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Addressing guideline and policy changes during pragmatic clinical trials

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Abstract

While conducting a set of large-scale multi-site pragmatic clinical trials involving high-impact public health issues such as end-stage renal disease, opioid use, and colorectal cancer, there were substantial changes to both policies and guidelines relevant to the trials. These external changes gave rise to unexpected challenges for the trials, including decisions regarding how to respond to new clinical practice guidelines, increased difficulty in implementing trial interventions, achieving separation between treatment groups, and differential responses across sites. In this article, we describe these challenges and the approaches used to address them. When deliberating appropriate action in the face of external changes during a pragmatic clinical trial, we recommend considering the well-being of the participants, clinical equipoise, and the strength and quality of the evidence associated with the change; involving those charged with data and safety monitoring; and where possible, planning for potential external changes as the trial is being designed. Any solution must balance the primary obligation to protect the well-being of participants with the secondary obligation to protect the integrity of the trial in order to gain meaningful answers to important public health questions.

Introduction

The National Institutes of Health's (NIH) Health Care Systems Research Collaboratory (''Collaboratory'') is conducting a series of large-scale pragmatic clinical trials (PCTs) in the United States. The Collaboratory's trials are designed to generate high-quality evidence needed to inform policy, best practice, and/or guidelines.[1] The nine trials range in size from 800 to 600,000 participants (average size ;105,000 participants) are conducted during the course of routine care or ''embedded'' in the health care system and use data from electronic health records, claims, and administrative sources (Table 1).

These PCTs address important, real-world questions that are relevant to public health where there is uncertainty about the effects of an intervention in everyday clinical practice settings when compared with other approaches.[2] However, during a trial spanning many years, emerging evidence can appropriately lead to new or revised guidelines or policies for medical treatment.

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Table 1. NIH Collaboratory Demonstration Projects[a].

Study name, ClinicalTrials.gov number	Project goal	Population	Intervention
Pain Program for Active Coping and Training (PPACT), NCT02113592	Help patients adopt self-management skills for chronic pain, limit use of opioid medications, and identify comorbid conditions and symptoms amenable to treatment	Patients with chronic pain on long-term opioid therapy (~800 patients) in primary care clinics of three health care systems	A multidisciplinary approach to cognitive behavioral therapy, a yoga-based movement component, support for patients to manage pain, and guidance and support for primary care providers
Strategies and Opportunities to Stop Colon Cancer in Priority Populations (STOP CRC), NCT01742065	Improve the rates of colorectal cancer screening in priority populations	Individuals eligible for screening (~41,000 patients) in 26 Federally Qualified Health Center clinics	Mailing fecal immunochemical test kits
Suicide Prevention Outreach Trial (SPOT), NCT02326883	Compare outcomes in patients who receive care management or online skills training for suicide prevention versus usual care	Individuals at elevated risk for suicide on a depression scale (~19,500 patients) in four health care systems	(1) Outreach and care management, (2) online skills training
Time to Reduce Mortality in End-Stage Renal Disease (TiME), NCT02019225	Determine whether increasing hemodialysis session durations reduces mortality and hospitalization rates	Adults initiating treatment with maintenance hemodialysis (~6800 patients) in 266 dialysis facilities	A minimum hemodialysis session duration of 4.25 h
Pragmatic Trial of Video Education in Nursing Homes (PROVEN), NCT02612688	Determine if showing advance care planning videos in nursing homes affects the rates of hospitalization	Two nursing home health systems serving long-stay (>12 months) patients with advanced comorbid conditions (~15,000 patients in 260 nursing homes)	Showing advance care planning videos
Lumbar Image Reporting with Epidemiology (LIRE), NCT02015455	Reduce subsequent spine-related tests and treatments (cross-sectional imaging, opioid prescriptions, spinal injections, or surgery)	Primary care patients with low back pain in 100 clinics (~250,000 patients) in four health care systems	Inserting epidemiological benchmarks for common findings into lumbar spine imaging reports
Active Bathing to Eliminate Infection (ABATE), NCT02063867	Reduce multidrug-resistant organisms and bloodstream infections	Patients in adult medical, surgical, oncology, and step-down units in 53 hospitals. (~600,000 patients)	Universal antiseptic bathing and targeted nasal mupirocin for patients harboring *methicillin-resistant Staphylococcus aureus* (MRSA)
Improving Chronic Disease management with Pieces (ICD-Pieces), NCT02587936	Improve care for patients with chronic kidney disease, diabetes, and hypertension	Patients with chronic kidney disease, diabetes, and hypertension in four health care systems (~11,000 patients)	A novel technology platform (Pieces) assigns practice facilitators to deliver best care interventions
Trauma Survivors Outcomes and Support (TSOS), NCT02655354	Coordinate care and improve outcomes for trauma survivors with post-traumatic stress disorder (PTSD) and comorbidity *and* inform regulatory policy	Trauma survivors with PTSD and comorbidity (~635 patients) treated in 25 US Level I trauma centers	A collaborative care intervention that includes care management, medication, and psychotherapy elements

