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Intervention Fidelity in Pain Pragmatic Trials for Nonpharmacologic Pain Management: Nuanced Considerations for Determining PRECIS-2 Flexibility in Delivery and Adherence

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Abstract

Nonpharmacological treatments are considered first-line pain management strategies, but they remain clinically underused. For years, pain-focused pragmatic clinical trials (PCTs) have generated evidence for the enhanced use of nonpharmacological interventions in routine clinical settings to help overcome implementation barriers. The Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2) framework describes the degree of pragmatism across nine key domains. Among these, “flexibility in delivery” and “flexibility in adherence,” address a key goal of pragmatic research by tailoring approaches to settings in which people receive routine care. However, to maintain scientific and ethical rigor, PCTs must ensure that flexibility features do not compromise delivery of interventions as designed, such that the results are ethically and scientifically sound. Key principles of achieving this balance include clear definitions of intervention core components, intervention monitoring and documentation that is sufficient but not overly burdensome, provider training that meets the demands of delivering an intervention in real-world settings, and use of an ethical lens to recognize and avoid potential trial futility when necessary and appropriate.

Keywords

pragmatic clinical trial; PRECIS-2; flexibility; treatment; adherence; pain

Introduction

Pain and co-occurring conditions are a serious public health challenge. In particular, chronic pain, typically defined as pain lasting 3 months or longer, affects about 20% of American adults.[32] It contributes to reduced mobility and quality of life, dependence on opioids, and mental health conditions such as anxiety and depression. Reflecting the multidimensional experience of pain, a seminal 2011 report from the Institute of Medicine[17] (now the National Academies of Sciences, Engineering, and Medicine) highlighted the need to transform pain management to be patient-centered, integrated, evidence-based, multimodal, and interdisciplinary. A substantial and growing evidence base supports the first-line use of various nonpharmacological pain management strategies. These include body-based approaches such as massage, acupuncture and spinal manipulation, and physical therapy; psychologically guided treatments; and others.[28] Despite clinical guidelines to support

these approaches,[24,31] most current pain management is still limited to medication-based approaches, due to numerous barriers that limit the widespread availability and integration of nonpharmacological approaches into routine care for chronic pain.[10,29]

Focus of this article: Maintaining intervention fidelity in pain pragmatic clinical trials

Pragmatic clinical trials (PCTs) have been used for years to generate evidence for the use of interventions in routine clinical settings.[7] PCTs differ from explanatory trials by addressing generalizability of results. PCTs test interventions in a real-world setting and measure clinical outcomes relevant to both patients and healthcare systems. Pragmatic research emerged in a research environment that for decades held the double-blind, placebo-controlled trial as the gold standard for evaluating treatment efficacy – a well-suited strategy for studies that evaluated single-modality treatments such as medications. Many researchers, clinicians, and patients continue to value elements of explanatory trials for determining efficacy but increasingly appreciate the value of pragmatic research to determine effectiveness.

Pain-focused PCTs are particularly suited to test the effectiveness of nonpharmacologic management strategies for multidimensional conditions like pain, which is unique among individuals based upon the highly variable contexts in which people live.[26] Conclusive results from pain PCT studies might encourage use of nonpharmacological strategies by demonstrating effectiveness along with ways to integrate these approaches into clinical pain care pathways. However, to maintain scientific and ethical rigor, PCTs must ensure that pragmatic elements such as patient-centered treatment flexibility do not compromise delivery of interventions as designed. Herein, we describe key considerations related to flexibility in delivery and adherence in pain-focused PCTs of complex, often multimodal nonpharmacological interventions. We focus in particular on the design, monitoring, and documentation of intervention core components and the related role of provider training in methodologically and ethically sound pain-focused PCTs.

The Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2) framework

The Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2) framework highlights key methodological areas that identify which aspects of a clinical trial are pragmatic or explanatory in nature. Use of the PRECIS-2 framework has been recommended as a way to improve reporting standards for all clinical trials.[22] It was conceived and developed to help investigators describe clinical trials based on the degree of pragmatism across nine key domains. Each domain is scored on a 5-point Likert continuum (from 1=very explanatory “ideal conditions” to 5=very pragmatic “usual care conditions”). They include eligibility, recruitment, setting, organization, flexibility (delivery), flexibility (adherence), follow-up, primary outcome, and primary analysis.[22] Decisions regarding PRECIS-2 design domains in PCTs can vary considerably based upon the key scientific question(s) examined, the specific pain management approach being tested, and the participating trial population and settings.

