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# Ethical responsibilities toward indirect and collateral participants in pragmatic clinical trials

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## Abstract

Pragmatic Clinical Trials (PCTs) are designed to inform decision makers about the benefits, burdens, and risks of health interventions in real-world settings. PCTs often use for research purposes data collected in the course of clinical practice. The distinctive features of PCTs demand fresh thinking about what is required to act properly toward people affected by their conduct, in ways that go beyond ensuring the protection of rights and welfare for “human research subjects” under conventional research ethics regulations. To stimulate such work, we propose to distinguish among categories of research participants in PCTs as follows: Direct participants: (1) Individuals being directly intervened upon and/or (2) individuals from whom personal identifiable data are being collected for the purposes of the PCT. 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. Collateral Participants: Patient groups and other stakeholder communities who may be otherwise affected by the occurrence and findings of the PCT. We illustrate these distinctions with case examples and discuss the distinctive responsibilities of researchers and PCT leadership toward each type of participant. We suggest that PCT investigators, Institutional Review Boards (IRBs), health systems leaders, and others engaged in the research enterprise work together to identify these participants. For indirect participants, 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.

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**Conflict of Interest**

Jaye Bea Smalley is an employee of the Patient-Centered Outcomes Research Institute.

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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.

**Keywords**

Human Research Subject; Indirect Participant; Direct Participant; Collateral Participant; Pragmatic Clinical Trials; Ethics; Cluster Randomized Trials; Research Ethics; Patient Engagement; Stakeholder Engagement

## Introduction

In clinical practice, some patients don't receive the best care possible, either because high-quality evidence is lacking or because evidence-based practices are not routinely implemented.[1] The use of electronic medical records and personal health records presents a significant opportunity to embed research in the continuum of care in order to learn what works in real-world settings and to understand the most effective dissemination and implementation approaches. Whereas traditional clinical trials typically evaluate health interventions in tightly restricted study populations using protocols not situated in the continuum of care under real-world conditions, Pragmatic Clinical Trials (PCTs) are designed to inform decision makers about the benefits, burdens, and risks of health interventions already used in clinical practice. Accordingly, PCTs often use data from clinical practice for research purposes. This feature of PCTs raises concerns about identifying research subjects and other participants.[2]

The issue of identifying research subjects has been outlined in the context of traditional research and in some cluster randomized trials (CRTs) where the unit of randomization is the facility, community, or a group of people.[2,3] Because PCTs typically occur in complex healthcare systems, additional questions arise. Many people are involved in various roles and with various interests at stake.[4] In this paper, we propose to distinguish among three categories of participants who deserve ethical consideration in the context of PCTs. Because much work has already been done on identifying and protecting direct participants, we will focus primarily on the need to identify, protect, and engage indirect and collateral participants. We will consider the ethical implications of involving them, and discuss communication and dissemination strategies for informing and engaging them. We hope to advance new considerations that expand the concept of research participation, encourage reflection on the provision of appropriate protections, and promote public trust and understanding for PCTs.

## Who Participates in Pragmatic Clinical Trials?

Ethically responsible implementation of PCTs requires a systematic approach to identifying: (1) people who may be exposed to associated risks or who, in some cases, may be afforded the prospect of benefit; and (2) parties with whom the leadership of a given PCT ought to collaborate and communicate routinely in planning and executing the trial. A helpful starting point is the current regulatory definition of a "human research subject" under the U.S. 45 CFR 46.102(f), also known as the Common Rule[3] (Table 1). For a given PCT protocol, a

central task of prospective ethical review will be to determine who is a human research subject in virtue of satisfying either categories (1) or (2) of the Common Rule definition (Table 1). Depending on the particulars of PCT protocol design, this task may often be less straightforward than it would be for a traditional clinical trial.[5]

A case in point is the question of how broadly to construe exposures to environmental manipulation in identifying human research subjects. The Common Rule defines a human research subject as:

