Received: 26 September 2023 | Revised: 22 December 2023 | Accepted: 16 February 2024

DOI: 10.1002/lrh2.10413

POLICY ANALYSES

Learning Health Systems

Post-trial responsibilities in pragmatic clinical trials: Fulfilling the promise of research to drive real-world change

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Funding information
NIH HEAL Initiative, Grant/Award Number: U24AT010961; Greenwall Foundation; National Center for Complementary and Integrative Health, Grant/Award Number: U24AT009676

Abstract

While considerable scholarship has explored responsibilities owed to research participants at the conclusion of explanatory clinical trials, no guidance exists regarding responsibilities owed at the conclusion of a pragmatic clinical trial (PCT). Yet post-trial responsibilities in PCTs present distinct considerations from those emphasized in existing guidance and prior scholarship. Among these considerations include the responsibilities of the healthcare delivery systems in which PCTs are embedded, and decisions about implementation for interventions that demonstrate meaningful benefit following their integration into usual care settings—or deimplementation for those that fail to do so. In this article, we present an overview of prior scholarship and guidance on post-trial responsibilities, and then identify challenges for post-trial responsibilities for PCTs. We argue that, given one of the key rationales for PCTs is that they can facilitate uptake of their results by relevant decision-makers, there should be a presumptive default that PCT study results be incorporated into future care delivery processes. Fulfilling this responsibility will require prospective planning by researchers, healthcare delivery system leaders, institutional review boards, and sponsors, so as to ensure that the knowledge gained from PCTs does, in fact, influence real-world practice.

KEYWORDS
post-trial access, post-trial obligations, pragmatic clinical trials, research ethics

1 | INTRODUCTION

Pragmatic clinical trials (PCTs) are becoming more prevalent, driven by the aspiration that they might generate knowledge more efficiently than traditional clinical trials and with greater relevance for the real-world healthcare decisions facing patients, clinicians, health system leaders, and other stakeholders. To support this promise, funders such as the National Institutes of Health and the Patient-Centered Outcomes Research Institute (PCORI) have invested considerable resources to develop a nationwide infrastructure to facilitate the initiation and widescale implementation of PCTs.

This attention focused on facilitating the *implementation* of PCTs has, to date, overshadowed the critical issue of how knowledge gained through a PCT should then be translated into future care delivery practices. If patients, clinicians, and broader health systems have assumed the risks and burdens associated with generating knowledge within a PCT, what responsibilities are then owed to those same stakeholders once the trial is complete?

Considerable scholarship has explored responsibilities owed to research participants (and/or to their broader communities) at the conclusion of explanatory clinical trials, such as those testing a new HIV medication. While the contours of post-trial responsibilities remain a source of debate,[1] existing scholarship and international research ethics guidelines have largely focused on post-trial access to study medications or interventions, particularly for trials conducted in low-resource settings. For example, the Declaration of Helsinki states that "sponsors, researchers, and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial."[2] Similarly, ethical guidelines from the Council for International Organizations of Medical Sciences (CIOMS) instruct researchers and sponsors to make plans for "providing continued access to study interventions that have demonstrated significant benefit."[3]

No similar guidance exists regarding responsibilities at the conclusion of a PCT. This is problematic because post-trial responsibilities in PCTs are likely to involve considerations that are distinct from those emphasized in existing ethics guidance and prior scholarship. For example, unlike trials involving new medications, many PCTs test lower risk interventions with fewer individual-level burdens for patient participants, potentially lessening duties owed on the basis of reciprocity, which is emphasized in some of the arguments for post-trial access in explanatory trials. Additionally, the interventions under study in PCTs are often delivered by and within healthcare delivery systems (including integrated delivery systems, hospitals, nursing homes, and community health centers),[4] and downstream access to successful interventions may therefore be less a function of whether an individual is insured or otherwise has the financial resources to pay for an intervention than about whether and how the health system in which that individual receives care chooses to implement it. Moreover, existing guidance largely focuses on responsibilities incurred for trials identifying interventions that demonstrate meaningful benefit over existing alternatives. Yet, fulfilling post-trial responsibilities must encompass situations when an intervention that has been incorporated into usual care proves instead to have no meaningful benefit—perhaps especially when that intervention involved substantial changes to a healthcare delivery system's clinical or operational activities. Guidance for post-trial responsibilities in a PCT should therefore also address issues of *de*implementation, or discontinuing interventions not found to be effective.

