any particular scheme desired
- Following subjects to understand their progression through the trial and the impact of intermediate events and behavior on outcomes
- Implementing clinical decision making to mimic real practice, including switches, treatment discontinuations, etc.
- Collecting information regarding outcomes
- Ending the trial in various ways (number of events, occurrence of specific events, maximum follow-up, calendar time, etc.)

- Rerunning a particular design many times to identify the impact of chance
- Varying the design to determine the consequences of changes

It should be noted that DES can also be applied to earlier-stage trials to predict efficacy and safety outcomes.

Hedging Your Bets

To test various designs and determine how likely they are to be successful, a Pragmatic Trial Simulation (PTS) should be done. This is not just another abbreviation; it is a tool that enables interested parties to explore the different paths a pragmatic trial can follow and understand the impact of each one on relevant outcomes. Possession of such information in advance will allow decisions to be made that maximize the likelihood of success and provide some justification for the high costs and long timelines typical of clinical trials.

PTS is akin to a lab bench where different assumptions and ideas and their consequences on specific measurable outcomes can be tested. Equations underlying PTS are developed based on a detailed understanding of the desired features of a clinical trial, data from previous trials and other studies, and knowledge of the disease itself. The model framework for analyzing the implications of various designs is constructed and a fast, user-friendly analytic interface is built to facilitate interaction with the model. As the project develops and potential changes are proposed or new questions arise, the flexibility of PTS allows modifications to be readily implemented. Depending on the need, it is possible to build in the cost components of the trial as well, which enables companies to better understand the implications of the various design decisions on their trial budgets. Some typical points of interest to explore are included in the table below.

Since every trial is unique, the questions will be different for each one. To ensure confidence in simulation predictions,

Question	Factors that can be considered in a PTS
What are the chances of success given design choices?	<ul style="list-style-type: none"> ■ Admissibility (inclusion/exclusion) ■ Response criteria, other outcomes ■ Duration of follow-up ■ Sample size ■ Adaptation ■ Other
What are the risks in the design?	<ul style="list-style-type: none"> ■ Critical limit of drop-outs and losses to follow-up ■ Potential cross-over effect ■ Pragmatic effects ■ Effects of concomitant treatments ■ Other
How much will it cost?	<ul style="list-style-type: none"> ■ Sample size ■ # visits, sites, duration of follow-up ■ Endpoints (measures) ■ Adaptation choices

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therefore, the model must take into account the relevant particulars of the disease area and the specific details of the proposed trial. It is critical that the PTS validly mimic the trial with the appropriate level of detail (note: not every detail!) so it is possible for the user to draw the same conclusions from the simulation outcomes as from a real clinical trial.

Close collaboration between the trial team and the modelers is essential to ensure that the questions of interest and design choices are addressed appropriately by the model, and that the model predictions are presented in a way that is informative to the stakeholders.

Since PTS is a tool to facilitate pragmatic trial design, it will be most beneficial to stakeholders the earlier it is initiated. PTS can still be useful, however, if initiated later in the planning of a pragmatic trial to inform last-minute adjustments or even to aid with the critical “go/no go” decision.

So the take-home message is: Wouldn't it feel good to be able to test your clinical trial design, explore the dangers and potential mistakes on the computer where the costs and time associated with mistakes are a fraction of those in a real trial?

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Investigator Recruitment

By L. Adam Simmons, DC, Study Start-Up Specialist

Investigator recruitment is a vital part of the start-up process for any new study. Identifying the appropriate site participants for a study can affect the ultimate success of the program, and as in any study, getting the right, high quality data is the ultimate goal.

There are many things to consider when selecting sites for a clinical or observational study; it is not a “one site fits all” situation. The first and key consideration, however, is the recruitment and choice of investigator sites. The qualifications and experience of the site staff, including the investigator, site coordinator and all staff involved in data collection

and patient interaction, needs to be evaluated. Experience with the disease or therapeutic area definitely has an impact on site selection, but also important to consider is past experience with implementing and coordinating a study. Study oversight requires management skills, problem solving abilities, and strong communication skills.

Investigators should cover a wide range of medical specialties and range from community-based physicians to academic research centers to site management organizations (SMOs). Having an investigator database that includes sites from across the world allows companies to implement feasibility assessments to determine the right sites, and in the right locations, for each specific study.

Sources for site selection can include proprietary databases of investigators through service providers, sponsor-provided lists, physician networks, professional societies and IMS and National Drug Code (NDC) prescription data. Access to investigator databases is invaluable. In most cases, entries are made into a database once sites and investigators have been identified and those entries are then tagged with specialties in which they have indicated interest or in which they have previously participated in specific types of trials. A list of investigators to target for a new program can then be generated based on specific criteria needed for a project.

Another way that sites can be identified is through the Internet. Companies can use their websites to recruit new investigators. Many medical professionals are interested in participating in clinical and observational studies to broaden their experience and opportunities in the health care industry, but they are not always sure how to go about getting involved. Website use allows physicians interested in participating in clinical trials the chance to visit these websites, provide their contact information, information about their study experience and the types of clinical trials in which they would like to participate, allowing new sites and staff to be added to databases on a regular basis. An example of this type of website interface can be found on the UBC website at www.unitedbiosource.com/clinical-trials-registration.aspx.