> "a living individual about whom an investigator (whether professional or student) conducting research obtains
>
> **(1)** Data through intervention or interaction with the individual, or
>
> **(2)** Identifiable private information.[3]"

The Common Rule defines "interaction" as including "both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject *or the subject's environment* that are performed for research purposes" (emphasis added). The Common Rule does not further elucidate possible types of environmental manipulations. Yet additional guidance is needed on this point because PCTs as well as other forms of health research can expose people more or less immediately, yet still intentionally, to environmental manipulations. For instance, a trial might be designed to study how increased room temperature affects patients' performance on certain standardized tests (as in, for instance, physical therapy protocols used to support recovery from injuries): those patients would be immediately exposed to the environmental manipulation. By contrast, a trial might be designed to study the effect of an educational intervention to promote evidence-based practice among hospital staff, with the expectation that some of their patients' environments will be altered in certain ways, so far as changes in the behavior of these staff are attributable to the intervention. Here, staff's exposure to the environmental manipulation would be immediate, and patients' (potential) intended exposure would be mediated through that of the staff. Recent recommendations from the Secretary's Advisory Committee on Human Research Protections (SACHRP) of the U.S. Department of Health and Human Services[5] holds (as do Mann and Reyes[6]) that the Common Rule definition of "human research subjects" should encompass people who undergo both types of exposure. This interpretation is arguably controversial. With respect to environmental manipulation, the Ottawa Statement, a consensus document on the ethical design and conduct of cluster randomized trials (CRTs)—a common but not universal type of trial design for some PCTs—explicitly restricts the identification of CRT "research participants" only to people who undergo immediate exposure ("direct target[s]");[7] (See Table 1, Ottawa Statement, point 2). McRae, et al., support this restrictive definition.[2] A recently published commentary by Van der Graaf and colleagues, however, recommends that the Ottawa statement be refined to relax this restriction. [8] (For further discussion of this topic, see *Harms, Benefits, and the Nature of Interventions in Pragmatic Clinical Trials*[9] in this series of papers.)

A further point critical to the ethically responsible conduct of PCTs is not addressed on either side of the debate about whether people who have only a mediated exposure to environmental manipulations (and who satisfy no other criterion listed in Table 1) should be

identified as human research subjects (or, in the parlance of the Ottawa Statement, CRT "research participants"). That debate focuses on people who are intentionally targeted, whether through immediate or mediated exposure, by the environmental manipulations under study. But in addition, environmental manipulations introduced by PCTs may create systematic risk and benefit exposures for people whom they do *not* intentionally target. By definition, PCTs are embedded in settings of routine clinical practice. The introduction of a PCT into a given clinical setting, such as a hospital unit or a whole clinical facility, may correspondingly alter the environment or experience of patients, clinicians, other employees, and visitors who are not themselves targets of trial-related interventions, interactions, or data collection.

Furthermore, the purpose of PCTs is to generate evidence that matters to patients, clinicians, and other constituencies served by the healthcare system, specifically by ensuring that enrollment is representative of the patients, populations, and clinical settings that are relevant to the decisions of interest. (See the introduction to this series of papers: *Exploring the ethical and regulatory issues in pragmatic clinical trials*.[10]) Relevant patient advocacy groups and healthcare professionals' associations may have good reason to want systematic engagement with PCT leadership in real time as the trial is designed, planned, and conducted, and as findings are disseminated. Accordingly, whereas the ethically responsible conduct of traditional clinical trials already requires investigators to work closely with relevant institutional authorities like the directors of clinics where patients are recruited, PCTs may introduce further distinctive responsibilities on the part of trial leadership to engage proactively with other parties, too. For example, the Patient-Centered Outcomes Research Institute (PCORI) requires patient and stakeholder engagement in a majority of the research initiatives and projects that it funds.[11] As more patients and stakeholders begin to take active roles in the research continuum, it is important to distinguish those who are participating as collaborators from those who are considered participants in the research strictly speaking.

