HHS Public Access

Author manuscript

Clin Trials. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

Clin Trials. 2015 October ; 12(5): 442–448. doi:10.1177/1740774515597699.

Gatekeepers for Pragmatic Clinical Trials

Danielle M. Whicher[1], **Jennifer E. Miller**[2,3], **Kelly M. Dunham**[1], and **Steven Joffe**[4]

[1]Patient-Centered Outcomes Research Institute, Washington, DC, USA

[2]Kenan Institute for Ethics, Duke University, Durham, NC, USA

[3]Edmond J. Safra Center for Ethics, Harvard University, Cambridge, MA, USA

[4]Department of Medical Ethics and Health Policy, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

Abstract

To successfully implement a pragmatic clinical trial, investigators need access to numerous resources, including financial support, institutional infrastructure (e.g., clinics, facilities, staff), eligible patients, and patient data. Gatekeepers are people or entities who have the ability to allow or deny access to the resources required to support the conduct of clinical research. Based on this definition, gatekeepers relevant to the United States clinical research enterprise include research sponsors, regulatory agencies, payers, health system and other organizational leadership, research team leadership, human research protections programs, advocacy and community groups, and clinicians. This manuscript provides a framework to help guide gatekeepers' decision-making related to the use of resources for pragmatic clinical trials. These include (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, and (3) stewardship of financial, human, and other organizational resources. Separate from these ethical considerations, gatekeepers' actions will be guided by relevant federal, state, and local regulations. This framework also suggests that to further enhance the legitimacy of their decision-making, gatekeepers should adopt transparent processes that engage relevant stakeholders when feasible and appropriate. We apply this framework to the set of gatekeepers responsible for making decisions about resources necessary for pragmatic clinical trials in the United States, describing the relevance of the criteria in different situations and pointing out where conflicts among the criteria and relevant regulations may affect decision-making. Recognition of the complex set of considerations that should inform decision-making will guide gatekeepers in making justifiable choices regarding the use of limited and valuable resources.

Address for correspondence: Danielle M. Whicher, PhD, MHS, Patient-Centered Outcomes Research Institute, 1828 L Street, NW, 9th Floor, Washington, DC 20036, dwhicher@pcori.org.

Declaration of Conflicting Interests

Dr Whicher is a Program Officer for the Clinical Effectiveness Research team at the Patient-Centered Outcomes Research Institute (PCORI), and Ms Dunham is the Program Manager for Research Portfolio Development in the Office of the Chief Science Officer at PCORI. Dr Miller has no conflicts of interest to disclose. Dr Joffe served on a data monitoring committee for Genzyme/Sanofi until November 2012.

Keywords

Gatekeeper; research ethics; pragmatic clinical trial; comparative effectiveness research; deliberative democracy

Introduction

Pragmatic clinical trials (PCTs) are randomized trials that seek to compare the effectiveness of two or more interventions in real-world settings. Generally, PCTs are closely integrated with clinical practice, incorporate outcomes that are relevant to patients and other relevant stakeholders, include a broad range of clinical settings, and have minimal exclusion criteria so that the patients reflect those receiving care outside of the trial. These trials seek clinically applicable evidence about the relative advantages and disadvantages of interventions to inform the decisions made by clinicians, patients, and others.1-4, [i] Recently, given pressures to improve healthcare quality and interest in transforming healthcare institutions into learning healthcare systems,[5] PCTs have received increased emphasis and support.[6-8]

Before implementing a PCT, researchers must secure financial support, including reimbursement for study interventions; access to institutional infrastructure, including facilities and staff; and access to study participants and data (Table 1).[9] Securing these resources requires the cooperation of gatekeepers, defined as people or entities who can allow or deny access to resources required to support the conduct of clinical research.[10] Thus, gatekeepers critically shape which PCTs are successfully implemented.

The topic of gatekeeping in clinical research has been discussed previously, especially in relation to individuals or entities that control access to groups for cluster randomized trials[11-14] or to physicians who offer trials to eligible patients.[10, 15-17] While important, this literature does not address the breadth of individuals or groups that can facilitate or preclude successful implementation of PCTs. In this paper, we describe the range of gatekeepers relevant to PCTs in the United States, offer criteria for them to consider when making decisions about resources, and provide recommendations regarding best practices for gatekeeping in the context of PCTs.

