The Drive Toward Pragmatism in Randomized Trials: Are We There Yet?

Debra A. Schaumberg, ScD, OD, MPH
Vice President, Scientific Affairs, Real-World Evidence, Evidera

Marissa Mihos, MPH
Research Associate, Real-World Evidence, Evidera

Krista Payne, MEd
Vice President, Late Phase Studies, Real-World Evidence, Evidera

Donny Chen, MBA
Senior Director, Medical Affairs Research Operations, PPD

What's Fueling the Drive Toward Pragmatism?

Suggestions on the need for pragmatism in clinical trials arose at least a half century ago, forming the backdrop for some of the earliest examples, such as the Physicians' Health Study and the GISSI trial, initiated in the 1980s. Yet evidence shows a trend since that time toward increasing complexity in trials[1] rather than widespread adoption of pragmatism. In a contravening trend, though still comprising only a small minority of the overall trial output globally *(Figure 1),* pragmatic trials have been the subject of increased attention and focused efforts of key stakeholders in the healthcare system. Among the factors contributing to the recent resurgence of dialogue around pragmatism, we think three factors have been crucial.

Increasing Capabilities in Real-World Evidence (RWE)

The dawning of the Information Age spawned a large and diverse impact on the healthcare system, including various dimensions of drug development and healthcare, and has enabled the possibility of more real-world evidence-based decisions on the part of drug developers, regulatory agencies, clinicians, health plans, and patients. The rapid and continuous development of information infrastructures and capabilities has resulted in an explosion in the amount and quality of real-world data (RWD) and linkages that have expanded the possibilities for how RWD can be built into RWE to inform decisions, creating a learning healthcare system. Conventional randomized controlled trials (RCTs), sometimes called explanatory trials, remain the gold standard for regulatory submissions for marketing authorizations across the globe, however, they come with a number of important costs and limitations. This has initiated conversations about the need for additional research with a more pragmatic focus designed to answer a somewhat different set of questions directed at real-world effectiveness and safety of interventions. **The goal has shifted to not only bringing to market safe and efficacious interventions, but those for which enough evidence exists that patients will ask, providers will prescribe, and payers will pay.** To meet this goal effectively, RWE is needed throughout the development cycle. Importantly, regulators including the U.S. Food and Drug Administration (FDA) and


Debra A. Schaumberg


Marissa Mihos


Krista Payne


Donny Chen

the European Medicines Agency (EMA), as well as other stakeholders such as the National Institutes of Health (NIH) and the Patient-Centered Outcomes Research Institute (PCORI), are active participants in a number of efforts aimed at incorporating RWE – including from pragmatic trials – into regulatory decision making.

Increased Attention to Patient Centricity

A renewed focus on patients and their involvement in healthcare, treatment decisions, and increasingly in designing research is also driving discussions of the role of RWE and pragmatic trials. We have moved from patients being viewed as recipients of healthcare interventions to being participants in the entirety of the healthcare spectrum. People are taking a much more proactive role in their healthcare choices, and technology has enabled patient empowerment, with patients now looking to find the right information at the right time. This search for information initiated by patients moves throughout the healthcare enterprise and has helped highlight existing evidence gaps that have exposed the necessity of generating and integrating RWE into the healthcare paradigm.

Limitations of RCT Evidence to Support Healthcare Decisions and Market Access

A third key factor relates to the recognition of the loss of both efficiency and knowledge that occurs when clinical trials are conducted outside of routine care settings. There is an inherent tradeoff that arises between RCT design choices aimed at enhancing internal validity with those more pragmatic choices that would aid generalizability. For example, registration trials increasingly tend to enroll relatively small samples of highly selected patients at sites with experienced investigators under ideal conditions, and collect large amounts of very specific data that are often not a routine part of clinical care. A spectrum of increasingly complex design features are being implemented primarily to 1) enhance internal validity, 2) maximize the chance of detection of efficacy signals when a true effect of the intervention exists, and 3) inform understanding of the biological basis of a treatment effect. However, such design features tend to result in high

> A renewed focus on patients and their involvement in healthcare, treatment decisions, and increasingly in designing research is also driving discussions of the role of RWE and pragmatic trials.

costs and the inclusion of only a small subset of patients and investigators who often differ substantially from the broader populations of patients and healthcare providers who would eventually be receiving and prescribing the new treatment. The number of registered interventional trials has increased over time,[1] however, most are small with 62% enrolling 100 or fewer participants,[1] and systematic reviews consistently find insufficient evidence to effectively inform the clinical decisions patients and their providers must make. Further, RCTs increasingly study surrogate markers as endpoints, and the relation between those and the outcomes of most importance to patients is not