In what follows, we present an overview of prior scholarship and guidance on post-trial responsibilities, including international guidelines, ethical rationales, and the nature and scope of these responsibilities. We then identify challenges for post-trial responsibilities for PCTs, along with insights to guide researchers, healthcare delivery system leadership, institutional review boards (IRBs), and trial sponsors.

2 | INTERNATIONAL GUIDELINES ON POST-TRIAL RESPONSIBILITIES

Several research ethics guidelines have addressed post-trial obligations, including those from CIOMS and the World Medical Association. This guidance has largely been framed around addressing research conducted in low-resource settings, particularly in the international context. Relevant excerpts from these documents are included in Table 1.

3 | ETHICAL RATIONALE FOR POST-TRIAL RESPONSIBILITIES

While numerous proposals have been offered, there remains no agreement regarding the ethical justification for post-trial responsibilities.[5,6] Justifications most commonly advanced in support of post-trial responsibilities include: avoiding exploitation; demonstrating reciprocity; respecting and recognizing the contribution of research subjects; and preventing harm, including feelings of abandonment.[5] There may be a further justification for post-trial responsibilities rooted in a broader expectation that research will generate social value, typically through production of knowledge that could lead to improvements in health or well-being of populations.[3,7] We briefly describe each justification below.

3.1 | Avoid exploitation

Exploitation occurs when researchers or sponsors take unfair advantage of research participants.[8] Avoiding exploitation might therefore require, among other things, that participants receive a fair share of benefits arising from their involvement in the research, and/or that they be ensured reasonable access to interventions proven efficacious by the trials in which they are involved.[9,10] Avoiding exploitation has similarly been presented as a justification for community benefit requirements in international research, given the potential for research to place burden on community resources (eg, using clinic space or diverting the attention of clinical personnel).[11]

3.2 | Reciprocity

Many arguments for post-trial responsibilities invoke the principle of reciprocity: as participants assist researchers in generating

TABLE 1 Examples of relevant language pertaining to post-trial obligations as described within international research ethics guidelines.

Document	Relevant language on post-trial obligations
Declaration of Helsinki, 2013	*Paragraph 34*: "In advance of a clinical trial, sponsors, researchers, and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process." *Paragraph 36*: "Researchers, authors, sponsors, editors, and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports…Negative and inconclusive as well as positive results must be published or otherwise made publicly available…"
CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, 2016	*Guideline 2*: "Before instituting a plan to undertake research in a population or community in low-resource settings, the sponsor, researchers, and the relevant public health authority must ensure that the research is responsive to the health needs or priorities of the communities or populations where the research will be conducted. As part of their obligation, sponsors, and researchers must also: Make every effort, in cooperation with government and other relevant stakeholders, to make available as soon as possible any intervention or product developed, and knowledge generated, for the population or community in which the research is carried out, and to assist in building local research capacity… Consult with and engage communities in making plans for any intervention or product developed available, including the responsibilities of all relevant stakeholders. *Guideline 24*: In accompanying guidance for the guideline on Public Accountability for Health-Related Research, researchers are stated as having "a duty to make the results of their health-related research involving human beings publicly available," including negative and inconclusive results. Further, researchers should ideally "take steps to promote and enhance public discussion" so as to make knowledge from the research "accessible to the communities in which the research was conducted…"
HIV Prevention Trials Network (HPTN) Ethics Guidance for Research, 2020	*Guidance Point 15*: HIV prevention researchers seeking to establish the efficacy of an intervention must have at minimum a preliminary plan regarding post-trial access to interventions proven to be safe and effective, which offer meaningful benefits for research participants and their communities.
UNAIDS Ethical Considerations in HIV Prevention Trials, 2021	*Guidance Point 14*: As part of the protocol, researchers and trial sponsors should have an agreed plan for post-trial access. In principle, trial sponsors should provide ongoing provision of HIV preventive products that have been demonstrated to be efficacious to all trial participants. The research team also has a special obligation to ensure the timely dissemination of study progress at regular intervals and to report and publish the final results in peer-reviewed journals. Dissemination of progress updates and results to national authorities, local communities, and study participants should be a priority and occur before or contemporaneously with international dissemination.

valuable data, researchers, in turn, should help to ensure that participants benefit from what is learned through their research.[3] A common formulation of this argument is that reciprocity demands that research participants be provided post-trial access to study medications. However, no consensus yet exists regarding what reciprocity actually requires, including whether providing post-trial access to medications is the best means by which to realize the principle of reciprocity (as opposed to, eg, providing compensation in return for assuming risk).[9] In PCTs, considerations from reciprocity are further complicated in that there may be reciprocity-based arguments for providing benefits to clinicians and other stakeholders within the health systems conducting the PCT who may have assumed burdens related to both the implementation of interventions under study, as well as from the collection of additional data to assess their impact.

