Pragmatic trials (PTs) promise to address much of healthcare’s urgent need for real-world evidence to inform and improve decision-making in patient care and health policy. Enabled by expanding access to real-world health data environments and operationalized by eHealth data technologies, pragmatic trials evaluate health technologies as they are used in actual medical practice, evaluating not only therapeutic benefits and risks in real-world populations, but also measuring economic impact, and elucidating other important contributing factors such as prescribing practices and patient compliance.

For the biopharma industry, these real-world studies can demonstrate product value, not only to regulators but also to patients, prescribers and payers. However, PTs also pose significant research design and operational challenges as sponsors extend product evaluation beyond the controlled setting of randomized clinical trials (RCTs) into the post-approval arena of real-world clinical settings and patient populations. This paper details key PT design characteristics and major considerations for sponsors related to study infrastructure and generation of real-world evidence necessary for the successful implementation of PTs and consequent generation of valid and relevant real-world evidence.
The Need for Real-World Therapeutic Evaluation

Since Austin Bradford Hill’s landmark 1946 trial of streptomycin against tuberculosis, the randomized controlled trial (RCT) has provided the methodology for therapeutic safety and efficacy evaluation. Using carefully selected populations to control for bias, RCT is the optimal design to demonstrate a therapy’s biological effects, but in many cases it is unable to answer a broad constellation of questions healthcare must answer to understand the value of a therapy in real-world medical practice.

Questions central to improving health outcomes and guiding policy decisions typically can only be answered by assessing a therapy’s effectiveness in large, heterogeneous populations and, in the case of interventions for chronic conditions, over longer periods of time. To ensure broader safety and effectiveness, drug effects must be evaluated in patients of various ages and ethnicities and in the context of multiple disease conditions and concomitant medications. To identify optimal health technologies and interventions, the benefits, risks and cost-effectiveness of competing therapies and programs must be compared in the broad target patient population and in the care settings where they are actually used. Escalating costs in both drug development and care delivery make it ever-more imperative to generate high-quality, real-world evidence of value in an efficient manner.

Pragmatic trials (PTs) are designed to extend scientific evaluation beyond the limits of the RCT research setting and into the realm of real-world medical practice. Non-interventional observational studies and registries generate useful information on real-world drug effects but lack randomization designed to reduce bias. Interventional PTs enable rigorous scientific evaluation in relatively short timeframes using designs that provide strong external validity to ensure that findings apply to real-world patient populations and care environments.

For the biopharma industry, PTs offer solutions to address the growing demands of care providers, payers and policy makers for high-quality evidence of therapeutic and economic value. PTs can provide evidence to:

- *Demonstrate product safety and effectiveness* in post-approval medical practice sought by regulators, especially for new therapies used in large chronic disease populations including diabetes, cardiovascular and respiratory diseases.
- *Support reimbursement and pricing* by demonstrating real-world product performance and economic value increasingly required by payers.
Enhance competitive position by demonstrating product benefits to prescribers and patients. Increase research efficiencies by applying new health data sources and advances in information technology to answer research questions pertaining to real-world performance faster, and at reduced cost.

Regulatory agencies have also expressed interest in using PT-generated evidence in regulatory decision-making. In a recent article, several leaders from the FDA, including then Commissioner, Dr. Robert M. Califf, MD, stated that the FDA is committed to robust policy development regarding the use of real-world evidence in regulatory decision making. The authors also stated that real-world evidence can more efficiently answer questions on how factors such as the clinical setting and provider and health-system characteristics influence treatment effects and outcomes.¹

**Characterizing the Pragmatic Trial: PT vs. RCT**

The critical distinction between randomized clinical trials and pragmatic trials lies in the questions they seek to answer. Pre-approval clinical trials are explanatory studies that seek better understanding of a biological effect by asking: Does this new health technology deliver a biological benefit in a population with a specific disease? Pragmatic studies seek better healthcare decision-making by asking: Which of two interventions is preferable—that is, which is more effective in a broad real world population?²

**Definition.** In 2015, Califf and Sugarman defined a pragmatic trial as a study “designed for the primary purpose of informing decision-makers regarding the comparative balance of benefits, burdens and risks of a biomedical or behavioral health intervention at the individual or population level.”³