A recent narrative review that employed the PRECIS-2 framework to assess published PCTs of nonpharmacological approaches for pain management identified and highlighted specific

design and methodological features that could inform planning for future PCTs.[13] For the most part, the characteristics that make a trial more or less explanatory or pragmatic are quite clear. For example, the most pragmatic of pain management trials employ broad eligibility criteria to mimic heterogeneity within a study population, including for example co-occurring medical and mental health conditions. In contrast, explanatory trials typically include more stringent exclusion criteria, aiming to recruit more homogenous study populations. To emulate real-world conditions, PCTs typically rely on support from a range of clinical and organizational partners, whereas highly pragmatic trials are embedded into existing clinical workflows. In PCTs, healthcare staff (rather than dedicated research personnel) assume greater responsibilities for recruitment, intervention delivery, and outcome assessment. In contrast, explanatory trials are more likely to have dedicated research personnel performing these functions outside existing healthcare staff workflows.

Why focus on flexibility (delivery) and flexibility (adherence)?

The review by Gordon and colleagues noted that some PRECIS-2 domains were challenging to define within pain-focused PCTs and may require a more nuanced view. In particular, the PRECIS-2 domains flexibility (delivery) and flexibility (adherence) raise several important issues. The PRECIS-2 framework articulates “flexibility in delivery” as, “How should the intervention be delivered?” and “flexibility in adherence” as, “What measures are in place to make sure participants received the treatment as intended and adhere to the intervention?” According to the PRECIS-2 framework, the most pragmatic design approach to flexibility in delivery allows usual care providers to decide how to deliver an intervention, with little to no monitoring of treatment delivery or adherence other than what is done in routine clinical care. Yet, the PRECIS-2 flexibility domain, as it relates to both delivery and adherence, requires nuanced interpretation.[13,16] Understanding intervention delivery and adherence fidelity in a PCT is ethically and scientifically important for establishing and maintaining a distinction between the trial interventions and usual care and/or other control conditions.

Tailoring Pragmatism to Reality: Flexibility Considerations

In 2017, the Pain Management Collaboratory (PMC), was established. It is a novel tri-government agency partnership, funded by and conducted in collaboration with the National Institutes of Health (NIH), the Department of Defense (DOD), and Department of Veterans Affairs (VA). The PMC supports the conduct of several large, multisite PCTs of nonpharmacological approaches for the management of pain and common co-occurring conditions within military and veteran health systems.[19] This major investment was informed by the awareness that military service members and veterans are particularly affected by pain[1] and that the DOD and VA, as integrated learning health systems, represent ideal settings for large-scale PCTs. Several PMC-supported trials are underway, and this community of investigators have become aware of challenges related to ensuring fidelity of treatment delivery and adherence in PCTs.

Defining core intervention components

Regardless of the level of pragmatism, PCTs should clearly define core components of an experimental intervention and usual care, control, or other comparison conditions.[5]

Defining core components prior to the trial starting provides guidance about the degree of flexibility that is acceptable within the context of intervention delivery and adherence during the trial. In trials testing psychologically based interventions, for example, it could be acceptable to vary the frequency and timing of treatment sessions and/or accommodating other modifications consistent with a patient-centered approach.

Behavioral protocols used for pain management rely on treatments informed by psychological and behavioral science theory and practice. These approaches rely on higher-than-normal levels of active engagement from patients and providers compared to providing educational materials as in usual care, which do not usually involve behavior change techniques. In PCTs, providers delivering such interventions must be attuned to a patient's psychological status, familiar with issues and approaches related to behavior change, and able to identify and manage emotional and behavioral concerns that arise during treatment. It is also true that staff providers in PCTs may augment an experimental intervention, offering trial participants information and support that goes beyond the core element(s) of the trial intervention. For example, routine chiropractic care or physical therapy for chronic back pain primarily involves manual therapy and structured exercise, but also features education, home exercise recommendations, and other ideas consistent with adaptive pain self-management.[11,20,21,30]

Monitoring and documenting intervention fidelity

Because PCTs operate within existing clinical environments, they rely on active engagement from staff providers and clinical teams as well as clinical and organizational administrative partners. In explanatory studies, investigators are expected to monitor and document intervention delivery and adherence using approaches that often require considerable time and effort from both research staff and participants. In contrast, and in keeping with the PRECIS-2 framework, an ideal PCT may rely solely on a flexible, nonburdensome approach to monitoring and reinforcing adherence to a trial intervention. This can be achieved by using a standard, or modified monitoring strategy, such as the template for intervention description and replication (TiDiER) checklist.[15] Several PMC PCTs collect trial-related information based on review of electronic health records, allowing monitoring of clinic visits (in-person or virtual) and stop codes, prescribed interventions, and other information such as psychologically based therapy session topics.[6,8,12,14,27] One PMC trial uses the electronic health record to monitor intervention fidelity as well as to inform future implementation strategies.[9] The approach assesses key process indicators for each care pathway, enabling tracking of time to first appointment (virtual or in-person), number of sessions attended, and whether participants were stratified by risk. Other sources of delivery and adherence data for PMC PCTs include interventionist and patient self-reports.

