

Workshop Summary:
Embedded Pragmatic Clinical Trials of Therapeutic A vs. B Interventions

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Workshop Report:

Embedded Pragmatic Clinical Trials of Therapeutic A vs. B Interventions

Background

On May 16, 2018, the National Institutes of Health (NIH) Health Care Systems Research Collaboratory convened a workshop to explore strategies and challenges related to planning and implementation of embedded pragmatic clinical trials (PCTs)[1] comparing two or more therapeutic medical interventions (i.e., “A vs. B”).

Since 2012, the Collaboratory, which is sponsored by the NIH Common Fund, has launched several large-scale PCTs embedded in U.S. health care systems. These trials are conducted in real-world settings of routine clinical care and intended to serve as case studies for addressing the challenges of pragmatic research. The present workshop focused on unique aspects of such trials and provided examples of ongoing or recently completed trials. Its five moderated discussions incorporated stakeholders from across the PCT landscape, including health care system leaders, oversight bodies, payers, research funders, clinical investigators, and clinicians. A videocast is available.[2]

Introduction and Keynote Address

From the National Center for Complementary and Integrative Health (NCCIH), NIH, which hosted the workshop, Dr. David Shurtleff, Acting Director; Dr. Catherine Meyers, Director of the NCCIH Office of Clinical and Regulatory Affairs; and Dr. Wendy Weber, NCCIH Acting Deputy Director, offered opening remarks.

Dr. Michael Lauer, Deputy Director of Extramural Research at NIH, opened his keynote address by likening PCTs to digital photography as “disruptive models” when they were first introduced. By embedding clinical research within routine care and generating real-world evidence (RWE) for interventions, the Collaboratory is, similarly, offering a new paradigm for NIH research.

The concept of a “learning health care system”[3] may be described as a health care system that not only provides care but also is continuously learning and thus continuously improving care to patients. The “learning research system” is another paradigm to consider. Although research funders have always collected data about their funded projects for learning and project-improvement purposes, this concept reaches a higher level in the Collaboratory, which uses its projects to glean generalizable knowledge in a systematic way. One outcome has been the Collaboratory’s *Living Textbook of Pragmatic Clinical Trials*,[4] which also reflects NIH’s efforts to improve the rigor of its funded research.

Although some may claim the opposite, several recent books have argued that human life has been improving over time in many ways, a development that may be underappreciated. These authors highlight the major roles played by science and technology in substantial societal improvements, particularly when scientific discoveries spur work in technology—as in the advancement of medical care and improvement of health care. PCTs play this kind of role and ultimately will improve public health and health care.

Panel 1: Partnering with Stakeholders to Conduct Trials

Dr. Richard Platt, Harvard Pilgrim Health Care Institute, moderated Panel 1, which opened with Dr. Mark Cziraky of HealthCore, Inc., a health outcomes research firm. HealthCore’s parent company is Anthem, Inc., a health insurance payer with 40 million members. Anthem sees an opportunity in leveraging its assets to better understand **in whom** a therapeutic intervention works and **is safe**—including by obtaining more information (and more granular information) to aid its decisionmaking and policymaking. Use of therapies and technologies often runs ahead of the evidence, yet the company must make decisions.

Anthem works on its own and in partnership with external investigators on evidence development, including through PCTs and safety and epidemiology research. Its PCTs are conducted in provider practices within Anthem’s integrated practice network. (Cultivating those relationships in advance is helpful.) Participating practices have shown a high level of interest in this activity and its results.

Dr. Kenneth Sands represented HCA Healthcare, a network of about 180 hospitals and 120 freestanding surgery centers in the United States and the United Kingdom (U.K.). HCA sees driving clinical operations and the quality of care in a reliable way as core to its business model and its mission. The company has successfully partnered in five cluster PCTs and is expanding this activity.

Positive lessons shared from HCA's PCT partnerships included that the learning health care system can be strengthened by academic-public-private partnership. Pragmatic research is feasible in an operationally sophisticated health care system. Collaboration between experts on research design and real-world implementation can be successful. Having an empowered, enthusiastic internal champion for a study is important. Sophistication in data management is stretched through these trial partnerships, which offer an opportunity above all to reinforce mission and define national practice.

HCA's challenges with PCTs have included substantial intangible costs (e.g., in terms of distraction and competing opportunities), complexity in defining partner relationships, a need to hold the line on competing interventions, possible loss of synchronicity in operational and research timelines, communication challenges within and between organizations, scope creep, and changes in requests.

