MEETING SUMMARY

Advisory Panel on Clinical Trials Meeting Summary

May 15, 2019

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OVERVIEW

On May 15, 2019, the PCORI Advisory Panel on Clinical Trials (CTAP) held its 13th meeting in Washington, DC.

CTAP's 15 members include patient representatives and experts in clinical trials, biostatistics, epidemiology, and ethics. Two members of PCORI's Methodology Committee serve ex officio on CTAP. The meeting was open to the public via webinar, and meeting materials were posted to the PCORI website in advance.

At the meeting, CTAP learned about federal regulations, expert panel recommendations, and PCORI policies on the return of aggregate and individual study results to study participants. Panel members offered several recommendations on sharing individual PCORI-funded study results with participants. Other presentations provided overviews of an NIH Collaboratory study on ethical issues associated with incidental findings in pragmatic studies and PCORI's pre- and post-award processes. CTAP reviewed the results of a study on the contributions of patient engagement in research and best practices for pragmatic clinical studies based on PCORI's experience with these studies. A CTAP discussion addressed the types of analyses the panel would like from PCORI to support the panel's work.

RETURNING STUDY RESULTS TO PARTICIPANTS

Allie Rabinowitz, M.P.H., Program Associate in PCORI's Office of the Chief Science Officer, explained that returning results to study participants shows appreciation for research participation, builds a sense of partnership between researchers and participants, and increases public trust and willingness to participate in research.

The U.S. Department of Health and Human Services and the Health Insurance Portability and Accountability Act (HIPAA) have no regulations on returning aggregate results to research participants. However, several rules and regulations do govern the return of individual research results to participants, including the following:

- The U.S. Food and Drug Administration endorses the good clinical practice guideline[1] of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. This guideline calls for investigators to inform participants when they need medical care for illnesses that the investigator has learned of during the research.
- HIPAA requires patients to have access to their personal health information on request.

[1] https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf

- The Clinical Laboratory Improvement Amendments Act of 1988 (CLIA) does not permit studies to release results from laboratories that do not have CLIA certification.

PCORI directs but does not require researchers to share study results with participants and partners. PCORI works with principal investigators (PIs) to prepare a 500-word lay-language summary of each completed project. PCORI posts these summaries on its website within 90 days after the study ends. Awardee institutions must make a reasonable effort to ensure that participants and partners receive these summaries.

CTAP discussed the importance of sharing results with participants in plain language and making sure that participants are aware that results are available. Several CTAP members disapproved of an expert panel suggestion that researchers not disclose individual results if data breaches or unauthorized disclosure could occur or when returning this information would be burdensome. They noted that data breaches and unauthorized disclosure are always possible. The presumption today is that research results should be shared, but investigators must determine how to do this and acknowledge that doing so might not make sense in some situations.

CTAP Recommendations for Returning Research Results to Participants

- Instruct investigators to discuss plans for sharing study findings with participants in their funding applications
- Offer no-cost extensions that allow pragmatic trials to share results with participants
- Review applicants' plans for sharing results with participants in PCORI's merit review process
- Explain that PCORI-funded studies must share results with participants for institutional review boards
- Find out how the National Institutes of Health *All of Us* Research Program[2] will return results to participants
- Share language with researchers for cover letters to journals stating that PCORI publishes research summaries and final reports

Exploration of Incidental Findings in Pragmatic Clinical Trials

Kevin Weinfurt, Ph.D., a CTAP member, explained that the NIH Collaboratory[3] provides an infrastructure for collaborative pragmatic trials in health care systems. As part of the Collaboratory, Dr. Weinfurt and Jeremy Sugarman, M.D., M.P.H., M.A., of Johns Hopkins University, are addressing ethical issues[4] associated with incidental findings in studies that might have implications for participants. For example, x-rays of spines collected in a Collaboratory study identified potential cases of osteoporosis. However, participants and their health care providers might not have known of this information, and they might have been unaware that these patients were part of a pragmatic study.

Dr. Weinfurt's study is interviewing the Principal Investigators (PIs) of all Collaboratory and other NIH-funded pragmatic trials as well as some PCORI-funded pragmatic trials. When a study is identified that produced clinically relevant incidental findings, the investigators will examine the decision process used and who decided whether to disclose the incidental findings.

[2] https://allofus.nih.gov
[3] https://rethinkingclinicaltrials.org
[4] https://rethinkingclinicaltrials.org/cores-and-working-groups/regulatory-ethics

Overview of PCORI Funding Processes: Opportunities

Dr. Trontell described PCORI's research-funding process. In the pre-award phase, the steps are:

- Gather information about a topic
- Issue a PCORI Funding Announcement (PFA)
- Solicit applications
- Conduct merit review
- Score applications
- Ask applicants to answer questions from the review
- Decide whether to fund each application
- Issue public announcements of awards

CTAP and other advisory panels can provide input on the guidance PCORI gives applicants, criteria for merit review, types of additional information to request from applicants, and criteria for approving an award.

Once an award is made, the study begins. Investigators must submit reports to PCORI at least every 6 months on their progress and milestones, although larger studies and those with certain risks might be required to submit reports every month. If a study has difficulties, such as with enrollment, PCORI opens a dialog with the investigator. In exceptional circumstances, PCORI might terminate a study. Areas for input from CTAP and other advisors in the post-award period include modifications to the study aims, scope, or duration; changes to reporting requirements; and remediation recommendations. Once the study and analysis of findings are complete, the final research report is issued, and the study summaries are released.

