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Harms, benefits, and the nature of interventions in pragmatic clinical trials

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Abstract

To produce evidence capable of informing healthcare decision making at all critical levels, pragmatic clinical trials (PCTs) are diverse both in terms of the type of intervention (medical, behavioral, and/or technological) and the target of intervention (patients, clinicians, and/or healthcare system processes). Patients and clinicians may be called on to participate as designers, investigators, intermediaries, or subjects of PCTs. Other members of the healthcare team, as well as the healthcare system itself, also may be affected directly or indirectly before, during, or after study implementation. This diversity in the types and targets of PCT interventions has brought into focus the need to consider whether existing ethics and regulatory principles, policies, and procedures are appropriate for PCTs. Specifically, further examination is needed to identify how the types and targets of PCT interventions may influence the assessment of net potential risk, understood as the balance of potential harms and benefits. In this paper, we build on scholarship seeking to align ethics and regulatory requirements with potential research risks and propose an approach to the assessment of net risks that is sensitive to the diverse nature of PCT interventions. We clarify the potential harms, burdens, benefits, and advantages of common types of PCT interventions and discuss implications for patients, clinicians, and healthcare systems.

Keywords

Research ethics; bioethics; harms; benefits; pragmatic clinical trials

Introduction

Pragmatic clinical trials (PCTs) often employ approaches to identify the impact of healthcare and systems interventions that have the potential to increase the quality, improve the experience, or reduce the cost of care.[1,2] To produce evidence capable of informing

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healthcare decision making, PCTs are diverse both in terms of the type of intervention (medical, behavioral, and/or technological) and the target of intervention (patients, clinicians, and/or healthcare system processes).[3] Multiple study designs are used to answer pragmatic research questions, with each design requiring different types and degrees of engagement with individuals in order to successfully test interventions and obtain necessary data.[4] Patients and clinicians may be called on to participate as designers, investigators, intermediaries, or subjects of PCTs. Other members of the healthcare team, as well as the healthcare system itself, also may be affected directly or indirectly before, during, or after study implementation.

This diversity in the types and targets of PCT interventions has brought into focus the need to consider whether existing ethics and regulatory principles, policies, and procedures—designed with traditional biomedical and behavioral research in mind—are appropriate for PCTs.[5,6] Recent scholarship has highlighted some of the ethics and regulatory issues raised by PCTs and comparative effectiveness research (CER);[7–19] however, there remains a need to examine how differences in the types and targets of PCT interventions can influence the assessment of potential net research risk, understood as the balance of potential harms and benefits.[20,21]

In this paper, we build on scholarship seeking better alignment of ethics and regulatory oversight with potential research risks.[22] While current ethics and regulatory frameworks, rooted in the protection of patient-subjects, advance an important perspective on potential harms and benefits, we propose a broader framework that also explicitly acknowledges potential harms and benefits that may accrue to other individuals and entities participating in PCTs, namely clinicians and healthcare systems. We clarify the types of potential harms, burdens, benefits, and advantages of common categories of PCT interventions for patients, clinicians, and healthcare systems. Theoretical and practical implications of this analysis for related ethics and regulatory constructs are also discussed.

Traditional ethics and regulatory focus: Potential harms and benefits to human subjects

Ethics and regulatory standards relating to the responsibilities of clinical researchers and the protection of research participants are well established in the United States. From a regulatory perspective, the U.S. Department of Health and Human Services (HHS) and the U.S. Food and Drug Administration (FDA) have enumerated basic investigator responsibilities.[23–28] Additional, nonbinding federal policy recommendations addressing investigators' responsibilities have also recently been proposed by the Presidential Commission for the Study of Bioethical Issues and the Secretary's Advisory Committee on Human Research Protections (SACHRP).[29] Regulatory requirements primarily aimed at safeguarding research participants are also detailed under HHS regulations (known as the Common Rule)[28] and FDA regulations[27,30] and include provisions relating to institutional review board (IRB) review, informed consent, privacy and confidentiality, proper selection of research subjects, minimizing risks and ensuring they are reasonable in relation to anticipated benefits, informing subjects about significant new findings, respecting the right to withdraw from research, protecting vulnerable subjects, and other substantive or

procedural elements that seek to protect research participants. Considerable official guidance pertaining to these protections has been issued by the U.S. Office for Human Research Protections (OHRP), and nonbinding policy recommendations have been proposed by SACHRP.[31,32]