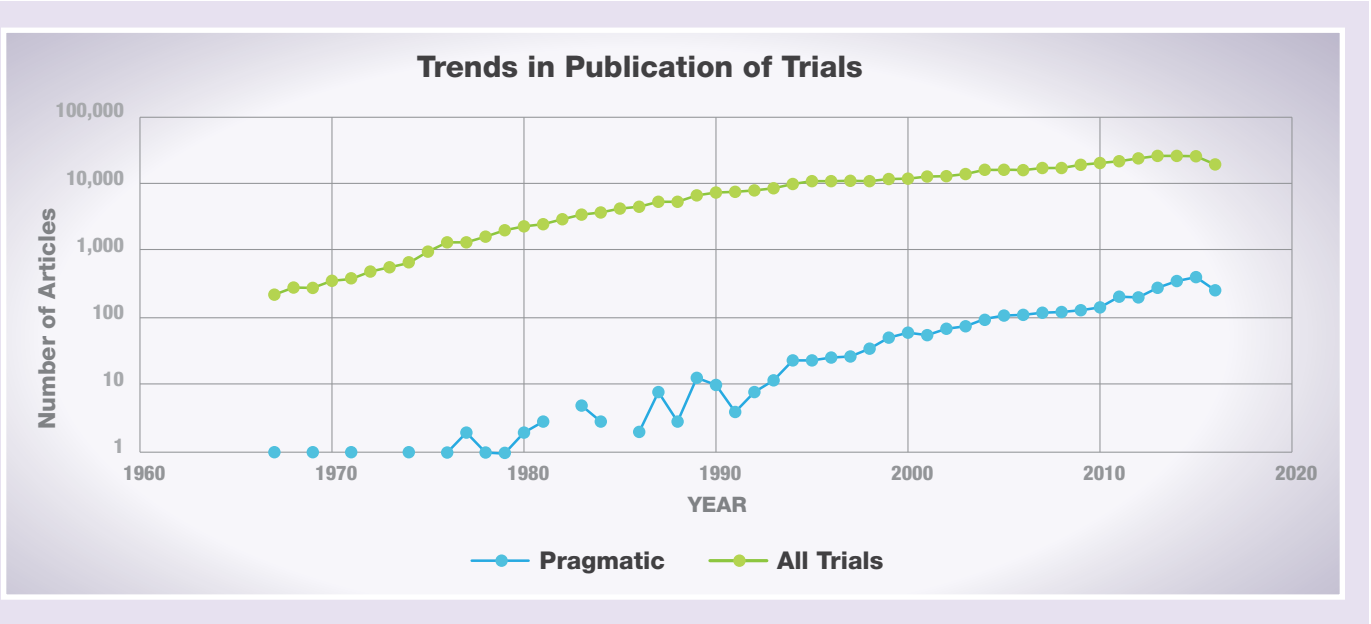


Figure 1. Articles per year from MEDLINE. In blue, resulting from search of the words *pragmatic* or *naturalistic* and *trial* in the title or abstract and tagged as "clinical trial." In green, articles with *trial* in title or abstract tagged as "clinical trial." Search is neither sensitive nor specific but meant to demonstrate trends and relative numbers of pragmatic trials versus RCTs in general.

Notably, the relative proportion of trials reported as pragmatic remains low (under 2%), and there is only a hint of a possible increase in the relative proportion of all trials that are reported as pragmatic.

always clear. In order to deliver healthcare interventions that maximize benefit, minimize harm, are cost-effective, and that patients will ask for, providers will prescribe, and payers will pay, it is crucial to understand the balance of benefits and risks of interventions within the context of the complexities of the whole system, including patient populations, provider behaviors, payers, and health systems. Gaps in such information are the rule rather than the exception at the time of market authorization. Filling such gaps is within the domain of RWE, and the pragmatic trial can be a crucially important mechanism to build the evidence required to inform decisions and support a transition to a learning healthcare system where RWE is collected and quickly fed back into clinical care, and clinical care itself would inform the further development of medical evidence.

Innovative Approaches to Trials

Achieving evidence needs to inform the move toward a learning healthcare system requires a diverse portfolio of observational *and* interventional RWE research methods. The case is more compelling than ever for the conduct of more efficient clinical research to enhance the value of healthcare. Innovative approaches to randomized trials can bridge the intersection of observational RWE and the conventional RCT and provide:

- Patients with better information on treatment options, benefits and risks, and health outcomes that matter to them
- Patients with multiple conditions the ability to compare the effectiveness of medical treatments
- Medical providers with evidence needed to more effectively treat patients with multiple conditions and to compare the effectiveness of medical treatments
- Medical product developers with new insights on both new and existing therapies and unmet medical needs
- Regulators with better information to understand the effectiveness and safety of medical treatment options in broader patient groups
- Payers with better information to understand the benefit, risk, and value of medical treatment options

Pragmatic Trials

Pragmatic trials improve generalizability of findings by evaluating health interventions in real-world settings that are more representative of the patients, providers, and health systems in which the intervention will be implemented.[2] Pragmatic trials draw on the substantial methodological, bias-reducing advantages of random allocation of health interventions combined with the real-world setting of an observational study to provide answers to questions that are relevant to clinical decision making. Randomization can be done at the patient level, or alternative designs such as cluster randomization or cohort multiple randomization can be adopted, particularly if there are concerns that individual level randomization would result in important changes to the routine care process. Due to the increased level of heterogeneity, pragmatic trials must be large enough to be sufficiently powered to detect small to moderate effect sizes.

Large Simple Trials

The large simple trial (LST) is a variation of a pragmatic trial with a sufficiently large sample size (often 10,000 or even 20,000 participants or more) designed to provide evidence on interventions with anticipated small to moderate effects. Characteristics of LSTs include:

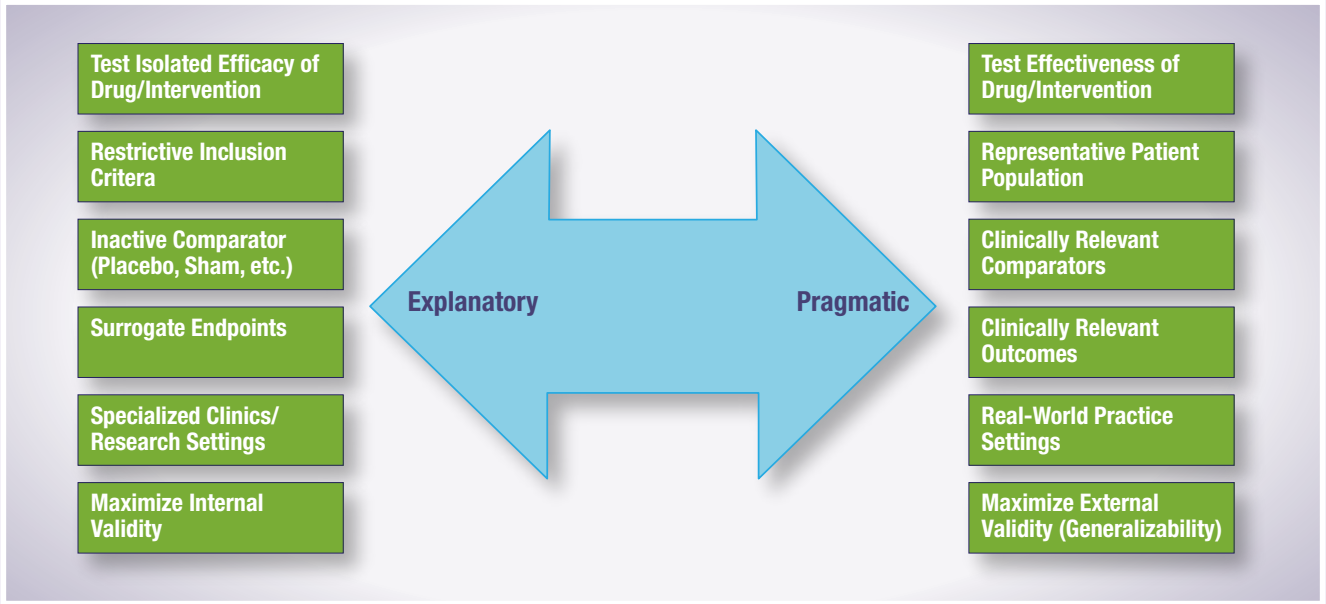
- Broad eligibility criteria
- Simple randomization scheme leading to a diverse patient population and enhanced generalizability
- Clinically meaningful outcomes
- Streamlined design with few or no departures from routine medical care
- Efficient and effective data collection mechanism for capturing outcomes and other relevant information

LSTs are generally Phase IV studies of already marketed health interventions for common health conditions and/or disease prevention, though other applications can be envisioned.

Expanding Body of Pragmatic/ Large Simple Trial Guidance

Only high-quality data can provide substantial evidence needed for regulatory approval, however, there is flexibility in the type of evidence that can be considered, and regulators have made progress in promoting the streamlining of trials.[3] In recent years, the FDA has issued guidance on "Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations"[4] (see Safety section), as well as "Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring,"[5] and issued a rule modifying investigational new drug safety reporting requirements. Other issues, notably including informed consent procedures, remain unresolved and guidance is

Figure 2. Some core distinctions between traditional explanatory RCTs and trials with more pragmatic elements



needed for institutional review boards (IRBs), sponsors, and investigators to help facilitate the conduct of pragmatic trials under existing regulations while alternatives are considered, such as a risk-based approach for informed consent. Among others, the ongoing NIH Health Care Systems Research Collaboratory supported ABATE Infection cluster randomized trial,[6] and the Patient-Centered Outcomes Research Institute ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness) trial[7] have highlighted considerations related to FDA regulations for informed consent, and should aid in provision of empirical data and knowledge in adapting informed consent processes to this new paradigm of research. The FDA has been actively engaged in a number of multi-stakeholder efforts aimed at the incorporation of RWE into regulatory decision-making.

In Europe, the Good Pharmacovigilance Practice (GVP) Module VIII on Post-Authorisation Safety Studies and Module V on Risk Management plans provide guidance for pragmatic trials. Additional information can be found in The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 6).[8]

Which Types of Research Questions

Where a trial falls on the explanatory – pragmatic spectrum should emerge from a careful depiction of the overall study question. If the primary aim is to demonstrate and understand the isolated effect of a drug/other intervention (efficacy and safety), tradeoffs aimed at enhancing internal validity will likely take precedence and the trial will likely comprise design choices incorporating more explanatory elements. Pragmatic design features should prevail

Consider Pragmatic Elements to Answer These Types of Study Considerations

- Trial population not representative of broader patient population that receives therapy
- Establishing effectiveness in subgroups of the general population, especially those excluded from conventional RCTs
- Administration of an intervention (e.g., differences in routine practice vs. RCT)
- Real-world adherence
- Acceptability for patients in real practice
- Evidence gaps for comparisons with routine standard of care
- Position of new treatments within current treatment paradigms
- RCT comparators that differ from routine standard of care
- RCT outcomes not considered to be the most relevant measures of effectiveness (e.g., surrogate endpoints used and data on clinically relevant endpoints desired)
- RCT treatment pathway is not representative of usual practice
- RCT sites are not representative of usual care settings

where the primary aim is to understand the effectiveness of a drug or other health intervention, and to empower patients, providers, and organizations to be able to make informed evidence-based choices to improve patient health and/or satisfaction. Depending on the research question, some pragmatic trials, especially large simple trials, may include placebo arms and, where multiple interventions are to be tested in a single trial population, also factorial randomization schemes. Evidence from pragmatic trials is not limited to a post-approval context (see Salford Lung Studies),[9] though it is a strong research design for comparative effectiveness research where approved treatments already exist, as well as when the

> One aim of trial design is to streamline study procedures, reduce complexity, and minimize the burden on participants, their clinical caregivers, and study sites.

real-life situation (patients, providers, care systems) is expected to influence the treatment effect. Interactions between elements of actual care, patient and disease characteristics, and health system policies may result in observed differences in effectiveness in a pragmatic trial versus efficacy demonstrations under a specific set of (often more ideal) conditions *(Figure 3),* the so-called efficacy-effectiveness gap.[10] It is important to anticipate any impacts on effectiveness that may arise and to explore these issues to increase understanding of drivers of effectiveness that may be amenable to modification to improve patient care.