Once sites have been initially identified, the process begins on contacting these sites regarding their interest and availability to participate in a specific study. Typically, blinded or abbreviated information is sent about the upcoming study project to gauge interest and obtain general information about the site contacted. This can be done through a mass fax, email or both. This correspondence can be personalized and sent in bulk, often thousands at a time depending on the scope and needs of the actual study. When reaching out to recruit sites, consideration should be given to making the process as convenient as possible for responders. To this end, the process should be designed to allow interested

sites to respond via a web portal, fax or toll-free phone lines so each person can respond in their preferred manner. Once a site has agreed to participate in a study, it is important to update the investigator database to indicate status or participation interest to ensure accurate record keeping for each database entry.

Coordination of study sites is most effective when an internal portal is developed and used to track all sites, allowing communication with sites and up-to-date records through call logs or other tracking vehicles. This also allows tracking of all regulatory documents such as the confidentiality agreements (CDA), Curriculum Vitae (CV), Medical Licenses, etc. Having standard operating procedures (SOPs) in place for investigator recruitment, feasibility process and clinical coordinating center activity is an important step to assure consistency in all recruitment efforts and easily identified procedures for new staff or audit purposes.

Site selection requires due diligence on the part of the sponsoring company, but also on the part of any service providers involved in the process, to ensure that the right criteria are met by each site to provide the expertise needed to collect the right, high quality data needed for your study.

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Study Coordinators as an Asset in Enrollment...and Ultimate Study Success

By Abbe Steel, Vice President, and Tess Drahzal, Account Director, Trial Enhancement

Successful studies hinge on several important factors — protocol development, site selection, infrastructure and technology processes, appropriate training, patient recruitment, etc. Because sites receive referrals from both within and outside of their practice, there should be a particular focus on activities that drive enrollment at the site level. In particular, this article addresses the role of the study coordinators and how their impact on enrollment can be maximized.

Many of us think of visibility when we think of patient recruitment — how many potential patients have seen our ad? There are certainly ways in which we can target media placement and deliver a compelling message. However, depending on the study, candidates may come from a variety of sources other than advertising. In many cases, the study coordinator plays a key role in driving recruitment by identifying patients from within their practice and community. Ideally, study coordinators use a variety of methods for patient identification, such as chart reviews, mailings, community events and reminders. In a community-based setting or with a novice

study coordinator, however, oftentimes all available methods are not employed. Regardless of where a referral is initiated, if the site staff is not making every effort to process these referrals, screen patients, and manage the informed consent process, full potential for enrollment will not be reached.

A survey of study patients was conducted in 2010 to gather information on what activities influenced their participation, and over three quarters of respondents said the site staff was the primary factor that convinced them to participate, and what kept them coming back. The takeaway is that the study coordinator is essential to patient recruitment and retention, and that fact should influence the approach to patient recruitment.

There are many reasons that studies do not enroll. Only about 20% of sites are actively enrolling patients.¹ This is often due to complex protocols and inclusion/exclusion criteria, multiple and competing trials at a study site, over-worked or research naïve study coordinators, study fatigue, or lack of support and resources. Many of these barriers and obstacles to enrollment can be removed at the site level by maximizing the impact of efforts made by study coordinators.

Site Assessments

Conducting site assessments as early as possible

can help initiate site-based recruitment efforts and set the groundwork for success. Some of the activities in a site assessment include providing useful, convenient, and effective tools; offering suggestions on tactics and the appropriate tools for implementation; and establishing a relationship with the study coordinator. It is commonplace to look at past performance when selecting sites. There are clearly quantitative aspects to site selection, such as the pool of patients, resources, etc., however, there is also a qualitative aspect to selecting and working with sites. Recruitment specialists talk to sites on a weekly, or sometimes daily, basis depending on the stage of the project, and those that are really good at their jobs often know the names of study coordinators' children and where they go on vacation. Developing this relationship early on will help the study coordinator rely on you for recruitment advice and help keep your study top of mind. Additionally, every site is different. During these calls, touch-points can be identified at each site. Who interacts with the patient at every point in their care? How is data collected?

There are many reasons that studies do not enroll. Only about 20% of sites are actively enrolling patients. Many of these barriers and obstacles to enrollment can be removed at the site level by maximizing the impact of efforts made by study coordinators.

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Where are the opportunities, and when is it appropriate, to introduce the study? Out of all of these efforts, developing a relationship with the study coordinator is the most important. It is what will make the difference down the road on whether your phone calls are returned and your suggested recruitment tactics are employed.

Some sites tend to overinflate their patient pool during the site selection process, so taking steps to truly understand each site's patient pool for a particular study is critical. There is also often significant variation of characteristics among sites participating in a given study, including research experience, number of physicians in the practice, technology, people, and space resources, and whether the site has the ability to stay open past normal business hours or on Saturdays to conduct screenings. This information will help formulate a recruitment plan for each site and calculate expected enrollment rates.

It is also important to keep track of potential staffing transitions. For example, if a sudden dip in screenings is seen when reviewing metrics from a site, it could be because the study coordinator transitioned. In this case, you need to treat the situation as if you are starting the study all over again — review the materials, patients, tools, etc. Studies can often be five to ten years in length, so remaining conscious of this possibility is necessary, especially in longer term studies.

Tools to Support Study Coordinators

Tailoring your approach to site management allows opportunities to be created for patient identification, recruitment, screening and enrollment. Sometimes a large part of this is offering suggestions on how the study coordinator can communicate with members of the site staff.