Research questions for studies may be generated inside or outside the company. HCA has developed its own list of principles for good partnerships, which also serve to filter ideas and define bandwidth. An example is, "How much extra burden can be placed upon the clinical operational environment and each unit?"

Dr. Joseph Chin of the Centers for Medicare & Medicaid Services (CMS), the Federal agency that oversees the Medicare and Medicaid programs, spoke on his agency's interest in collaborating with other entities to develop evidence specifically relevant to its beneficiary populations and covered providers and settings.

Medicare takes an evidence-based approach to coverage and payment and critiques published evidence, including for strengths and generalizability to its population. Gaps have been particularly apparent when reviewing evidence for coverage determinations involving newly developed U.S. Food and Drug Administration (FDA)-approved technologies. CMS also examines inclusion/exclusion criteria; for example, it has

encouraged inclusion of older adults in early-stage studies, but the numbers of these participants remain suboptimal. Survival, mortality, and morbidity are three examples of CMS-relevant outcomes.

CMS offers three mechanisms for coverage of items and services within the clinical study context: coverage with evidence development (CED),^[5] investigational device exemption,^[6] and routine costs in clinical trials.^[7] The agency encourages contacts and meetings about study concepts of potential interest.

Panel 2: Examples in Action

Dr. Beverly Green, Kaiser Permanente Washington, moderated this panel featuring the experiences of three investigators of pragmatic studies. Dr. Ryan Ferguson, Veterans Affairs (VA) Boston Healthcare System, opened with the Diuretic Comparison Project, a VA PCT comparing chlorthalidone (CTD) to hydrochlorothiazide (HCTZ) for reduction of major, adverse cardiovascular events in older military veterans with hypertension.^[8] Although both drugs are diuretics, CTD has advantages over HCTZ, such as a longer half-life (thus, more continuous control of blood pressure); however, it is costlier. This randomized study with concealed allocation is being done within the VA Point of Care program, whose mission is to deliver state-of-the-art care while enrolling patients in pragmatic studies that help redefine that care.

The trial has many pragmatic features. Researchers maximally leverage the VA's electronic health record (EHR); for example, all aspects of the trial are embedded in the EHR, and it is used for subject identification, recruitment, enrollment, primary care providers' clinical notes, and outcome collection. Accuracy of VA data is high, but its cleanliness is not perfect and mitigations/controls must be built into the system. All research activities take place as part of providers' normal workflow (with minimal perturbation). The research, institutional review board (IRB), and VA ethics groups chose a scripted, telephone-based process for informed consent, with a fact sheet sent to patients post consent. Reductions in barriers to participation have had a positive real-world impact, and the trial costs "pennies on the dollar" compared with traditional trials.

Dr. Susan Huang, University of California, Irvine School of Medicine, discussed the ABATE (Active Bathing To Eliminate Infection) trial. This PCT has been comparing

routine bathing care vs. a minimal-risk decolonization regimen of universal chlorhexidine bathing and targeted mupirocin nasal ointment for methicillin-resistant *Staphylococcus aureus* (MRSA) carriers. The goal is to reduce bloodstream infections and multidrug-resistant bacteria in non-critical-care hospital units.

The health system in ABATE is HCA, and this partnership has been a major driver in making the trial possible and successful. Corporate communication, endorsement, and support aided engagement and recruitment, for example, and an extensive amount of clinical data was able to be gathered from the 53 participating hospitals through HCA's centralized data warehouse. The study team worked behind HCA's firewall to access centralized data for standardization, feedback reports, and analysis. ABATE queries were embedded in the EHR and in routine nursing documentation. The study team also used centralized IRB approval with a waiver of informed consent, and IRB ceding was completed rapidly because there was a corporate compliance leader. HCA created a focused, computer-based training module customized to this trial.

ABATE required development of new processes to ensure chlorhexidine compatibility with use of other skin products in the central supply chain, to monitor new or proposed interventions to check for conflict with the trial outcomes (such conflicts led to withdrawal of three sites), and to track potential adverse events.