Source: Adapted from the NIH Collaboratory Living Textbook (rethinkingclinicaltrials.org), used with permission.
[a]All studies are conducted in the United States with usual care as the control arm.

Such external changes can have profound effects on the standard of care, clinical trials in general, and PCTs in particular. Although external changes (sometimes termed ‘‘history effects’’) may affect the outcome of interest and threaten the internal validity of any trial,[3–5] the problem is particularly acute with PCTs because they are conducted as part of routine care and often have ‘‘usual care’’ as a control arm,[6–8]

which is intentionally not tightly controlled and is therefore quite likely to be influenced by evolving guidelines and policies. However, although the control arm is not ‘‘controlled,’’ it is monitored in the same manner as in the intervention arm to help ensure trial validity. Because causal relationships are context dependent,[4] elucidating an experimental effect in a PCT conducted in a changing health system can also be challenging.

In addition, PCTs may be conducted under a waiver of conventional written informed consent and/or use altered consent,[9] as is the case with six of the nine Collaboratory trials, so that patients may be receiving care without awareness about being in a trial. In the face of external changes, PCT investigators and sponsors must evaluate what, if any, changes to the trial are appropriate, balancing the best interests of participants enrolled in the trial with preserving the evidence being generated by the trial.

Using actual case examples from the Collaboratory's trial portfolio, we illustrate two important types of external changes that can have profound effects on clinical practice and the conduct of PCTs: (1) clinical practice guidelines and (2) medical reimbursement policies that affect behavior of providers. We provide specific examples of how these types of changes posed challenges for the Collaboratory's PCTs and offer recommendations for those faced with these types of challenges based on our aggregate experience in the context of these trials.

Methods

Leadership from the Collaboratory Coordinating Center conducted several meetings with the Principal Investigators of the Collaboratory Demonstration Projects and NIH personnel who were involved in oversight of them to develop and discuss the recommendations, which were then drafted and circulated for further revision and refinement.

Clinical practice guidelines

Clinical practice guidelines are intended to scientifically support clinical decision-making. However, guidelines are ubiquitous, with myriad often-conflicting guidelines being developed and revised by professional societies, disease advocacy groups, health care systems, commercial companies, governmental bodies, and others in response to public health crises and evolving evidence.[10,11] Not all clinical practice guidelines have or arguably should have the same impact on practice. Of the 3700 entries in the Guidelines International Network,[10] many are based on low-quality evidence or expert opinion, and in most cases, the actual effectiveness of guidelines on the quality of care is unknown.[10,12,13] Complicating the matter, in the United States, funding for the National Guidelines Clearing House, which housed 2700 guidelines, was stopped in July 2018, and the guidelines are no longer readily available. In addition, when there is lack of consensus across different guidelines, specific practice recommendations may be different.[14] This creates confusion and complexity not only for clinical practice, but also for PCTs, especially ones that include patients with multiple chronic conditions and/or common conditions, such as hypertension, that may be addressed in multiple guidelines. This situation occurred during the conduct of the Collaboratory's Improving Chronic Disease management with Pieces (ICD-Pieces) trial (NCT02587936).

