Oversight Challenges with Patient Centered Outcomes Research

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- PhD in Philosophy/Ethics from University of Toronto; MA in Religion from Yale Divinity School
- Most recently was Senior Researcher at Harvard Law School and prior to that completed a Postdoctoral Fellowship in Bioethics at National Institutes of Health
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- Work has been published in several academic journals, including *New England Journal of Medicine*, *Annals of Internal Medicine*, *Hastings Center Report*
I have no relevant COIs to declare

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Learning Objectives

1. Understand Patient Centered Outcomes Research (PCOR)
   • What is it? How does it differ from traditional clinical research?

2. Present and discuss empirical research on ethical and oversight challenges with PCOR
   • Results from qualitative interviews and national survey of IRB chairs

3. Overview of evidence-based recommendations addressing areas of oversight uncertainty and need
   • Results from a consensus-building Delphi process among an expert stakeholder panel
What Is Patient Centered Outcomes Research?
“...and the ACA begat the Patient Centered Outcomes Research Institute (PCORI)”

- The Evolution/Revolution of Patient Centeredness In Healthcare and Outcomes Research
- PCC mentioned over 40 times in ACA, echoed in initiatives by FDA and IOM to grant patient perspective a central role in drug development
What Is PCOR?

PCORI describes its mandate:

To “improve the quality and relevance of evidence available to help patients, caregivers, clinicians, employers, insurers, and policy makers make better-informed health decisions. To do this, we work with those healthcare stakeholders to identify critical research questions and answer them through comparative clinical effectiveness research...focusing on outcomes important to patients.”

Source: https://www.pcori.org/about-us/our-story
What Is PCOR?

PCORI

• Departs from the traditional clinical research paradigm, in which investigators drive the conceptualization and implementation of research...

• Embraces an approach on which patients are involved throughout the entire life cycle of research projects—“from proposal development to research design and dissemination of the study results”

Source: https://www.pcori.org/research-results/how-we-select-research-topics
What Is PCOR?

The 21st Century Cures Act, passed in 2016:

• Patients are “in a unique position to contribute to an understanding of benefit and risk considerations throughout the medical product development process”

• Recognizes “the need for systematic collection of direct patient input” to guide choices about drug development

What Is PCOR?

The underlying assumption of these efforts

- Research meaningfully informed by the patient perspective is more likely to be used by patients to inform their decision-making and, in the end, to improve patient outcomes
What Is PCOR?

PCOR refers to the evaluation of questions and outcomes that are meaningful and important to patients and caregivers, and that engages patients beyond their traditional role as research subjects.
What Are the Oversight Challenges with PCOR?
Background

The Patient Centered Outcomes Research Oversight Study (PCOROS)

- PCORI-funded, 2-year, mixed methods study
- Led by Joel Weissman, PhD at Brigham and Women’s/Harvard Medical School
PCOROS Project Aims

Aim 1
Describe the human subjects-related challenges posed by PCOR and learn how, if at all, IRBs in major research institutions are responding to those challenges.

Aim 2
Develop guidelines and recommendations for IRBs, investigators and patient advisors to employ when designing or reviewing human subjects research aspects of PCOR.
Three Phases

1. Qualitative research – interviews with various stakeholders
   • Largent et al. “PCOR: Stakeholder Perspectives and Ethical and Regulatory Oversight Issues.” *IRB*, 2018; 40: 7-17

2. National survey of IRB chairs

3. Development of evidence-based recommendations and policies
Phase 1: Qualitative Aspect

- 3 onsite case studies
  - 1 school of medicine
  - 1 school of public health
  - 1 research hospital
- 13 individual interviews
- 6 focus groups
  - 2 groups of IRB chairs and members (AER 2015)
  - 2 groups of PCOR investigators
  - 2 groups of patient and family advisors

In all, we spoke with more than 100 individuals engaged in various aspects of PCOR
Respondents identified widespread engagement of patients in non-traditional roles (study staff such as PI, sub-I, recruiter, consultant or advisor) as the novel aspect of PCOR from an ethical and regulatory oversight perspective.

**Findings**

- Involvement of patients in non-traditional roles was seen as a novel issue
  - Disparate views on whether and to what extent these patients need to be protected
  - Question of whether the institution needs protection
Respondents perceived many barriers to the meaningful engagement of patients in non-traditional roles but did not widely view lack of meaningful engagement as a problem for IRBs to resolve.