Dr. Michael Kappelman, University of North Carolina School of Medicine, discussed his COMBINE (Clinical Outcomes of Methotrexate BINary Therapy in PracticE) trial, which is comparing anti-tumor necrosis factor (anti-TNF) monotherapy and combination therapy with low-dose methotrexate in pediatric patients with Crohn's disease. As pediatric Crohn's is a rare disease cared for by specialty physicians and not all patients start anti-TNF therapy, no single health care delivery system is large enough provide a sufficient sample size. Therefore, COMBINE was designed as a multisite trial that leverages ImproveCareNow, a network of clinicians, researchers, parents, and patients collaborating to advance care of Crohn's and ulcerative colitis in children and youth. Use of the ImproveCareNow registry allows repurposing of data already being collected as standard of care at outpatient visits.

The study team struggled with multiple design challenges, including the subjective nature of many outcomes and a concern that knowledge of treatment assignment might affect the reporting of study outcomes. Although the investigators initially considered a cluster

randomized trial (CRT) as a way to minimize differential outcome reporting, clinicians, patients, and families provided feedback objecting to this approach. Ultimately, the researchers decided on a double-blind, placebo-controlled RCT, prioritizing internal validity over pragmatism. Other challenges they have faced are common ones, such as site workloads, provider buy-in, and data cleaning.

COMBINE has offered the pediatric gastroenterology community an opportunity to change its culture. The specialty has done very few large, rigorous trials and thus evidence to inform care decisions has mostly been lacking. The trial and the related network are providing an opportunity to learn and share best practices, embed a clinical trial into everyday care, answer an important clinical question, and establish comparative effectiveness research and PCTs in this specialty.

Panel 3: Maximizing the Pragmatic: Understanding Approaches to Design

Dr. Gregory Simon, Kaiser Permanente Washington, moderated this panel of three speakers who used different design strategies to capture RWE on distinct medical therapeutic interventions.

Dr. Scott Solomon, Harvard Medical School and Brigham and Women's Hospital, described INVESTED, a trial comparing high-dose vs. standard-dose influenza vaccination in patients with high-risk cardiovascular disease, which places them at higher risk for complicated or severe influenza.[10] INVESTED has incorporated some pragmatic elements, such as broad inclusion criteria, minimal exemptions, and use of several formal networks (e.g., that of the VA) in addition to nonnetwork hospitals.

Nonpragmatic (traditional) elements are present as well. For example, outcome ascertainment included participant surveys as well as EHR data because of concerns about completeness with EHR data alone. INVESTED has an Investigational New Drug exemption but also a regulatory requirement for adverse event reporting. Safety data collection can be onerous, making PCTs more appealing for Phase IV than as pivotal registration trials.

Recommendations included that specific aspects of trial design be matched to specific scientific questions. The less information collected, the fewer questions can ultimately be answered. The noisier the data, the larger the trials need be. One may ask, is the research question better suited to a larger, simpler trial or a smaller, more carefully done trial?

More broadly, how can the trial community incorporate more pragmatic elements into trials while retaining the ability to obtain the answers they need?

Dr. Rachael Fleurence of the National Evaluation System for Health Technology Coordinating Center (NESTcc), a public-private partnership between FDA and the medical device industry, presented a trial platform and mechanism for obtaining RWE with regard to premarket and postmarket studies of medical devices. Regulatory and clinical contexts for devices are different from those for drugs, which has implications for feasibility of PCTs. The NESTcc Data Network is being expanded, including through the evaluation and use of high-quality, real-world data from various collaborators.

Registries can be the key player in PCTs. Interest in their coordination has been growing, and some successful initial studies have been done, including to inform RWE decisions by FDA. However, challenges include typical limitation of registries to a single disease or category of device; failure to capture all relevant outcomes; high cost of developing a data infrastructure separate from clinical and billing records; and often, multi-stakeholder governance. PCTs using electronic health data for e-identification, e-consent, e-randomization, and e-follow-up should be possible in the device space, and not just with registries, but directly with certain clinical trial sites. Proof-of-concept studies using this approach are needed.

Dr. Kourtney Davis, GlaxoSmithKline, discussed the Salford Lung Studies (SLS) in chronic obstructive pulmonary disease (COPD) and asthma populations, with a specific focus on the COPD study.[11,12] This large, randomized, pragmatic, Phase III real-world effectiveness trial was conducted in the U.K. during a drug's prelicensure and post-licensure periods. SLS compared a once-daily inhaled corticosteroid and long-acting beta2-agonist fixed-dose inhaler (fluticasone furoate combined with vilanterol) against usual care in patients with COPD. In the trial's catchment area—Salford and two contiguous areas near Manchester—primary and secondary care data were available in integrated EHRs at the system level and had been used previously for diabetes care management research. The region was also chosen because of its higher burden of disease related to socioeconomic deprivation (e.g., cigarette smoking) and the presence of study champions in the medical community.