These distinctive features of PCTs demand fresh thinking about what is required to act properly toward people affected, in ways that go beyond ensuring the protection of rights and welfare for "human research subjects" under the Common Rule (or CRT "research participants" under the Ottawa Statement). To stimulate and support the fresh thinking that's needed, we introduce a set of distinctions among *direct*, *indirect*, and *collateral* research participants in PCTs (Table 2). To illustrate the proposed distinctions and their import, we will use real-world cases.

Our definition of *direct* participants in PCTs corresponds to the Common Rule definition of a human research subject (Table 1) and accepts the broad construal of environmental manipulation endorsed by SACHRP recommendations[5] and by Mann and Reyes.[6]"

Those who prefer the narrow construal (as proposed for CRTs in the Ottawa Statement[7] and by McRae, et al.[2]) might consider the possibility of classifying as *indirect* participants in PCTs people who undergo mediated but intentional exposure to PCT-imposed environmental manipulation.

For PCTs, direct participants by our definition are typically patients and the clinicians administering the interventions under study in the units or healthcare facilities intentionally targeted by the PCT. For purposes of ethical and regulatory oversight, they should be regarded as "human research subjects" under the Common Rule definition. Our category of *indirect* participants is meant primarily to support exploration of a distinctive territory of ethical commitments on the part of researchers, health system leaders, clinical staff, and other gatekeepers who have prior, institutionally defined ethical responsibility to protect the rights and well-being of certain constituencies who may also be exposed to PCTs.

What do these distinctions imply for the ethical review and oversight of PCTs? The accompanying paper by Ali and colleagues considers appropriate human subjects protections for those whom we call *direct* participants in PCTs.(See *Harms, Benefits, and the Nature of Interventions in Pragmatic Clinical Trials*.[9]) Accordingly, we do not further discuss *direct* participants in this paper. In the following discussions of *indirect* and *collateral* participants, respectively, we clarify the ways in which it makes sense to think of them as truly 'participating' in a PCT, even though they are not participating as human research subjects, and we explore what these further forms of participation mean for the ethical responsibilities of PCT investigators and other PCT leadership.

## Indirect Participants

In PCTs, the rights and welfare of people other than direct participants may be affected by the intervention under study through their routine exposure to the environment in which the intervention is being deployed. We propose to define these people as indirect participants (Table 2). Whereas direct participants' rights and welfare must be considered and protected by the Institutional Review Board (IRB) of record,[5] research regulations do not determine who is responsible for protecting the rights and welfare of indirect participants in PCTs. We suggest that PCT investigators, IRBs, health systems leaders, and others engaged in the research enterprise should work together to identify these participants, delineate the risks to which they are exposed by the conduct of the PCT, and ensure that their rights and welfare are protected accordingly. The operative ethical obligations are primarily those that are institutionally defined for the leadership of participating health systems and clinical facilities, but these leaders may need the assistance of PCT investigators and IRBs to understand fully how they should act on their obligations.

We are not suggesting that traditional informed consent be routinely required for indirect participants. While individuals are broadly recognized to have a liberty right not to be experimented on without their consent, indirect participants are not in any sense the people who are being experimented on in PCTs. Their exposure is due to happenstance, not to study design. Nonetheless, PCT-imposed exposures have the potential to infringe unduly on the autonomy of indirect participants in ways other than by their being experimented on. To avoid undue infringement on the autonomy of indirect participants, possible forms of protection include broad notification, the ability to opt out of entering the study environment, and other strategies that would enable indirect participants to make well-informed decisions.

In particular, novel interventions introduced by PCTs may infringe on existing agreements and/or contracts that are in place to protect the rights and welfare of clinicians, hospital staff, and regular visitors. In order to maintain the institution's compliance with these prior arrangements, relevant information about PCTs should be adequately communicated and disseminated to indirect participants, and to the institutional officials who already bear responsibility, *ex officio*, for protecting their rights and welfare with respect to routine activities in the environment where the PCT will occur.