**Key characteristics.** PTs typically compare marketed therapies or medical interventions in settings that represent, as closely as possible, their routine clinical use. PTs are designed to answer questions to support treatment and policy decision-making rather than to evaluate a therapy’s biological effects. They collect large volumes of real-world health data and, where possible, they rely on advanced digital technologies to support data collection, management and analysis, which take the burden of data collection away from the practice.
Depending on the study design, population studied, setting of clinical care, etc., PTs can sit along a spectrum from highly pragmatic to minimally pragmatic but all seek to answer the question of how the product is likely to perform under real-world conditions. Characteristics that define PTs include:

- Interventions may be medical, behavioral or technical and may be measured in patients, clinicians or across healthcare systems.
- PTs rely on patient heterogeneity to maximize generalizability to real-world care; minimal exclusion criteria are used.
- PTs typically are large-scale studies to ensure adequate statistical power and require streamlined research operations.
- Endpoints encompass a broad array of health outcomes, health behaviors and economic impacts, with a major focus on patient-centered outcomes.
- Healthcare decision-makers are often involved in the design of pragmatic trials, which routinely include cost-effectiveness analyses.

**Figure 1. Explanatory (RCT) vs. Pragmatic Trials (PT)**

<table>
<thead>
<tr>
<th>Design Characteristics</th>
<th>RCT</th>
<th>PT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validity</td>
<td>Strong Internal</td>
<td>Strong External</td>
</tr>
<tr>
<td>Study Population</td>
<td>Homogeneous</td>
<td>Heterogeneous</td>
</tr>
<tr>
<td>Study Sites</td>
<td>Clinical Research/Academic</td>
<td>Real-World Medical Practice</td>
</tr>
<tr>
<td>Comparators</td>
<td>Rx vs. placebo/standard-of-care</td>
<td>Clinically relevant alternatives</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Symptoms; biomarkers</td>
<td>Health/ behavioral/ economic outcomes</td>
</tr>
</tbody>
</table>

**Key Considerations: When to Conduct PTs**

PTs pose significant challenges for sponsors, not least of which obtaining agreement across the organization as to the need for and value of this type of study. The design, set-up, and conduct of PTs require special consideration regarding:

- Research infrastructure to provide ready access to a real-world practice network and data environment;
- PT design to ensure time- and cost-efficient operations;
- Regulatory issues pertaining to both methodological and ethical practices.
Ideally, all new drug products can benefit from PTs that more fully characterize post-approval safety and effectiveness profiles and provide real-world evidence to support reimbursement and pricing. PTs can be of special value in the development of therapies intended for wide and long-term use, those most likely to pose safety issues in heterogeneous populations, and products that will require compelling evidence of cost-effectiveness to support adoption.

Given limited research budgets, the decision to conduct a pragmatic trial often focuses on therapies in which Phase III trials do not provide needed evidence to differentiate them in the marketplace: for example, if Phase III trials do not adequately reflect real-world use and are likely to fall short of payer and HTA decision-making needs, or if they mask some important attribute of the product that helps drive its value or utility. PTs are also recommended for wide-use products when the proportion of the overall target population included in Phase III trials is small. In the case of rare disease therapies, it may be necessary to conduct a PT to evaluate real-world performance and cost-effectiveness if the context of Phase III trial is substantially different from the real-world setting.

**Infrastructure Requirements to Access and Implement Real-World Evidence.**

The greatest operational challenge of PTs is access to, and management of high-quality real-world data via a network of practices with linked electronic health record systems. Efficient conduct of PTs relies on two expanding sources of electronic data—administrative health claims data and electronic health records (EHRs), and on the ability to link and integrate these two datasets at the individual patient level, to unlock the understanding and insights that accrue from the therapeutic intervention or change in health policy.