An Ethical Framework for Gatekeeping

Given their critical role in PCTs, gatekeepers require a set of criteria to help guide their decision-making. Many gatekeeping functions are also mandated by regulation. Relevant criteria, presented without any implied priority, include:

(1) Concern for the interests of individuals, groups, and communities affected by the gatekeepers' decisions, including protection from harm and maximization of benefits;

[i]This paper relies on the definition of pragmatic clinical trials described in: Califf RM, Sugarman J. Exploring the ethical and regulatory issues in pragmatic clinical trials. *Clin Trials* 2015 (in press).

(2) Advancement of organizational mission and values; and

(3) Stewardship of financial, human, and other organizational resources.

Each of these criteria can represent an ethically significant justification for gatekeeping actions. Their relevance and weight may vary, however, depending on the particular gatekeeping role and decision at hand.

On the first criterion, gatekeepers should generally respect, promote, or represent the interests of various individuals, groups, or communities likely to be directly or indirectly affected by their decision-making. This may include protecting entities or individuals from trials that are overly risky or burdensome or are unlikely to generate valid and valuable evidence. Based on their knowledge of those they represent, many gatekeepers should be able to identify local risks, benefits and concerns.

On the second criterion, as organizational representatives, some gatekeepers are charged with ensuring that the use of specific research resources promote their organization's mission and values. Organizational mission statements are generally publicly available and, in the case of organizations that are gatekeepers for PCTs, often articulate goals related to advancing patients' well-being or public health. Relevant values may include promotion and support of robust clinical research; delivery of high-quality, patient-centered, and affordable healthcare; treatment or prevention of specific diseases or conditions; or reduction of health disparities.

Finally, since the resources available to conduct PCTs are limited, implementing a PCT competes with the ability to pursue other clinical research or to serve other organizational priorities. Gatekeepers must steward resources under their purview, including money, infrastructure, personnel, patients, and data (Table 1). This responsibility extends to consideration of the organization's financial sustainability so that it may fulfill its mission over time. It may also include ensuring that sufficient external funds are available to complete the trial without excessive need for subsidy from other organizational resources.

Regulatory requirements also influence gatekeepers' decisions. Relevant regulations include federal human subjects protections regulations; US Food and Drug Administration (FDA) requirements; and legally enforceable fiduciary obligations of certain gatekeepers, such as organizational officials with responsibilities to shareholders and clinicians with responsibilities to patients.

Although each is important, these criteria frequently exist in tension. Gatekeepers must often balance competing considerations when deciding whether to allow access to resources, and individuals affected by their decisions may raise questions of legitimacy or trust. Drawing on frameworks such as the theory of accountability for reasonableness[18] and the more general concept of deliberative democracy,[19] to foster legitimacy, gatekeepers should follow transparent decision-making processes and be prepared to justify their decisions to those they represent. Stakeholder engagement in relevant decisions may also promote responsible decision-making.

Gatekeepers for Pragmatic Clinical Trials

Because the relevance of the criteria, regulatory context, and types of conflicts that arise vary across gatekeepers, we apply the framework to the range of gatekeepers that influence the successful implementation of PCTs in the United States (Table 1).

Research Sponsors

A necessary step for conducting any PCT is securing financial support (Table 1). Organizations that fund PCTs include federal agencies such as the National Institutes of Health (NIH);[20] nonprofit organizations such as the Patient-Centered Outcomes Research Institute (PCORI);[8] and private and for-profit organizations, including companies that manufacture medical products.[21]

When developing research priorities, sponsors must represent the interests of relevant stakeholders and ensure coherence with organizational missions and value statements. Stakeholders will often have conflicting interests. In these situations, research sponsors must make choices about which research priorities to pursue. A sponsor's mission and values will assist it in prioritizing research topics. For instance, as the largest public funder of research, the NIH consists of 27 institutes and centers, each with a mission oriented towards a set of diseases, a spectrum of life, or a type of research. To enhance the legitimacy of research prioritization, most public funding agencies have transparent and publicly accessible processes, including publicly appointed advisory committees operating under Sunshine laws.[22, 23]