Focus on Patient-Centered Outcomes

Clinically Relevant Endpoints

One aim of trial design is to streamline study procedures, reduce complexity, and minimize the burden on participants, their clinical caregivers, and study sites. To answer the primary research question, pragmatic trials focus data collection activities on a limited number of variables that are both clinically meaningful and important to patients. Such trials often make use of composite endpoints comprised of a collection of clinical events that presumably share an underlying biological basis. Composite endpoints can be particularly useful when the disease being studied has a variety of clinical consequences, and can be used to either reduce the sample size or increase the sensitivity of the trial to detect moderate levels of effectiveness (e.g. JUPITER trial,[11] Physician's Health Study,[12] and Women's Health Study[13]).

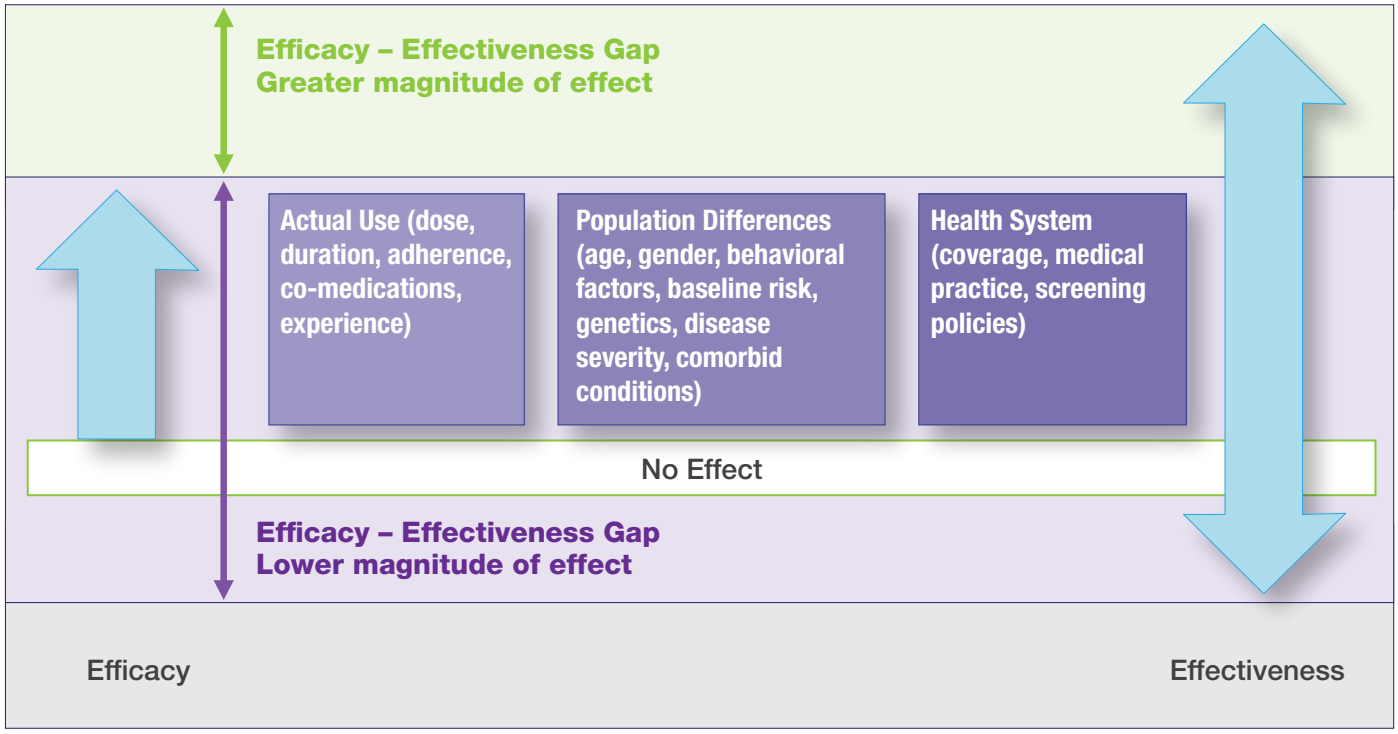
Patient-Reported Outcomes

Patient-reported outcomes are increasingly incorporated into explanatory trials, and their place in pragmatic trials is central. It is important to give thoughtful attention to inclusion of patient outcomes including securing the necessary expertise to assess existing patient-reported outcomes (PROs), the potential need for development of novel PROs, and the collection and integration of patient-centric information across various dimensions of the patient experience.

Ambient Physiological Measures

A burgeoning selection of patient/physiological monitoring devices with the potential to provide real-time data on important indicators is an emerging area of innovation with likely applications in the pragmatic trial setting. When there

Figure 3. The Efficacy – Effectiveness Gap



is no major difference in clinical outcomes, differences in symptoms, common adverse events, and quality of life are critically important to patients and caregivers. For certain indications physiological monitoring may be highly predictive of a clinically relevant endpoint and real-time collection of symptom scores is another potential application. Regulatory guidance on use of mobile apps for reporting of adverse drug reactions (ADRs) and use of social media is under development.

Safety

Ensuring the safety of medicines or other health interventions is a fundamental requirement for continued market authorization, with increasingly active and data-driven scrutiny in the post-approval period (e.g., the FDA's SENTINEL system). Whereas well tested procedures for assessing the safety risk in new medicines exist and are required for regulatory review, approval, and post-approval monitoring, the limitations of pivotal RCTs in terms of restrictions in patient populations studied, ideal conditions versus actual use, and monitoring, etc., and passive pharmacovigilance highlight the importance of a transition to active real-world safety (safety epidemiology) assessments post-approval. These can be done through observational epidemiology techniques using available datasets such as in the SENTINEL model, and there may also be a role for the pragmatic trial in certain cases to actively investigate potential safety issues (e.g., in a comparative safety trial) while overcoming potential bias that may arise in database studies, such as prognostic incomparability between patient groups. In the more