With some exceptions (e.g., added protections for pregnant women, human fetuses and neonates, prisoners, or children involved in research),[33–37] health research regulations typically do not define norms and obligations in relation to the individual capabilities or characteristics of human subjects. Individuals who possess greater or lesser knowledge, skills, or acumen are not, as a rule, given special status. For example, a healthcare professional who is asked to share, for research purposes, data about her referral preferences and practices is afforded the same regulatory protections as any other member of society. Instead, regulatory jurisdiction—the limits of which are codified in exclusions, exceptions, and exemptions[38,39]—has been based primarily on determinations of whether particular activities constitute HHS-supported/conducted or FDA-regulated research involving human subjects. It is noteworthy that HHS and FDA definitions of "research" ("clinical investigation" under FDA regulation) and "human subject" differ.[40–42]

From a scholarly perspective, the potential and actual risk of harm to patient-subjects enrolling in "traditional" explanatory clinical research (i.e., research designed to understand biological mechanisms and processes) has been heavily reviewed and discussed.[43,44] The focus on protecting patient-subjects from potential harm is primarily rooted in concerns over the introduction of new and sometimes unknown risks associated with experimental medical interventions, and the possibility that researchers may be divided in their loyalty to individual research participants when driven significantly by the desire to produce generalizable knowledge for the benefit of others.[45,46] Well-known historical examples of unethical research, largely involving vulnerable individuals who were exposed to significant and unjustifiable harms in pursuit of scientific goals, underscored the drive to maintain strong protective oversight measures.[47–49] Ethics and regulatory requirements established in the wake of these events seek to ensure that the risks of research are minimized and justified, and that the rights and interests of individual research participants are prioritized and respected. As a result, in the context of explanatory clinical trials where one can typically draw relatively clear boundaries between the types and targets of interventions, patient-subjects have been the central focus of concern, with other research stakeholders implicitly considered marginally and primarily with respect to how their role affects, or is affected by, patient-subjects.

With respect to pragmatic clinical trials, which seek to generate actionable evidence to inform common clinical practices,[1] approaches used to analyze net risk in explanatory clinical trials may yield an incomplete assessment of the potential impact of PCTs on the multiple stakeholders who bear the burdens and stand to benefit from research.[50] While it is likely unwarranted to suggest that PCTs are deserving of broad alternative ethics and regulatory consideration when assessing net risk, a more sensitive itemization of the potential harms, burdens, benefits, and advantages of various PCT interventions can inform future policy development and facilitate more efficient and effective ethics review.

A broader look at potential harms and benefits for interventional pragmatic clinical trials

National and local efforts to advance evidence-based medicine, the clinical translation of science, and the development of a learning healthcare system have led to an increase in clinical research networks and pragmatic clinical trials to improve the quality and value of healthcare.[51–53] Large-scale national efforts, including the NIH Health Care Systems Research Collaboratory[54] and the National Patient-Centered Clinical Research Network (PCORnet),[55] have emerged seeking to better understand and coordinate pragmatic clinical research systems to advance effective and efficient PCTs and patient-centered CER.

