Exploring the Ethical and Regulatory Issues in Pragmatic Clinical Trials: Introducing a Special Series in *Clinical Trials*

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Background Conditions

- High-quality medical evidence is needed by all stakeholders—patients, families, physicians, and policy-makers—to support decisions about health and healthcare.
- Technological advances and access to rich sources of patient data are enabling pragmatic research on wider scales.
- PCTs that use novel designs and leverage these data sources hold promise for improved care and outcomes.
Types of Trials

• Mechanistic
  • Intent to evaluate a biological or mechanistic hypothesis

• Pragmatic
  • Aimed at answering questions that inform decision-makers about health and healthcare
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.

NIH Health Care Systems Research Collaboratory

- Pragmatic trial design
- Electronic health record as core data collection instrument
- At least 2 integrated health systems collaborating
NIH Health Care Systems Research Collaboratory

Collaboratory Coordinating Center
LIRE – Lumbar Image Reporting and Epidemiology
SPOT – Suicide Prevention Outreach Trial
TSOS – Trauma Survivors Outcomes and Support
TiME – Time to Reduce Mortality in End-Stage Renal Disease (sites to be selected from units across all 50 states)

STOP CRC – Stop Colorectal Cancer in Priority Populations
PPACT – Collaborative Care for Chronic Pain
PROVEN – Pragmatic Trial of Video Education in Nursing Homes
ABATE – Active Bathing to Eliminate Infection
ICD-Pieces – Improving Chronic Disease Management with Pieces
Additional sites to be determined

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Why PCORI Was Created

Patients, their families, and clinicians face a wide range of complex and often confusing choices when it comes to addressing their health and healthcare concerns. They need trustworthy information to decide which option is best for them.

Unfortunately, traditional medical research, for all of the remarkable advances in care it produces, hasn’t been able to answer many of the questions that patients and their clinicians face daily. And even when reliable information does exist, it’s not always available to patients, or those who care for them, in ways they can understand or use most effectively.

PCORI was established to help address these challenges. Our job is to close the gaps in evidence needed to improve key health outcomes. To do this, we identify critical research questions, fund patient-centered comparative clinical effectiveness research, or CER, and disseminate the results in ways that the end-users of our work will find useful and valuable.
CDRNs and PPRNs

This map depicts the number of PCORI-funded Patient-Powered or Clinical Data Research Networks that have coverage in each state.

Modified, http://www.pcornet.org/

Broadening the Inquiry

• Formed multi-stakeholder writing groups to produce academic manuscripts addressing 11 ethical and regulatory issues related to PCTs
  • Iterative drafting and review process
  • Leadership by Drs. Jeremy Sugarman and Robert Califf
  • Operational support from Coordinating Center, including professional writing/editing support

• Goals of the manuscripts
  • Review the ethical and regulatory complexities related to PCTs
  • Provide guidance for future pragmatic clinical trials where possible
  • Describe issues that remain to be resolved
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Guest Editors: Jeremy Sugarman and Robert Califf

http://ctj.sagepub.com/content/early/recent
Development Process

• Initial discussions by teleconference

• Convened week-long face-to-face meeting
  • January 5-9, 2015
  • 78 attendees from 50 organizations
    • Ethicists, clinical trialists, IRB professionals, regulatory experts, patient representatives
    • Included participants from PCORnet and CTSAs
  • Each writing group met for 1.5 days
    • Included time for cross-group discussions

• Cycles of internal review followed by external peer review
Gatekeepers for pragmatic clinical trials

Danielle M Whicher¹, Jennifer E Miller²,³, Kelly M Dunham¹ and Steven Joffe⁴
Key Issues

• Various gatekeepers control access to resources necessary to implement a PCT.
  • *Gatekeepers*: research sponsors, regulatory agencies, payers, health system and other organizational leadership, research team leadership, human research protection programs, patient advocacy and community groups, clinicians
  • *Resources*: financial support, reimbursement for care, interventions, infrastructure (e.g., physical, informational, human), data, patients/participants

• Outlining best practices for gatekeepers can help guide ethical decision-making and foster transparency and trust in the research enterprise.
Findings & Conclusions

• Ethical framework for gatekeeping actions:
  1) Concern for the interests of individuals, groups, and communities affected by the gatekeepers’ decisions, including protection from harm and maximization of benefits
  2) Advancement of organizational mission and values
  3) Stewardship of financial, human, and other organizational resources

• There may be conflicting considerations; federal, state, and local regulations also apply.