3.3 | Respect and recognizing participants' contributions

Respecting those included in research throughout the duration of a research study is a central requirement for it to be ethical.[7] Fulfilling post-trial obligations can be a way to further respect and recognize participants' contributions.[5] Relevant mechanisms for recognizing contributions include considering participants' needs after trials and sharing research products fairly.[12]

3.4 | Prevent harm

A core tenet of research ethics is that participants should not be made worse off as a result of trial participation.[5] For example, a research

participant may receive clinical benefit from a medication or intervention being tested in a trial. If no provisions are made to facilitate continued access to such a study medication or intervention (or a similarly effective alternative) following completion of the trial, that individual may experience a setback in health status and/or psychological loss.

3.5 | Social value

PCTs are often assumed to have high potential for contributing social value. The social value of PCTs results from generating "real world knowledge that is directly applicable to decision-making."[13] While the potential to generate social value is an ethical requirement for all clinical research, it has been argued that PCTs have a greater potential than explanatory trials to yield results that are "immediately applicable to clinical practice."[13,14] This promise of greater social value cannot be realized, however, if actions are not taken to ensure that PCTs do, in fact, influence real-world practice. This influencing of real-world practice includes (but is not limited to) deliberate efforts to implement or deimplement interventions based upon the findings of a given PCT within the healthcare delivery system(s) in which the trial is conducted.

4 | NATURE OF POST-TRIAL RESPONSIBILITIES

While early debates about post-trial responsibility focused on access to medications demonstrated to be beneficial at the conclusion of a study, access to medications is only one among a broader set of potential responsibilities that might be owed to research participants at the conclusion of a trial. For example, access to medications can be understood as part of an umbrella of broader responsibilities related to "responsible transitioning of participants"[15] following trial completion. Responsible transitioning can encompass a range of support types or implementation strategies to facilitate a smooth transition from a research study to the healthcare sector, including helping to arrange clinical care or social services, providing referrals to appropriate follow-up care or to another trial, or providing alternative interventions to the study medication.[15] For PCTs, some of what is required for responsible transitioning when an intervention is shown to be beneficial can be led by research teams, including developing implementation toolkits, providing trainings, and technical assistance. However, other components of responsible transitioning will likely require healthcare delivery system-level resources (eg, ensuring relevant clinical personnel have the training and other resources needed to incorporate beneficial therapies into existing clinical delivery systems).[16,17]

An additional and related type of responsibility is capacity-building. As explained in guidance on Guideline 2 of CIOMS, "benefits other than those associated with study participation may accrue to the community or population…such benefits can include improving the health infrastructure, training laboratory personal, and educating the public about the nature of research and the benefits resulting from a particular study."[3] While it could be argued that capacity building is a closely related but separable obligation that goes beyond the life-cycle of any particular clinical trial, for PCTs, this reasoning might provide further support for arguments that investigators and/or research funders adequately support research sites. PCTs involving clinical settings with limited resources, such as federally qualified health centers and other community health centers, should not only avoid imposing burdens on clinical care activities underway within these settings but also look for ways to enhance capabilities, whether by providing technical assistance with EHRs or testing interventions designed to help clinics meet quality metrics.

A third type of post-trial responsibility relates to dissemination, so as to provide access to study results and the resultant knowledge gained. Without dissemination, it's as if the study did not take place. The Declaration of Helsinki, CIOMS, and The Joint United Nations Programme on HIV/AIDS (UNAIDS) guidelines all explicitly describe an obligation to communicate findings with relevant authorities, communities, and individuals (See Table 1). Similar arguments have been made for implementation research and health systems research.[18,19] These rationales likewise support dissemination of the results from PCTs, although the appropriate mechanisms for facilitating access to study results will likely vary by stakeholder group.