As noted above, the constituency served by such PCTs is broader than that served by explanatory trials.[56] Patients, clinicians, and healthcare systems may all be targeted directly in PCTs, depending on the nature of the intervention. To illustrate, PCTs may focus on changes to health outcomes that result from medical and behavioral interventions targeting *patients*, such as comparing the effects of two or more commonly used drugs, diet or exercise regimens, or medical advice compliance strategies. PCTs may also focus more directly on *clinician practices*, such as determining whether introducing readily available epidemiological evidence into lumbar spine imaging reports has an impact on physician diagnostic and therapeutic recommendations,[57] or whether automatically notifying clinicians about alternative generic drug options changes prescription practices. Countless other pragmatic studies could be conducted with the goal of identifying the most effective approaches for improving health communication between clinicians and patients or others. *Healthcare systems* may also be the primary target of PCT interventions; for example, comparing workflow models to determine the most efficient staffing arrangement to decrease medical expenses while meeting patient expectations and maintaining satisfactory health outcomes. Also, as with other types of research, society more broadly can be an important stakeholder in terms of the potential treatment benefits from increased knowledge generated by PCTs and resulting health policy decisions.

These illustrations lead to a further observation that PCTs not only target multiple different kinds of individuals and entities but also fall within three broad interventional categories: medical, behavioral, and information technological. *Medical interventions* can be understood as any activity that is directly related to the treatment of patients; for example, PCTs examining the use of different drugs, devices, or procedures. *Behavioral interventions* include efforts to alter habits, compliance with clinical instructions, and the management of beliefs or attitudes that could affect clinical care or psychological and physical well-being. The integration of *information technology interventions* in PCTs allows for greater understanding of the interface between health management and electronic data coordination, measurement, and communication.

While these distinctions can be important to ethics and regulatory analyses, perhaps more critical to acknowledge is that multiple types and targets of PCT interventions often overlap within a single study. A PCT introducing new electronic decision support tools for primary care physicians to reduce the unnecessary prescription of antibiotics can be viewed as a medical, behavioral, and technological intervention that will have an impact on not only

clinicians but also healthcare system processes and the health of current and future patients.[58] Similarly, a smoking cessation behavioral intervention could be undertaken using various technological aids, such as devices designed to allow participants to taper-off cigarette use through informational alerts signaling when they can use a nicotine replacement. Such a study would assess the medically relevant behavioral outcomes resulting from the use of the new technology. Under these types of cross-cutting studies, it will be necessary for careful evaluation of potential harms/burdens and benefits/advantages that may accrue to *all* direct and indirect interventional targets.[59]

The variability and overlap in the types and targets of interventions compels a more nuanced and differentiated look at potential harms and benefits of PCTs. The variety of interventions and stakeholders in PCTs increases the potential for far-reaching benefits, advantages, harms, and burdens. Table 1 provides a framework and examples of potential harms or burdens and possible benefits to members of the three target groups who may be the subject of medical, behavioral, and technological PCT interventions. As illustrated in the table, medical and behavioral interventions share many of the same potential burdens and benefits such as increased or decreased privacy, physical health, or psychological well-being at the patient level; increased or decreased time commitment, confidence, reputation, or autonomy at the clinician level; and increased or decreased cost, staff/patient satisfaction, workflow efficiency, ranking/reputation, and liability at the healthcare system level. When medical and behavioral interventions incorporate significant information technology components, additional important considerations arise including whether the technology is likely to materially change (positively or negatively) the way in which healthcare is personalized, accessed, delivered, combined, communicated, or measured (Table 1).

These and other benefits and burdens can be expected or unexpected. For example, at a systems-level, some short-term inconveniences associated with testing a new electronic prescribing system may be expected and accepted based on anticipated long-term advantages. But unexpected inefficiencies, such as those associated with frequent system updates necessitating significant retraining, or additional efficiencies, such as those associated with the integration of real-time patient-reported medication data, also may emerge. While some PCTs may be more predictable in their anticipated burdens and benefits, others are intentionally adaptive—making it even more difficult to anticipate precisely who will be affected and how. Further, given the traditional focus on potential harms and benefits to patient-subjects in clinical research, it can be particularly easy to overlook or minimize the potential harms and benefits of PCT interventions for clinicians and healthcare systems.