• Gatekeepers can help enhance the legitimacy of their decisions by having transparent decision-making processes and engaging stakeholders to better understand those they represent.
Harmonization and streamlining of research oversight for pragmatic clinical trials

P Pearl O’Rourke¹, Judith Carrithers², Bray Patrick-Lake³, Todd W Rice⁴, Jeremy Corsmo⁵, Raffaella Hart⁶, Marc K Drezner⁷ and John D Lantos⁸
Key Issues

• The oversight of research involving human subjects is complex and “owned” by many. It requires both IRB review and non-IRB institutional review, also called the human research protection program.

• Researchers and policymakers have proposed using a single IRB of record, or central IRB (CIRB), as a solution to the complexity of multisite research. While this proposal has merit, the use of a CIRB for multisite research does not address the larger problem of coordinating the interdependence of non-IRB and IRB reviews across multiple sites.
Findings & Conclusions

• Several issues present opportunities for harmonization of research oversight—yet most of these are issues of institutional policy/review and not specific to IRB review (eg, HIPAA, COI, biosafety, FWA reporting).

• With coordinated effort and constructive progress, every aspect of research oversight could be streamlined. But without such effort, the overall process may in fact become more difficult. True harmonization and streamlining will require attention to each component of the review.
Oversight on the borderline: Quality improvement and pragmatic research

Jonathan A Finkelstein¹, Andrew L Brickman², Alexander Capron³, Daniel E Ford⁴, Adrijana Gombosev⁵, Sarah M Greene⁶, R Peter Iafrate⁷, Laura Kolaczkowski⁸, Sarah C Pallin⁹, Mark J Pletcher¹⁰, Karen L Staman¹¹, Miguel A Vazquez¹² and Jeremy Sugarman¹³
Key Issues

- Pragmatic research that compares interventions to improve the organization and delivery of health care may overlap with organizational Quality Improvement.
- For these activities, confusion often arises about what ethical oversight is, or should be, required.
- Appropriate ethics oversight differs according to the type of activity. The following categories may be useful to consider:
  - *Routine QI* activities aim to more reliably deliver intended care processes in health care organizations, and policies for QI oversight vary across health systems.
  - *QI research* seeks to produce generalizable knowledge using accepted scientifically valid inferences or qualitative research, and typically requires oversight by an IRB.
  - *Non-routine QI* activities are designed both to improve care locally and to contribute to knowledge more generally.
Findings & Conclusions

• Health care organizations should have systematic policies and processes for designating activities as routine QI, non-routine QI, or QI research, and determining what oversight each will receive.
• Health care organizations should have formal and explicit oversight processes for non-routine QI activities that may include input from institutional QI experts, health services researchers, administrators, clinicians, patient representatives, and those experienced in the ethics review of health care activities.
• QI research requires review by an IRB; for such review to be effective, IRBs should develop particular expertise in assessing QI research.
• Stakeholders should be included in the review of non-routine QI and QI-related research proposals.
Harms, benefits, and the nature of interventions in pragmatic clinical trials

Joseph Ali¹, Joseph E Andrews², Carol P Somkin³ and C Eglad Rabinovich⁴
Key Issues

• Pragmatic clinical trials 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 interventions compels a more nuanced assessment of net potential risk, understood as the balance of potential harms and benefits.

• A narrow focus on the harm (and benefits) that traditionally arise in explanatory clinical trials may be inadequate for pragmatic clinical trials.
Findings & Conclusions

• 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 ongoing regulatory developments and may also prompt stakeholder engagement efforts that seek to identify the ethical acceptability of particular types of tradeoffs (e.g., understanding when it may be acceptable for a PCT to introduce potential risks for clinicians, given a potential for benefit to patients and/or health systems).
Ethical responsibilities toward indirect and collateral participants in pragmatic clinical trials

Jaye Bea Smalley¹, Maria W Merritt², Sana M Al-Khatib³, Debbe McCall⁴, Karen L Staman⁵ and Carl Stepnowsky⁶
Key Issues

• Research subjects, or “direct participants,” have been explicitly defined in the context of cluster randomized trials as:
  • Individuals being directly intervened upon; and/or
  • Individuals from whom personal identifiable data are being collected for the purposes of the research.