- **Support materials** can also be provided to study coordinators to assist them in targeting appropriate patients. These can include tools for patient identification, such as chart stickers to provide a visual reminder to discuss the study when patients visit, and patient recruitment materials such as brochures, letters and posters. For example, a recent study in pregnant women was under-enrolling. It was discovered that a critical inclusion criteria was not being tracked at the time the women were receiving an ultrasound. The simple act of placing a flyer near the ultrasound machine reminded staff to let the study coordinator know if the women they were treating fit the inclusion criteria. As a result, an immedi-

ate jump in enrollment was seen. In another case, a site participating in a pediatric study did not have a very “kid friendly” office. Placing books and making floor space for kids to play helped encourage parents to participate and to return for study visits.

- **Call centers** can be a useful tool in studies, but a call center is not always the answer for every site or every study. The key is to find out what is missing from study recruitment operations and then to use a call center to fill potential gaps. Utilizing a call center to reduce site burden and manage site and patient reminders can be a huge asset. A call center can play a variety of roles, including motivation, reminders, referral tracking, data collection and enrollment monitoring. Initial phone screenings help provide sites with more qualified referrals, reducing the time spent screening for appropriate patients, and providing encouragement to potential participants and site staff. The call center can also assist with appointment scheduling, reminder calls to both sites and patients, and transportation arrangements for study visits.
- **Recruitment portals** help service providers, sponsors, and sites track the status of referrals, while allowing all approved parties to assist in entering this information if sites are behind on status updates. In addition, receiving feedback from sites through a tool like a portal on how they prefer to receive referrals also helps ease their involvement in the study. The general rule is that if patients are not contacted within 24-48 hours of being referred, the chance that they will be responsive when they are eventually reached is very small.
- **Study coordinator workshops** can be conducted at an investigator meeting, at strategic time-points during the enrollment period, or as a contingency if enrollment is lagging. A study coordinator workshop provides an opportunity to identify challenges, opportunities, and suggestions; discuss best practices; and to conduct role playing exercises to facilitate the enrollment and informed consent process. Study coordinators are also often asked to complete certain assignments prior to the workshop such as preparing a blinded patient list to bring with them to the workshop. Offering encouragement in the form of a gift certificate or token of appreciation for participation can also go a long way. Workshops can be particularly useful if there is caregiver involvement or added difficulty managing informed consent. These meetings have the best impact when study coordinators are truly involved and engaged.
- **Teleconferences** focused on study coordinator activities create a forum for coordinators to share their experiences and provide suggestions on what has worked and what has not. Often these teleconferences will include a case study from a site that has done particularly well or offer guidance on finding study coordinators to fit a

niche request. As an example, a past study was being developing in an extremely competitive therapeutic area where there was an emphasis on recruiting a minority population. Study coordinators were identified that were experienced and specifically interested in working with minorities. By using the teleconference forum to outline this specific need, champion study coordinators ended up making this study immensely successful.

It is critical that service providers and sponsors create an environment of teamwork with study coordinators. This means demonstrating commitment and establishing credibility and reliability early on in the process. There is an opportunity to empower study coordinators to play a critical role in recruitment by providing suggestions and tools to facilitate their involvement. Part of this strategy is creating a game plan – something they can refer to throughout the process. Study coordinators are busy and have multiple responsibilities, so making information readily accessible will encourage the measures that contribute to enrollment. Among sponsors, service providers, and sites, roles and responsibilities need to be clarified, defined and recognized. The approach should be tailored and comprehensive to ensure sites optimize their recruitment efforts.

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Clinical Trials 2.0: Using Home Health Nurses in the “Change”

By Jennifer M. Allen, RN, BSN, MBA, Senior Manager, Site of Care Services and Mary James, BS, Business Administration, Client Account Manager

Just as the technology industry routinely reinvents itself (think “Web 2.0”), so too must the clinical trial industry. Recently, there was an industry article published describing a “Clinical Trial in a Box” concept that just may be the start of Clinical Trial 2.0.¹ This trial design is characterized as a streamlined study design that leverages telemedicine and remote patient monitoring in order to control costs of managing post-approval studies.

Protocol designs that reduce site burden and accelerate study start up timelines are essential components to cost containment. A variety of new operational techniques, such as utilizing home health nurses and direct-to-patient data collection, are now being integrated as core components of study execution.

In the typical site-centric clinical trial model, patients travel to investigator sites for study visits and administration/dispensing of the trial drug. In a direct-to-patient clinical trial model, however, the trial comes to the patient via home health nurses and technology. As a way to reduce cost impact, companies are starting to consider a combination of site and home nurse visits or all home nurse visits. There are many advantages to this more innovative, flexible, hybrid study approach, including: expanded geographic reach, reduced payments to sites, consistent data collection, improved patient retention and the reduction of transportation barriers.

Leveraging Home Health Nurses

Next to recruitment, retention of enrolled patients is the fundamental challenge to ensure the timely completion of clinical trials.

Furthermore, when the study is to continue for a number of years, the drop-out rate can be considerable, causing timeline delays and increasing trial budgets. Patients that consent to participate in a study do not always realize the commitment they have made, and when they see little to no value, their motivation to remain in the study dramatically decreases.