Once they determine research priorities, public research sponsors solicit research proposals and select projects most likely to address the defined priorities. Many public funding agencies have established merit review processes whereby individuals with expertise in the relevant topics review and score research applications based on pre-defined criteria to identify those most likely to promote public interests and the organization's mission.[24, 25]

The medical products industry, which provides approximately 60% of research funding,[26] must address many of the same issues as public funders. However, the research priorities of these organizations are often shaped by regulatory agencies and payers. Furthermore, industry sponsors must reconcile their legal accountability to shareholders and other investors with organizational mission statements and the interests of the people with diseases or conditions that their products address. As post-marketing PCTs expand, such as in the field of diabetes,[27] companies' interactions with regulatory authorities and patient advocacy groups can create complex tensions between profitability and public health. Another important development is the increase in industry co-funding with federal sponsors. Investigators often must pass peer review at the NIH while also convincing company decision-makers that the trial merits financial or in-kind support.

Regulatory Agencies

Relevant regulatory bodies include federal agencies, such as the Office for Human Research Protections (OHRP), the FDA, and Department of Health and Human Services Office for Civil Rights (OCR), as well as state and local agencies. In some cases, these agencies serve

a gatekeeping function for an individual PCT. For example, the FDA might decide whether or not a trial that involves an off-label use of an approved agent requires an Investigational New Drug application, and if so, whether or not to approve the application. More generally, these agencies play upstream roles in establishing the rules that other gatekeepers must apply in carrying out their responsibilities. Although the particular resources to which regulators control access vary across agencies and trials, at the most general level, investigators and research teams cannot access experimental interventions, patient data, or prospective participants without satisfying the agencies' substantive and procedural requirements (Table 1).

Agencies' decision-making is predominantly guided by regulations. However, when regulations do not provide adequate guidance, regulators may benefit from the framework we provide in this paper.

Payers

Payers are organizations that finance the cost of health services provided to patients. Payers that may play gatekeeping roles in PCTs include those run by federal or state governments, such as the Veteran's Health Administration, Medicare, and Medicaid; not-for-profit managed care and health insurers such as Kaiser Permanente; and for-profit insurers such as WellPoint. Payers may support PCTs by covering trial-related costs, including routine clinical costs, costs of interventions being used off-label, or costs of services that fall outside the payer's formulary (Table 1). Payers may also encourage PCTs by restricting reimbursement for certain services to patients participating in trials.[28] Finally, they may facilitate trials by making data regarding patients' outcomes available to investigators.

Payers have an interest in PCTs for a variety of reasons, including the mission-driven goal of increasing their ability to make efficient, evidence-based coverage decisions.[29] When making decisions about whether to pay for health services delivered in a PCT, payers must weigh the potential for knowledge gained against other research or organizational priorities.

Health System and Other Organizational Leadership

Even when funded by an external sponsor, some PCTs require additional financial subsidies from the healthcare systems or hospitals in which they are conducted.[30, 31] PCTs also require the use of physical, informational, and human infrastructure, each a limited organizational resource. Health system and other organizational leaders must steward their organizations' financial resources, make decisions about the use of other valuable institutional resources including patient data, and mediate interactions between researchers and patients (Table 1).

When making these decisions, health system leaders must consider the organization's financial sustainability, the interests of individuals within the organization, coherence with the organization's mission and values, and relevant regulatory requirements. These considerations often conflict. System leaders must weigh effects on workflow and personnel time commitments against the benefits of participation. In other instances, a PCT may address a question of relevance to individuals within a healthcare institution, but leaders might question the consequences of participation. Potential adverse effects on an

organization's reputation, trustworthiness, operations, financial stability, or opportunities to pursue other research interests are legitimate concerns for system leaders. While these issues are difficult and complex, health system leaders can enhance the legitimacy of their decision-making by engaging relevant stakeholders and adopting transparent processes. Despite these considerations, little information exists regarding the processes institutions use when reviewing research commitments.

Institutional leaders are also typically responsible for oversight of electronic health records (EHRs) and claims data. Although many PCTs rely on such data to address important research questions, data breaches can result in patient harm, adversely affect trust and institutional reputation, and result in punitive legal and administrative actions, including substantial fines.