• Because PCTs are embedded in routine care settings where exposure may be happenstance, there is an ethical responsibility to also identify and engage indirect and collateral participants in order to evaluate the impact of the trial on their rights and welfare.
Findings & Conclusions

• **Indirect participants**: Individuals who are (1) not identified as direct participants and (2) whose rights and welfare may be affected by the intervention through their routine exposure to the environment in which the intervention is being deployed.
  • Risks and benefits to which they are exposed should be weighed to ensure that their rights and welfare are protected accordingly; and communication strategies should be considered to help them make well-informed decisions.

• **Collateral Participants**: Patient groups and other stakeholder communities who may be otherwise affected by the occurrence and findings of the PCT.
  • Collateral participants could provide input on the design, planning and conduct of a PCT, and offer insights regarding the best way to communicate the trial’s results to their constituencies.

• Regardless of distinctions among direct, indirect, and collateral participants, there should be no distinction in our imperative to build trust and consider protections for all participants.
Considerations in the evaluation and determination of minimal risk in pragmatic clinical trials

John D Lantos¹, David Wendler², Edward Septimus³,⁴, Sarita Wahba⁵, Rosemary Madigan⁶ and Geraldine Bliss⁷
Key Issues

• Federal regulations require IRBs to classify riskiness.
• If an IRB determines that a clinical trial constitutes “minimal risk” as defined by these regulations, it may:
  • Allow a waiver or alteration of the informed consent process;
  • Permit the study to be performed in certain vulnerable populations;
  • Use an expedited review process.
• IRBs vary in their determinations of risk.
• Variation may hamper multicenter research.
Findings & Conclusions

• Causes of confusion and disagreement:
  • Different levels of risk-averseness among IRBs
  • Differences in classifying risk as “attributable” to the study
    • In studies of risky interventions, the risks of the interventions themselves should not be considered as risks of the research if those interventions would be used outside the research protocol.
    • Only risks that are “attributable” to the research protocol itself should be graded as minimal or greater than minimal risk
  • Studies are needed to understand how prospective participants think about the acceptable risk levels.
  • An optimal balance of transparency, accuracy, and empowerment requires clearly differentiating the risks and potential benefits of therapies from the risks and benefits of evaluating those therapies.
Use of altered informed consent in pragmatic clinical research

Ross E McKinney Jr¹, Laura M Beskow², Daniel E Ford³, John D Lantos⁴, Jonathan McCall², Bray Patrick-Lake⁵, Mark J Pletcher⁶, Brian Rath⁷, Hollie Schmidt⁸ and Kevin Weinfurt²,⁹
Key Issues

- Pragmatic clinical trials, including comparative-effectiveness studies and cluster-randomized trials, may present situations in which the need to obtain “traditional” written informed consent can present significant barriers to conducting needed research.

- Although federal regulations governing research allow for an altered consent process to be used in some cases, the same stringent interpretations of these standards are typically applied regardless of whether the process is being modified or waived altogether.

- Adopting a more flexible interpretation of existing rules can help enable pragmatic clinical research while still protecting research participants’ rights and interests.
Findings & Conclusions

• Excessively cautious interpretation of federal regulations governing altered consent poses an important but remediable barrier to conducting pragmatic research.

• Current regulations permit IRBs to make nuanced determinations about the degree of risk imposed by participation in research.

• Revising existing regulations could make this permission even clearer and afford additional interpretive guidance, but it remains important to communicate with patients about these issues and to work with them to find the best options.
The ethics and regulatory landscape of including vulnerable populations in pragmatic clinical trials

Mary Jane Welch¹, Rachel Lally², Jennifer E Miller³,⁴,⁵, Stephanie Pittman⁶, Lynda Brodsky⁷, Arthur L Caplan⁵, Gina Uhlenbrauck⁸, Darcy M Louzao⁸, James H Fischer⁹ and Benjamin Wilfond¹⁰,¹¹
Key Issues

• PCTs are conducted in real-world settings. The real world includes populations considered “vulnerable”:
  • Pregnant women, fetuses, neonates, children, prisoners, persons with physical handicaps or mental disabilities, and disadvantaged persons
  • Ethical and regulatory guidelines designed to protect vulnerable populations in traditional clinical trials may not be translatable, feasible, or ethical for PCTs.
• Approaches are needed that will provide appropriate protections while allowing equitable access to PCTs that can inform clinical decision-making in these populations.
Findings & Conclusions

• There is an ethical argument for inclusion.
  • Being part of a vulnerable population should not be an exclusion criterion in PCTs.
  • Consider how to manage ethical & regulatory requirements for vulnerable populations during study design.