Electronic administrative claims data provide broad, population-level data that enable researchers to evaluate the impact of an intervention across the healthcare delivery system. The capability to integrate these patient level electronic claims data with patient level clinical data is a key differentiator of PTs compared to randomized clinical trials. While EHRs do not contain the same breadth of patient level data as administrative claims data, they do provide deep, patient-level data to support the conduct of PT’s safety and effectiveness evaluation in real-world care settings. Although comprehensive EHRs would be ideal, data necessary for a PT may be supplemented with electronic case report forms (eCRFs) in cases where some data elements are not available through direct linkage to EHRs.
In addition, effective PT design and implementation requires that sponsors have in-house or outsourced access to the necessary scientific disciplines and operational expertise, together with an in-depth understanding of health systems. When selecting a contract research organization (CRO), it is important that the CRO have both the technical capability and the research knowledge and experience relevant to the healthcare setting and clinical environment. Research operations require both the human resources and processes (SOPs) needed to implement a PT as well as technology platforms with capabilities to operationalize data collection, sharing and analysis.

**Figure 2. Infrastructure Required to Access and Implement Real-World Evidence Generation**

**Design Considerations.** Similar to pre-registration clinical trials, PTs require special expertise to design a study that answers the relevant research questions in a scientifically robust manner; but also to satisfy operational needs for efficiency in the context of large-scale enrollment in real-world practice settings. Efficient designs are aimed at generating the most valid and relevant real-world evidence to address research objectives with generalizability to real-life
practice. PTs include randomization at the patient or the practice level (in the case of cluster randomized trial designs) and appropriate patient populations and provider populations.

In the most simple and pragmatic form, a PT utilizes either individual or cluster randomization techniques, applied to either the new (investigational) technology or to the usual medical care a patient would receive. All the required data for the study would be gathered electronically, with no additional input from either patient or physician. Physicians participating in the study would be informed about the investigational therapy or technology in accordance with the product’s approved label—or, in the case of a pre-licensed drug, the labeling likely to be approved. Thereafter, physicians would be free to prescribe the investigational product and manage and instruct the patient as they see fit. Physicians and patients would not be required to follow a defined schedule of visits or assessments. Other than receiving the normal instructions from their physician, patients would be required to do nothing other than behave as they would normally. PTs therefore have minimal impact on patients and are designed to minimize the burden on the physician and physician’s practice.

In contrast to RCTs, PT design often involves more varied research input, adding to the complexity of the design process. In addition to the necessary expertise in statistics, data analysis, trial operations and therapeutic specialties, successful PT design can require the involvement of clinicians, epidemiologists, health economics and outcomes research experts, real-world data management experts, and input from patients and clinical practice site management.

Tools are available to help implement design across the complex PT environment. One is PRECIS, which can help sponsors develop fit-for-purpose designs consistent with study goals. PRECIS-2, for example, uses nine domains to design trials on a continuum ranging from explanatory to pragmatic approaches. It guides decision-making regarding trial elements including eligibility criteria, recruitment, participant adherence and outcomes.\textsuperscript{5}.

**Practice network sites.** Using one or more existing practice networks makes study set-up, start-up and conduct much more efficient. Ideally each network would have a comprehensive EHR system in place, and the data from all the practices in the network would be easily aggregated into a single study database for data capture and analysis. If more than one network
is being included in the study (e.g., in a multi-country PT) it will be necessary to have the capability to easily and accurately aggregate the data from all the networks.

Having a pre-existing practice network facilitates other elements of study execution, such as patient recruitment and consent, practice training and study initiation. In the absence of a pre-existing practice network site, building this component would add significantly to the time and cost of a PT.

**Electronic health data.** Access to electronic health records is essential for the efficient capture of study data. Beyond efficient data capture, using the EHR system normally used in clinical practice makes the study more reflective of the real-world patient management. The study also mirrors real-world practice more closely if it does not require capture of supplemental data elements, either by the treating physician or study patients. In this case, physicians, practice staff and patients are not regularly reminded that they are participating in a study and are less likely to behave differently as a result of participating in the research, thus minimizing the Hawthorne Effect.