## Direct participants vs. indirect participants: three illustrative examples

The planning phase for the **Pr**agmatic **T**rial **o**f **V**ideo **E**ducation in **N**ursing Homes (PROVEN) trial[12] is underway to evaluate the effectiveness of advance care planning (ACP) videos in reducing hospitalizations, hospice election, and other burdensome transitions among seriously cognitively and functionally impaired nursing home residents with multiple co-morbidities served by two large healthcare systems. The control facilities will use their usual ACP practices, and the treatment facilities will show one of five videos to all newly admitted and long-stay residents of participating facilities. The video topics include goals of care, advanced dementia, hospitalization, hospice, and a general ACP educational video. In PROVEN, the unit of randomization is the nursing home, and the outcomes are obtained from patient level data using existing data sources such as the electronic medical record (EMR) and Medicare Vital Status data. The research team obtained a waiver of individual consent as the research intervention was deemed to meet criteria for minimal risk and the study could not be practicably carried out without the waiver. The research team is using a train-the-trainer approach, and will train the designated contact for each system, who will then deploy the training for the staff who show the videos. In PROVEN, the direct participants are: (1) the patients in the intervention units of the facilities participating in the trial; and (2) the nursing home staff who have received training on showing the video. The Brown University IRB has determined that these staff are not serving as researchers; we consider them to be direct participants because they are directly intervened upon. The indirect participants are the families and/or caregivers of patients being cared for in these units where the intervention is being deployed and all other nursing home staff who may routinely work in the participating units. All families have the opportunity to be shown the video and have the right to decline watching the video, as do patients. Although families of the patients may be exposed to the intervention, they are not the targets of study and there is no data collection on these family members. Their rights and welfare may nonetheless be affected by their exposure to the intervention under study. For instance, the video may alter the workflow of staff in the facilities and may affect the level of care that they typically provide, and families who don't view the video with their loved ones may still benefit from knowing about the use of these videos to better inform discussions with loved ones around ACP.

The **L**umbar **I**maging with **R**eporting of **E**pidemiology (LIRE) trial[13] is underway to reduce overtreatment of back pain patients. In this study, at clinics randomly assigned to receive the intervention, epidemiologic benchmarks are inserted into lumbar spine imaging reports to provide context to the findings. The primary outcome will be the number of subsequent spine-related diagnostic and therapeutic interventions reported at the clinic level. Here,

direct participants are the patients and the clinicians. Both patients (those who access their electronic medical records) and physicians will be exposed to the modified imaging reports. Also, research data will consist of individual subjects' medical record data and information on clinics and providers.[14] The indirect participants include the informatics personnel, radiologists, healthcare operations personnel, and relevant department chairs (Table 2). While the study may not pose any additional risk to these indirect participants' welfare, its implementation may unintentionally impose significant administrative burden on one or more of these groups of participants, thereby affecting workers' well-being.

The **A**ctive **Bat**hing to **E**liminate (ABATE) Infection trial[15] is underway to reduce multidrug-resistant organisms and hospital infections by comparing usual bathing of non-critically ill hospitalized patients to universal bathing with chlorhexidine plus nasal mupirocin for those who are carriers of methicillin-resistant *Staphylococcus aureus* (MRSA). In the ABATE Infection trial, the unit of randomization is the hospital, and the outcomes will be unit-attributable clinical cultures of MRSA and vancomycin-resistant enterococci (VRE). The direct participants are (1) the patients in the intervention and control units of the hospitals participating in the trial and (2) the nurses and nursing assistants on participating units because they have received training on trial protocol. The indirect participants are all other hospital staff who may routinely work in the participating units and regular visitors of patients being cared for in these units where trial protocol is being deployed. Their rights and welfare may be affected by their exposure to the intervention under study or the maintenance of routine care since control units were not permitted to adopt competing interventions. For example, participants of intervention units could potentially be exposed to a strain of bacteria resistant to chlorhexidine or mupirocin that emerged during the intervention.