> Incorporation of pragmatic trial characteristics may lead to operational challenges that differ from those typically encountered in explanatory trials.

pragmatic setting, it can be more challenging to study and understand drug safety when relevant data were not systematically collected as part of the original data collection process. For trials primarily designed for effectiveness, the FDA's guidance document "Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations" gives clear guidance to sponsors that it may be appropriate to adopt a selective approach to safety data collection when the safety profile of the drug for common, non-serious adverse events has been established.[14] This is most likely to be the case for investigations of new indications for approved drugs, post-marketing commitments, large late-stage pre- or post-marketing outcome trials (such as most pragmatic trials), and post-approval investigations on a different population, etc. Three types of selective safety data collection are outlined, including: 1) no collection of certain safety data; 2) less frequent collection of certain safety data; and, 3) collection of certain safety data from only a fraction (e.g.,10%) of the total trial enrollment.[14] However, as requirements remain more restrictive in some countries, sponsors of a multinational trial would need to conform to the most restrictive regulatory regime. Indeed, the guidance speaks directly to the benefits of selective safety monitoring to facilitate the conduct of large trials. As always, a sponsor should consult with the FDA to determine whether selective safety data collection would be appropriate, and, if so, develop its plan for implementation.

Operational Aspects/Challenges

Incorporation of pragmatic trial characteristics may lead to operational challenges that differ from those typically encountered in explanatory trials. Nearly all trials will impact usual care in some way, and depending on the design, upfront engagement with leadership of the healthcare systems may be needed to enable investment of managerial time and systems support to minimize the impact of a trial on frontline providers. (Notable exceptions include some LSTs such as the Physicians' Health Study where participants are contacted and enrolled directly, outside of their healthcare system, and then followed-up using a combination of self-reported information, medical record review, and linkages to claims data.) Getting support from health system leaders and frontline providers can be facilitated if the trial is designed to test a question of interest that will help inform clinical decision-making. Since they are conducted in more real-world settings, cultural differences among the variety of disparate teams from different professional cultures (academia, clinical, pharmaceutical industry, operations, etc.) may require proactive mechanisms to define ways of working, accountabilities, etc.

To garner a representative sample that better approximates the real world, a pragmatic trial needs to appeal to a broad range of site participants. This involves a balanced cross section of academic centers and community-based sites. While the former may be well versed in the rigorous standards of clinical research, the latter may be dabbling in research for the very first time. A well-thought-out study training curriculum is highly advisable, in addition to basic clinical training such as Good Clinical Practice (GCP) and informed consent (ICF) procedures. This will ensure that even the least experienced participant is astute and knowledgeable enough to provide quality data and pass regulatory inspection.

The observational nature of a pragmatic trial means the pace of enrollment cannot be wholly driven by the protocol. Despite randomization, a subset of study participants will typically be prescribed the sponsor product. Enrollment, therefore, cannot be encouraged to the extent that it is perceived as inducement. As such, expectations around study milestones and publication planning need to be kept relatively flexible, with contingencies in place should enrollment prove to be more languid than desired.

Examples

Case Study 1: Label Change[15-17]

Study Overview: *While debatable where the JUPITER trial (safety and effectiveness of rosuvastatin vs. placebo) lies on the exploratory-pragmatic spectrum, several pragmatic design elements led the FDA to grant a new indication for this cholesterol lowering medication.*

Pragmatic Design Elements:

- ***Eligibility:*** *diverse, representative patient population (~18,000 enrolled across 26 countries)*
- ***Primary Endpoint:*** *composite measure of time to first occurrence of cardiovascular events – actionable, patient-centered, and relevant – was important to stakeholders and to health/needs of patients*
- ***Streamlined Collection of Safety Endpoints:*** *Studying a large group of patients led to a surprising safety finding – an increase in the number of individuals receiving rosuvastatin who developed diabetes. Because statins are so widely used, there was a heightened public awareness around this finding.*

Case Study 2: "Site-Less" Clinical Trial[18]

Study Overview: *VITAL Study investigates the correlation between daily supplement intake and risk reduction for developing cancer, heart disease, or stroke in 20,000 individuals with no prior history of these conditions*

Pragmatic Design Elements:

- ***Eligibility/Recruitment:*** *broadly represented patient population (20,000 ethnically diverse men and women) selected on basis of age not risk factors (e.g., diabetes)*
- ***Setting:*** *a true representation of usual care setting; study-site free approach*
- ***Data Collection:*** *annual patient completed questionnaire to assess treatment compliance, use of non-study drugs, occurrence of endpoints, cancer and vascular risk factors*

This study represents a cost-effective option to study marketed, low-risk interventions in a real-world setting. Benefits of this trial design include reduced costs and time, and enhanced patient adherence to protocol. Through this pragmatic trial, the opportunity exists to create a platform of integrated, ancillary studies to generate a wealth of observational real-world data.

Case Study 3. Pre-Approval Pragmatic Trial[9]

Study Overview: *The Salford Lung Studies (SLS) evaluated the benefit-risk profile of a combination medication for COPD and asthma. The SLS represent the first pre-approval pragmatic trials. The intent was to maintain the scientific rigor of a traditional RCT while reflecting everyday clinical practice to the best possible extent. The studies were designed to include patients who often would have been excluded from a traditional RCT.*

Pragmatic Design Elements:

- ***Eligibility:*** *Minimal exclusion criteria; trial population was more realistic of everyday practice and was representative of a much broader population*
- ***Setting:*** *minimal disruption to everyday clinical care; patient experience as normal as possible*
- ***Outcome Measures:*** *endpoints collected were relevant to patients and healthcare decision makers; treatment was compared with 'usual care'*

Challenges included the need for ongoing training and support for investigators with minimal prior research experience and the variable quality of EHR data. This pre-approval pragmatic trial realized the opportunities associated with a digitally enhanced RCT in integrated, real-time data from a variety of sources, complementing existing data provided by the conventional RCT and generated findings that are generalizable beyond the Salford general practitioners.