While more complex trials may continue to require subjects to travel to traditional investigator sites for their study office visits, other trials can utilize a version of the novel concept of a “mobile trial” to achieve the desired goals of improved patient retention and cost control. Common reasons for drop-out rates include transportation issues, inconvenience of traveling to a study site for scheduled appointments, fatigue when attending site appointments, and lack of familiarity with the environment at the site. Studies show that individuals in their home or similar familiar environments provide more consistent baseline data and eliminating transportation issues can increase study participation to greater than 80%.^{2,3}

Home care services offer flexibility of scheduling and follow up, thus decreasing missed appointments. While providing increased convenience to subjects, home care can also

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help decrease the impact of rising study costs and increase investigator participation. Home health nurses can provide a variety of services in support of a clinical trial including:

- Patient assessments
- Patient education for diary completion and self administration
- Administration of study drug
- Specimen collection
- Data collection

The ability to provide innovative solutions to barriers encountered in traditionally designed study protocols, such as home health nursing services, increases the potential subjects available for recruitment, the ability to gather consistent data, and decreased study costs. As costs of clinical trials continue to increase, the availability of home health resources provide cost efficiency and recruitment reach that will be critical to the success of future drug development and complement current practices for clinical trials. Clinical Trial 2.0 is overdue, and creative solutions are paving the way to development of a crucial model in care.

Case Study Illustration I

A 66-year-old male Caucasian with Myelodysplastic Syndrome, participating in a Phase II open label, dose escalation study to evaluate the safety and efficacy of study drug in thrombocytopenic subjects with low or intermediate-1 risk Myelodysplastic Syndrome provides an example of how new initiatives can address the needs of the patient and increase participation. The investigator was located in Ohio and the patient traveled between Ohio, Florida, and Kentucky. The trial required sample collection on week one at 24, 48, 72, and 120 hours post subcutaneous injection of study drug for pharmacokinetic and platelet analysis. Sample collection occurred again on week seven at the same intervals as week one with additional sampling at 192 hours and 240 hours post injection. Site visits were required every one to two weeks.

Due to the subject’s travel requirements, the subject would have declined participation or dropped from the study prior to completion if required to adhere to conventional study protocols. Because of a broad home health care coverage footprint, the subject successfully completed the trial protocol.

Case Study Illustration II

A 77-year-old male Caucasian with atrial fibrillation, agreed to participate in a comparative research study, comparing the outcomes of a traditional medication therapy utilizing genetic testing versus the usual management practices of physicians when genetic testing is not incorporated into their regime. During the enrollment period of the study, the subject was on an extensive vacation touring the country in a recreational vehicle and only resting in one location for two to three days. The trial required only one lab draw but it had to be thoroughly coordinated in order to find the suitable location and meet the courier service requirements.

Again, due to a broad national footprint of home health care coverage, the subject was able to participate in the study and the lab specimen arrived intact at the central lab in accordance to the protocol requirements. The investigator was able to obtain the genetic test results in order to prescribe an appropriate dose of medication therapy.

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Technology Considerations in Registries and Observational Studies: One Size Doesn’t Fit All

By Othniel Badea, Director and Chief Information Architect, Information Technology and Jennifer Kelly, Associate Director, Coordinating Center

There are obviously a variety of factors that need to be considered when designing and implementing registries and observational studies. While these studies do have some similarities to traditional clinical trials, there are definite differences and considerations that need to be accounted for when providing technology platforms and support for these programs.

Audience

For the most part, the sites and investigators that participate in registries and observational studies are not familiar with the terminology or the platforms available in the clinical trial world. Most have not been exposed to terms or activities such as “Data Correction Queries” or “Site Monitors” before, and some may not even be accustomed to logging into a system on a periodic basis or having to reset their password at predefined intervals. Although many of these things are considered routine in a clinical trial environment, the same assumption cannot be made in observational studies. All details, including application, navigation and presentation elements, should be considered when designing the studies.

Burden

Another element to consider is the burden that is placed on the site. These program types would not be economically feasible if they had to support additional staff at sites, so the burden falls on the existing staff to incorporate the data collection process into their already busy schedule. Technology can play a major role in keeping the additional burden to a minimum, and educating the staff by holding one-on-one or group trainings and offering application training manuals abets user acceptance.

The application should be simple to use with specific user preferences, allowing quick access to the patient or collection form needed for a given patient. Having the ability to save partial information and then have the system be able to return the user to the same location at a later time to complete the data entry is a critical feature that must be considered. In a busy practice, the person entering the data may have many interruptions that could interfere with the entry process, and having the ability to start and stop when needed is imperative. The platform should have the ability to automatically maintain a patient workflow, allowing investigators to see an instant “snapshot” of each patient upon login which would show a listing of upcoming, incomplete or missing forms that need to be completed for a given patient.

In a traditional system, the data collection tools are displayed on the screen in a consistent format. In observational studies, data should be displayed very similarly to the design of the paper form, including breaking the forms into multiple pages or screens in order to simulate the paper form. This feature becomes critical when related questions need to be displayed side by side or in a specific location. A simple example would be data collection about organs that are on different sides of the body and having the need to display all questions related to the left side of the body on the left, and all questions related to the right side of the body in parallel on the right.

Observational studies, like clinical trials, sometimes require data to be collected directly from the patient or other stakeholders. Having the ability for the patient or the stakeholder

to enter the data directly into the platform is a necessary feature for registries. This design should accommodate both entry from a remote location as well as entry from the physician’s site, where a kiosk would be provided for patients to complete data. This also often requires a multilingual interface for the patients in order to simplify data entry and maximize compliance and accuracy.