During the discussion, Dr. Trontell explained that when PCORI changes a PFA from previous cycles, the new PFA highlights those changes. PCORI has learned that many incremental changes are more disruptive than several changes at the same time. PCORI is asking applicants how to make the application process easier. PCORI wants to attract good applicants and to avoid imposing barriers to good research ideas.

CTAP encouraged PCORI to develop guidelines on potential challenges that might arise in studies with certain designs. Dr. Trontell explained that when a study needs a new design because it will not reach its recruitment goal, PCORI can offer resources and the collective wisdom of its staff to meet this need.

Contributions of Patient Engagement in Research: PCORI's Findings

Kristin L. Carman, Ph.D., M.A., Director of Public and Patient Engagement at PCORI, shared the results of a study on the contributions of patient engagement in research that was recently published in *Health Affairs*.[5] With guidance from PCORI's Advisory Panel on Patient Engagement,[6] Dr. Carman and colleagues extracted information from 127 articles with details on contributions of engagement to PCORI-funded comparative effectiveness research (CER) studies.

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[5] https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2018.05067?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&

[6] https://www.pcori.org/engagement/engage-us/join-advisory-panel/advisory-panel-patient-engagement

The article describes the contributions of engagement of participants and other stakeholders in all phases of a study, including research focus and design, interventions, recruitment and retention, data collection and analysis, and dissemination of research findings. The study showed that many kinds of stakeholder engagement can have an impact, sometimes on a study's entire course.

Dr. Carman concluded that PCORI funding is driving change in research through stakeholder involvement, which can influence research value, relevance, and utility. Although engagement cannot address all of the challenges of CER, it can improve many aspects of this research. Engagement can also help balance the tradeoffs involved in responding to end user needs while maintaining study quality.

Dr. Carman briefly summarized a recent meta-analysis[7] of seven randomized clinical trials showing that engagement in research increases enrollment in clinical trials.

CTAP suggested that PCORI assess the impact of engaging study coordinators or nurses in PCORI research. Panel members asked about gaps related to stakeholder engagement that could be filled by research. A PCORI statement on the return on investment of participant engagement is needed to help health system leaders understand the need to support this engagement.

Pragmatic Clinical Studies: Learning from Experience

Dr. Trontell explained that PCORI has three types of CER funding announcements: Broad, Targeted Topic Areas, and Pragmatic Clinical Studies (PCS). All PCORI research must have a pragmatic focus. PCORI has published a Guidance[8] for all CER conducted in real-world settings, which was developed with help from the CTAP.

After 11 funding cycles to date, PCORI has awarded 43 PCS awards totaling $494 million. These studies are all currently ongoing so results are not yet available. The median PCS sample size is17,000, and have ranged from 425 to 100,000. In addition to the usual clinical trial challenges with start-up, recruitment, enrollment, and retention, the challenges of research in real-world settings include the time required for staff to complete their clinical and research tasks, fidelity of intervention implementation, adherence to study protocols by participants and providers, and variations during study performance.

Best practices identified by PCS studies include:

- Strong and frequent engagement of multiple research partners is invaluable.
- Networks of research relationships can accelerate start-up processes and problem solving.
- Data can be used to simulate enrollment and event rates from one or more sites to help researchers anticipate changes in participant characteristics over time.
- Investigators sharing their experiences from pragmatic studies (e.g., through PCORI Learning Networks) can be helpful.

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[7] https://www.bmj.com/content/363/bmj.k4738.long

[8] https://www.pcori.org/research-results/about-our-research/guidance-design-and-conduct-trials-real-world-settings-factors

Potential Future Topics for CTAP Discussion

Dr. Trontell listed several potential topics for future CTAP discussion, including the following:

- Descriptions of ongoing and/or completed studies, including outcomes and study characteristics
- Analyses of outcomes and other aspects of completed clinical trials
- How studies can best manage variation and adaptations of interventions, intervention fidelity, and participant adherence

Dr. Trontell asked CTAP to weigh in on which types of information the panel would like to receive on ongoing or completed studies and whether case studies are helpful. PCORI must be selective about the types and numbers of analyses it conducts to use PCORI staff time efficiently.

Analyses of PCORI-funded studies suggested by CTAP

- Rates of staff turnover
- What types of study and study features need to be more or less pragmatic along each PRECIS dimension
- Urgency of research questions
- Assumed versus actual interclass correlations (ICC) of completed studies
- Contributors to study success according to investigators
- Why health systems participate in research
- Pros and cons of research in health systems
- Challenges during the PCORI-funded study conduct
- Planned analyses versus those published in study reports
- How new measurement tools affect what is assessed

CTAP would like to identify the factors that make trials successful, but this would require a definition of a successful trial. The factors that contribute to lack of success often include recruitment or retention difficulties or missing data. Successful studies are often those with a PI and project manager who are dedicated to the trial, but PCORI cannot ask for this type of personnel in a PFA. Large pragmatic trials need a great deal of planning, and preparation is probably one of the most important success factors. Another success factor is existing research infrastructure that allows new studies to start quickly.

CTAP recommended that PCORI encourage investigators to spend 1 year on planning and assessing the feasibility of their studies. They also suggested that PCORI help researchers determine the best position along each PRagmatic Explanatory Continuum Indicator Summary (PRECIS) dimension for their study given their research question and real-world environment characteristics.

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