• Two types of PCTs may include vulnerable populations:
  • PCTs where a vulnerable population is the focus of study
    • Address protections for that population
  • PCTs where vulnerable subjects may be part of a larger population
    • Generally should not have to identify vulnerable subjects for the purpose of creating differential burden or exclusion
    • Consider incremental risk of the study when assessing need for additional safeguards
    • Revisit the regulations to address above issues
The Food and Drug Administration and pragmatic clinical trials of marketed medical products

Monique L Anderson¹,², Joseph Griffin³, Sara F Goldkind⁴, Emily P Zeitler¹,², Liz Wing¹, Sana M Al-Khatib¹,² and Rachel E Sherman³
Key Issues

• FDA has broad jurisdiction over drugs and medical devices whether or not they are approved for marketing.

• Current FDA requirements for obtaining individual informed consent may impede or delay the conduct of PCTs intended to develop reliable evidence of comparative safety and effectiveness of approved medical products regulated by the FDA.

• Under current regulations, there are no described mechanisms to alter or waive informed consent to make it more practicable to conduct low-risk PCTs.
Findings & Conclusions

• We recommend that FDA adopt a risk-based approach to its jurisdiction for IND- and IDE-exempt trials, recognizing that formal implementation of a risk-based approach to informed consent will require a change to FDA regulations, which is typically a lengthy process.

• In the interim we propose that FDA provide guidance to facilitate the conduct of PCTs under existing regulations:
  • Guidance for acceptable innovative methods of obtaining and documenting consent (e.g., simple-to-use, interactive electronic options)
  • Guidance for alternatives to traditional informed consent for low-risk cluster-randomized trials where individual consent may not be feasible
  • Empirical data will be imperative in guiding the FDA to this new paradigm of research.
Privacy and confidentiality in pragmatic clinical trials

Deven McGraw¹, Sarah M Greene², Caroline S Miner³, Karen L Staman⁴, Mary Jane Welch⁵ and Alan Rubel⁶
Key Issues

• We must balance the need to improve the evidence base for health care through PCTs and to protect privacy: both are important and one should not be compromised for the sake of the other.

• This requires a re-examination of our ethical framework and innovative approaches for protecting autonomy and privacy in sharing information in the context of PCTs.
Findings & Conclusions

• Reaping benefits of digital health data and PCTs will require balancing—not trading off—the need to protect the privacy of individuals while allowing health data to be leveraged for the common good.

• Modified approaches to “consent” and engagement in minimal risk interventions may prove effective at honoring individual’s privacy interests in their data. These include:
  • Greater stakeholder input into research and research policies
  • The ability to opt out (instead of opting in as with traditional informed consent)
  • Broad notification through posters, emails, brochures, social media or web portals
  • Individual notification to increase transparency and inform patients
  • Community consultation (people agree to be governed by the decisions of community representatives with respect to research uses)
Data monitoring committees for pragmatic clinical trials

Susan S Ellenberg¹, Richard Culbertson², Daniel L Gillen³, Steven Goodman⁴, Suzanne Schrandt⁵ and Maryan Zirkle⁵
Key Issues

• Certain characteristics of PCTs may have implications for data monitoring committees (DMCs) to consider.
  • Examining the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) can help identify potential areas for attention.

• Additional questions include:
  • Which PCTS will require an independent DMC?
  • What are the analytical considerations?
  • Is there special expertise needed on DMCs for PCTs?
Findings & Conclusions

• Many PCTs will warrant an independent DMC for monitoring the quality of trial conduct and evaluation of interim data by treatment arm.

• Special considerations for DMCs monitoring PCTs include:
  • Being comfortable monitoring subjective outcomes
  • Paying greater attention to site-specific data
  • Addressing how protocol adherence will be monitored and acted upon
  • Examining ineligibility rates by treatment arm to prevent bias
  • Monitoring intracluster correlation coefficient over time (cluster designs)

• Questions remain regarding criteria for consideration of early termination for effectiveness or futility.

• In addition to usual DMC expertise, consider role of a biomedical informatician and patient representative.
Next Steps

• Derivative products
• Dedicated Grand Rounds sessions
Concluding Comments

• Addressing the ethical and regulatory challenges of PCTs is surprisingly complex
• Additional experience, data and deliberation should help inform the development of appropriate policies and procedures
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- Informed consent
- Defining minimal risk
- Data monitoring
- Research/quality improvement distinction
- Vulnerable subjects
- IRB harmonization
- Identifying direct and indirect subjects
- Gatekeepers
- FDA-regulated products
- Nature of intervention
- Privacy

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