The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard Bioethics Collaborative

Tuesday, February 11th, 2020 | 10:00am- 3:00pm
Ropes & Gray LLP | 800 Boylston Street, Boston, MA, 02199

Pragmatic Clinical Trials and Real-World Evidence
Executive Summary

The February 11th, 2020, meeting of the MRCT Center Bioethics Collaborative convened stakeholders from academia, industry, patient advocacy organizations, foundations, and Institutional Review Boards (IRBs) to examine the topics of **Pragmatic Clinical Trials and Real-World Evidence.**

Introduction

Pragmatic clinical trials (PCTs) compare or assess interventions in real-world practice settings, hoping to deliver data that is readily applicable to real-world decisions faced by patients. PCTs can be contrasted with explanatory clinical trials that attempt to demonstrate efficacy in a highly controlled setting. Prospective PCTs may utilize different randomization techniques (randomizing at the individual or cluster level, or not at all) and/or evaluate observational data collected through the usual course of care. PCTs blur the distinction between research and clinical care more than traditional randomized control trials (RCTs), which in turn raises novel ethical questions concerning informed consent, incidental findings, and other issues. The analysis of real-world data (RWD) to generate real-world evidence (RWE) in PCTs raises additional ethical questions concerning the definition of human subject research, data privacy on the individual and institutional level, data quality, and others. The convened meeting of the Bioethics Collaborative engaged and expanded upon these ethical issues and considered strategies for addressing the theoretical and practical challenges that they raise for investigators, sponsors, IRBs, participants, and other stakeholders.

Meeting Summary

Pragmatic clinical trials attempt to merge research and care seamlessly. Informed consent can be seen as a time-consuming obstacle to realizing the potential that pragmatic clinical trials, and the learning health systems in which they often take place, promise. Nonetheless, informed consent is a requirement for ethical research participation, and any waiver or alteration to consent has to meet the following regulatory criteria, in the U.S.:

1) the research involves no more than minimal risk to subjects;
2) the waiver or alteration will not adversely affect the rights and welfare of subjects;
3) the research could not practicably be carried out without the waiver or alteration; and

> 4) when appropriate, the subjects will be provided with additional pertinent information after participation.
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> *(45 C.F.R. §46.116 (e), 2018)*

Meeting these regulations is not easy or clear. PCTs typically test standard-of-care (SOC) interventions. In order to determine whether the SOC intervention involves 'no more than minimal risk,' one first must determine the appropriate baseline for measuring research risk. Views that measure research risk by reference to risks ordinarily experienced by *healthy* individuals are likely to conclude that PCTs involve more than minimal risk, since healthy individuals will not take, or experience the risks of, the interventions being tested. However, if research risk is referenced to the risks experienced by the *sample population* (e.g., a population afflicted with the same condition and burdens as the research population), one may conclude that the PCT is minimal risk, since the study population would likely be receiving one or other of the approved interventions outside the research. In a draft guidance on risk disclosure in research evaluating standard of care procedures, the U.S. Office for Human Research Protections (OHRP) supports the former position (*Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care*, 2016), in other words, that the reference population should be normal individuals. The tension between the nature of PCTs, ethical intuition, and the aforementioned guidance was explored at the Bioethics Collaborative.

Many of the meeting attendees agreed that the right comparator for determination of minimal risk is a person with the condition in question since they entered the healthcare setting to receive treatment for that condition. This interpretation may justify increased use of waiver or alteration of informed consent in PCTs if the research interventions are comparable. However, it is difficult to find two interventions with exactly the same risks, potential benefits, and burdens. Perhaps more importantly, attendees opined that most people would want to know if their care were being determined through randomization; therefore, informed consent is best practice whenever practicable. Although the empirical literature on this point is limited, this conclusion was bolstered by empirical evidence suggesting that patients generally want to be informed of their participation in research and when their treatments are determined in randomized or non-personalized ways. While most patients wish to be informed, there is variation among patients on how they wish to be informed—either verbally, through traditional written consent forms containing all required elements of informed consent, or through abbreviated or altered consent forms and methods. Verbal or abbreviated consent would constitute an alteration of informed consent in the United States, and thus would still require the determination of minimal risk by an IRB.