**Findings**

- Most patient and family advisors reported that they were meaningfully engaged.
- **BUT** other respondents perceived patient involvement as just “checking a box”.
- Respondents felt that it was the role of investigators and funders to ensure that patients were more meaningfully engaged in PCOR, rather than the IRB.
Respondents reported that, although the ethical and regulatory oversight issues associated with PCOR are largely familiar, PCOR oversight is nevertheless relatively challenging as compared with traditional clinical research.

Findings

- Scale presents oversight challenges
- PCOR studies are often conducted at multiple sites, which can lead to variations in IRB review
- **Rise of PCOR corresponds with growth in new technologies that raise unresolved oversight challenges**
Phase 2: National Survey

Sample: All IRB chairs who were registered with OHRP, at...
- 138 medical schools, 61 schools of public health, 68 independent hospitals: n = 267 institutions
- Total sample size: n = 436 chairs

Domains covered challenges and needs of IRBs in PCOR review and oversight

Mail and online response options, with modest incentive

61% response rate
Patients Engaged in Research – Are They Researchers or Subjects?

- Nearly 26% of respondents said that their IRB considers patients in non-traditional roles to be research subjects even if not formally enrolled as subjects in same study.
- 37% of respondents said that their IRB requires informed consent from patients in non-traditional (non-subject) roles.
### PCOR Features Chairs Find Challenging for IRB Review and Management

<table>
<thead>
<tr>
<th>Patient Roles</th>
<th>% Challenging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients' access to identifiable data</td>
<td>84%</td>
</tr>
<tr>
<td>Patients in dual roles</td>
<td>78%</td>
</tr>
<tr>
<td>Patients as co-investigators</td>
<td>69%</td>
</tr>
<tr>
<td>Patients on advisory boards</td>
<td>24%</td>
</tr>
</tbody>
</table>

### PCOR Characteristics

- Inadequately trained investigators: 73%
- Creation of local patient registries for recruitment: 31%

### Digital Health

- Social Media for recruitment: 56%
- Wearable devices to collect data: 22%
Are Some IRBs Being Overly Protective?

Perceived level of IRB responsibility to...

- Protect patients in non-traditional roles:
  - A lot of responsibility: 60%
  - Some or little responsibility: 34%
  - No responsibility: 6%

- Protect institutions from problems due to patients in non-traditional roles:
  - A lot of responsibility: 55%
  - Some or little responsibility: 41%
  - No responsibility: 4%
Summary of Empirical Results

- Key stakeholders and IRBs find oversight of PCOR relatively more challenging than non-PCOR research.
- IRBs wrestle with standards for appropriate training and oversight of patients in non-subject roles, and can be over-protective.
- Use of social media, digital devices and apps is common in PCOR (e.g., data security and privacy issues), yet PIs and IRBs may lack relevant expertise.
- Identification and quality engagement of patient partners can be challenging, though not within purview of oversight bodies.
Addressing PCOR Oversight Challenges
Recommendations on 3 Main Topics

1. Patients in non-traditional study roles
2. Widespread use of emerging technologies in PCOR
3. Identifying and engaging patient partners, with a focus on potential conflicts of interest for patients in non-traditional roles
The Modified-Delphi Consensus Process

- Expert stakeholder panel evaluates standards for some domain (typically, clinical care)
- Multiple rounds of qualitative and quantitative evaluations
- Participants made aware of each others’ (anonymized) responses after rounds and given chance to re-evaluate their initial view
- 17 expert stakeholders recruited
  - IRB chairs, patients and patient advocates, PCOR principal investigators, experts in bioethics and law, policymakers
Consensus reached on 21 recommendations

- 10 addressing oversight of patients in non-traditional study roles
- 6 addressing oversight of emerging technologies in PCOR
- 5 addressing challenges in patient engagement and COI
PCOR features patients in non-traditional and sometimes multiple roles

- As part of the research team, i.e., someone who interacts with human subjects or identifiable data
- As recruiters, who invite family, friends and/or other patients to participate in PCOR
- As consultants, who contribute to the development of meaningful endpoints for patient populations
- Potentially as subjects, when they are a source of data for the research team
Topic 1. Patients in Non-Traditional Roles