5 | SCOPE OF POST-TRIAL RESPONSIBILITIES

Similar to the lack of uniformity of ethical justifications for post-trial responsibilities, there is also no agreement regarding their scope.[1] Questions remain regarding to whom responsibilities should be owed, including, for example, whether responsibilities should be limited to trial participants vs to broader communities, and whether and how responsibilities might differ for those randomly assigned to treatment vs to control groups during a trial. Prior debates over these issues signal relevant questions that merit further exploration regarding the scope of post-trial responsibilities in PCTs, including in what circumstances responsibilities should be limited to those enrolled in PCTs vs to the broader patient populations within the healthcare delivery systems into which the PCT was embedded.

Furthermore, a range of factors have been proposed as influencing the scope of post-trial responsibilities. These include the risk to participants from discontinuation of a study intervention; the potential benefits to participants from post-trial provision of an intervention; the trial outcome, including both the magnitude and clinical relevance of the effect[20]; the financial and opportunity costs, including those related not only to the intervention itself, but also the infrastructure needed to deliver it; the corresponding risks of disincentivizing socially valuable research if research sponsors shy away from undertaking research out of concern for downstream costs associated with sustained implementation[1,20]; the duration and nature of the intervention modality, such as whether an intervention involves a single point-in-time interaction, such as vaccination, or requires prolonged delivery and substantial ancillary supports[21]; the participant's vulnerability and/or dependence on the research team; and the available alternatives with similar effectiveness. These factors may be similarly relevant for PCTs.

6 | CHALLENGES FOR PCTs

While existing literature and guidance about the nature and scope of post-trial responsibilities may suggest some insights for PCTs, several features of PCTs present distinct challenges.

First, who bears the duty to fulfill post-trial responsibilities in PCTs? Existing literature and guidance have often emphasized the role of researchers, trial sponsors, and host governments. Several characteristics of PCTs, however, limit the relevance of prior guidance. One key distinction is that healthcare delivery systems have generally not been a focus of post-trial responsibilities. Yet, these systems are integral to the conduct of PCTs—and therefore play a central role in what happens when trials end.[1] Additionally, scholarship on post-trial responsibilities often is predicated on the view that research and clinical care are distinct activities, bearing different duties. From this view, researchers are understood as having a more limited responsibility to trial participants than that of physicians to patients. However, the integration of research and care within a PCT may complicate assessments of the nature and scope of researchers' responsibility.[22] On the one hand, this integration may lessen the distinction between research and care so as to make the responsibilities owed to PCT patient subjects more akin to those owed to patients in clinical care. Yet integration also often means PCTs are less demanding of patient subjects, which may mitigate responsibilities owed on the basis of reciprocity.

Second, to whom are those responsibilities owed? Specifically, what responsibilities might be owed to clinicians or staff within the health systems in which PCTs were or are conducted? Prior literature and international guidance documents have largely concentrated on the responsibilities owed to research participants (and, in some cases, their broader communities).[1] However, the embedding of PCTs into ongoing clinical care creates the need to also consider potential obligations to other parties who might be affected by the research. This is perhaps especially true for clinicians and staff, who may themselves be research subjects, and who may have assumed additional burdens related to trial interventions and data collection activities.

Third, how might those responsibilities vary across study sites? Many PCTs are deliberately designed to involve partnerships across multiple health systems, so as to inform effectiveness across a range of contexts. Yet this presents the potential for heterogeneity of resources and priorities across study sites that may influence decision-making about the feasibility or desirability of sustaining or de-implementing an intervention following trial completion. This challenge may be further complicated with the rise of decentralized or virtual trials, in which patient participants may be physically distanced from trial hubs and/or the interventions themselves may be delivered remotely. Actualizing post-trial responsibilities in such a context may require, for example, consideration of whether the virtual capabilities of the trial need to be carried over post-trial, and if so, whether those elements ought to remain centrally supported.

Finally, what is required to transition a participant responsibly from a medication trial—the core of existing literature and guidance—is logistically and ethically distinct from that required for the types of interventions that are often under study in PCTs. For example, the Multi-Regional Clinical Trials Center's guidance on post-trial responsibilities specifies that post-trial researcher responsibilities include, if needed, contacting an appropriate treating physician and arranging for the responsible transition of a research participant to follow-up care.[23] In the case of an explanatory medication trial, such referrals may facilitate access for participants to medications (acknowledging the range of potential barriers to access, including insurance status and/or the ability to pay out of pocket for the medication and any related services such as office visits or laboratory testing). Such referrals seem likely to have little relevance, however, for many PCTs, which may involve complex interventions that require substantial redesign of clinical delivery systems to facilitate broad implementation. For example, facilitating continued access to interventions from a PCT testing a multi-level intervention involving artificial intelligence-based chatbot text messaging and proactive pharmacist support to facilitate self-management for cardiovascular disease risk would require coordination of multiple service lines and/or information technology services.[24] Consequently, responsible transitioning from PCTs may require involvement of a broader set of stakeholders, including clinical and operational leadership of the health systems in which the trials were conducted.