Since PCTs occur in the context of routine patient care, health system leaders also mediate access to patients as research participants. Few data exist regarding leaders' views about whether research positively or negatively affects patients' experiences and attitudes towards their health systems. Some leaders may worry that admitting uncertainty could be viewed negatively, whereas others might argue that integration of research activities signals a "cutting-edge" program that provides high-quality healthcare.

Research Team Leadership

PCTs may take place within academic medical centers, health systems, or community-based office settings. Within these organizations, identified individuals are often responsible for leading research programs, such as by serving as site principal investigators (PIs) or directing research infrastructures. Research team leaders often have a more defined role than health system or other organizational leaders in overseeing specific research-related organizational components such as study coordinators, data management systems, and research finances. Considerations for such leaders include scientific priority, ability to serve specific patient populations, and the financial stability of the research component of the organization. Like health system leaders, research team leaders may also control access to EHR and claims data (Table 1).

Permission to approach patients usually requires the agreement of research team leaders, in addition to approval by institutional review boards (IRBs), as discussed below. For example, in the National Patient-Centered Clinical Research Network (PCORnet) aspirin dosing trial,[32] the PIs of member research networks constitute the first level of gatekeeping. Each interested PI must then seek approval of other institutional leaders.

Human Research Protection Programs

Human research protection programs (HRPPs), including but not limited to IRBs, perform several crucial gatekeeping functions.33, [ii] They determine whether investigators may employ study interventions for research purposes; may use institutional infrastructure and

[ii]We focus on IRBs here because they most directly influence which PCTs are implemented. However, once a PCT is implemented, radiation safety, biosafety, data monitoring committees, and other committees within HRPPs also play a crucial role in determining whether the PCT is successfully completed.

resources for research; may generate or access data for analysis; and may offer study enrollment to prospective participants (Table 1). They are empowered not only to approve or disapprove study protocols, consent forms, and associated documents, but also to require modifications. HRPPs typically exercise their gatekeeping functions with respect to groups of prospective participants, but may occasionally make decisions that affect individuals, such as whether a patient is competent to consent to study participation.

In performing their gatekeeping roles, HRPPs focus on the interests of individuals, groups, and communities affected by the research, including those who might participate and those who might be affected by the knowledge gained. HRPPs are charged with considering both potential benefits and harms. They promote clear and accurate communication with prospective participants and protect their autonomy to decline or accept entry into research. They also attend to fairness in research, ensuring that disadvantaged groups do not unfairly bear its burdens and that privileged groups do not disproportionately reap its benefits.[34] To enhance the legitimacy of their decision-making, HRPPs generally include representation from different stakeholder groups and maintain records justifying their decisions.

Patient Advocacy and Community Groups

Patient advocacy groups typically focus on advancing the interests of a specific population based on a disease or condition. While community groups may also advocate for a specific cause, they are typically defined by shared interests or identity or by geographic proximity. These groups may control access to certain patient or community populations and data, or relevant infrastructure (Table 1). In these situations, group leaders bear some responsibility for protecting group members from trials that are unlikely to promote their interests or that may cause them harm. Leaders of patient advocacy groups are also responsible for promoting the mission and values of the organization.

Some advocacy groups, such as those addressing cystic fibrosis and multiple myeloma, have become powerful in shaping decisions about which research projects are funded and the study designs that ensue (Table 1).[35, 36] When patient advocacy groups act as research sponsors, their responsibilities mirror those of other sponsors previously discussed.

Leaders of patient advocacy and community groups can enhance the legitimacy of their decisions by engaging in a transparent decision-making process with group members and relevant stakeholders. This process could include an open dialogue with PCT investigators to communicate the interests and priorities of the group, or even extend to a partnership in implementing the trial.

Clinicians

Clinicians are often asked to identify eligible individuals and to offer them the opportunity to enroll in an ongoing PCT. Clinicians may also control information reported about patients in, for example, case report forms or EHRs (Table 1).