Cluster randomized trials (CRTs) are randomized at the cluster level (e.g. clinic, hospital, community, etc.), and institutional or relevant authorities (e.g. senior hospital leader, community elder, medical center board, etc.) are typically positioned to make the decision for the cluster to participate. CRTs may present an easier setting to waive individual consent since the entire cluster would be randomized to one intervention, and "approval" would have been attained by the appropriate authority. Attendees, however, concluded that participants should generally be

made aware of research participation in some way when doing so is practicable. The notion of being "made aware" of research participation would not serve as informed consent (and whether it would rather constitute an alteration to informed consent might then depend upon whether the potential participant could opt out of the research). The extent to and manner in which participants are alerted may be dependent, at least in part, on the risk of the trial. For example, a hallway flier may be appropriate for a hospital studying Purell® vs. a new alcohol-based sanitizer but would not be appropriate for a study randomizing patients to receive one anesthetic or another. Attendees briefly considered the proposition that patients have an obligation to participate in pragmatic research, and thus broadly waive their right to consent, before rejecting it due to its limited applicability. Further, typically an obligation to participate in research only applies to minimal risk research.

Meeting attendees further explored the appropriateness of waiving or altering consent by enumerating the ways in which clinical care and pragmatic research operate similarly. For example, a pragmatic clinical trial may arbitrarily randomize patients to receive one of two different standard-of-care interventions. The research is not apparently different than physicians who may prescribe one of two standard-of-care interventions based on intuition rather than data or evidence. A patient at a hospital may randomly be seen by one physician who prefers intervention X, but if traffic had delayed their arrival by 10 minutes, they would have been seen by a physician who prefers intervention Y. Pharmacies may not have the prescribed intervention X available at the time ordered, and the patient will thus receive intervention Y. Finally, hospital systems regularly make decisions about which medications to list on formulary based in part on cost without notifying their patient population. If clinical decisions are sometimes made arbitrarily (e.g. physician preference or familiarity), randomly (e.g. formulary decisions, timing in the queue to be seen), or intuitively (e.g. not based on analysis of the best evidence), then pragmatic research involving randomization does not introduce a higher or different level of arbitrariness into the clinical setting and may actually provide an evidence base for future decision-making.

Clinical equipoise, the genuine uncertainty over which intervention is best, is a requirement for conducting ethical research. Efficacy and safety are the primary criteria for the assessment of clinical equipoise. Attendees suggested that efficacy and safety might be insufficient categories for clinical equipoise, particularly in the absence of informed consent. Extending the criteria in the context of pragmatic clinical trials appears important. For example, it may be unjust for someone to be randomized to receive a medication that is much more expensive than an alternative medication, even if there is equipoise over health-related risks and benefits. If funding is not available to cover the cost difference, a participant should not have to bear the cost burden of research participation. Participants should also know if the side effect profile or practical burden is not equivalent between the two arms of research. Equipoise assessments will vary between IRBs and among care providers and investigators.

Meeting attendees considered the role of RWD both within and outside the context of PCTs. Despite the scientific desire for institutions and trialists to share de-identified data, attendees

expressed concern that data sharing may violate the rights of patients that did not authorize the use of their data for a particular research study. Anonymized data has not been considered human subjects research, but attendees questioned whether this exempt designation remains appropriate as data sources proliferate, data analytic techniques mature, and genetic research evolves. Further, while anonymizing data can alleviate the requirement for informed consent currently, an individual may still wish to withhold consent from research if they morally disagree with the research question.

Institutionally, data are a business value or asset even in the absence of an immediate purpose and can include proprietary information about confidential institutional operations. The scientific enterprise has to balance calls for transparency through data-sharing with the realities of business and privacy. Interestingly, some journals have mandated data-sharing as a requirement for publication. Data stewardship was suggested as a topic for a future Bioethics Collaborative.

An expert investigator with extensive experience designing and conducting PCTs shared several insights. First, PCTs present an important opportunity for stakeholder input as multiple parties, including both investigator and patient, have a clear interest in answering the question at hand. Shared decision-making between the investigator and patient-participant is one way to manifest collaboration in PCT design and conduct. Further, recruitment may be easier in PCTs than other trials since patients have significant interest in the research question. Experience has shown that pragmatic conclusions may be well-supported, evidence-based, and persuasive, yet they may not be adopted. Implementation is difficult if the research does not originate from those with the authority to make the changes in clinical care. The investigator emphasized that pragmatic research may enhance routine clinical care since outcomes are better tracked.

Potential Future Work

- Decision-tree for waiver or alteration of informed consent in PCTs
- An academic contribution that reorients pragmatic trials to put patient-collaborator at the center of research rather than policymakers or trialists at center
- Deliverable that outlines pertinent PCT definitions such as minimal risk and practicability in the context of informed consent
- Outlining good practice for informed consent and data usage
- Clinical decision framework to help patients understand clinical influences and more broadly understand differences between clinical care and research
- Bioethics Collaborative on appropriate data stewardship

References

Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care. (2016, March 21). [Text]. HHS.Gov. https://www.hhs.gov/ohrp/regulations-and-policy/requests-for-comments/draft-guidance-disclosing-risk-in-standards-of-care/index.html

General requirements for informed consent, 45 C.F.R. *§46.116 (2018)*.