As a practical matter, therefore, variation in the design and target of PCT interventions poses challenges for ethics review by IRBs. Each protocol can present unique interpretive issues resulting in research delays, especially for multisite research where inconsistencies across IRBs require reconciliation.[60] PCTs may require a more complex calculation to arrive at a decision on whether to approve a study and what risk minimization measures must be implemented, if any. For example, a cluster-randomized PCT of contagious disease treatment protocols could introduce potential risks for clinicians, such as increased risk of exposure to infectious diseases, or disparagement of a clinician or team for not supporting

the intervention. At the same time, the PCT could offer a chance to improve patient outcomes and decrease exposure rates by refining the treatment approach and reducing the spread to clinicians and others. In such a study, it can be difficult to weigh and compare potential risks and benefits to the multiple affected parties. These multidimensional risk assessments are not unique to PCTs, but are common to pragmatic research questions. Given that such risk assessments can lead to important determinations about whether, to what extent, and from whom informed consent or authorization is required, additional guidance seems warranted to clarify how the types and targets of interventions in PCTs ought to inform the analysis of net risk.

IRBs have traditionally played an important role in evaluating the net risks of PCTs. The Common Rule requires IRBs to ensure that:

> [R]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.[61]

In order to adequately assess the net risk of complex PCTs involving multiple types of interventions and target groups, the ratio of potential harms and benefits for each type of participant must be examined thoroughly, and IRBs, sponsors, and investigators must ensure that the risks to each participant are reasonable in relation to the possible benefit. Investigators and institutions should also evaluate the risks to others who may be affected by the clinical trial even though they are not directly participating; for example, studies involving drugs with teratogenic effects or those that could expose others to live virus vaccination risks.[62] While IRBs, by regulation, are required not to consider the possible long-range effects of applying knowledge gained in research, it is important that they systematically assess the degree and possible impact of risks, and indeed potential benefits, posed by PCTs to any participant or other potentially affected person. During the course of research, continuous monitoring and reporting, when appropriate, of “unanticipated problems involving risks to subjects or others,” as required under HHS and FDA regulations, is equally critical.[62–65]

IRBs have become familiar with these review and reporting requirements; however, with large multisite PCTs that potentially involve several IRBs, the coordination of review and reporting processes often requires prioritization if efficiency-related goals are to be realized.[60] Challenges associated with multisite review and reporting have been described previously,[66] and various models for streamlining coordination across institutions are being considered, with single or lead IRB review approaches currently being proposed by entities such as the NIH[67] and PCORI for some studies.[68] It is noteworthy that SACHRP recommendations to OHRP and FDA, while generally supportive of “single IRB review models” for research in which multiple sites follow a common study protocol, also

emphasize the need for "material local variations [to] continue to be recognized and accommodated in study design and conduct."[69] Existing and emerging models for broader coordination of oversight *within* institutions may also help to inform network-level coordination. For example, institutional systems for coordination across IRB, research risk, quality improvement, or biosafety committees could be modeled at a more central level or leveraged to reserve local review for particular oversight needs.

Additional implications for stakeholder engagement and responsibilities

Moving beyond the implications for IRBs and regulatory requirements, a broader perspective on the potential risks and benefits of PCTs can inform stakeholder and public engagement efforts to identify the value of PCTs, to discuss the ethical acceptability of particular types of tradeoffs, and to build trust in healthcare systems research. Consistent with existing stakeholder engagement recommendations and frameworks,[70,71] we believe wider community discussions, structured forums, and deliberative sessions are necessary to clarify the nature of different PCT interventions and the range of associated potential benefits and burdens. This is important not only for "buy-in," but also to support institutional and national policy development and policy evaluation to ensure regulatory interpretations align with societal expectations and values. Further, because PCTs often seek to improve clinical practices that may be deeply entrenched at multiple levels, engagement and partnership within healthcare systems is essential, both ethically and practically, to identify and address relevant values and ensure effective implementation both during and after pragmatic trials.[4,72,73] These engagement practices are increasingly becoming a part of nationally coordinated pragmatic research efforts, such as PCORnet, capable of aligning clinical, public health, and healthcare systems research goals.