Overall Takeaway: *Demonstrated value of an intervention in the real-world can be generated earlier in the product development cycle by means of a pragmatic trial design.*

Site and patient engagement is another key challenge with a pragmatic trial. From the site's perspective, given the standard of care treatment, study remunerations are more modest compared to explanatory studies. Also, pragmatic trials are unlikely to involve novel therapies, so may be less motivating from an innovation perspective. From the patient's perspective, active product is typically not study-provided, which is one of the incentives missing compared to explanatory studies. Furthermore, treatment randomization eliminates a patient and his/her physician's control over the treatment of choice. A patient may be randomized to a treatment he/she prefers less and incur a higher insurance copay. The latter can be mitigated by employing copay cards to equalize out-of-pocket expenses between treatment arms.

> The most naturalistic pragmatic trials typically involve one or more supplemental data sources such as administrative claims databases or electronic medical records.

The most naturalistic pragmatic trials typically involve one or more supplemental data sources such as administrative claims databases or electronic medical records. Incorporating these data sources minimizes the likelihood of the Hawthorne effect, a phenomenon where patients (or physicians) change their behavior due to their awareness of being observed. By utilizing external data, prospective data collection can be minimized and thereby reduce the likelihood of this effect. A key challenge with external datasets is integration complexity. This can be relatively straightforward such as harmonizing field names between data sources to something more complex such as data imputation and adjusting for time lag.

Technology / Infrastructure

Existing clinical data collection platforms present opportunities to both enable and enhance patient enrollment in pragmatic trials and minimize data-collection needs. In the U.S., the NIH's Health Care Systems Research Collaboratory (https://www.nihcollaboratory.org) and the Patient-Centered Outcomes Research Institute's National Patient-Centered Clinical Research Network (http://www.pcornet.org) have undertaken large-scale efforts to empower such opportunities. These efforts will strengthen research capabilities by providing infrastructures that enable healthcare systems to collaborate through shared data, resources, and best practices while safeguarding patient privacy and security.

Discussion

Through the combined individual and collaborative efforts of diverse stakeholders, the stars are aligning for wider adoption of pragmatic approaches to trial design, and not necessarily limited to the post-approval setting. A core strength of the pragmatic trial is the enhancement of external validity and ability to inform clinical decision making. Pragmatic trials should be considered to fill evidence gaps for medicines with known benefit/risk profiles to inform the clinical relevance of new medicines to patients, providers, regulators, and payers. Most traditional RCTs focus on the safety and efficacy of investigational drugs and/or devices and, to meet these goals, enroll a highly selected patient population that is often not representative of the target population and are highly controlled in ways that depart from usual care. Pragmatic approaches apply the methodological advantage of randomization to a variety of study design and operational choices to increase generalizability and reduce as much as possible the burden the study imposes on patients and their doctors. Evidence derived from these approaches has great potential to help improve patient care through understanding the real-world effectiveness and safety of drugs and devices, which aids clinical decision making in a number of possible areas, including, for example, appropriate patient selection (comorbid diseases and therapies, disease severity, etc.), timing of therapy, duration of therapy, comparative effectiveness (e.g., electronic health records [EHR] versus standard of care), and others. Such information adds to available efficacy and safety to better inform the clinical relevance of new drugs and devices to patients, providers, regulators, and payers.

To fully realize the value that can be added through more widespread conduct of pragmatic trials, the field must realize a paradigm shift to incorporate data and operational platforms that can capitalize on data capture through EHRs, registries, PROs, etc., and enrollment infrastructures within integrated health systems. Moving forward, more pragmatic elements will begin to be introduced during the formulation of the clinical development plan. Relevant stakeholders must address challenges to internal validity and analysis of subgroups, treatment changes and multiple comparators, and operational aspects. Important questions that still pose challenges include development and adoption of novel, more streamlined approaches for ethical review, institutional requirements, consent and involvement of patients without putting research participants at risk, or creating the perception of increased risk, as well as both efficient and precise endpoint ascertainment and safety monitoring.

For more information, please contact Debra.Schaumberg@evidera.com, Marissa.Mihos@evidera.com, Krista.Payne@evidera.com, or Donny.Chen@ppdi.com.