ICD-Pieces was designed to assess the possibility of improving care for patients with chronic kidney disease, diabetes, and hypertension using a novel technology platform (Pieces), by assigning practice facilitators within primary care practices or community medical homes.[15] In the implementation arm, practice facilitators aim to promote a set of specific targets, one of which is maintaining blood pressure less than 140/90 mmHg; the control group receives usual care, which is determined by individual primary care physicians according to local practice at the individual sites. During the trial, new blood pressure guidelines from the American College of Cardiology/American Heart Association lowered the definition of high blood pressure to 130/80 mm Hg and recommended this as a new standard of care.16

Of note, patients with the triad of conditions of concern in ICD-Pieces were not included in the recent studies that prompted the new guidelines, and some, but not all, professional societies relevant to patients in ICD-Pieces adopted the new guidelines. The research team reviewed the issue with the Data Safety and Monitoring Board (DSMB) to consider making changes in the protocol based on the new guidelines. In discussing the possibility of making changes to the protocol in response to these changes in guidelines, the DSMB recommended that investigators not modify the protocol given the lack of consensus across the guidelines. Regardless, the investigators may be able to assess changes in clinical management that occurred after the guidelines were released.

The introduction of a new guideline also posed challenges for the Collaboratory's Pain Program for Active Coping and Training (PPACT) trial (NCT02113592). PPACT was designed to assess the potential benefit of helping patients adopt self-management skills for chronic pain, limit use of opioid medications, and identify factors amenable to treatment in the primary care setting.[17,18] Due to the increasing attention to the opioid crisis, the Centers for Disease Control (CDC) published prescribing guidelines regarding chronic opioid treatment in March of 2016, 23 months into the 46 month implementation period of PPACT.[19] Because the PPACT intervention is non-pharmacotherapeutic, the new guidelines did not directly address the PPACT intervention. However, the CDC guidelines received significant press coverage and spurred numerous local quality improvement initiatives within the study's participating health care systems, such as attempts to broadly reduce the opioid dose threshold in patient populations. This contributed to confusion among both patients and frontline clinical staff. Specifically, there was fear and confusion among some patients eligible for PPACT, all of whom were on chronic opioid treatment and many of whom did not have a satisfactory response to other pain-related treatments. Patients were concerned that their chronic opioid treatment would be reduced or altogether discontinued, and they shared their concerns with study staff during PPACT recruitment. In response, the investigators intensified upfront orientation efforts to ensure that potential participants fully understood their care options and the trial intervention. Frontline clinical staff were managing changes and restrictions to opioid prescribing and required enhanced communication from the PPACT study team around the intervention. These changes to clinical practice affected participants in both study arms equally but their presence underscores the importance of understanding usual care in a pragmatic trial.

Changes to policy

Policy changes can affect how existing care strategies are reimbursed and influence when a particular treatment strategy becomes available. Such policy changes can compromise PCTs in several ways. First, when reimbursement for an intervention changes during the conduct of a PCT, subsequent changes in behavior in the control and/or intervention arms can potentially compromise the ability to detect an intervention effect. Second, uptake of and adherence to a new policy can vary across sites, and in a group- or cluster-randomized trial, differential uptake of new policies across clusters can create spillover effects that may substantially change or overwhelm treatment effects.[20] Likewise, delays in implementation due to slow-to-change cultures, lack of process flows to facilitate adoption, and competing priorities may affect the time to change both the control and intervention arms. Conversely, changes to reimbursement policy can also accelerate the implementation of an intervention.

One example of the potential impact of a policy change comes from the Collaboratory's Time to Reduce Mortality in End-Stage Renal Disease (TiME) trial (NCT02019225). Designed to determine whether increasing hemodialysis session duration reduces mortality and hospitalization rates for patients receiving maintenance hemodialysis, the TiME trial compared a default hemodialysis session duration of at least 4.25 h with usual care for patients with end-stage renal disease.[21] Shortly before the initiation of the TiME trial, a Technical Expert Panel was convened by the Centers for Medicare & Medicaid (CMS), the major payer for dialysis in the United States, to provide recommendations to CMS about quality measures for dialysis.[22] The expert panel initially recommended hemodialysis session durations of at least 4 h for individuals without residual kidney function, a session duration similar to the TiME trial

intervention. The panel later amended their report to remove the 4 h minimum hemodialysis session recommendation, recognizing that there was not sufficient supporting evidence.[23] Had the preliminary recommendation been maintained by the panel and adopted by CMS as a quality measure, there could have been widespread increase in hemodialysis session durations across the country. Such an increase could have altered usual care and limited the ability to answer the TiME trial's research question. While this potential threat to the trial was not realized, the substantial influence of CMS quality measures on clinical practice could also have been a powerful facilitator of sustainability if the intervention was found to have clinical benefits in the trial.

