MEETING SUMMARY

Advisory Panel on Clinical Trials Meeting Summary

November 5, 2019

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Overview

On November 5, 2019, the PCORI Advisory Panel on Clinical Trials (CTAP) held its 14th meeting in Washington, DC.

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

At the meeting, CTAP received a welcome from Josephine Briggs, M.D., PCORI's new interim Executive Director. Dr. Briggs described her priorities, which include serving as a public champion for PCORI and ensuring that PCORI has the resources needed to continue its work. CTAP learned about PCORI's plans to encourage awardees to return results to study participants. Andrea Troxel, Sc.D., CTAP's chair, described PCORI's new methodology standards for studies of complex interventions (SCIs) as well as implementation science frameworks and study types. CTAP discussed the potential to form a learning network that could address the challenges of investigators conducting PCORI-funded pragmatic studies. The final session focused on the potential for new staged or phased research awards that might improve the quality and success of PCORI-funded trials.

PCORI Updates

Anne Trontell, M.D., M.P.H., Associate Director, Clinical Effectiveness and Decision Science at PCORI, reported that Joe V. Selby, M.D., M.P.H., PCORI's Executive Director, plans to retire at the end of 2019. PCORI's Board of Governors announced that Dr. Briggs would become PCORI's Interim Executive Director and Acting Chief Science Officer starting on November 1.

As PCORI seeks Congressional reauthorization, the institute remains open for business. PCORI continues to fulfill its obligations to research that it has funded or plans to fund. Although PCORI is optimistic about its reauthorization, it will not fund major new initiatives until it is reauthorized, but it will continue to welcome and develop new research topics.

Dr. Briggs explained that PCORI is undergoing a complex transition. As interim Executive Director, Dr. Briggs's top priority is to be a public champion for PCORI. A search is underway for a permanent Director, and this individual will be appointed as soon as PCORI is reauthorized. Dr. Briggs's second priority is to ensure that PCORI's components have the staffing and resources required to continue doing their work. In this transition

period, Dr. Briggs will identify process changes that could make her successor's job easier. However, she does not plan to make major changes or establish a strategic vision for PCORI's next decade.

Follow-Up from Previous Meetings

Allie Rabinowitz, M.P.H., Senior Program Associate at PCORI, reminded CTAP of its discussion in May 2019 on sharing aggregate and individual research results with study participants. PCORI guidelines encourage awardees to return aggregate study results to study participants, and a new internal PCORI workgroup is discussing how to make this recommendation clearer and more prominent. Once a strategy is finalized, it will be included in future PCORI funding announcements.

In Fall 2020, a new CTAP Chair and Co-Chair will be appointed, and Ms. Rabinowitz encouraged CTAP members to volunteer or nominate a fellow member for these positions. The Chair's responsibilities include oversight, meeting agenda development, and moderation of CTAP meetings.

Implementation Science: Potential Applications to PCORI's Complex Intervention Standards

Dr. Troxel reported that PCORI's Methodology Committee issued Standards for Studies of Complex Interventions in April 2018. A rough definition of a complex intervention is one that has multiple components that might depend on one another and be active at several levels.

Implementation science is a field that formalizes process evaluations and other ways of assessing the intervention's reach, adoption, and scalability. This is especially relevant to complex interventions. Implementation science considers barriers to and facilitators of successful implementation at the systems, individual practitioner, and participant levels. Implementation science also evaluates effects of changes to or adaptations of interventions as well as intervention adoption and scalability.

Dr. Troxel reviewed some commonly used implementation science frameworks that can be useful for evaluating aspects of complex interventions:

- Consolidated Framework for Implementation Research (CFIR), which has five domains: intervention characteristics, inner setting, outer setting, characteristics of implementing individuals, implementation process
- RE-AIM, which has five dimensions: reach, efficacy/effectiveness, adoption, implementation, and maintenance

CTAP discussed the differences among the various hybrid types of implementation science studies. They noted that Type I studies emphasize effectiveness, whereas Type II studies give equal weight to effectiveness and implementation. In Type I studies, the primary outcome is the health impact and the secondary outcomes are implementation variables. The reverse is true for Type III studies, which might assess, for example, whether an intervention that worked in an urban setting is equally effective in a rural setting.

CTAP pointed out collecting patient perspectives is critical before developing an intervention to address a health issue. PCORI might work with patient organizations to identify implementation science study designs that are patient centered. Patient engagement could, for example, help identify how accomplishing a health goal could help patients meet personal or professional goals.

Dr. Trontell reported that PCORI-funded investigators have had difficulty in identifying the appropriate scope for process evaluations and asked for suggestions for these investigators. CTAP suggested that the choice of a framework be based on the elements that are most relevant to what is being studied, and the causal model should drive the process evaluation. If, as Dr. Troxel recommends, the causal model has two active pathways, these pathways should be clearly identified so that they can be measured. A CTAP recommendation was for PCORI to develop a taxonomy for the domains to use in process evaluations described in the Methodology Standards for Studies of Complex Interventions.

The PCORI methodology standards are the minimum set of standards for PCORI-funded research and are not intended to be prescriptive. Investigators must determine the appropriate causal model and how to assess an adaptation using the framework they believe best fits their project, so they have flexibility to implement the methodology standards in the way that best fits their project. Researchers have been asking for guidance on how to do this, and, although PCORI does not promote a particular framework, providing some structure is useful. New awards will need to comply with the Methodology Standards for Studies of Complex Interventions.

