Harms, benefits, and the nature of interventions in PCTs

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Attributes of PCTs

1. an intent to inform decision-makers (patients, clinicians, administrators, and policy makers), as opposed to elucidating a biological or social mechanism;

2. an intent to enroll a population relevant to the decision in practice and representative of the patients/populations and clinical settings for whom the decision is relevant;

3. a focus on outcomes of relevance to patients and clinicians; and

4. either an intent to:
   (a) streamline unnecessary procedures and data collection so that the trial can focus on adequate power for informing the clinical and policy decisions targeted by the trial, or
   (b) measure a broad range of outcomes.

Key Issues

Pragmatic clinical trials (PCTs) are diverse in terms of the type of intervention—medical, behavioral, and/or technological—and the target of intervention—patients, clinicians, and/or healthcare system processes.

Variability and overlap in the types and targets of PCT interventions compels a more nuanced assessment of net potential risk, understood as the balance of potential harms and benefits.

A narrow focus on the harms that traditionally arise in explanatory clinical trials may be inadequate for PCT oversight and policy development.
Three Core Questions

1. What are the relevant potential burdens or harms and advantages or benefits for key stakeholders engaged in PCTs?

2. Do different types of interventional PCTs draw out particular kinds of potential harms and benefits?

3. What are the implications for ethical review, stakeholder decision-making, and the development of policies and norms for PCT oversight?
Scope

We sought to

- Highlight equally the potential *harms and benefits* of PCTs

- Discuss these in context of several *interventional PCTs*, including from Collaboratory & PCORnet

- Provide a broad *preliminary framework* to help organize discussions of harms/benefits for many types of interventional PCTs
Scope

We did not

- Distinguish harms from burdens, and benefits from advantages

- Give greater or lesser value to particular harms or benefits

- Give greater or lesser value to the “claims” of particular stakeholders
  E.g., did not propose that potential harms to patient-subjects are more/less important than potential harms to clinician-subjects
“Traditional” Ethics/Regulatory Focus

US regulations consider most anyone a potential human subject ... however...

Much ethics scholarship has examined risk of harm to patient-subjects involved in clinical research

Concerns have focused on

◦ Introducing new and unknown risks associated with experimental medical interventions
◦ Implications of divided loyalty (to patient vs. to generate knowledge for benefit of others)
◦ Imbalance in knowledge and access to information

As such

◦ Attention given to patient protection, informed consent, therapeutic misconception, privacy, etc...
◦ Relatively little discussion of potential benefits, and the risks/benefits encountered by clinicians and health systems
Yet... Belmont Report (1978)

**Beneficence**

“Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.”

“In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.”

“Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous.”

**Risks/Benefits to Others**

“Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society).”
PCTs – Broader Constituency

*Patients, clinicians* and *other members of care team* may serve as
- Designers
- Implementers
- Intermediaries
- Subjects
- Beneficiaries

*Healthcare systems* (processes and administrators) may also be affected directly or indirectly before, during, or after study implementation

*Information technology* permits conducting large scale research and cohort finding for rare diseases and special populations, often with minimal incremental risks and burdens and less cost
Common *Targets* of PCT Interventions

**Patients**
- E.g., Comparing two or more commonly used diet regimens – impact on patient weight

**Clinicians**
- E.g., Determining whether automatic clinician notifications about alternative generic drug options changes prescribing practices

**Healthcare systems**
- E.g., Comparing workflow models to determine the most efficient staffing arrangement to decrease medical expenses while maintaining satisfactory health outcomes
Common Types of PCT Interventions

Medical
• Interventions directly related to the physical treatment of patients

Behavioral
• Efforts to alter habits, compliance with clinical instructions, and the management of beliefs or attitudes that could affect clinical care or psychological and physical wellbeing

Information technology
• Integration of IT to allow for greater understanding of the interface between health management and electronic data coordination, measurement and communication
Lines are Often Blurred

Multiple types and targets of PCT interventions often overlap within a single study