The appropriate type of responsible party for protecting the rights and welfare of indirect participants is not an IRB, because IRBs do not generally control routine operations in the relevant institutional environments. Rather, we recommend that gatekeepers such as hospital and facility administrators be systematically involved in the design, planning, and conduct of PCTs. They are best able to help investigators identify features of the study design that ought to be modified to avert or minimize conflicts with pre-existing institutional protections afforded to indirect participants.

In the research ethics literature, "gatekeepers" have been defined as people or entities who have the ability to allow or deny access to resources or people who are required to support the conduct of clinical research.[16] Specifically for PCTs, the systematic involvement of gatekeepers may be critically important to identifying ways in which the conduct of a trial might infringe on the rights of indirect participants, and helping to ensure that the necessary protections are in place. A full discussion of gatekeepers' responsibilities to community members can be found in an accompanying paper in this series by Whicher and colleagues *(Gatekeepers for Pragmatic Clinical Trials*[17]).

## Collateral Participants

Collateral participants are patient groups and other stakeholder communities who may be affected by the occurrence and findings of a PCT. They include patient advocacy groups, patient forums, other intentionally formed stakeholder organizations focused on patient and community health, healthcare professionals, and healthcare stakeholders such as payers and health system administrators. Vayena and colleagues call for a new social contract for what they have termed participant led research (PLR).[18] PLR is inclusive of people who are looking to "acquire health information, whether about themselves or more generally." Collateral participants may contribute greatly to PCTs. Not only can they provide input on the design, planning and conduct of a PCT, but they could also offer insights regarding the best way to communicate the trial's results to their constituencies. Advance Care Planning is an example of a healthcare issue that is at the forefront of advocacy agendas for both healthcare professional and patients/caregivers organizations. The Coalition to Transform Advanced Care (C-TAC)[19] is a coalition of organizations representing a variety of professional and lay stakeholders. They indicate ACP as a key organizational initiative. These groups are examples of collateral participants in relation to research studies like PROVEN, which evaluates the effectiveness of ACP interventions.

PCORI's Patient Centered Outcomes Research Network (PCORnet) has taken explicit efforts to engage patients, caregivers, and professional societies. In PCORnet, these stakeholders are informing and prioritizing PCORnet's research agenda and have developed dissemination and communication strategies to inform the lay and medical community. Within PCORnet, collateral participants have contributed effectively to considerations for PCTs through both Patient Powered Research Networks (PPRNs) and Clinical Data Research Networks (CDRNs), in which patients and other stakeholders play an active role in informing the design and conduct of research, including PCTs focused on important clinical conditions like obesity, diabetes, arthritis, chronic obstructive pulmonary disease and sleep apnea.

PCORnet's first clinical trial for the Optimal Aspirin Dose for Patients with Coronary Artery Disease demonstrates the involvement of collateral participants throughout the continuum described above. Aspirin dosage for coronary artery disease was selected from 41 topics initially suggested by network members. The topic was ranked highest among all those evaluated by PCORI's Advisory Panel on Assessment of Prevention, Diagnosis, and Treatment Options, an advisory group whose 21 members represent a broad range of healthcare stakeholders.[20] The research topic was also prioritized by the Health eHeart PPRN Steering Committee and several of the members supported the development of a protocol to respond to PCORI's limited request for proposals to PCORnet partners.

The Health eHeart Alliance is a PPRN building a network of patients, caregivers, family members, doctors and researchers who all share the goal of working together to formulate new research ideas and improve health outcomes in ways that matter to patients. Several patient advocacy organizations belong to the Alliance including American Heart Association, Stop A-Fib.org, SADS Foundation, Mended Hearts and Mended Little

Hearts.[21] These organizations participate on the steering committee and some are involved in the governance of the network.