Major challenges during SLS included recruitment of eligible participants, and training of health care providers to take on clinical research responsibilities. Concerns regarding

study-induced improvements in usual care (i.e., the Hawthorne effect) were addressed in an observational companion study using the linked EHR from a matched cohort of the U.K.'s population-based Clinical Practice Research Database. Other challenges of a pioneering real-world trial embedded into primary care included managing time constraints of clinician workload, monitoring and safety reporting, ethical and regulatory approval, generalizability, and a fixed population of EHR systems and involved pharmacies (i.e., less flexibility to add sites or patients). The team also found that relevant endpoints may not be routinely or systematically collected, and trade-offs can exist between what is measured in routine care and meaningful, differentiating endpoints that may require electronic case report forms for systematic health care provider or patient reporting.

The increased use and quality of EHRs as a core part of delivering U.K. health care provided records of high enough quality to facilitate this pragmatic study, as did having a unified record, data-sharing agreements, simplified operational processes, the U.K.'s Quality and Outcomes Framework, validated data linkage and flows, and strong partnerships between the treating and research communities. The trials and observational designs both provided useful data for interpreting the drug's benefit-risk profile, with the SLS data fulfilling a postauthorization safety study requirement. To perform this kind of pragmatic trial at scale requires increased linkages, as well as availability and quality of EHRs married with advanced methods. The study nurses were very important in the study's success and represented a large investment.

Research-naive investigators needed extensive Good Clinical Practice training and support, which added length to the study. EHR data quality varies by provider and time—evaluation should start early in the feasibility stage, and one may still need to augment data collection for key variables. (Mobile data collection solutions may be an option.) Allowing “usual care” as the comparator can create unforeseen challenges if it changes considerably over the course of the study or if the “usual care” patterns are not generalizable; specifying sensitivity analyses and stratification in the analysis plan can help to explore subgroups and specific comparators of interest. EHRs with alerts triggered by trial participants' hospital encounters provided robust safety monitoring.

The SLS experience showed that ordinary patients were enthusiastic about taking part in these trials. Having good management support is critical, especially in the scenario of innovation, to escalate problems and communicate solutions. Flexibility and creativity are

key for success. Interpretation of final results may require more context to impact decisionmaking across multiple stakeholders.

Panel 4: Regulatory Aspects of Clinical Research and the Regulation of Products

Regulation and ethical oversight of the clinical research enterprise are essential components of PCT planning and implementation. Therefore, Panels 4 and 5 addressed the regulatory aspects and ethical oversight aspects of embedded A vs. B PCTs. Dr. Adrian Hernandez, Duke University School of Medicine, moderated Panel 4, which featured three presenters from two Federal oversight agencies.

Dr. Jacqueline Corrigan-Curay of the Center for Drug Evaluation and Research, FDA, addressed regulation in the drug space. Congress has asked the FDA to take concrete steps to evaluate the use of RWE in regulatory decisions, and the agency has been moving to launch a framework, a program, and ultimately guidance.

“Pragmatism” in clinical studies is often defined as a range of characteristics (represented, e.g., by a wheel or spider web) and not as a single design. A key question is whether some or all of the potential flexibilities work for particular regulatory questions. For example, when considering applicability and simplification of trials, how can trials be moved away from a separate, traditional infrastructure into clinical practice and substantial evidence be obtained for a labeling claim? Large, simple cardiovascular trials conducted in the 1980s may provide a model.[13] The current challenge is in trying to overlay all the electronic health or digital information being gathered on a routine basis, and for regulators, ascertaining which data are accurate and reliable.

Potential components of RCTs for label expansion in real-world, clinical practice settings include attention to elements of study design; data accuracy and completeness, especially for outcomes of interest (a major focus in FDA review); and study monitoring (e.g., streamlined adverse event reporting may be acceptable depending on FDA guidance).[14] FDA often sees noninferiority studies, but these may be a challenge in the real-world setting because of the potential bias to the null if there is noise in the data. Certain designs for PCTs may be more appropriate in this setting than others, as described recently in the literature.[15]

To FDA, the question is not, “Is a trial pragmatic or not?” Many trials can have pragmatic elements—in fact, FDA encourages this—and can maintain the rigorous standards for

data collection and assessment that will allow the agency to make evidence-based decisions. The speaker's suggestions included identifying relevant questions for practitioners and patients; selecting an intervention that can be appropriately delivered in a clinical setting; normalizing the integration of clinical practice with research; achieving greater integration of clinical data across health care systems, with appropriate patient protections to maximize data capture; and potentially bringing in mobile technologies to fill gaps, as in patient-reported outcomes.