Ethical questions and uncertainty arise when patients occupy these roles

• What criteria should be used to differentiate roles?
• What level of ethics and scientific training do patients in these roles require?
• Should patients be permitted to occupy multiple roles or change roles during the course of a study?
Patients in Non-Traditional Roles: General Themes

- Tension between providing guidance on how IRBs can provide effective oversight for patients in potentially unfamiliar study roles and refraining from unnecessarily exceptionalizing patient engagement in research
  - General agreement that patients should not be held to different standards just because they are patients
- Who is responsible for what? Proper scope of IRB oversight?
- Oversight implications of patients in multiple/switching roles in same study
RECOMMENDATION 1

- PCORI (or another funding or regulatory body) should endorse a **formal taxonomy** for differentiating research-related roles patients and other stakeholders might assume, in order to systematize decision-making and policy
RECOMMENDATION 2

➢ **Study Personnel:** Patients and other stakeholders should be considered “study personnel” when they *interact with research subjects in a study-related capacity and/or have access to identifiable data*. This category would include patient co-investigators as well as patients in other roles, such as patients who collect data via surveys, obtain consent from research subjects, and recruit research subjects.

➢ **Advisor:** Patients and other stakeholders should be considered “advisors” when they do not have access to research subjects and/or identifiable data but do *formally advise* on protocol development, study endpoints or recruitment strategies, or participate in activities that may inform study design or conduct.

➢ **Research subject:** Patients and other stakeholders should be considered “research subjects” whenever they satisfy the *definition provided in the federal regulations*. 
Principal investigators should classify patients and other stakeholders participating in their research in accordance with the above taxonomy and follow standard procedures for reporting study personnel to the IRB in accordance with IRB policies.
RECOMMENDATION 4

- Patients and other stakeholders who are study personnel should receive required **standard ethics training** (CITI, GCP, etc.) as a baseline.
PCORI (or another funding or regulatory body) should endorse and make available educational modules aimed at facilitating and improving the ability of patients and other stakeholders to serve effectively in study personnel roles, providing guidance on ethical, scientific/methodological, and logistical challenges that they may encounter.
RECOMMENDATION 9

IRBs should **not require informed consent** or the application of other relevant human subjects protections for patients and other stakeholders in research roles who do **not** satisfy the regulatory definition of “research subject”
Address a matter of practical import to IRB review:

- When, if ever, is it acceptable for one and the same person/patient to occupy multiple research roles simultaneously, or switch between roles, in the same study?
- Not entirely unique to PCOR but likely more common
Potential Roles

▷ Study personnel
  • Access to data, interaction with subjects

▷ Study advisor
  • No access to data or contact with subjects; input on study design

▷ Research subject
  • Regulatory definition
Simultaneous Roles

- Subject and study personnel
- Subject and advisor
Switching Roles

- Subject → study personnel
- Subject → advisor
Simultaneous or Switching Roles?

What is the concern?
Simultaneous Roles for Patients?

Subject and study personnel

- Certain interests as a patient-subject
- Certain interests as a researcher

These interests might conflict
Subject and study personnel

- As a patient-subject, you might have an interest in receiving active intervention, or knowing whether you are receiving investigational drug or placebo
- As a researcher, you have an interest in randomization and maintaining the blind
The nub of research ethics...

The aims of clinical research and the aims of personalized patient care can diverge

When someone occupies researcher and subject roles simultaneously, this tension can be realized in the same individual and potentially force conflicts of commitment
Simultaneous Roles for Patients?

At the same time, there could be benefits...

• The whole point of PCOR is to let the experience of the patient guide the research

• What more immediate way to realize this ideal than having someone use their experience as a subject in a study to inform their actions as researcher for that study?
Would it be acceptable for a patient stakeholder to be both a subject and study personnel (i.e., someone with access to data and subjects) in the same study?
Principal investigators should not invite, and IRBs should not permit, patients and other stakeholders to occupy the “research subject” and “study personnel” roles simultaneously in the same study, due to concerns about scientific integrity (e.g., potential for un-blinding or other forms of bias) as well as potential conflicts of commitment for these individuals (e.g., if the individual’s own interests as a patient were to conflict with the aims of research).