PCORI's Advisory Panels are an example of integrating collateral participants into the research process. They provide recommendations to help plan, develop, implement, improve, and refine the research agenda, and while they do not hold decision-making authority, they provide substantive input into the refinement of the Institute's research portfolio and other activities.[22]

Effective communication and dissemination of research information to potential collateral participants is of critical importance. An important ethical responsibility for those who lead the conduct of PCTs is to inform collateral participants of the gaps in knowledge that the research is intended to address, and of the progress and results of ongoing trials, in language they can understand. This concept builds on existing literature that discusses the increasing importance and obligation to consult with communities. Weijer and Emmanuel[23] suggest a strategy for the development of protections for communities in biomedical research. Their approach distinguishes between the various types of communities involved in research, their characteristics, and appropriate protections for each. Dickert and Sugarman point out that differences of communities require customized approaches to consultation.[24] However, the ethical goals should always remain consistent. They advance 4 ethical goals to assist researchers, regulators, and IRBs when considering community consultation: enhanced protection, enhanced benefit, legitimacy, and shared responsibility.

There are increasing opportunities to leverage technology, embed research into care, and move toward a learning health system.[4] Patients, caregivers, the public, and some clinicians may not understand how little evidence there is about the safety and effectiveness of available drugs, therapies and other procedures. In interviews with patients, few interviewees grasped the notion that there might be no evidence-based reason for choosing one therapy over another.[25] Educating them about the importance of addressing these issues in PCTs and soliciting their input on the design and conduct of such trials may increase their effective participation in PCTs and potentially increase trust in implementation of study findings.

When a clinic or site is participating in a PCT, this fact could be communicated to patient groups through email, brochures, social media, posters, social media and patient support communities for a specific disease. This will help empower patient organizations and communities with information about the research and afford opportunities for further engagement in the design and conduct of PCTs. Additionally, participation in research that is important to patients and other key stakeholders may help build the credibility and prestige of the participating organization.

Disseminating information on the identification, development, and progress of research studies as well as their findings to collateral participants is equally important for PCTs. Further research is required to evaluate when engagement of collateral participants is most effective over the course of a PCT and to understand how best to engage these participants. Through ongoing communication about study milestones and the eventual results with

collateral participants, clinicians and researchers may foster trust and may gain a bigger pool of potential direct participants for future studies. Also, with timely and clear communication with collateral participants, information on ongoing studies and the findings of completed ones could be disseminated more widely to patients, clinicians and other stakeholders.

## Conclusion

We have proposed to distinguish among direct, indirect, and collateral participants of PCTs. We hope that recognizing these distinctions will support PCT funders, sponsors, investigators, host sites, patient/caregiver organizations, and other interested parties in acting rightly toward various people affected in various ways by PCT research programs. An important early step in the implementation of a PCT is to identify direct and indirect participants, and to ensure appropriate protections for each group. Another important early step is to identify, engage, and inform collateral participants about the need for evidence-based practice and the opportunity to address the evidence gap with PCTs. Engagement and communication may increase understanding of the research process and build trust, and may also support the ethical conduct of research and enhance acceptance of, participation in, and retention in research trials and recruitment for future trials.[26] If culture change occurs such that participants are indeed more active participants in the process, we hope all participants, direct, indirect, or collateral, will be empowered and informed. 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.