To be most pragmatic on the PRECIS-2 scale, PCT investigators should incorporate monitoring that uses routine documentation in clinical records and does not add burden to clinician workflows. For example, the Defense Health Agency (DHA) and its military health system and Veterans Health Administration's (VHA) pain management policies require clinicians to incorporate a plan for timely "pain reassessment" after starting a new treatment. Documentation of pain reassessments could help capture important information

about patients' enactment and adherence to interventions being examined. One PMC trial evaluating stepped care management of low back pain in the military health system refers to an electronic health record during trial visits and review of medical records at the end of the trial.[8]

Valid interpretation of treatment effect size requires careful tracking and reporting of disruptions to intervention delivery and adherence. If no participants are receiving the intended dose of an intervention, further investigation is warranted to better understand the reason why. In this pragmatic approach, clinicians are not asked to document intervention delivery and adherence beyond their normal practices.

Provider training

Within the PRECIS-2 framework, the "organizational" domain encourages PCTs to consider how an intervention is delivered in a trial as well as how the intervention would be made available to patients in usual care settings.[22] Multimodal nonpharmacological pain management strategies require the expertise and experience of a range of healthcare providers and affiliated staff with specialized roles in pain management. These include pain medicine physicians, nurses, rehabilitation specialists, behavioral health specialists, and complementary and integrative health providers, among others. Cognitive-behavior therapy and other evidence-based psychological approaches for chronic pain management are typically multicomponent, focusing on skills training and targeting maladaptive thinking and behaviors.[3] Due to the complexity of these approaches, a key concern in PCTs of nonpharmacological pain care is the level of training, experience, and expertise of the person(s) delivering a trial intervention.[18]

Because pain-focused PCTs test already established interventions or care pathways based on previously demonstrated efficacy, protocols often are already available or have been adapted to describe both a trial intervention and its intended delivery and adherence. These types of interventions are considered "validated" care.[2] For example, evidence-based psychological interventions for managing chronic pain and common co-occurring conditions often follow published provider and patient guidance, toolkits, and/or manuals that support promoting fidelity of treatment delivery. The VHA evidence-based psychotherapy initiative, for example, includes a programmatic effort to promote veterans access to cognitive-behavioral therapy for chronic pain.[23] This clinical programmatic initiative offers intensive training in the delivery of this intervention with fidelity and provides ongoing support and supervision for therapists. Several PMC PCTs incorporate similar models of clinician training to increase the likelihood that core elements of an intervention are delivered. For example, one PMC trial is using telehealth to enable a small pool of physical therapists deliver psychologically informed treatment to ensure training consistency among providers that will deliver a trial intervention.[9]

Altering scheduling practices or changing site-delivery locations may also be necessary during a PCT, as long as they do not compromise the core components of an intervention being evaluated in a trial. Two such adjustments were made in a PMC trial[8] in which patients with chronic low back pain are initially randomized to receive physical therapy or a holistic approach across eight health domains.[25] First, staff deployment to prioritize

community COVID-19 vaccination efforts meant that those staff were not available to deliver the trial intervention. Scheduling and attendance within treatment sessions were disrupted to such an extent that a decision was made to deliver the experimental intervention in alternative clinic settings that had sufficient staffing to deliver the treatment sessions. Second, a higher rate of suicides at one military installation and the need to address psychological consequences slowed trial enrollment and reduced the availability of trained behavioral health providers to deliver the trial intervention. The research team decided to deliver the intervention in a different facility that had more staff available.

Ethical and statistical considerations

Clinical trials are often monitored based on ethical, administrative, and economic factors. Periodic reviews of accumulating data are conducted to document potential evidence of harm, efficacy, futility, and feasibility. Whether explanatory or pragmatic, it is considered unethical to continue a trial if a treatment is i) unsafe, ii) clearly beneficial, iii) ineffective, or iv) unable to generate a valid answer to a scientific question. Any of these outcomes can affect interventions being tested in PCTs, although there are nuances to consider when compared to explanatory trials. First, safety concerns are typically minimal with nonpharmacological pain management, especially when delivered within an existing clinical workflow. Therefore, there may be less of an emphasis on monitoring safety for a PCT. Second, the issue of whether a PCT generates a valid answer may require in-depth consideration of how the treatment was delivered; especially if the trial is embedded into existing clinical workflow. This issue is not as much of a consideration for explanatory trials where treatment delivery is under the direct control of the research team. Indeed, the issue of “how the treatment was delivered” and that linkage to trusting PCT results is one of the primary reasons for highlighting the flexibility domains in this focus article.