**Research Operations.** While the practice network and EHR data are central requirements for a PT, expertise in research operations is also critical to success. Having the right people and processes to utilize the technology and implement other critical study elements is essential. For example, in many cases the study sites and participating physicians may have little or no prior experience in conducting clinical research. Having appropriately experienced field staff, together with training and support materials, will be required to ensure that the study is implemented according to the study plan and protocol. Depending on the study design, there may also be a requirement to train health professionals beyond the practice. For example, in the recently completed Salford Lung Study (discussed below), the sponsor had to train community pharmacists and home health nurses to ensure that they were able to carry out their duties in accordance with Good Clinical Practice and the study protocol.

**Ethical and Regulatory Considerations**

PTs are conducted in a data-driven healthcare environment that integrates clinical practice with medical research in ways that challenge traditional regulation governing ethical practice and oversight. Sponsors should be aware of issues regarding informed consent and patient
protections in the context of PTs to ensure the highest levels of ethical practice and to comply with evolving regulation.\textsuperscript{2}

**Informed consent.** Regulatory requirements designed to obtain informed consent in pre-approval clinical trials can be a barrier to large, low-risk PTs comparing marketed therapies. The U.S. Food and Drug Administration has been asked to consider development of a risk-based approach to informed consent to facilitate PTs.\textsuperscript{6}

**Vulnerable populations.** Regulations protecting vulnerable populations—including pregnant women, infants and children, prisoners, poor and mentally and physically handicapped subjects—generally result in their exclusion from clinical trials. Exclusion from PTs may actually be harmful, since no real-world evaluation of drug effects will be available to inform better treatment and health policy decisions for these groups. Recommendations have been made for regulatory revisions aimed at protecting vulnerable populations while allowing participating in PTs.\textsuperscript{7}

**Privacy and confidentiality.** Use of patient medical records and health claims data is fundamental to PTs. Anonymization is an important safeguard, but multiple applications in digital environments including social media increase risks for breaching confidentiality and data rights protections. Current regulatory protections, such as HIPAA requirements, are burdensome in the context of PTs, and new approaches are attempting to streamline consent-to-use practices to balance individual privacy with data use.\textsuperscript{8}

**Advances in Pragmatic Research: The Salford Lung Study**

The milestone Salford Lung Study represents an important advance in evolving PT practice. The Salford Lung Study is the world’s first Phase IIIb pragmatic trial. The trial was conducted before market registration to develop a novel asthma therapy—a once-daily, long-acting B agonist corticosteroid combination (fluticasone furoate/vilanterol, FF/VI).

Sponsor GlaxoSmithKline (GSK) designed the pragmatic trial to overcome significant limitations of traditional RCT evaluation of therapies targeting asthma and COPD. The proportion of patients who meet the common inclusion/exclusion criteria for traditional Phase III clinical trials is estimated to be as low as 3\% for asthma and 7\% for COPD. To obtain better evidence of drug performance in clinical practice, GSK designed a pragmatic Phase IIIb trial to generate a
rigorous safety and efficacy profile that incorporated assessment of patient adherence, co-morbidities, polypharmacy and other real-world factors. The practice network of the UK’s Salford and South Manchester region gave researchers access to electronic health data through the North West EHealth linked database and alert systems. This provided comprehensive, daily updated, electronic patient-level data from a variety of sources.

The COPD study, completed and reported in 2016, was conducted at 75 primary care sites; 2799 COPD patients were enrolled and randomized either to receive FF/VI or to continue on their existing maintenance therapy. Eligible patients were recruited in their GPs’ offices, and during the study, their GP’s adjusted dosage of all medications and provided care in the usual way. The primary effectiveness endpoint was the mean annual rate of moderate or severe exacerbations. In the primary effectiveness analysis, there was a statistically significant reduction of 8.4% (confidence interval 1.12 to 15.17) in the rate of moderate or severe exacerbations in patients treated with FF/VI 100/25mcg, compared with those receiving usual care (p=0.025).