Finally, an open and comprehensive accounting of the potential harms, burdens, benefits, and advantages of PCTs can also inform ongoing discussions around reasons and obligations to participate in PCTs. Some scholars have explored whether patients and members of society have a *prima facie* moral duty (or social obligation) to participate in research,[18,74–78] but few have discussed this duty in relation to either clinicians[79] or healthcare systems.[18,80] The rationale for supporting a duty to participate has been based on various ethics principles including beneficence, contributing to the common good, and justice. However, the obligation to participate in research is not typically considered to be absolute, and just as considerations of potential harms and benefits of research play a central role in determining consent, authorization, and notice requirements, we believe these considerations should also play a central role in determining whether broader duty-based obligations to participate in PCTs exist. What can be expected of a patient, clinician, or healthcare system in the name of research (e.g., take medication at a particular time of day, receive automated reminders, furnish a particular kind of hand sanitizer) depends on the net risk of the particular intervention and who bears the burdens and benefits of participation. A clearer articulation of how PCTs can affect multiple levels of stakeholders (both positively and negatively) allows for more informed debate around whether implied authorization may exist for particular stakeholders under certain types of studies. Examination of the impact of the intervention on the clinician-patient relationship and on patient expectations is also critical to any analysis of the obligation to participate in research.

Conclusion

Thorough assessment of potential harms and benefits of PCTs requires the application of a framework that is sensitive to the multiple and overlapping types and targets of PCT interventions. IRBs, clinical investigators, sponsors, and others often struggle to evaluate net risk to patients, clinicians, and healthcare systems engaged in PCTs. The framework discussed in this paper may inform a more systematic and comprehensive approach to risk assessment and support broader efforts to navigate the range of ethics and regulatory challenges and obligations emerging in PCTs. Sustained involvement of diverse PCT stakeholders in these efforts can help ensure that ethics and regulatory policies and practices are relevant, sustainable, and supportive of patient, clinician, healthcare system, and societal priorities.

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Table 1

Examples of potential harms/burdens and benefits/advantages of PCTs by type and target of intervention

Target of Intervention or Interaction	Potential Harms/Burdens	Potential Benefits/Advantages
Medical and Behavioral Interventions (drug, device, or procedure; educational, attitudinal, or adherence)		
Patient	• Inconvenience of regimen • Loss of privacy • Poorer health outcomes • Psychosocial discomfort	• Commitment to regimen • More time with care teams • Better health outcomes • Fulfillment of altruistic desires
Clinician	• Increased time commitment • Additional professional oversight • Decreased confidence/reputation • Decreased clinical autonomy • Increased medical error	• Advancing the field • Improved care delivery • Increased confidence/reputation • Increased patient trust • Decreased medical error
System	• Increased financial costs • Decreased staff/patient satisfaction • Decreased workflow efficiency • Decreased ranking/reputation • New liabilities	• Decreased financial costs • Improved staff/patient satisfaction • Increased workflow efficiency • Improved ranking/reputation • Better management of liabilities
Information Technology Interventions (electronic data management, measurement, or communication)		
Patient	• Increased potential for loss of privacy • Decontextualization of disease • Depersonalization of care and communication • Lower accessibility (limited resources or tech capabilities)	• Better adherence to regimen • Better health outcomes • Improved continuity of care • Greater access to clinicians • More thorough understanding of disease condition • Better opportunity to report patient-level outcomes
Clinician	• Greater security-associated liabilities • Increased frustration and inconvenience • Depersonalization of care • Increased dependence • Insufficient communication or understanding • Increased medical error	• Increased efficiency and optimization of care delivery • Improved communication accuracy • Improved communication speed • Broadened medical skill set • Decreased medical error
System	• Perceived endorsement of experimental technology • Unforeseen stresses to system resources • Incompatibility with existing information technologies	• Better staffing synergies • Fewer care redundancies • Faster rollout/uptake of system-wide improvements • Better data interoperability • Increased monitoring capabilities