Previous literature describes reasons why clinicians may experience conflict when discussing a clinical trial with eligible patients. For instance, the time required to discuss a PCT may interfere with their ability to care for other patients. Additionally, clinicians may

feel that research responsibilities could spark distrust by patients or could conflict with other clinical and fiduciary responsibilities.[37] Clinicians may also be concerned about certain individuals' vulnerability or ability to understand aspects of the trial design.[15]

Some scholars have argued that clinicians' decisions to not discuss trials with eligible individuals fail to respect patient autonomy.[38] Instead, it may be more appropriate for clinicians to mention the trial to eligible individuals and engage in a discussion about the benefits and potential harms of participation. This approach would promote transparency and demonstrate respect for patient autonomy. Additionally, early clinician engagement in trial design may minimize the likelihood that trial participation will conflict with clinicians' fiduciary obligations to their patients.[17]

A distinct issue, related to clinicians' roles as stewards of finite resources, arises when patients are eligible for several trials. It may be unrealistic for a clinician to take the time to review each of those trials with the patient. If clinicians are aware of patients' interests, they will be better equipped to identify for discussion those trials that most likely align with those interests. However, clinicians should also inform patients about sources of information regarding other available trials. Alternatively, some institutions have developed policies for prioritizing trials enrolling patients with the same medical condition.[39]

Discussion and Conclusions

In the US healthcare system, many gatekeepers influence which PCTs are implemented through controlling access to resources. We have articulated criteria that gatekeepers should use to inform their decision-making. While not every gatekeeper will play a role in implementing every PCT, we describe the range of gatekeepers that may be relevant and the considerations that likely affect their decision-making processes. We emphasize that all gatekeepers can enhance the legitimacy of their decision-making by developing transparent decision-making processes, offering justifications for decisions, and engaging with those whose interests they represent. Although some gatekeepers already have well-defined and transparent decision-making processes, others, such as healthcare executives, may be less transparent.

Given the recent focus on deliberation and shared decision-making, gatekeepers should also consider whether adopting more formal mechanisms of stakeholder engagement would better equip them to understand the interests of those they represent. When appropriate, investigators should engage prospectively with relevant gatekeepers to understand their decision-making processes. For instance, engagement with payers during the conceptualization of a PCT may help ensure that the trial meaningfully addresses knowledge gaps relevant to coverage and reimbursement decisions; engagement with clinicians may help minimize conflicts with fiduciary obligations; engagement with patient advocacy groups can help clarify the relevance of the proposed trial to patients' priorities; and discussions with health system leaders may illuminate ways to design PCTs that minimally alter institutional workflow.

Finally, although we have focused on considerations that gatekeepers should use to guide decisions on whether or not to allow a PCT to be implemented, it is important to note that many gatekeepers continue to be relevant to the successful completion of these trials and to the implementation of findings. Additionally, as the clinical research enterprise evolves, the landscape of relevant gatekeepers may change. For instance, patients and their advocates increasingly conceptualize, fund, and initiate PCTs. When this occurs, these patient advocacy groups will need to develop expertise in clinical investigation or partner with experienced investigators before the PCT can be implemented.

As stewards of valuable resources, gatekeepers play a critical role in the success of PCTs. Their decisions have an enormous impact on those they represent and on the ability to improve healthcare through research. The framework proposed in this article can promote responsible, transparent, and accountable decision-making by gatekeepers and foster trust in the larger research enterprise.

Acknowledgements

We thank Kelly Clayton, Jim Sabin, MD, and Susan Surovec for their helpful input. We thank Gina Uhlenbrauck for editorial assistance in the preparation of this manuscript. Gina Uhlenbrauck is an employee of the Duke Clinical Research Institute, Durham, North Carolina, and received no compensation for her work on this article other than her usual salary. We also thank Robert M Califf, MD, for his contributions while Director of the Duke Translational Medicine Institute. The views presented here are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health or the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee, or other participants in the National Patient-Centered Clinical Research Network (PCORnet).

Funding

This work is supported by the National Institutes of Health (NIH) Common Fund, through a cooperative agreement (U54 AT007748) from the Office of Strategic Coordination within the Office of the NIH Director. Dr Joffe's work was supported by a grant from the Greenwall Foundation.