The Way Forward: Harnessing the Benefits of Pragmatic Trials
The Salford Lung Study illustrates the potential value of pragmatic trials and may play an important role in advancing PT practice in the industry. One hypothesis regarding the value of GSK’s novel therapy was that patients would be more adherent to this therapy, which would translate into improved effectiveness over standard-of-care. A traditional Phase IIIb study would not have demonstrated this benefit. In a traditional Phase IIIb, patients’ adherence to therapy in both study arms is monitored. Patients are required and encouraged to adhere, thereby eliminating (or reducing) this benefit over standard-of-care. To demonstrate and leverage this value driver as soon as possible after product approval, GSK took the bold step of undertaking a pre-approval PT, in which no requirement or encouragement of patient adherence would be conducted.

The Salford Lung Study demonstrates the feasibility and benefits of conducting a PT in a peri-approval setting. Given this success, other sponsors will be more likely to consider including PTs in their product development and commercialization planning. Regulatory compliance coupled with the high costs of failure tend to discourage risk-taking in product development research methodologies, but the biopharma industry is also extremely competitive. This leads to
slow innovation in research methods, but rapid adoption once proven to be acceptable and of value.

We expect to see significant growth in the number of PTs being conducted, as well as significant growth in EHR-enabled practice networks, thereby increasing access to more and better electronic health data, and much-improved technologies for generating, capturing, storing and analyzing real-world health data.

**Pragmatic Trials in Current Practice: PPD-HealthCore Experience**
Among the real-world evidence studies undertaken by HealthCore, a thought leading healthcare research company, and a key partner with PPD in providing real-world and outcomes research services, pragmatic studies point to decision-makers’ needs and the utility of the PT approach.

**Randomized controlled evaluation of an activity tracking device.** Wearable devices that track physical activity are potential tools to encourage health-promoting exercise. Although these devices are highly successful consumer products, there is controversy regarding their ability to increase physical activity for wearers. This real-world study conducted between 2011 and 2013 was a randomized controlled trial designed to determine if there are differences among three interventions aimed at helping people be more active: using a wearable activity tracking device alone; using a tracker combined with coaching; and exercising without either a tracker or coaching. Endpoints included persistence using Activity tracker, Daily step count, Daily active minutes, Weight, Nottingham Health Profile (NHP)-Quality of Life, Health care costs between the groups. The pragmatic nature of this study was due to the minimally intrusive interventions, electronic data capture and real-world setting of the research.

**Pragmatic site-based prospective observational study of a novel delivery system.** The primary objective of this study was to collect prospective real-world information on the use of a new insulin delivery system compared to the standard delivery system in patients with type 2 diabetes. HbA1c results will be compared at three months among patients using three delivery insulin systems: syringe, pen and the new test system. Patients report treatment satisfaction scores specific to insulin delivery. The study was conducted in physician practices across the United States who were randomized to either standard of care or the novel delivery system. Administrative claims data were used where possible to identify physicians with a patient
population appropriate for the study. The study was conducted in a real-world setting with diabetic patients being managed in primary care practices and standard of care data collection.

**Real-world pragmatic trial to evaluate product efficacy and health outcomes.** Initiated in 2015, this randomized, interventional study is designed to demonstrate clinical benefit of a newly introduced therapy in achieving individualized HEDIS HbA1c targets after six months of use in patients with type 2 diabetes. Primary endpoints are patient persistence with assigned therapy and changes in HbA1c, fasting plasma glucose and body weight. The study will compare differences in patient-reported and provider-reported outcomes, with a focus on utilization of healthcare resource including hospitalizations, emergency department and other provider visits, and healthcare costs. Healthcare resource utilization will utilize administrative claims data where possible to minimize the impact on patients and practices and the primary endpoints are typical endpoints captured as a standard of care for type 2 diabetic patients.

**Conclusion**

As healthcare systems transition to evidence-based practices, there is a growing need for, and acceptance of real-world data. As access to electronic claims data and EHRs expand, and as trial design and data analysis evolve to support studies based on real-world evidence, the increasing conduct of pragmatic trials will drive greater understanding of what is required to generate scientifically robust and relevant evidence to improve healthcare decision-making.

In the emerging practice of real-world drug development, the Salford Lung Study has broken new ground that is likely to attract fast-followers to PT methodology. Life science companies need to support the development of pragmatic trial infrastructure and methods. In this effort, CROs have an opportunity to advance and provide PT design and execution expertise as well as research operations capabilities.

**References**