Notifications / Compliance

Most registries and observational studies follow patients for a much longer period of time than clinical trials. Some safety registries can follow each patient for as long as 15 years; other disease registries are indefinite. The largest problem this poses is compliance. Fatigue and lack of interest over time will lead to patients that are lost to follow-up and reduction in data collection.

In order to ensure optimal follow-up rates, the platform used should support a robust notification mechanism as well as a robust follow-up portal that allows call center personnel to obtain the missing information. Most patients have preferences for methods and times of communication, and those preferences need to be taken into consideration when reaching out to them. The number of calls and/or notifications should be kept to a minimum. Having a tool that can give a holistic view of the patient is critical, allowing the personnel responsible for contacting patients to resolve all outstanding issues with the patient in a single communication. The most common methods of communication should be supported: e-mail, fax, text messaging, and automated calls.

Dashboard

Developing a customizable, action-driven dashboard allows a call center to manage program workload. Patient and site outreach follows a programmed algorithm for each touch point. Tasks are assigned allowing call center personnel to manage their daily call volume. The platform links the dashboard task list with the corresponding patient or site profiles, allowing for real-time data entry and edit capabilities during the live contact.

Managers have the ability to monitor performance based on task completion and compliance rates, and workloads can be easily modified to fit targeted goals and service level

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agreements. For example, the dashboard provides a concise snapshot of the number of patients in a window to complete their registry follow up, thus allowing management to develop realistic, longer term staffing models.

Data Cleaning

In a registry study, the chance of receiving a data correction form is minimal, making it critical to collect data as completely and cleanly as possible up front. In order to accomplish this, the platform used needs to support edit checks that can execute against each data collection field, can compare data to fields on other pages, and can compare data to fields on other forms from other visits. Having the ability to run these edit checks in real time as data is being entered will provide quicker feedback on fields that are out of range and minimize data entry time.

Because of the large number of fields collected in a registry or observational study, some fields, pages, or even forms might not apply based on the answers provided by the patient previously. The platform used should have the ability to hide fields, pages or forms that are not relevant. This will ensure data that does not apply is not collected and will not have to be queried later for a resolution.

Supporting documentation is sometimes needed for these types of programs, ranging from simple lab results to MRI images. The platform should support the ability to upload a variety of documents that can then be reviewed either together with the patient records or anonymously across all patients by an adjudicator.

Size / Length

Unlike clinical trials that are very specific in size and length, most registries and observational programs have a very large patient population and can have a very long follow-up period. The platform utilized needs to have a defined upgrade path that will allow it to execute and stay current for more than 10 years, and it will need to be tested and proven with very large amounts of data to ensure there is no performance degradation as more data is being collected.

Because of the length, the platform also needs to be able to adjust to dynamic program changes and dynamic follow-up algorithms. Since the analysis cannot wait until the end of

the study, being able to identify locked forms at any time and having the ability to extract the interim locked data for analysis is a must for such programs.

Customization / Flexibility

Flexibility and rapid change are critical components of these types of programs. The platform needs to have the flexibility of customizing any behavior and workflow in order to quickly react to changes. The data collection forms need to be extremely flexible and quick to change. Because data fields will be updated after the release of the program, the platform will also need to intelligently define the impact on the current data or data collection form based on a given change, eliminating potential data loss as a result of the changes.

Reporting

One of the benefits for the investigator in these types of studies is the advancement of medicine. The data they are collecting is beneficial to advances in patient treatment, and thus, ultimately is very important to these investigators. The platform needs to be able to bring this data to life for them, having the ability to extract investigator specific data and provide them access to their own data in real time. Reports that compare site data to aggregated national data, and that graph events over time to show improvement versus degradation of patients, are integral tools in the analysis and interpretation of study results.

The platform must maintain historical data for all call center activities on a project and individual basis. A browser-based interface needs to provide a rich set of standard real-time and historical reports. This reporting system helps call center managers observe and control the performance of their personnel. Being able to report, measure, review and interpret the results of call center-based observational studies and registries is paramount to the ongoing success of your recruitment and retention strategies.

The increased use and importance of observational studies has created the need for companies to evaluate the standard operating procedures for clinical trials and assess how those procedures need to be amended for these new programs. Often the focus of that evaluation is on methodology, structure, and resulting evidence, but it is just as critical that the technology details be evaluated as well to support all other considerations. Information technology experts should be included in the early stages of decision making and design to ensure the right data is collected in the right ways from the right people with the least amount of burden or potential for error.

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Publication Planning — Extending the Value of Data

By Linda Gorman, PhD, UBC-Envision Group

Clinical trials are a complex and costly undertaking, not only from the perspective of the sponsor or funder but also in consideration of the time and dedication of the participants — from investigators to site managers to study participants. The way data dissemination is planned, managed, and delivered to target audiences is critical. Findings from clinical trials are typically first presented at congresses as poster or oral presentations and subsequently reported in a primary manuscript published in a peer-reviewed journal. However, additional publication opportunities exist that may enable further dissemination of the data or provide additional perspectives related to the clinical context of the disease or therapeutic area in which the research is conducted. Including these considerations during the publication planning process will better ensure the highest educational impact and broadest informational reach of available data.