Differential uptake in response to a change in reimbursement policy affected the Collaboratory's Pragmatic Trial of Video Education in Nursing Homes (PROVEN) (NCT02612688), a trial designed to determine whether showing advance care planning videos in nursing homes affects the rates of hospitalization of frail, multi-morbid patients for whom aggressive medical interventions are not likely to be effective.[24] Around the time the trial began, CMS introduced a new billing code for advance care planning which reimbursed physicians and nurse practitioners for their time discussing advance directives with patients and their family members. The investigative team thought this would be an incentive for their intervention and they worried that both intervention and control sites would increase such discussions, undermining the investigators' ability of detecting an effect of showing the videos to all appropriate admissions and long-stay residents. However, the CMS requirement that a nurse practitioner or physician have the discussion meant that this new option could not be integrated into the PROVEN intervention as it was being implemented largely by facility social workers. Since the recruitment period for PROVEN was extended by 6 months, the risk of this policy change affecting the study outcome was increased because provider responses to these kinds of reimbursement policy changes are not usually immediate. In addition, some providers responded more quickly than others to the change in reimbursement, resulting in differential uptake of advance care planning.

Policy changes that increased incentives for health systems to increase colorectal screening rates affected the Collaboratory's Strategies and Opportunities to Stop Colon Cancer in Priority Populations (STOP CRC) trial (NCT01742065), designed to assess the possibility of improving the rates of colorectal cancer screening by mailing fecal immunochemical testing kits to patients at Federally Qualified Health Centers.[25] For clinics in Oregon, new Medicaid health plan incentives raised the prioritization of colorectal cancer screening across health centers. Intervention sites naturally became more engaged because they were interested in improving rates of colorectal cancer screening; concurrently, usual care settings also became motivated to increase their rates of colorectal cancer screening through usual methods. Because the goal of the trial was also to increase screening rates, these policy changes potentially changed outcomes in both the active intervention and control arms.

Recommendations

PCTs are conducted in complex and ever-changing health systems, so solutions to challenges created by external changes will not always be the same. In addition, when conducting research in health systems, patient care and the priorities of the organization can (and should) supersede the needs and interests of the trial. Nevertheless, based on the aggregate experiences in the NIH Collaboratory in actual PCTs, the following broad recommendations and strategies may help overcome such challenges.

1. The well-being of the participants must be privileged in deciding appropriate courses of action. Consider clinical equipoise when changes occur. When guidelines or policies change, clinical equipoise should be explicitly re-considered to ensure that ethical responsibilities to patients within a trial are still being met.[2] If a new guideline perturbs clinical equipoise, then it might be unethical to continue the study.
2. Include relevant stakeholders in the decision-making process. Where possible include those affected by the trial, such as clinicians and patients. However, doing so in the setting of PCTs in

which explicit consent may not have been obtained may make it challenging to engage patients and clinicians in such processes, since they may be unaware of the trial and their involvement in it.

3. Involve the entity charged with data and safety monitoring when unanticipated changes occur. These independent bodies can provide critical recommendations when external changes occur during a PCT.[26]
4. Engage health system leaders. Because PCTs are embedded in health care systems, Chief officers (executive, financial, operations, medical), directors, and other executive-level leaders or senior management within health systems, hospitals, skilled nursing facilities, and/or other health care delivery organizations should be continuously engaged during the conduct of PCTs.[27] Change is common, and these leaders bear responsibility for providing optimal care of patients and ensuring that it is appropriate for a particular trial to be conducted or continued within their institutions.
5. Investigators need to actively monitor guideline and policy changes, ask sites about their plans to respond to those that occur, and assess the multilevel context that influences the adoption of such changes. Factors such as external incentives (quality assurance metrics), organizational readiness, provider and patient knowledge, attitudes, and beliefs may lead to more nuanced adoption of new guidelines.
6. Monitor and document site-level responses to guideline and policy changes as well as the impact of the external change on care over time. There may be considerable heterogeneity in the implementation of interventions, different levels of adoption of various activities, and change over time in both the intervention and control units that may necessitate conducting additional sensitivity analyses. If guidelines or policies do change, in addition to the data already being collected for the trial, additional information may need to be collected through surveys[28] or other methods.
7. If nationally accepted changes to best practice or guidelines need to be implemented across all participating arms during the course of the trial, there should be equal opportunity and implementation support of the recommended changes. For example, if a national guideline changes, one option is to implement training across all sites to ensure they have equal access to and understanding of the change. That way, patients will be afforded the opportunity for better care, and the change will be more consistent across sites.
8. Consider during the design phase the possible effects on the trial of a change in practice in response to new guidelines. If possible, discuss the trial with the producers of guidelines or policy to see (1) if changes to guidelines are anticipated and (2) if the trial can supply evidence regarding the potential change. If guideline changes are anticipated, rules surrounding when to stop and when to change the protocol can be developed in advance. Such a plan should include a means of monitoring both fidelity of the intervention and changes to policies and guidelines, and respond to practice changes in response to new or revised guidelines and/or medical policy in participating sites.