Abbreviations

The following abbreviations are used in this manuscript:

EHR	electronic health record
FDA	US Food and Drug Administration
HRPP	human research protection program
IRB	institutional review board
NIH	National Institutes of Health
OCR	Office for Civil Rights
OHRP	Office for Human Research Protections
PCORI	Patient-Centered Outcomes Research Institute
PCORnet	National Patient-Centered Clinical Research Network
PCT	pragmatic clinical trial

PI	principal investigator

References

1. Califf RM, Sugarman J. Ethical and regulatory issues in pragmatic clinical trials. Clin Trials. submitted for this issue.
2. Mullins CD, Whicher D, Reese ES, et al. Generating evidence for comparative effectiveness research using more pragmatic randomized controlled trials. Pharmacoeconomics. 2010; 28:969–976. [PubMed: 20831305]
3. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic–explanatory continuum indicator summary (PRECIS): a tool to help trial designers. J Clin Epidemiol. 2009; 62:464–475. [PubMed: 19348971]
4. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. JAMA. 2003; 290:1624–1632. [PubMed: 14506122]
5. Institute of Medicine. [accessed 22 January 2015] The learning healthcare system: workshop summary. 2007. http://www.iom.edu/Reports/2007/The-Learning-Healthcare-System-Workshop-Summary.aspx
6. National Institutes of Health. [accessed 24 November 2014] NIH Health Care Systems Research Collaboratory website. www.nihcollaboratory.org
7. [accessed 24 November 2014] National Patient-Centered Clinical Research Network (PCORnet) website. www.pcornet.org
8. Patient-Centered Outcomes Research Institute. [accessed 24 November 2014] Funding opportunities: pragmatic clinical studies and large simple trials to evaluate patient-centered outcomes. 2014. http://www.pcori.org/announcement/pragmatic-clinical-studies-and-large-simple-trials-evaluate-patient-centered-outcomes
9. Chalkidou K, Tunis S, Whicher D, et al. The role for pragmatic randomized controlled trials (pRCTs) in comparative effectiveness research. Clin Trials. 2012; 9:436–446. [PubMed: 22752634]
10. 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]
11. 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]
12. Weijer C, Grimshaw JM, Taljaard M, et al. Ethical issues posed by cluster randomized trials in health research. Trials. 2011; 12:100. [PubMed: 21507237]
13. Gallo A, Weijer C, White A, et al. What is the role and authority of gatekeepers in cluster randomized trials in health research? Trials. 2012; 13:116. [PubMed: 22834691]
14. Taljaard M, Weijer C, Grimshaw JM, et al. The Ottawa Statement on the ethical design and conduct of cluster randomised trials: précis for researchers and research ethics committees. BMJ. 2013; 346:f2838. [PubMed: 23661113]
15. Newington L, Metcalfe A. Researchers' and clinicians' perceptions of recruiting participants to clinical research: a thematic meta-synthesis. J Clin Med Res. 2014; 6:162–172. [PubMed: 24734142]
16. Fletcher B, Gheorghe A, Moore D, et al. Improving the recruitment activity of clinicians in randomised controlled trials: a systematic review. BMJ Open. 2012; 2:e000496.
17. Donovan JL, Paramasivan S, de Salis I, et al. Clear obstacles and hidden challenges: understanding recruiter perspectives in six pragmatic randomised controlled trials. Trials. 2014; 15:5. [PubMed: 24393291]
18. Daniels, N. Just health: meeting health needs fairly. Cambridge University Press; New York, NY: 2007.
19. Gutmann A, Thompson D. Deliberating about bioethics. Hastings Cent Rep. 1997; 27:38–41. [PubMed: 9219023]