Dr. Owen Faris of the FDA's Center for Devices and Radiological Health discussed implications for PCTs in the medical device space as a means for obtaining RWE. Devices differ from drugs in multiple ways. FDA has issued guidance on RWE to support regulatory decisionmaking for devices[16] and is used to seeing trials that are not gold standard RCTs. Opportunities exist related to flexibility, innovation, and collaboration. Clinical trial innovation has been occurring in the device space in the past few years, including in nontraditional clinical data. Whether an A vs. B trial is pragmatic or not, the data submitted should be fit for purpose, relevant, and reliable.

Obtaining RWE through pragmatic approaches has both pros and cons compared to traditional trials; one can ask what they are for a particular data set. Regulatory uses for RWE include for a control arm for a pivotal clinical study, new indications for approved devices, studying new improvements to devices, replacing a postapproval study, adverse event reporting, and shifts to pre- and postmarket balance. Current areas of exploration include "what we know vs. what we think we know" and which information is reliable (e.g., in EHRs); the answers will be important for successfully embedding trials.

Julie Kaneshiro of the Office for Human Research Protections (OHRP), U.S. Department of Health and Human Services, discussed PCTs in relation to the Common Rule. When determining whether the rule applies to a PCT, it is important to look at the particular activities and who is doing which pieces, in decisions about jurisdiction. One should ask: (1) Does the activity involve a research intervention? (2) Does the research involve human subjects? (3) Is the human subjects research exempt? If a cluster design is proposed, consider whether it is truly necessary and the impact upon consent. (OHRP rules present a challenge for cluster studies when it is not easy to get informed consent, especially for greater-than-minimal-risk research.) Further, is the intervention "research"? Who are the subjects? What role, if any, should a patient's treating physician have in

determining whether patients should be asked to enroll? The existence of equipoise does not necessarily mean that the study poses minimal risk or consent can be waived.

All collaborating institutions on a study do not necessarily need IRB review, only those “engaged” (a key term to understand) in the research. Two aspects of the upcoming, revised Common Rule particularly have implications for PCTs: new informed consent provisions, such as presenting the consent information in a more understandable, targeted way, and the requirement for single IRB review (sIRB). sIRB applies to U.S. institutions engaged in cooperative research for the portion of the research conducted in the United States; has a compliance date of January 20, 2020; and does not apply when more than a sIRB is required by law, or a Federal component supporting or conducting the research determines and documents that a sIRB is not appropriate for the context. Overall, the speaker described the issues in this topic area as difficult, with neither all the questions nor their answers fully known at present.

Panel 5: Ethical Aspects of Clinical Research and the Regulation of Products

The fifth session was moderated by Dr. David Wendler of the Department of Bioethics, NIH Clinical Center, and featured perspectives from specialists in three segments of the field: bioethics research; a consulting company; and a research setting comprising academic, hospital, clinical, and translational research.

Dr. Spencer Philips Hey, Harvard Medical School, presented a draft unified framework for identifying and addressing ethical challenges posed by pragmatic trials. His work was part of a collaborative project funded by the Canadian Institutes of Health Research and aimed toward eventual publication of guidance documents.

PCTs are being conducted, but the relevant ethical issues are not yet well recognized or understood and there is no consensus or widely used guidance on addressing them. PCTs are not all the same; for example, they can be seen as more pragmatic in some ways and explanatory in others, or on a continuum with “pragmatic” at one end and “explanatory” at the other. It is more important to evaluate a specific study than to focus on its label.

His group has developed a hypothesis that the PICO (Population, Intervention, Comparison, Outcome) framework [17] widely used in evidence review, systematic

reviews, and trial design can also be applied to a trial’s research question (Figure 1). They also use the NIH PRECIS-2 tools [18] created to help design clinical trials that are fit for purpose, to assess their pragmatism, and to later assess implications of the design choice. It is hoped that the approach Dr. Hey presented will also facilitate communication among stakeholders. Thinking about all the groups engaged in the trial outcomes and aiming toward using a common language whenever possible are recommended.