REFERENCES

1. Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010. *JAMA.* 2012 May 2;307(17):1838-47. doi: 10.1001/jama.2012.3424.
2. Schwartz D, Lellouch J. Explanatory and Pragmatic Attitudes in Therapeutical Trials. *J Chronic Dis.* 1967 Aug;20(8):637-48.
3. Anderson ML, Griffin J, Goldkind SF, et al. The Food and Drug Administration and Pragmatic Clinical Trials of Marketed Medical Products. *Clin Trials.* 2015 Oct;12(5):511-9. doi: 10.1177/1740774515597700. Epub 2015 September 15.
4. U.S. Food and Drug Administration. Guidance for Industry: Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations. February 2016. Available at: https://www.fda.gov/downloads/drugs/guidances/ucm291158.pdf4. Accessed September 29, 2017.
5. U.S. Food and Drug Administration. Guidance for Industry: Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring. August 2013. Available at: https://www.fda.gov/downloads/Drugs/Guidances/UCM269919.pdf. Accessed September 29, 2017.
6. Active Bathing to Eliminate Infection (ABATE Infection) Trial (ABATE). Available at: https://clinicaltrials.gov/ct2/show/study/NCT02063867. Accessed September 29, 2017.
7. ADAPTABLE, the Aspirin Study - A Patient-Centered Trial. Available at: http://theaspirinstudy.org/. Accessed September 29, 2017.
8. European Network of Centres for Pharmacoepidemilogy and Pharmacovigilance (ENC3PP). ENCePP Guide on Methodological Standards in Pharmacoepidemiology. Revision 6, July 2017. Available at: http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml. Accessed September 29, 2017.
9. Vestbo J, Leather D, Diar Bakerly N, et al. for the Salford Lung Study Investigators. Effectiveness of Fluticasone Furoate-Vilanterol for COPD in Clinical Practice. *N Engl J Med.* 2016 Sep 29;375(13):1253-60. doi: 10.1056/NEJMoa1608033. Epub 2016 Sep 4.
10. Eichler HG, Abadie E, Breckenridge A, et al. Bridging the Efficacy-Effectiveness Gap: a Regulator's Perspective on Addressing Variability of Drug Response. *Nat Rev Drug Discov.* 2011 Jul 1;10(7):495-506. doi: 10.1038/nrd3501.
11. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. *N Engl J Med.* 2008 Nov 20;359(21):2195-207. doi: 10.1056/NEJMoa0807646. Epub 2008 Nov 9.
12. Physicians' Health Study. Available at: http://phs.bwh.harvard.edu/. Accessed September 28, 2017.
13. Women's Health Study. Available at: http://whs.bwh.harvard.edu/. Accessed September 28, 2017.
14. U.S. Food & Drug Administration. Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations. Guidance for Industry. February 2016. Available at: https://www.fda.gov/downloads/drugs/guidances/ucm291158.pdf. Accessed October 9, 2017.
15. U.S. Food & Drug Administration. Questions and Answers for Healthcare Professionals: CRESTOR and the JUPITER Trial. Available at: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm199891.htm. Accessed September 28, 2017.
16. Scudder L, Egan A. Statins: The Story Behind the Label Changes. *Medscape* 2012. Available at: http://www.medscape.com/viewarticle/759736. Accessed September 28, 2017.
17. Bankhead C. Cholesterol-Busting Statins: Study Raises New Concerns. 2010. Available at: http://abcnews.go.com/Health/HeartHealth/cholesterol-busting-statins-study-raises-concerns/story?id=11037926. Accessed September 28, 2017.
18. Manson JE, Bassuk SS, Lee IM, et al. The VITamin D and OmegA-3 TriaL (VITAL): Rationale and Design of a Large Randomized Controlled Trial of Vitamin D and Marine Omega-3 Fatty Acid Supplements for the Primary Prevention of Cancer and Cardiovascular Disease. *Contemp Clin Trials.* 2012 Jan;33(1):159-71. doi: 10.1016/j.cct.2011.09.009. Epub 2011 Oct 2.

Resources for the Design and Conduct of Pragmatic Trials

Refinements in concept and consensus building to incorporate pragmatism in randomized trials have accelerated in recent years. Some useful resources are listed below.

PRagmatic Explanatory Continuum Indicator Summary (PRECIS-2) offers a framework to help understand and visually represent where trials fall on the pragmatic/explanatory RCT spectrum across nine domains using a graphical representation.[a] PRECIS-2 guides decision making on the design of trial domains and enables trialists to think about how applicable trial results will be in the real world, and how trial design choices determine the applicability of a trial (e.g., the ability for a trial result to be applied or used in a particular situation).[b]

Eligibility - to what extent are the participants in the trial similar to those that would receive the intervention as part of usual care?

Recruitment - how much extra effort is made to recruit participants over and above what would be used in the usual setting?

Setting - how different is the setting of the trial and the usual care setting?

Organisation - how different are the resources, provider expertise, and the organisation of care delivery in the intervention arm vs. those available in usual care?

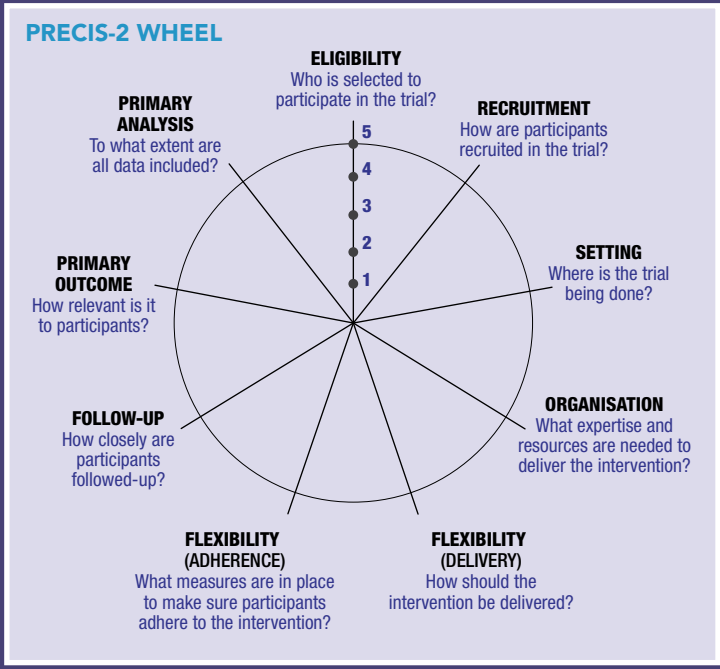
Flexibility (Delivery) - how different is the flexibility in how the intervention is delivered vs. usual care?

Flexibility (Adherence) - how different is the flexibility in how participants must adhere to the intervention vs. usual care?

Follow-up - how different is the intensity of measurement and follow-up of participants in the trial vs. usual care?

Primary Outcome - to what extent is the trial's primary outcome relevant to participants?

Primary Analysis - to what extent are all data included in the analysis of the primary outcome?