A strategic publication plan should 1) be founded on evidence-based medical and scientific direction; 2) include a diversity of tactical outputs appropriate for the therapeutic area and clinical applicability of the product; and 3) strive to reach target audiences unique to the associated disease or condition. Aside from dissemination of primary data, clinical trial data can be extended through post-hoc (subset) analyses, integrative (pooled) data analyses, exploratory data analyses, review articles (narrative or structured/systematic), commentaries and expert opinion pieces, and journal supplements (See Figure 1). Other types of secondary data can also be presented, for example, observational research (various insurance/care databases, patient registries, and epidemiological data) and health economics and outcomes research. All publications developed as part of a publication plan involving industry-sponsored research should follow the Good Publication Practice for Communicating Company Sponsored Medical Research (GPP2) guidelines. These guidelines require author direction, participation, and final determination/approvals of all publications.

Primary data dissemination

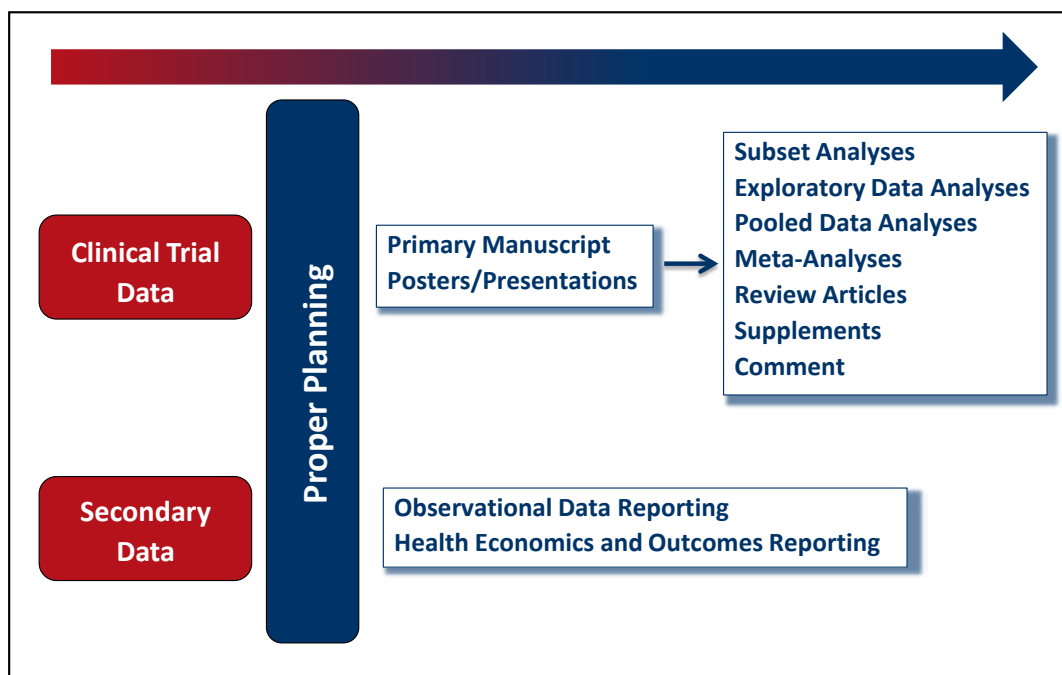
As a result of the enactment of the U.S. Food and Drug Administration Amendments Act (FDAAA) and the European Union Drug Regulating Authorities Clinical Trials (EudraCT), results of all clinical trials of an approved drug (except for Phase 1 trials) must be posted on a publicly accessible, searchable database within one year after the trial's primary completion date, defined as last patient last visit. Publication of a primary manuscript before posting of trial results in the public database is desirable to prevent misinterpretation of the posted raw data; this has led to greatly accelerated manuscript development timelines. These shorter timelines have in turn necessitated rapid distribution of trial data at relevant congresses. Publication planning is critical at this stage to ensure abstract submission/congress presentation prior to publication of primary data. Not only is it important to submit abstracts to the major conferences in the relevant therapeutic area, it is also a good strategy to submit primary data to congresses with different target audiences (related or sub-specialties, regional medical groups, etc.) to maximize exposure. This will enable study data to be presented to both specialists and other groups involved in health care decision-making with patients (such as primary care physicians, pharmacists, nurses, nurse practitioners and physician assistants, and patient educators).

Primary data have been presented – Now what?

Additional Analyses of Primary Data

- **Post-hoc analyses** of existing data may offer novel insights or provide a rationale for a new clinical study. Primary data for pre-specified clinical endpoints are