E.g., A PCT that cluster randomizes health systems to use of new electronic decision support tools to reduce unnecessary prescription of antibiotics amongst primary care physicians

- Medical,
- Behavioral,
- Technological,
- Impacting health systems, clinicians, and the health of current/future patients

Important to consider harms/burdens and benefits/advantages that may accrue to all direct and indirect interventional targets
Sample PCT Harm/Benefit Considerations

Medical & Behavioral Interventions

Patients
- Increased or decreased privacy, physical health, psychological wellbeing

Clinicians
- Increased or decreased time commitment, confidence, reputation, autonomy

Healthcare Systems
- Increased or decreased cost, staff/patient satisfaction, workflow efficiency, ranking/reputation, liability

Information Technology Interventions/Components
- Is the technology likely to materially change (positively or negatively) the way in which healthcare is personalized, accessed, delivered, combined, communicated or measured?
# Organizing Framework

**Table 1.** Examples of potential harms/burdens and benefits/advantages of PCTs by type and target of intervention.

<table>
<thead>
<tr>
<th>Target of intervention or interaction</th>
<th>Potential harms/burdens</th>
<th>Potential benefits/advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical and behavioral interventions</strong></td>
<td>(drug, device, or procedure; educational, attitudinal, or adherence)</td>
<td><strong>Medical and behavioral interventions</strong></td>
</tr>
<tr>
<td>Patient</td>
<td>Inconvenience of regimen</td>
<td>Commitment to regimen</td>
</tr>
<tr>
<td></td>
<td>Loss of privacy</td>
<td>More time with care teams</td>
</tr>
<tr>
<td></td>
<td>Poorer health outcomes</td>
<td>Better health outcomes</td>
</tr>
<tr>
<td></td>
<td>Psychosocial discomfort</td>
<td>Fulfillment of altruistic desires</td>
</tr>
<tr>
<td>Clinician</td>
<td>Increased time commitment</td>
<td>Advancing the field</td>
</tr>
<tr>
<td></td>
<td>Additional professional oversight</td>
<td>Improved care delivery</td>
</tr>
<tr>
<td></td>
<td>Decreased confidence/reputation</td>
<td>Increased confidence/reputation</td>
</tr>
<tr>
<td></td>
<td>Decreased clinical autonomy</td>
<td>Increased patient trust</td>
</tr>
<tr>
<td></td>
<td>Increased medical error</td>
<td>Decreased medical error</td>
</tr>
<tr>
<td>System</td>
<td>Increased financial costs</td>
<td>Decreased financial costs</td>
</tr>
<tr>
<td></td>
<td>Decreased staff/patient satisfaction</td>
<td>Improved staff/patient satisfaction</td>
</tr>
<tr>
<td></td>
<td>Decreased workflow efficiency</td>
<td>Increased workflow efficiency</td>
</tr>
<tr>
<td></td>
<td>Decreased ranking/reputation</td>
<td>Improved ranking/reputation</td>
</tr>
<tr>
<td></td>
<td>New liabilities</td>
<td>Better management of liabilities</td>
</tr>
</tbody>
</table>

**Information technology interventions** *(electronic data management, measurement, or communication)*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Patient Benefits</th>
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</thead>
<tbody>
<tr>
<td>Increased potential for loss of privacy</td>
<td>Better adherence to regimen</td>
</tr>
<tr>
<td>Decontextualization of disease</td>
<td>Better health outcomes</td>
</tr>
<tr>
<td>Depersonalization of care and communication</td>
<td>Improved continuity of care</td>
</tr>
<tr>
<td>Lower accessibility</td>
<td>Greater access to clinicians</td>
</tr>
<tr>
<td><em>(limited resources or tech capabilities)</em></td>
<td>More thorough understanding of disease condition</td>
</tr>
<tr>
<td></td>
<td>Better opportunity to report patient-level outcomes</td>
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</table>