NIH Collaboratory Living Textbook on Pragmatic Trials is a virtual home for knowledge about pragmatic clinical trials using health systems, acting as a living resource to guide various stakeholders with an interest in pragmatic clinical trials via a reflection of expert consensus regarding special considerations, standard approaches, and best practices in the design, conduct, and reporting of pragmatic clinical trials (PCTs).[c]

Center for Medical Technology Policy Effectiveness Guidance Document, Pragmatic Phase 3 Pharmaceutical Trials: Recommendations for the Design of Clinical Trials that are More Informative for Patients, Clinicians, and Payers[d] guides the implementation of pragmatic study designs by providing recommendations for incorporating pragmatism into Phase III clinical trials, while simultaneously meeting regulatory requirements of the FDA. Recommendations focus on the broad topic areas of:

- Enhancing stakeholder engagement in study design
- Aspects of trial design
- Other operational, analytical, and ethical aspects of using pragmatic designs for regulatory approval trials

A concluding output from this guidance indicates that any incremental steps taken to improve the pragmatic nature of trial design by "improving the generalizability of the patient population, selecting active comparators and selecting consistently measured, clinically-relevant outcomes, can markedly improve the utility of information obtained from clinical studies designed for regulatory approval."[d]

The **PragMagic** tool, a recently available tool developed by the GetReal consortium of the Innovative Medicines Initiative, builds on prior work, including PRECIS-2, and uses an interactive game-like setting to aid understanding of how various pragmatic design choices impact operational feasibility, study validity and generalizability, and acceptability to patients, prescribers, regulators, health technology assessment bodies, and ethical considerations.[e]

The **GetReal consortium of the Innovative Medicines Initiative** has carried out literature reviews and extensive interviews with stakeholders leading to:

- An eight-article series on pragmatic trials published in the *Journal of Clinical Epidemiology* focused on specific design choices[f-l]
- RWE Navigator, a web-based information hub to aid and understand study design choices by clarifying the issues and finding purpose-appropriate RWE options
- A special 12-article issue of *Clinical Trials* focused on ethical and regulatory issues in pragmatic trials[m]

Institute of Medicine workshop output: Large Simple Trials and Knowledge Generation in a Learning Health System: Workshop Summary.[n]

REFERENCES

a. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 Tool: Designing Trials That are Fit for Purpose. *BMJ.* 2015 May 8;350:h2147. doi: 10.1136/bmj.h2147.

b. PRECIS-2.org. PRECIS-2. Available at: http://precis-2.org/. Accessed October 9, 2017.

c Weinfurt K. Welcome: Welcome. In "Rethinking Clinical Trials: A Living Textbook of Pragmatic Clinical Trials. Available at: http://www.rethinkingclinicaltrials.org/welcome/. Accessed 19 September 2017.

d Center for Medical Technology Policy Effectiveness Guidance Document - Pragmatic Phase 3 Pharmaceutical Trials: Recommendations for the Design of Clinical Trials that are More Informative for Patients, Clinicians and Payers. September 14, 2010. Available at: http://www.cmtpnet.org/docs/resources/PCT3_EGD.pdf. Accessed September 27, 2017.

e PragMagic. Available at: http://www.pragmagic.eu. Accessed September 19, 2017.

f Zuidgeest MGP, Goetz I, Groenwold RHH, Irving E, van Thiel G, Grobbee DE, GetReal Work Package 3. Series: Pragmatic Trials and Real World Evidence: Paper 1. Introduction. *J Clin Epidemiol.* 2017 Aug;88:7-13. doi: 10.1016/j.jclinepi.2016.12.023.

g Worsley SD, Oude Rengerink K, Irving E, et al. Series: Pragmatic Trials and Real World Evidence: Paper 2. Setting, Sites, and Investigator Selection. *J Clin Epidemiol.* 2017 Aug;88:14-20. doi: 10.1016/j.jclinepi.2017.05.003.

h Oude Rengerink K, Kalkman S, Collier S, et al. Participant Eligibility, Recruitment, and Retention in Pragmatic Trials. *J Clin Epidemiol.* 2017 May 11. pii: S0895-4356(17)30480-8. doi: 10.1016/j.jclinepi.2016.12.021. [Epub ahead of print].

i Welsing PM, Oude Rengerink K, Collier S, et al. Outcome Selection and Measurement in Pragmatic Trials. *J Clin Epidemiol.* 2017 May 11. pii: S0895-4356(17)30481-X. doi: 10.1016/j.jclinepi.2016.12.022. [Epub ahead of print].

j Irving E, van den Bor R, Welsing P, et al. Collecting and Reporting Safety Data and Monitoring Trial Conduct in Pragmatic Trials. *J Clin Epidemiol.* 2017 May 11. pii: S0895-4356(17)30482-1. doi: 10.1016/j.jclinepi.2017.05.004. [Epub ahead of print].

k Meinecke AK, Welsing P, Kafatos G, et al. Data Collection in Pragmatic Trials. *J Clin Epidemiol.* 2017 Jul 14. pii: S0895-4356(17)30776-X. doi: 10.1016/j.jclinepi.2017.07.003. [Epub ahead of print].

l Kalkman S, van Thiel GJMW, Zuidgeest MGP, et al. Challenges of Informed Consent for Pragmatic Trials. *J Clin Epidemiol.* 2017 May 11. pii: S0895-4356(17)30479-1. doi: 10.1016/j.jclinepi.2017.03.019. [Epub ahead of print].

m Anderson ML, Griffin J, Goldkind SF, et al. The Food and Drug Administration and Pragmatic Clinical Trials of Marketed Medical Products. *Clin Trials.* 2015 Oct;12(5):511-9. doi: 10.1177/1740774515597700.

n *Large Simple Trials and Knowledge Generation in a Learning Health System: Workshop Summary.* Washington (DC): *National Academies Press (US).* 2013 Dec 5. Available at: https://www.ncbi.nlm.nih.gov/books/NBK201274/. Accessed September 28, 2017.