7 | INSIGHTS FOR PCTs

As noted earlier, one of the key rationales for PCTs is their promise of generating real-world social value, including by facilitating uptake of results by relevant decision-makers.[13] Consequently, there should be a presumptive default for PCTs that study results (whether positive or null) be incorporated into future care delivery processes.

Operationalizing this commitment will require prospective planning for post-trial responsibilities by a range of actors, including researchers, healthcare institutions, IRBs, and sponsors. Key considerations that should be addressed as part of this planning include the level of benefit/effect and the type of study outcome that would merit intervention continuation or other related investment; the types of benefits that should be provided, and by whom, after a trial concludes; the relevant stakeholders for supporting continued implementation (and/or de-implementation), and, relatedly the relevant policy levers. With respect to this latter consideration, recent scholarship exploring the translation of PCTs into practice has identified the importance of aligning policy incentives to support real-world implementation of interventions demonstrated as effective through PCTs, including through proactively partnering with professional societies to influence practice guidelines, or with payers to inform coverage determinations.[25]

The argument from social value also provides justification for another post-trial responsibility, namely, dissemination of study results, including sharing aggregate results with affected stakeholders. Study results cannot be implemented into practice if they are not made publicly available. Given that PCTs are designed to influence real-world practice, there is a compelling argument that PCT

researchers have an even greater responsibility to disseminate study results as an act of good faith toward benefit sharing.[13] While the specific stakeholder groups to whom results should be disseminated will vary by trial, relevant groups include patients, clinicians treating the studied condition(s), and others who may shape decision-making about (de)implementation, including operational leaders, policymakers, and payers.[26]

As discussed previously, dissemination approaches that include sharing aggregate results with affected stakeholders are also supported by the principle of respect, demonstrating recognition for, and appreciation of, participants' contributions to research. Similarly, appropriately recognizing the contributions of those involved with PCTs may require looking beyond patient subjects, including clinicians and staff.[27] While there is broad recognition of the ethical arguments supporting sharing aggregate results with research participants in an understandable manner, such dissemination has not been widely adopted. Furthermore, several features characteristic of many PCTs may challenge the applicability of existing best practices for sharing aggregate results with research participants. Large study populations across multiple healthcare systems add logistical complexity. Additionally, the use of waivers of informed consent raises the question of how to approach those who do not realize that they were included in a research study. Future work will be needed to inform strategies for sharing aggregate results from PCTs, with communications tailored to the interests of different stakeholder groups as well as to the circumstances of the research.

Fulfilling post-trial obligations will require proactive involvement of a range of actors, including researchers, health system leaders, institutional review boards, and trial sponsors. Input from research participants should also inform this process. Below, we outline considerations for each.

7.1 | Researchers

While policy and practice leaders (including legislators, healthcare administrators, payers, and institutional leaders) have the primary responsibility to implement changes in healthcare, researchers should nevertheless work to ensure that PCTs are designed with implementation in mind as early as possible, so as to increase their probability of influencing real-world practice. Relevant strategies include: designing trials with an eye toward influencing (de)implementation; identifying and engaging with the relevant policy processes and stakeholders who influence whether and how the intervention under study will be used as the study is being designed; engaging relevant decision-makers to understand the factors shaping decisions about implementation, and incorporating these factors, as feasible, into trial design; presenting findings so as to be both useful to and accessible by those with the responsibility to (de)implement practices based on the study results; providing technical assistance to sustain or scale the intervention after the trial concludes; and engaging with relevant decision-makers following study completion about sustaining or deimplementing interventions, as appropriate.