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## References

1. Tricoci P, Allen JM, Kramer JM, et al. Scientific evidence underlying the ACC/AHA clinical practice guidelines. JAMA. 2009; 301:831–841. [PubMed: 19244190]
2. McRae AD, Weijer C, Binik A, et al. Who is the research subject in cluster randomized trials in health research? Trials. 2011; 12:183. [PubMed: 21791064]
3. [8 October 2014] Code of Federal Regulations | HHS.gov. http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html
4. Committee on the Learning Health Care System in America, Institute of Medicine. Best Care at Lower Cost: The Path to Continuously Learning Health Care in America. Washington (DC): National Academies Press (US); 2013. http://www.ncbi.nlm.nih.gov/books/NBK207225/ [28 January 2015]

5. U.S. Department of Health and Human Services. [8 October 2014] Attachment C: Recommendations on Regulatory Issues in Cluster Studies | HHS.gov. http://www.hhs.gov/ohrp/sachrp/commsec/attachmentcjul32014:recommendationsonregulatoryissuesinclusterstudies.html
6. Mann H, Reyes M. Identifying the human research subject in cluster randomized controlled trials. IRB. 2008; 30:14–18. [PubMed: 18953772]
7. Weijer C, Grimshaw JM, Eccles MP, et al. The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials. PLoS Med. 2012; 9:e1001346. [PubMed: 23185138]
8. Van der Graaf R, Koffijberg H, Grobbee DE, et al. The ethics of cluster-randomized trials requires further evaluation: a refinement of the Ottawa Statement. J Clin Epidemiol. 2015
9. Ali J, Andrews JE, Somkin CP, et al. Harms, benefits, and the nature of interventions in pragmatic clinical trials. Clinical Trials. 2015; 12:467–475. [PubMed: 26374680]
10. Califf RM, Sugarman J. Exploring the ethical and regulatory issues in pragmatic clinical trials. Clinical Trials. 2015; 12:436–441. [PubMed: 26374676]
11. Methodology Committee of the Patient-Centered Outcomes Research Institute (PCORI). Methodological standards and patient-centeredness in comparative effectiveness research: the PCORI perspective. JAMA. 2012; 307:1636–1640. [PubMed: 22511692]
12. Mor, V.; Mitchell, SL.; Volandes, A. [5 May 2015] Pragmatic Trial of Video Education in Nursing Homes (PROVEN). NIH Collaboratory Website. https://www.nihcollaboratory.org/demonstration-projects/Pages/PROVEN.aspx
13. Jarvik, JG. [3 February 2015] Lumbar Imaging With Reporting of Epidemiology (LIRE) trial. NIH Collaboratory Website. https://www.nihcollaboratory.org/demonstration-projects/Pages/LIRE.aspx
14. Jarvik, JG. LIRE Supplementary Material. 2013. https://www.nihcollaboratory.org/Products/JerryJarvik-PragmaticTrialLumbarImageReportingEpidemiology-LIRE.pdf
15. Huang, SM. [2 February 2015] Active Bathing to Eliminate (ABATE) Infection trial. NIH Collaboratory Website. 2014. https://www.nihcollaboratory.org/demonstration-projects/Pages/ABATE.aspx
16. Patterson S, Mairs H, Borschmann R. Successful recruitment to trials: a phased approach to opening gates and building bridges. BMC Med Res Methodol. 2011; 11:73. [PubMed: 21595906]
17. Whicher DM, Miller JE, Dunham KM, et al. Gatekeepers for pragmatic clinical trials. Clinical Trials. 2015; 12:442–448. [PubMed: 26374683]
18. Vayena E, Brownsword R, Edwards SJ, et al. Research led by participants: a new social contract for a new kind of research. J Med Ethics. 2015
19. Coalition to Transform Advanced Care. [12 April 2015] Advanced Care Project. http://www.thectac.org/key-initiatives/advanced-care-project/
20. Patient-Centered Outcomes Research Institute. [15 April 2015] Optimal Aspirin Dose for Patients with Coronary Artery Disease Approved as Topic for First PCORnet Research Trial. PCORI. Jul 29. 2014 http://www.pcori.org/content/optimal-aspirin-dose-patients-coronary-artery-disease-approved-topic-first-pcornet-research
21. [15 April 2015] The Health eHeart Alliance. http://health-eheartalliance.org/
22. [16 January 2015] PCORI Advisory Panels FAQs | PCORI. http://www.pcori.org/content/pcori-advisory-panels-faqs
23. Weijer C, Emanuel EJ. Ethics. Protecting communities in biomedical research. Science. 2000; 289:1142–1144. [PubMed: 10970227]
24. Dickert N, Sugarman J. Ethical goals of community consultation in research. Am J Public Health. 2005; 95:1123–1127. [PubMed: 15983268]
25. Sabin JE, Mazor K, Meterko V, et al. Comparing drug effectiveness at health plans: the ethics of cluster randomized trials. Hastings Cent Rep. 2008; 38:39–48. [PubMed: 18947140]
26. Okello G, Jones C, Bonareri M, et al. Challenges for consent and community engagement in the conduct of cluster randomized trial among school children in low income settings: experiences from Kenya. Trials. 2013; 14:142. [PubMed: 23680181]