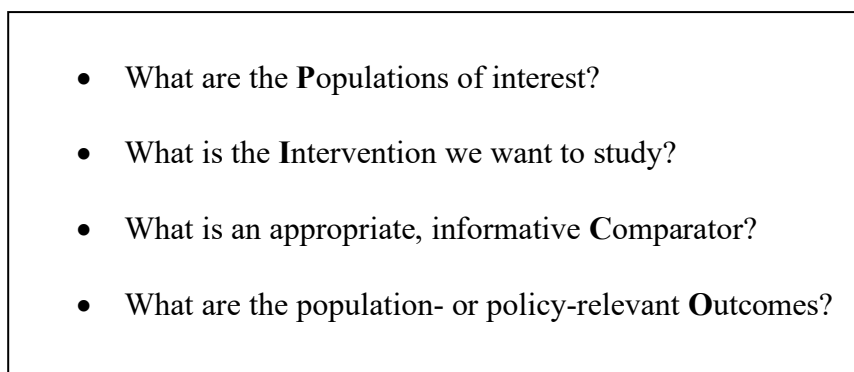
- 
- What are the **P**opulations of interest?
 - What is the **I**ntervention we want to study?
 - What is an appropriate, informative **C**omparator?
 - What are the population- or policy-relevant **O**utcomes?

Figure 1. PICO Framework [17]

Judith Carrithers of Advarra, an independent IRB, summarized the Common Rule and FDA regulations as applied to PCTs. The standard of “full” informed consent (containing the eight elements required under Federal regulations) may not always be feasible for PCTs and CRTs. Satisfying these regulatory requirements may disrupt clinical practice and add costs and delays that could make PCTs difficult or impossible to execute.

Federal regulations permit alterations or waivers of informed consent when a study satisfies four conditions. The two most important for PCTs are the requirements that the study pose no more than minimal risk and that the research could not practicably be carried out without the alteration or waiver. Some PCTs will not meet these conditions—they will not qualify as minimal risk and/or the IRB may determine that it is practicable to conduct the research with informed consent.

Several alternative consent models have been suggested for PCTs. For example, for studies comparing two standard-of-care treatments (treatments that in clinical practice require only oral consent), where the only research component is randomization, it may be possible to integrate clinical and research consent with a brief explanation of the intervention, rationale, alternatives, risks, and benefits, with the research component described (as a verbal or written consent documented in the EHR). Other alternative

models, such as site-specific broadcast notification, delaying consent, and waiving consent, are being discussed, although they need further discussion and ultimately may require changes to Federal regulations.

Dr. Barbara Bierer of Harvard Medical School and Brigham and Women's Hospital focused on whether and when individual consent and IRB review are necessary in relation to the session theme. Although institutional practice may vary, neither individual consent nor IRB review and approval are necessary in the setting of quality improvement or health operations. However, the approach is more complicated in the context of embedded PCTs conducted as research when the objective of the research is generalizable knowledge. If individual informed consent is practicable and will allow collection of data from a representative population, it is preferred. The considerations of elements of practicability require greater analysis, as discussed below.

The current regulatory framework does not address the threshold between explanatory and pragmatic trials, and in many instances there is no “bright line” to distinguish between them. As Dr. Corrigan-Curay and Dr. Hey previously described, many trials exist on a spectrum and have both explanatory and pragmatic elements. Further, the current regulatory framework does not address issues attendant in cluster randomized trials nor whether consent is feasible at the “cluster level.”

Whenever it is feasible and practicable to secure individual informed consent, it is desirable. Even in the context of minimal-risk studies that are not funded by Federal funds, it is often advisable for the IRB to deliberate and review a submitted formal clinical protocol; the security of external and independent review is worthwhile. While Dr. Hey used the term “less stringent ethics review” for minimal risk research and pragmatic trials, Dr. Bierer emphasized that the appropriate review is not in fact less stringent but rather is performed differently. The language used to describe the IRB review is important: IRB review is robust whether performed as an expedited or full board review.

IRB inefficiencies should be corrected if they exist and not be used as an excuse for avoiding IRB review. In this context, sIRB review of multisite trials is transforming how IRB review takes place. Time, experience, and NIH and Federal policy will be helpful in furthering familiarity with sIRB and efficiency. SMART IRB (www.SMARTIRB.org) is

an available methodology.[19] That said, education and flexibility are necessary to transition to sIRB review. The posture of the IRB system needs to evolve from “existential paternalism” to a participant-centered focus.