A lack of attention to intervention delivery and adherence, and the inability to monitor and document these domains, introduces ethical concerns and statistical challenges – some of which can be addressed. In explanatory clinical trials, a Data Safety Monitoring Board (DSMB) reviews intervention delivery and adherence and identifies issues of concern that may threaten a trial’s integrity. Many PCTs similarly require a DSMB to protect the interests and safety of participants.[4] Additional monitoring of intervention delivery and adherence by DSMBs provides another opportunity to ensure scientific and ethical rigor (half of the DSMBs for the PMC PCTs include monitoring of intervention delivery and adherence as part of their charter). The failure to identify and correct for major concerns about fidelity of delivery or adherence early in the conduct of a PCT could bias the findings toward a null result that may not reflect a reliable test of the relative effectiveness of the intervention. In some cases, pre-specified and carefully planned and executed interim futility analyses can manage such outcomes.

Formal statistical procedures can be defined in advance and usually performed after sufficient information has been collected in a trial (usually at least 50%) to make an informed decision. However, futility can arise in a trial when there is a failure to maintain separation of interventions. Developing thresholds to trigger action by a research team can improve fidelity of intervention delivery and/or adherence or trigger a futility analysis.

If separation of interventions cannot be maintained, formal statistical analyses can be employed that may signal intervention futility. These futility concerns may come into focus during the conduct of PCTs that have not been designed to monitor fidelity of delivery and adherence and intervene in a timely fashion if necessary. A proper assessment and formal report of feasibility barriers also informs future implementation considerations.

Conclusion

Flexibility in intervention delivery and adherence is a hallmark of high-quality, patient-centered care. In PCTs, the critical components of an intervention must be preserved. Therefore, PCTs must balance patient-centered treatment flexibility with the ability to ensure trial participants receive interventions as intended so data collected provide valid results. In either routine care or PCTs, it is ethically problematic to expose individuals to an unintended treatment, which limits clinical benefit and may also negatively influence future healthcare decisions.

Relatedly, quality assessment methods for clinical trials prioritize internal validity to maintain rigor (e.g., blinding interventions). These methods were developed with explanatory trials in mind and can be harder to apply to PCTs. The increased emphasis of PCTs on generalizability and estimating effectiveness enable PCTs to inform clinical practice and policy. However, there may be a need to develop alternative quality assessment methods specific to PCTs before they are used to inform clinical practice guidelines.

PCTs are intended to evaluate the effectiveness of interventions that have been previously subject to rigorous randomized controlled efficacy trials, potentially broadening the knowledge base to populations excluded from initial studies. Even when effectiveness is not demonstrated, PCT results still can be used to inform practice patterns and treatment delivery by revealing previously underrecognized barriers that can be addressed through further research. They also offer an opportunity to include populations who may have been excluded from explanatory trials, expanding the evidence base and understanding of outcomes. Although rigorously conducted PCTs with clearly positive results do not guarantee widespread adoption, they do offer scientific evidence needed to support decisions about insurance coverage, clinician training, policies to address access, and other implementation barriers.

Ensuring ethical rigor and scientific validity in pragmatic research is critical for their value in guiding clinical practice, including analyses of failed trials to reveal system-level inequities that could be approached further with new research. Investigators designing and conducting PCTs, and using PRECIS-2 as a guide, must recognize the need to protect the fidelity of interventions with flexibility in intervention delivery and adherence required for patient-centered care. Key principles include clearly defining intervention core components, sufficient but not overly burdensome intervention monitoring and documentation, and provider training that meets the demands of delivering the treatment in real-world settings. Each of these principles should be viewed through an ethical lens, enabling investigators to recognize and avoid factors that limit the ability to trust a trial’s results.

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Highlights

- Pragmatic clinical pain trials are increasingly important to address clinical practice gaps
- Pragmatic pain trials must ensure that flexibility does not compromise intervention fidelity
- This article highlights key principles for balance flexibility and fidelity in pragmatic trials

Perspective

This article presents nuances to be considered when applying the PRECIS-2 framework to describe pragmatic clinical trials. Trials must ensure that patient-centered treatment flexibility does not compromise delivery of interventions as designed, such that measurement and analysis of treatment effects is reliable.