## Table 1

Definitions of “Human Research Subject” (Common Rule) and “Research Participant” (Ottawa Statement).

| **45 CFR 46.102(f) (Common Rule)[3]** | **Recommendations on Regulatory Issues In Cluster Studies (SACRP, March 13, 2014)[5]** | **Ottawa Statement[7]** |
|---|---|---|
| Human Research Subject: A living individual about whom an investigator (whether professional or student) conducting research obtains<br>**1** Data through intervention or interaction with the individual, or<br>**2** Identifiable private information. | When the individual s environment has a reasonable possibility of being manipulated by the existence of the research, then the individual is a research subject. | CRT Research Participant: An individual whose interests may be affected as a result of study interventions or data collection procedures, that is, an individual (1) who is the intended recipient of an experimental (or control) intervention; or (2) who is the direct target of an experimental (or control) manipulation of his/her environment; or (3) with whom an investigator interacts for the purpose of collecting data about that individual; or (4) about whom an investigator obtains identifiable private information for the purpose of collecting data about that individual. Unless one or more of these criteria is met, an individual is not a research participant. |

**Table 2**

Definitions of research participants

| Participant type | Definition | Responsible Parties | Examples |
|---|---|---|---|
| **Direct** | **1** Individuals being intentionally targeted by a study intervention, whether through immediate or mediated exposure; or<br>**2** Individuals on whom personal *identifiable* data are being collected for the purposes of the PCT. | IRB | PROVEN:[12] Direct participants are the patients in the intervention of the systems participating in the trial. Nursing home staff who receive training on delivering the video are also direct participants.<br>LIRE:[13] Direct participants are the patients of primary care providers, physician assistants and other non-physician primary care providers; the providers themselves are also direct participants.<br>ABATE:[15] Direct participants are the patients in the intervention and control units of the hospitals participating in the trial. Nurses and nursing assistants are also direct participants because they received protocol training. |
| **Indirect** | Individuals (other than direct participants) whose rights and welfare may be affected by the intervention through their routine exposure to the environment in which the intervention is being deployed. | Gatekeepers | PROVEN:[12] Indirect participants are all other nursing home staff and patient s families.<br>LIRE:[13] Indirect participants are informatics personnel, radiologists, healthcare operations personnel, relevant department chairs and gatekeepers, and non-trial patients in need of services.<br>ABATE:[15] Indirect participants are all other hospital staff and patient visitors to participating units, and healthcare facilities that receive transferred patients from participating hospitals |
| **Collateral** | Patient and other stakeholder communities who may be affected by the occurrence and findings of the PCT. | Gatekeepers, patient advocacy groups, patient forums, patient-powered research networks, community members involved through community engagement & community consultation. | PROVEN:[12] Collateral participants include other nursing home professionals, attorneys involved in ACP, community members and caregiver advocacy groups who work with patients and their families, and professional associations for nursing home administrators and staff.<br>LIRE:[13] Collateral participants include community members served by the hospital, patients with a similar condition, and professional associations for health-care providers.<br>ABATE:[15] Collateral participants include other hospital units, the community served by the hospital, and professional associations for healthcare providers. |