Feedback from Pragmatic Clinical Studies Investigators

Dr. Trontell reported that PCORI conducted an in-depth needs assessment of the investigators of PCORI-funded Pragmatic Clinical Studies to determine the potential value of establishing a learning network for them. This network would offer a structured approach for peer-to-peer learning through meetings, collaborations, and shared resources. The needs assessment used in-depth discussions with awardees and PCORI stakeholders, an awardee survey, and an in-person meeting of Principal Investigators.

The top challenges identified in the survey were:

- Flexibility and real-world implementation while maintaining fidelity
- Patient recruitment, enrollment, and retention
- Study site start-up and onboarding

Meeting participants identified the following factors that contribute to these challenges:

- Site or provider adherence
- Flexibility or standardization of the intervention
- Patient adherence

Meeting participants also noted that investigators need to manage the range of collaborator expectations, write protocols that allow typical variations in the standard of care without leading to protocol deviations, and identify methods to measure adherence. Participants agreed that patient stakeholders contribute important perspectives, understanding of obstacles, and suggestions for language or framing.

During the discussion, CTAP supported the creation of a learning community for pragmatic trial investigators to share their challenges. To make the learning community effective, PCORI could explain that it will not cut off funding if an investigator admits having a problem that has no solution yet. Once one investigator admits to vulnerability, "the floodgates open" and others may start sharing their challenges. If PCORI creates a learning network, it should engage CTAP in discussing how to overcome the challenges that network members identify.

Staged or Phased Research Funding to Improve the Quantity, Quality, and Success of Funded Trials

Dr. Trontell explained that this session would focus on preliminary PCORI research on different mechanisms for developmental studies, pilot studies, or phased research funding to inform PCORI 2.0.

Courtney Clyatt, M.A., M.P.H., Program Officer for Engagement at PCORI, described lessons learned from two phased PCORI programs. PCORI's Pipeline to Proposal (P2P) program was designed to increase the involvement of underrepresented communities and other stakeholders in research through successive tiers of funding and technical support. P2P initially offered three tiers of funding for partnership development, research capacity, and research infrastructure development. After two cycles of awards, PCORI decided to shorten the original 33-month period for all three tiers to 21 months with just two tiers. However, the program ended before funding any second-tier projects.

The P2P program helped stakeholders learn how to engage partners in creating a multi-stakeholder environment to prepare for research. The P2P partnerships successfully engaged underrepresented stakeholders and facilitated sustainability by helping develop governance documents as well as communication and sustainability plans.

PCORI's Eugene Washington Engagement Award program offers two types of awards to scale up capacity for patient-centered outcomes and comparative effectiveness research and for multi-stakeholder gatherings to form collaborations for these types of research.

Ms. Rabinowitz identified phased awards used by other funders. The National Institutes of Health (NIH) offers several types of funding to develop research projects by supporting infrastructure and capacity building, small grants, and planning grants. The Department of Veterans Affairs has a phased funding model to identify priority areas for innovative and disruptive research. This model uses a rapid review process to evaluate and fund early studies, and it predefines progress milestones in phases for transitional funding to implement or scale up research. The Wellcome Trust offers seed awards to develop compelling and innovative ideas for larger grant applications to Wellcome or other funders. The trust's small grants program helps researchers build professional networks and develop new research agendas.

PCORI's consideration of developmental research awards offers the possibility to foster novel, innovative, or high-risk research project development or to assess research feasibility before a larger research funding investment. The awards can be small and/or time limited and offer proof-of-concept testing, pilot or feasibility studies, research planning, and/or additional competition to carry out research. The tools by NIH and other funding organizations often use cooperative research development with substantial guidance provided by funding organization staff, criteria or milestones to monitor progress, and rapid-cycle reviews of early-stage research development.

Discussion

CTAP discussed the purposes of phased funding. The initial phase of funding can show that the proposed study design is feasible. The phased approach also allows assessments of proof of concept, fidelity to the new comparator, and recruitment achievability. Phased funding could help PCORI fund more and better research, including more research on understudied issues.

CTAP noted that having to stop after the first phase; develop a protocol, application, and budget for the second phase; and wait for the notice of award results in loss of momentum and engagement of research partners and slows the process down. Furthermore, institutions must pay for the intervals between phases, and some might not be able to cover these costs. Ms. Clyatt confirmed that P2P awardees experienced atrophy and loss of momentum between phases.

CTAP offered the following recommendations for PCORI in considering developmental or phased funding:

- Develop a mechanism to make the staged process more efficient. For example, PCORI might offer up to 3 years of funding for the initial phase and allow investigators who complete the first phase early to move onto the second phase sooner.
- Issue contracts with built-in "if-then" mechanism to allow funding for the second phase to happen without re-competition but contingent on achieving phase 1 milestones on time
- Make decisions about the second phase before the first one ends
- Consider platform trial designs that address a disease or goal, such as tobacco use cessation. These platform trials set up the infrastructure to allow adding or dropping arms as new treatments or ideas are made available. The trial might accept a broad population of patients but assign them to arms depending on their characteristics and the interventions.

Next Steps and Closing

Dr. Trontell reported that CTAP members will receive a survey on topics for future meetings and on what did and did not work well in this meeting. CTAP suggested that PCORI distribute definitions of acronyms commonly used at CTAP meetings to help new panel members.