<table>
<thead>
<tr>
<th>Clinician</th>
<th>Clinician Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater security-associated liabilities</td>
<td>Increased efficiency and optimization of care delivery</td>
</tr>
<tr>
<td>Increased frustration and inconvenience</td>
<td>Improved communication accuracy</td>
</tr>
<tr>
<td>Depersonalization of care</td>
<td>Improved communication speed</td>
</tr>
<tr>
<td>Increased dependence</td>
<td>Broadened medical skill set</td>
</tr>
<tr>
<td>Insufficient communication or understanding</td>
<td>Decreased medical error</td>
</tr>
<tr>
<td>Increased medical error</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>System</th>
<th>System Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived endorsement of experimental technology</td>
<td>Better staffing synergies</td>
</tr>
<tr>
<td>Unforeseen stresses to system resources</td>
<td>Fewer care redundancies</td>
</tr>
<tr>
<td>Incompatibility with existing information technologies</td>
<td>Faster rollout/uptake of system-wide improvements</td>
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<tr>
<td></td>
<td>Better data interoperability</td>
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<td></td>
<td>Increased monitoring capabilities</td>
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PCT: pragmatic clinical trial.

Expected vs Unexpected Harms/Benefits

E.g., Testing an electronic prescribing system

**Expected**
- High up front costs, but long-term efficiencies

**Unexpected (?)**
- Real-time patient-reported medication data can be fairly easily integrated
- Frequent system updates lead to overwhelming re-training needs

Not unique to PCTs, but *adaptive trial design* may make it more difficult to pinpoint *who* may encounter harms/benefits, and *what* the magnitude or likelihood of their occurrence will be
Challenges for IRBs and HRPPs

Very little guidance on assessing harms/benefits in general
  ◦ Must maximize benefit/minimize harm, and
  ◦ Ensure risks of research are reasonable in relation to anticipated benefits to subjects, if any, and the importance of the expected knowledge to be gained

Complex (multi-level) harm/benefit assessment common in PCTs
  ◦ PCTs often require examination of whether risks have been minimized and are acceptable in light of potential benefits for multiple different types of participants. Must also assess risks to others who may be affected indirectly by the PCT.
  ◦ Less clear what IRBs should do when multiple types of participants are involved in PCTs and there isn’t “convergence” in risk/benefits. E.g., If a PCT presents direct burdens/risks for clinicians, but also potential direct benefit for patients, how should an IRB weigh and compare such risks/benefits?

Coordination of review, monitoring and reporting is essential in multi-site PCTs
  ◦ Significant potential for site-level variations in risk/benefit assessments (which may not be attributable to variations in local laws/policies/norms)
Broader Implications (for Individuals)

Enhancing autonomy
• Clear articulation of potential burdens, harms, benefits and advantages of a PCT is critical if relevant stakeholders are to make informed decisions about whether to participate or partner

Identifying role-responsibilities
• Researchers, clinicians, health system administrators and patient-partners may all have capacity to help reduce identified risks and maximize benefits, in different ways and depending on roles
Broader Implications (for Institutions & Society)

Building policies and norms
• A clearer perspective on risks and benefits of PCTs can
  o inform ongoing federal regulatory and institutional policy development
  o inform discussions about whether stakeholders ought to be expected to conduct or participate in particular types of PCTs given nature/balance of risks and benefits
• Important considerations include
  o What do patients, clinicians, public expect and how have/will they be engaged?
  o What is the net risk of specific types of PCTs?
  o Who bears the burdens and stands to benefit from specific types of PCTs?
• Need more public conversation about the nature of PCTs and the various potential burdens and benefits

“The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research.” (Belmont Report)
Summary

A **broader framework** is proposed to clarify the types of potential harms and benefits for patients, clinicians, and healthcare systems who may be engaged in different kinds of PCT interventions.

The **balance of potential harms and benefits for each type of participant must be examined thoroughly**; and IRBs, sponsors, and investigators should ensure that the risks to each type of participant are reasonable in relation to the possible benefit.

A clearer perspective on risks and benefits of PCTs can inform individual and shared decision-making, ongoing regulatory developments, and stakeholder engagement efforts that seek to identify the ethical acceptability of particular types of tradeoffs.