7.2 | Health system leaders

Health systems play a distinctive role in PCTs, serving not only as research sites, but often also as research gatekeepers, shaping access to potential research subjects, and determining whether the proposed research is an appropriate use of system resources.[28] Prior scholarship has suggested the need to account for this distinctive role of health systems when identifying obligations owed to PCT patient subjects.[22] Therefore, when assessing whether or not to partner in embedded PCTs, health systems should consider not only the impact of the trial on health system operations, but also whether the health system would change practice based on trial results—and, importantly, what metrics would be relevant for that assessment. This suggests the need for a more robust process of institutional sign-off for research protocols than typically exists within many systems, involving not only department chairs or division leaders, but also operational leadership, who are key to decision-making about whether to sustain or deimplement interventions following trial completion. Lack of buy-in from operational leadership to use the results of a PCT to inform decisions about future care delivery undermines the likelihood that the trial will generate social value—and therefore may militate against initiating the trial at all. During the life of the study, it is important to keep health system leaders informed about the progress of the research: even with enthusiastic institutional buy-in for a specific project, leadership and priorities may change and ongoing dialogue should be helpful.

Further, PCTs are embedded in health systems that often struggle with delivering equitable care. As others have described, inadequate attention to these inequities during the design and implementation of PCTs can risk reifying or even exacerbating their impacts.[29-31] Similar concerns may exist during the post-trial phase. For example, in order for post-trial commitments to be equitable a health system's commitment to continue access post-trial to an intervention shown to be effective may require additional attention to disparities in access identified during the trial. Consequently, equity metrics should be among those tracked and considered by health system leaders, with appropriate resources allocated to facilitating post-trial (de)implementation across diverse care settings. This is especially relevant given that, for some, a key motivation to advance post-trial access is a commitment to distributive justice.

7.3 | IRBs

In addition to existing processes for assessing the ethical conduct of PCTs, IRBs should consider incorporating questions about post-trial responsibilities in protocol reviews, including plans for downstream implementation or de-implementation based on study results, as well as for making research findings available and accessible to key stakeholders, including patient-subjects. Such considerations would benefit from attention on initial review, during continuing reviews, and at study closeout; post-trial interests and capabilities may evolve over the course of a trial.

7.4 | Sponsors

To support the likelihood that research results are used by relevant decision-makers to inform clinical and operational practice, sponsors should require discussion in grant proposals about how trial results will be used, as well as how investigators will ensure appropriate dissemination to support that use. Consideration should also be given to including this information in contracts and clinical trial agreements where relevant. Sponsors might also consider offering continuation grants to support interventions shown to be successful, including the development of necessary infrastructure to translate and deliver findings across stakeholder groups.

8 | CONCLUSION

We have argued that existing scholarship on post-trial responsibilities provides incomplete guidance for PCTs, due to the need to consider both the responsibilities of the healthcare delivery systems into which PCTs are embedded, as well as responsibilities for deimplementation when interventions integrated into usual care settings do not demonstrate meaningful benefit. We propose that identifying and fulfilling post-trial responsibilities will require planning by diverse research partners, including researchers, health system leaders, institutional review boards, and sponsors. Our goal for this article is that it can expand conversations about how to ensure that the knowledge gained from PCTs does, in fact, influence real-world practice, while demonstrating respect for those who contribute to that knowledge generation.

FUNDING INFORMATION

This work was supported within the National Institutes of Health (NIH) Pragmatic Trials Collaboratory through cooperative agreement U24AT009676 from the National Center for Complementary and Integrative Health (NCCIH), the National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute (NCI), the National Institute on Aging (NIA), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Nursing Research (NINR), the National Institute of Minority Health and Health Disparities (NIMHD), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the NIH Office of Behavioral and Social Sciences Research (OBSSR), and the NIH Office of Disease Prevention (ODP). This work was also supported by the NIH through the NIH HEAL Initiative under award number U24AT010961. Dr. Morain received additional support through a grant from The Greenwall Foundation.

CONFLICT OF INTEREST STATEMENT

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NCCIH, NIAID, NCI, NIA, NHLBI, NINR, NIMHD, NIAMS, OBSSR, or ODP, or the NIH or its HEAL Initiative. Dr. Morain received support for this work through a Making a Difference grant from The Greenwall Foundation. Jeremy Sugarman is a member of Merck KGaA's Ethics Advisory Panel and Stem Cell Research Oversight Committee; a member of IQVIA's Ethics Advisory Panel; a member of Aspen Neurosciences Clinical Advisory Panel; was a member of a Merck Data Monitoring Committee and a consultant to Biogen. None of these activities is related to the material discussed in this manuscript. The other authors have no conflicts to declare.

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How to cite this article: Morain SR, O'Rourke PP, Ali J, et al. Post-trial responsibilities in pragmatic clinical trials: Fulfilling the promise of research to drive real-world change. *Learn Health Sys*. 2024;8(3):e10413. doi:10.1002/lrh2.10413