Figure 1. The Publications Plan — Extending the Value of Data



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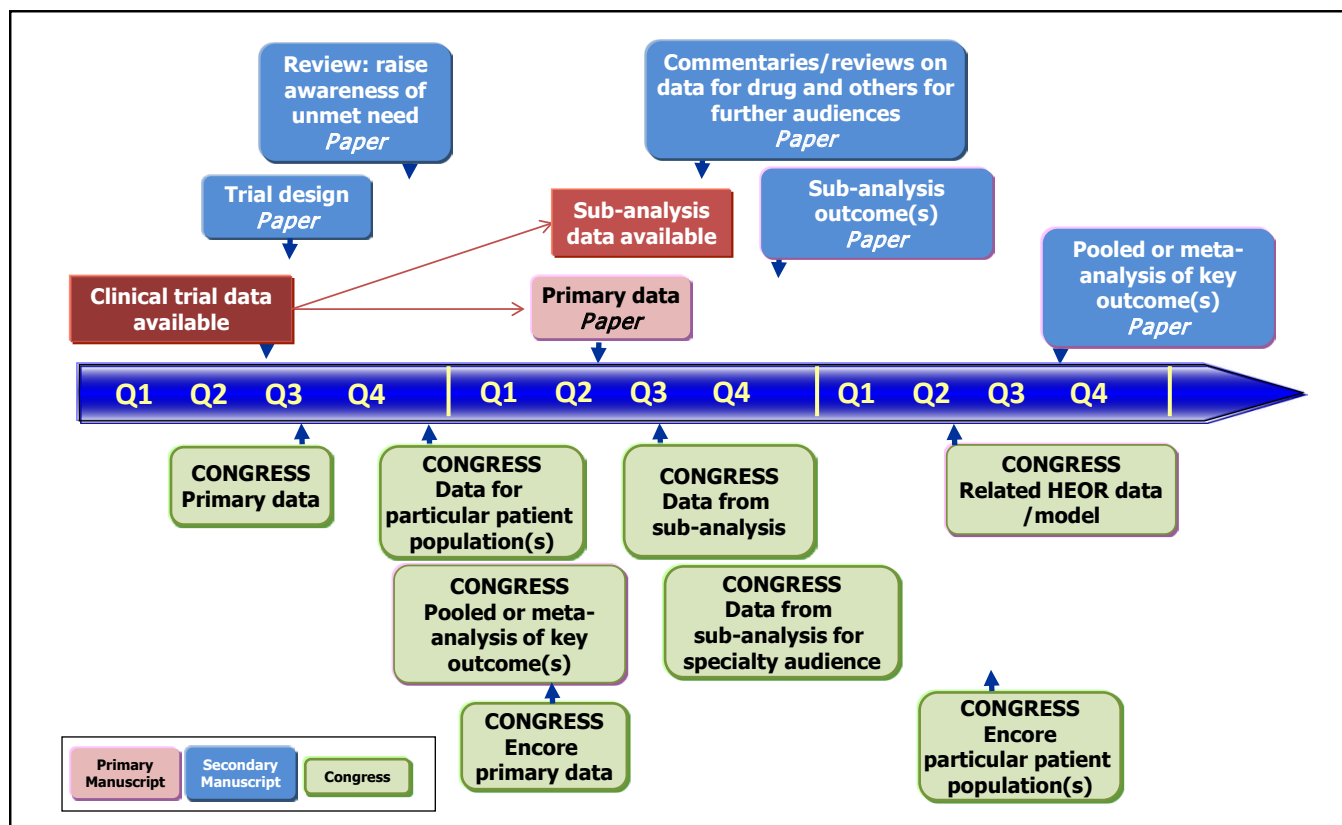
Publication Planning — Extending the Value of Data

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more statistically rigorous and clinically relevant than subsequent analyses or approaches using existing data. Accordingly, presenting and publishing primary data before publishing any data from post-hoc analyses is imperative. Post-hoc analyses are conducted in a subgroup of patients with defined baseline characteristics such as age, sex, race, comorbidity, or disease severity. Subgroup analyses can yield valuable information when properly planned, reported, and interpreted. Data gathered from such analyses may not be as statistically rigorous as the primary clinical trial data but may be important for identifying patterns or trends in the data, or for providing the basis for planning a new trial with relevant pre-specified endpoints. These analyses can result in new presentations and publications (i.e., manuscripts, research letters, short communications) if the data are noteworthy and clinically relevant.

- **Integrative data analysis (IDA)** is defined as the analysis of multiple individual data sets that have been pooled together. This type of analysis can only be performed when the original data are available. If the complete data are unavailable, a meta-analysis can be performed on the summary study statistics (as described below). By increasing the overall sample size, an IDA has the potential to provide substantial increases in statistical power for testing research hypotheses. This approach also allows a determination of whether treatment effects are consistent across independent studies.
- For **exploratory data analysis (EDA)**, data collected in a clinical trial are analyzed with the goal of developing an appropriate model. EDA techniques are usually graphical: scatter plots, character plots, box plots, histograms, bihistograms, probability plots, residual plots, and mean plots. The models developed might serve several purposes, from validating previous research findings to providing the basis for the design of future clinical trials to more rigorously investigate these associations through actual hypothesis testing.
- **Narrative review** articles often present a broad range of issues related to a given topic rather than addressing a particular issue in depth. Narrative reviews are appropriate for describing the history or development of a variety of potential medical topics (e.g., the etiology and management of a disease, mechanism of action of a therapeutic class, cutting-edge advances in the setting of scant research, or the conceptual integration of two independent fields of research). Literature included in a narrative review is not always identified by a methodological approach, though some journals may require a detailed description of how searches were conducted, including identification of databases and keywords used. Authors may selectively choose only references that support their viewpoint, while excluding other articles. Although these types of review articles can be educational and provide a broader background on a medical topic, they are more likely to reflect author opinion and be potentially biased.
- Qualitative **systematic reviews** apply standards for gathering, analyzing, and reporting evidence. Inclusion and exclusion criteria can be based on study topic, patient population and setting, or study design. The methodology used for selecting references is clearly defined at the beginning of the review and is usually described in detail. Relevant literature is assembled and critically appraised, and a synthesis of all relevant studies is generated. Conclusions are more reliable and accurate than those of narrative review articles because the use of the explicit search criteria limits bias in identifying and rejecting studies.
- A **meta-analysis** is a specific type of systematic review that uses statistical methods to combine and summarize the results of several studies. Unlike a pooled analysis, which relies on the original study data, a meta-analysis quantitatively combines the summary statistics drawn from multiple studies that address a set of related research hypotheses. This type of review can be undertaken when the data used in previous studies are inaccessible (e.g., in the case of multiple sponsors and proprietary interests) or if they are simply no longer available. This approach overcomes the problem of reduced statistical power in studies with small sample sizes by using a weighted average for the estimated treatment effect. Selection of studies is based on specific predefined criteria, for example, the requirement of randomization and blinding in a clinical trial. Analyses are performed using standard statistics software packages or specialized software packages designed for meta-analysis.
- A **comment** is written to discuss, support, or dispute a previous publication. Such a short publication may take the form of an article, letter, or editorial. Most journals have specific formats and requirements for the submission, review, and publication of such pieces.
- **Journal supplements** can support publication plans by establishing a current, in-depth, single-source compilation on selected topics of interest while also providing citable references. Supplements provide different benefits to different audiences. Supplements come in different forms: educational supplements (disease state and management), symposium or roundtable proceedings, consensus panels — guidelines or recommendations developed by expert thought-leaders — highlights from key symposia on selected topics of interest, or focused