However, in exceptional circumstances, such as where significant research would otherwise be impracticable, the IRB may consider permitting the practice after consultation with relevant institutional officials and development of adequate protections appropriate to the circumstances.
RECOMMENDATION 7

- Principal investigators should take precautions when inviting patients and other stakeholders to occupy the “research subject” and “advisor” roles simultaneously in the same study, due to potential conflicts of commitment for these individuals (e.g., if the individual’s own interests as a patient were to conflict with the aims of research).

- These precautions might include notifying and consulting with the IRB on appropriate safeguards.
Principal investigators may invite, and IRBs should permit, patients and other stakeholders to switch from the “research subject” role to a “study personnel” or “advisor” role in the same study once their active study participation is complete, provided that steps are taken to avoid conflicts and inappropriate incentives for patients and other stakeholders while occupying the research subject role (such as might occur if the prospect of earning advising fees once participation is complete were to inappropriately motivate enrolling or remaining in a study).
PCOR often features the use of relatively new technologies, such as social media, wearables and mobile apps

• As part of study design to monitor or collect data about study participants
• To engage potential participants and the public in recruitment efforts
Topic 2. Emerging Technologies

- Ethical issues and uncertainty arising from widespread use of emerging technologies in PCOR
  - What steps should be taken to ensure that the privacy and confidentiality of participants are protected?
  - And that investigators have adequate training to collect and handle data via these technologies on a large scale?
Emerging Technologies: General Themes

- Challenges not unique to PCOR
  - Panel concluded that the prevalence of these technologies in PCOR rendered the topic important enough to address

- PCOR investigators should explain to IRBs:
  - Which emerging technologies they will use
  - How they will use them
  - Proactively identify how they will address common privacy and confidentiality concerns

- High-level national regulatory or funding body should issue guidance on best practices for data collection in research
Due to the prevalence of emerging technologies in PCOR, PCORI (or other relevant funding or regulatory agencies) should develop training modules aimed at educating researchers, patient research partners, and IRB members on common emerging technology platforms (e.g., Twitter, Fitbit) and the ethical and regulatory issues associated with them.
For studies that plan to collect data using emerging technologies, investigators should submit a statement to the IRB detailing measures to safeguard privacy and confidentiality, addressing such things as who will have access to the data and safeguards around inadvertently collecting data unrelated to the study aims.
Meaningful patient collaboration may be challenging and raise ethical issues

- Rose SL, Highland J, Karafa MT, Joffe S. *Patient advocacy organizations, industry funding, and conflicts of interest.* JAMA Intern Med, 2017; 177: 344-50
Meaningful patient collaboration may be challenging and raise ethical issues

- Patients most accessible to PCOR investigators may be affiliated with drug companies or other commercial entities that stand to benefit from the research, which may raise conflicts of interests
- Should investigators and/or IRBs screen patient research partners for conflicts of interest?
- What steps, if any, should be taken to mitigate conflicts of interest among patients in PCOR?
- Should existing COI policies and practices be applied to patients with conflicts, or are different approaches required?
Patient advisors/consultants not within scope of IRB
  • Recommendations aimed at higher-level funding or regulatory bodies

Rejected notion that quality patient engagement requires patient to be “representative” of study population
  • Importance of diversity

Financial and non-financial COIs are important and require mitigation strategies
PCORI (or another funding or regulatory body) should address the importance of striving for a diverse mix of patient partners, including, where appropriate, consideration of characteristics such as race/ethnicity, sex, socioeconomic status, advocacy group affiliation, or health status.
PCORI (or another funding or regulatory body) should provide guidance on identifying and mitigating financial and non-financial conflicts of interest among patients and other stakeholders involved in research.
RECOMMENDATION 20

Investigators should identify and disclose conflicts of interest among patients and other stakeholders who are study personnel, as with other study personnel, to the IRB.
RECOMMENDATION 21

IRBs should hold patients and other stakeholders who are study personnel with conflicts of interest to the same disclosure and mitigation standards as other study personnel.
Takeaways

➤ Patients in NTRs perhaps biggest oversight challenge
  • PIs and IRBs should strive for clarity on which roles patients will be occupying, which will permit adequate training without over-protecting
  • Caution needed for occupying multiple roles simultaneously or switching between them

➤ Continued reflection and further guidance needed on ethical implications of emerging technologies in context of PCOR

➤ Be aware of potential COIs of patient partners
  • Follow standard reporting and mitigation strategies for patients on study staff
  • More guidance and work needed on handling COIs for patient advisors