Specific attention was directed to two criteria in OHRP guidance.[20] First, IRBs should evaluate the risks and benefits of the proposed research over and above those of planned or necessary clinical care. Currently, IRBs appear to evaluate the risks of the clinical care and treatment itself, not the added or incremental risks of the research, a more difficult assessment. Second, with regard to practicability, the emphasis is whether the study itself is practicable without the waiver of consent, not whether or not one can obtain informed consent when face-to-face with a patient. This difference is often misunderstood. The concept of practicability applies to whether the findings derived from the research will be generalizable, and thus an important threshold consideration is the potential impact of obtaining informed consent upon representativeness in recruitment. Options and questions with respect to informed consent for research in several risk categories were also presented.

For any embedded PCT, one should address respect for persons. In developing any model for an embedded PCT or any specific PCT study, patient engagement is essential. Patient engagement may be achieved through formal community consultation and engagement or other means. However, respect for persons also implies embracing data minimization so that only those data needed for the study are collected and shared, and ensuring the study’s social value is clear. Education and notification were also themes. Education of the public on the roles of clinical research and clinical trials is important. If the research is not practicable without waiver of consent, then consideration of public education and institutional notification of any ongoing study to possible participants are needed.

Notification can, for example, take the form of signage in appropriate clinical settings, news placed on hospital video channels, or other communication strategies. Principles of health literacy and attention to translation should be considered. At the end of a study, health literate communication of the results and other key information should take place.

The current regulatory environment is one of uncertainty but also opportunity. Despite commentary from the community during revision of the Common Rule, regulations specific to consent in PCTs, CRTs, and adaptive trial designs were not included in the final rule. Although there is no regulatory guidance or draft guidance in this respect, there is an opportunity: OHRP and FDA are willing to engage in dialogue with the community.

The regulated community should avail itself of this offer. Federal regulators can apply enforcement discretion if they wish.

A summary list of major points from Session 5 appears in Figure 2.

- PCTs of A vs. B raise important ethical issues.
- Those issues depend more on the nature of the specific study than on whether it is categorized as pragmatic.
- Full regulatory consent can be an obstacle to some PCTs.
- IRBs may be reluctant to find that PCTs satisfy the conditions for waiver or alteration of full regulatory consent. Minimal risk and practicability may be the most difficult conditions to satisfy.
- Practicability is often misunderstood. It should be considered in the context of the generalizability of the study results, as should the impact of individual informed consent on recruitment of a representative population.
- It is important to consider abbreviated ways to satisfy requirements for full regulatory consent.
- The level of IRB review and the nature of the consent process should be tailored to specific studies and be based on added or incremental risks of the study.
- Researchers should engage with the community and public during all phases of their research.

Figure 2. Key Points on Ethical Oversight of PCTs

Summary Expert Panel Discussion

The closing summary panel was moderated by Dr. Meyers, NCCIH, and composed of Dr. Hernandez, Duke University School of Medicine; Dr. Platt, Harvard Pilgrim Health Care Institute; Drs. Green and Simon, Kaiser Permanente Washington; and Dr. Wendler, NIH Clinical Center.

Emerging information from the NIH Collaboratory and other trials groups conducting PCTs is providing strategies that will facilitate gathering RWE for medical interventions. Lessons learned from embedded PCTs conducted thus far demonstrate that many stakeholders play a role in planning and implementing these trials. Strategies that can align the goals of research funders and regulators, investigators, health care system leaders, clinicians, and patients will continue to expand the PCT portfolio and provide answers to questions that inform public health. The diverse trials discussed in the

workshop demonstrate that clinical investigators have many degrees of flexibility in both design and implementation of PCTs, and must modify aspects of a study to ensure it can be successfully implemented and address the research question. Indeed, a fully pragmatic PCT is not always the optimum strategy to answer all questions.

Incorporating health care system leaders, regulators, health care system leaders, and research funders into study planning can be a daunting challenge. However, the expanding portfolio of PCTs supported by NIH and the lessons learned from them are providing a strong foundation for future work. Identifying challenges and apparent obstacles for large-scale A vs. B trials is clearly an important step for addressing issues and outlining a pathway for future studies. Collecting RWE on distinct therapeutic interventions in settings in which they are typically administered is critical for learning how best to use interventions and maintain support for the RWE enterprise.

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