Figure 2. The Publications Plan – Timing is Everything



collections of complementary research or studies that are epidemiologic-, pharmaco-economic-, or clinical research-based. Supplements are a means for clinical experts who are authors to educate their peers on the current knowledge, recent data, and state-of-the-art in treatment paradigms. Supplements enable exploration of related topics of interest in greater depth than primary manuscripts might allow (these typically are not published together). Supplements may be published more rapidly compared with single peer-reviewed manuscripts. Although some readers may perceive industry-sponsored supplements as inherently biased or lacking in credibility, selecting a journal that requires external peer review for the component articles helps address this concern. Similarly, as noted previously, multi-company-sponsored journal supplements provide further balance and credibility.

Secondary Data

- **Observational data** are used to identify 1) risk factors for disease, incidence, prevalence, and mortality rates; and 2) possible effects of treatment or care modalities on patients in a clinical setting. Studies can range from the examination of a single patient (case study) to an analysis of data from a large population (e.g., insurance databases or patient registries). Examination of these types of data may lead to novel discoveries, such as new diseases and comorbidities, unexpected treatment

effects (adverse or beneficial), or previously unidentified disease mechanisms.

- **Health economics and outcomes research (HEOR)** compares both the costs and consequences of different treatments and care strategies. Such studies may include economic modeling and analyses (e.g., burden of illness, cost effectiveness, cost utility), utilization analyses (e.g., treatment patterns, switching), productivity outcomes, post-marketing safety assessments, patient-reported outcomes, and comparative effectiveness research.

Conclusion

Publication planning has moved well beyond the requisite development of one abstract and one presentation per clinical trial (See Figure 2).

Further analysis of trial data, either through examination of smaller subsets or in combination with other similarly designed trials, can yield important insights or aid in the development of future trials. The many publication options available also enable researchers to present data to a broad range of target audiences. Secondary data sources and publication types can aid in providing context, history, and expert opinion on current issues. Combined, all these publication options enable data to be leveraged to its fullest potential.

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Top Ten Reasons to Conduct Research after Product Approval Value, Value, Value!

- 1. Real-world value**
Observe and document real-world effectiveness tailored towards demonstrating product value.
- 2. Comparative effectiveness**
Determine how a product (drug, biologic, device, diagnostic) compares with the “standard of care” or other competitors in actual use.
- 3. Patient-reported outcomes**
Evaluate patient (and/or caregiver) reported outcomes, including health-related quality of life impacts of diseases and treatments, patient and caregiver satisfaction, adherence and other patient-centric data to inform or support market access.
- 4. Cost implications**
Collect resource utilization and other relevant data to understand the economic impact of disease and how it can be reduced by alternative therapies. Measure and assess the differential economic impact of a product versus an alternative intervention or other health care service.
- 5. Prescriber and/or patient preference**
Identify the decision making process around why prescribers and/or patients prefer certain treatment characteristics and behave the way they do.
- 6. Safety**
Gather data on the adverse effects of a product versus other treatments as they are used in real-world populations, with a broader set of clinical and demographic characteristics than studied in clinical trials.
- 7. Disease and patient heterogeneity**
Understand how conditions, including orphan diseases, vary in terms of presentation and progression over time.
- 8. Health services research**
Understand the impact that health systems, plans and provider organizations have on the delivery and outcomes of health care.
- 9. Practice patterns**
Document practice patterns of physicians and other health care providers – how they may differ by health system, provider and patient characteristics, and how they may compare to national or international norms or guidelines.
- 10. Longitudinal outcomes**
Lengthen the duration of follow-up to better understand the consequences of a product, including effectiveness and safety, cost and patient-reported outcomes; or to evaluate outcomes with long latency.

Top Study Designs for Post-Approval Research

- Case-control Studies
- Chart Reviews
- Cross-sectional Studies
- Large Streamlined Trials/
Pragmatic Trials
- Modeling/Simulation
- Observational Prospective Cohort Studies
- Patient and Health Care Provider
Knowledge, Attitude and Behavior Surveys
- Registries
 - Product and/or Pregnancy Exposure
 - Multi-Faceted
 - Natural History of Disease
- Randomized, Blinded
Clinical Trials
- Resource Utilization
Questionnaires
- Retrospective Database Studies
- Time and Motion Studies

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