Limitations

While we have identified a set of preliminary recommendations that derive from our actual aggregate experience, other recommendations are likely to surface as more PCTs are fielded across different conditions, with different sponsors, and in different locations. After all, our experience is grounded in large-scale US-based PCTs, which may have different characteristics than those conducted in other health care systems. Consequently, we encourage similar discussion from those with experience elsewhere. In addition, while we focused here on policy and guideline changes that might influence the ability of a PCT interventions to be properly interpreted, there are other changes that may raise similar challenges such as quality improvement initiatives. Future work may want to examine such issues.

Concluding comments

Health care practices are understandably influenced by external changes in guidelines and policy, which can affect the conduct and validity of PCTs. This creates a problematic cycle: health systems participate in PCTs to generate the high-quality evidence needed to identify best practice, and changes to guidelines or policy based upon observational or small intervention studies can interfere with the conduct of PCTs and threaten the development of much-needed high-quality evidence that trials provide.[2] Other forces may also threaten PCTs by swaying general opinion or challenging the staffing of interventions. For example, partner health care systems may not be willing to sustain support of staff to continue implementing a trial intervention in the face of other external pressures. Nevertheless, strategic planning and communication between the investigators, the Institutional Review Board and the entity charged with data and safety monitoring and institutional leadership, are critical for determining the appropriate actions needed in the face of ever-shifting evidence, reimbursement priorities, and guidelines. The ability to appropriately address the tension between modifications to clinical guidelines and the need to generate quality evidence to support those guidelines is a crucial consideration for the fulfillment of a learning health system.[29] A healthy collaboration of key stakeholders should help delineate the circumstances that would necessitate changing a protocol, dropping participating sites, notifying participants, or terminating the trial.

PCTs are an important means of producing high-quality evidence needed to better inform clinical practice. However, when guidelines or reimbursement policies change during the conduct of a PCT, the ethical obligation to gather information to develop evidence-based practices may conflict with the primary ethical obligation to participants.[2] Just as in conventional clinical research in general, the primary obligation must be to protect the well-being of the participants; a secondary, yet also crucial obligation, is to protect the integrity of the trial question and design.[2]

Declaration of conflicting interests

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Disclaimer

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References

1. Weinfurt KP, Hernandez AF, Coronado GD, et al. Pragmatic clinical trials embedded in healthcare systems: generalizable lessons from the NIH Collaboratory. *BMC Med Res Methodol* 2017; 17(1): 144.
2. Cohen MS, McCauley M and Sugarman J. Establishing HIV treatment as prevention in the HIV Prevention Trials Network 052 randomized trial: an ethical odyssey. *Clin Trials* 2012; 9(3): 340–347.
3. Shadish WR, Cook TD and Campbell DT. *Experimental and Quasi-experimental Designs for Generalized Causal Inference*. Boston, MA: Houghton Mifflin, 2001.
4. Campbell DT and Stanley JC. *Experimental and quasi-experimental designs for research.* 2nd print. Boston, MA: Houghton Mifflin, 1967.
5. Cook TD and Campbell DT. *Quasi-experimentation: design & analysis issues for field settings*. Boston, MA: Houghton Mifflin, 1979.
6. 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.
7. Loudon K, Treweek S, Sullivan F, et al. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ* 2015; 350: h2147.
8. Johnson KE, Neta G, Dember LM, et al. Use of PRECIS ratings in the National Institutes of Health (NIH) Health Care Systems Research Collaboratory. *Trials* 2016; 17: 32.
9. McKinneyRE Jr, Beskow LM, Ford DE, et al. Use of altered informed consent in pragmatic clinical research. *Clin Trials* 2015; 12(5): 494–502.
10. Institute of Medicine. *Clinical practice guidelines we can trust.* Washington, DC: National Academies Press.
11. Weisz G, Cambrosio A, Keating P, et al. The emergence of clinical practice guidelines. *Milbank Q* 2007; 85: 691–727.
12. Tricoci P, Allen JM, Kramer JM, et al. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA* 2009; 301(8): 831–841.
13. Califf RM and Sugarman J. Exploring the ethical and regulatory issues in pragmatic clinical trials. *Clin Trials* 2015; 12(5): 436–441.
14. Shekelle PG. Clinical practice guidelines: what's next. *JAMA* 2018; 320(8): 757–758.
15. NIH Health Care Systems Collaboratory Demonstration Project. Improving chronic disease management with pieces (ICD-PiecesTM). *NIH Health Care Research Collaboratory*, https://www.nihcollaboratory.org/demonstration-projects/Pages/ICD-Pieces.aspx (accessed 4 February 2015).
16. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2017; 138: e426–e483.
17. Debar LL, Kindler L, Keefe FJ, et al. A primary care-based interdisciplinary team approach to the treatment of chronic pain utilizing a pragmatic clinical trials framework. *Transl Behav Med* 2012; 2(4): 523–530.