20. National Institutes of Health. [accessed 15 December 2014] New NIH research awards to address multiple chronic conditions. 2014. http://www.nih.gov/news/health/aug2014/nccam-20.htm
21. Buesching DP, Luce BR, Berger ML. The role of private industry in pragmatic comparative effectiveness trials. J Comp Eff Res. 2012; 1:147–156. [PubMed: 24237375]
22. The Government in the Sunshine Act. 5 U.S.C. §552b.
23. Federal Advisory Committee Act Amendments. 5 U.S.C. app.
24. Patient-Centered Outcomes Research Institute. [accessed 15 December 2014] Merit review process. 2014. http://www.pcori.org/content/merit-review-process
25. National Institutes of Health. [accessed 15 December 2014] Grants & funding: peer review process. http://grants.nih.gov/grants/peer_review_process.htm
26. Moses H 3rd, Matheson DH, Cairns-Smith S, et al. The anatomy of medical research: US and international comparisons. JAMA. 2015; 313:174–189. [PubMed: 25585329]
27. Nathan DM, Buse JB, Kahn SE, et al. Rationale and design of the glycemia reduction approaches in diabetes: a comparative effectiveness study (GRADE). Diabetes Care. 2013; 36:2254–2261. [PubMed: 23690531]
28. Pearson SD, Miller FG, Emanuel EJ. Medicare's requirement for research participation as a condition of coverage: is it ethical? JAMA. 2006; 296:988–991. [PubMed: 16926358]
29. Ratner J, Mullins D, Buesching DP, et al. Pragmatic clinical trials: U.S. payers' views on their value. Am J Manag Care. 2013; 19:e158–165. [PubMed: 23781914]
30. Commonwealth Fund Task Force on Academic Health Centers. [accessed 27 April 2015] From bench to bedside: preserving the research mission of academic health centers. Apr. 1999 http://www.commonwealthfund.org/usr_doc/AHC_cwf_bench_312.pdf
31. Britt, R. National Center for Science and Engineering Statistics InfoBrief. National Science Foundation; Arlington, VA: Feb 4. 2015 Higher education R&D expenditures resume slow growth in FY 2013. Report No. NSF 15-314
32. Fleurence, R.; Rotter, JR. [accessed 23 January 2015] Proving the concept: moving ahead with PCORnet's first clinical trial. Oct 29. 2014 http://www.pcori.org/blog/proving-concept-moving-ahead-pcornets-first-clinical-trial
33. Institute of Medicine Committee on Assessing the System for Protecting Human Research Participants. Responsible research: a systems approach to protecting research participants. National Academies Press; Washington, DC: 2002.
34. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA. 2000; 283:2701–2711. [PubMed: 10819955]
35. Cystic Fibrosis Foundation. [accessed 20 January 2015] Research overview. http://www.cff.org/research/
36. Giusti K. The Multiple Myeloma Research Foundation's evolving focus on drug R&D. Nat Biotechnol. 2012; 30:600–603. [PubMed: 22781678]
37. Miller FG, Rosenstein DL, DeRenzo EG. Professional integrity in clinical research. JAMA. 1998; 280:1449–1454. [PubMed: 9801009]
38. White C, Gilshenan K, Hardy J. A survey of the views of palliative care healthcare professionals towards referring cancer patients to participate in randomized controlled trials in palliative care. Support Care Cancer. 2008; 16:1397–1405. [PubMed: 18449574]
39. National Cancer Institute. [accessed 20 January 2015] An overview of NCI's National Clinical Trials Network. http://www.cancer.gov/clinicaltrials/nctn

Table 1

Gatekeepers in Pragmatic Clinical Trials and the Resources They Directly Control

	Financial support for research	Reimbursement for care	Interventions (drugs, devices, etc.)	Physical, informational, and human infrastructure[a]	Data[b]	Patients/ participants[c]
Research sponsors[d]	X	X	X[e]			
Regulatory agencies[f]			X		X	X
Payers	X	X			X	
Health system and other organizational leadership	X	X[g]		X	X	X
Research team leadership[h]				X	X	X
Human research protection programs[f,i]			X	X	X	X
Patient advocacy and community groups	X			X	X	X
Clinicians					X	X

[a] Includes buildings, clinic space, equipment, information technology infrastructure (e.g., servers, computers, software), and staff.

[b] May include data from electronic health records, pharmacy records, insurance claims, patient registries, biospecimen repositories, and trial datasets.

[c] Or their surrogate (e.g., parents of minors).

[d] Sponsors may be public entities, nonprofit organizations, or private, for-profit companies.

[e] Sponsors sometimes provide interventions.

[f] Although these entities do not directly manage resources necessary for the conduct of PCTs, they control access to certain resources by providing oversight over the appropriate use of those resources and by establishing rules that many other gatekeepers use when making decisions about access to resources. Without approval from these entities, research teams are unable to access the resources identified in this table.

[g] For example, capitated or global-payments systems.

[h] Examples include chair of a large network or site principal investigator.

[i] Includes institutional review boards and their offices, radiation safety and biosafety committees, and data monitoring committees.