18. DeBar L, Benes L, Bonifay A, et al. Interdisciplinary team—based care for patients with chronic pain on long—term opioid treatment in primary care (PPACT)—protocol for a pragmatic cluster randomized trial. *Contemp Clin Trials* 2018; 67: 91–99.
19. Dowell D, Haegerich TM and Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *MMWR Recomm Rep* 2016; 65: 1–49.
20. Murray DM. *Design and analysis of group-randomized trials*. New York: Oxford University Press, 1998.
21. Dember LM, Archdeacon P, Krishnan M, et al. Pragmatic trials in maintenance dialysis: perspectives from the kidney health initiative. *J Am Soc Nephrol* 2016; 27(10): 2955–2963.
22. Centers for Medicare & Medicaid Services. Medicare program; end-stage renal disease prospective payment system, payment for renal dialysis services furnished to individuals with acute kidney injury, and end-stage renal disease quality incentive program (82 FR 50738), https://www.federalregister.gov/documents/2017/11/01/2017-23671/medicare-program-end-stage-renal-disease-prospectivepayment-system-payment-for-renal-dialysis (2017, accessed 12May 2018).
23. Arbor Research Collaborative for Health and the University of Michigan Kidney, Epidemiology and Cost Center. End stage renal disease (ESRD) quality measure development and maintenance hemodialysis adequacy clinical technical expert panel summary report, https://www.cms.gov/Medicare/Quality-Initiatives-Patient-AssessmentInstruments/MMS/Downloads/Hemodialysis-Adequacy-TEP-Summary-Report-and-Addendum.pdf (2013, accessed 11 May 2018).
24. Mor V, Mitchell SL and Volandes A. Pragmatic trial of video education in nursing homes (PROVEN). *NIH Collaboratory*. https://www.nihcollaboratory.org/demonstration-projects/Pages/PROVEN.aspx (accessed 5 May 2015).
25. Coronado GD, Vollmer WM, Petrik A, et al. Strategies and opportunities to STOP colon cancer in priority populations: design of a cluster-randomized pragmatic trial. *Contemp Clin Trials* 2014; 38(2): 344–349.
26. Ellenberg SS, Culbertson R, Gillen DL, et al. Data monitoring committees for pragmatic clinical trials. *Clin Trials* 2015; 12(5): 530–536.
27. Fraser J, Moloney RM, Tambor ES, et al. Engaging stakeholders and building partnerships to ensure a successful trial. In: *Rethinking clinical trials: a living textbook of pragmatic clinical trials.* NIH Health Care Systems Research Collaboratory, https://rethinkingclinicaltrials.org/chapters/engaging-stakeholders/engaging-stakeholdersand-building-partnerships-to-ensure-a-successful-trial/ (2017, accessed 22 October 2017).
28. Swaby L, Hind D, Gossage-Worrall R, et al. Adherence to NICE guidance on lifestyle advice for people with schizophrenia: A survey. *BJPsych Bull* 2017; 41(3): 137–144.
29. Faden RR, Kass NE, Goodman SN, et al. An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics. *Hastings Cent Rep* 2013; 43: S16–S27.