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BRIEF REPORT

Adapting to disruption of research during the COVID-19 pandemic while testing nonpharmacological approaches to pain management

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Abstract

The COVID-19 pandemic has slowed research progress, with particularly disruptive effects on investigations of addressing urgent public health challenges, such as chronic pain. The National Institutes of Health (NIH) Department of Defense (DoD) Department of Veterans Affairs (VA) Pain Management Collaboratory (PMC) supports 11 large-scale, multisite, embedded pragmatic clinical trials (PCTs) in military and veteran health systems. The PMC rapidly developed and enacted a plan to address key issues in response to the COVID-19 pandemic. The PMC tracked and collaborated in developing plans for addressing COVID-19 impacts across multiple domains and characterized the impact of COVID-19 on PCT operations, including delays in recruitment and revisions of study protocols. A harmonized participant questionnaire will facilitate later meta-analyses and cross-study comparisons of the impact of COVID-19 across all 11 PCTs. The pandemic has affected intervention delivery, outcomes, regulatory and ethics issues, participant recruitment, and study design. The PMC took concrete steps to ensure scientific rigor while encouraging flexibility in the PCTs, while paying close attention to minimizing the burden on research participants, investigators, and clinical care teams. Sudden changes in the delivery of pain management interventions will probably alter treatment effects measured via PMC PCTs. Through the use of harmonized instruments and surveys, we are capturing these changes and plan to monitor the impact on research practices, as well as on health outcomes. Analyses of patient-reported measures over time will inform potential relationships between chronic pain, mental health, and various socioeconomic stressors common among Americans during the COVID-19 pandemic.

Keywords

Pain management, COVID-19, Disruption of research, Pragmatic clinical trials, Interventions

Implications

Practice: As a result of the COVID-19 pandemic, the way we deliver nonpharmacological pain interventions has changed, prompting that we recognize and respond to shifting needs in patient care.

Policy: Shifts in care delivery during and beyond the COVID-19 pandemic may deepen disparities in undertreatment of pain, and policymakers must be conscious of this effect, especially in at-risk populations.

Research: Pragmatic clinical trials are well-suited in many ways to adapt to disruption, like that caused by the COVID-19 pandemic, but researchers should be sensitive to potential mediation of treatment effects caused by these disruptions.

INTRODUCTION

By late winter of 2020, the COVID-19 pandemic had overtaken our lives, changing how we live, work, and take care of each other. The enormity and gravity of COVID-19 have eclipsed thousands of carefully planned research projects underway, affecting the conduct—and, probably, outcomes—of thousands of clinical studies of numerous health conditions [1]. Amid the breakneck pace of efforts to stem the disruption from COVID-19, we must pause to recognize that its urgency punctuated other ongoing and serious crises. Two of them are the opioid epidemic [2] and the enormous, unsolved problem of managing chronic pain [3,4]. These issues are interdependent: insufficient and underinformed pain management can contribute to minimally effective (and potentially addictive) prescriptions and/or unproven procedures. These complex problems require complex and multipronged solutions in a rapidly changing, overtaxed health care environment. Each challenge has also revealed pressure points in health systems that may worsen health disparities [5].

Chronic pain and its management are significant concerns for military service members and veterans living in the USA, many of whom were among the 2.5 million active military deployed since 2001 in Operations Enduring Freedom, Iraqi Freedom, and New Dawn in Iraq and Afghanistan [6–8]. Among this population, chronic pain frequently coexists with other problems, including mental illness, substance abuse, and sleep disturbances [8–10]. Research has

shown that evidence-based, nonpharmacological approaches to pain management, including complementary and integrative health approaches, reduce pain intensity and heighten physical and emotional function and well-being—with minimal risks compared to the use of opioids. However, currently, there is insufficient evidence for maximally effective use of these modalities (as well as for multimodal, integrated therapies) in routine clinical management of chronic pain [3,11].

The National Institutes of Health (NIH) Department of Defense (DoD) Department of Veterans Affairs (VA) Pain Management Collaboratory (PMC) is currently supporting 11 large-scale, multisite, embedded pragmatic clinical trials (PCTs) in military and veteran health systems to evaluate nonpharmacological approaches and integrated pain care models to manage pain and important comorbidities [12]. PCTs offer the opportunity to develop and test interventions in "real-world" health care environments: a strategy that blurs the distinction between research and care and which thus offers the opportunity for rapid implementation of effective practices within study populations in their usual-care health systems [13]. Formed in 2017, the PMC consists of a research core of 11 PCTs, a coordinating center (Pain Management Collaboratory Coordinating Center [PMC^3]), seven domain-oriented Work Groups, a Military Treatment Facility Engagement Committee (MTFEC), and a Steering Committee, which operate within two integrated health systems: the Veterans Health Administration (VHA) and the Defense Health Agency (DHA). Currently, 3 years into its efforts, most PMC PCTs are transitioning between their planning (UG3) phase and implementation (UH3) phase. In this current crisis within a crisis, the PMC is aggressively developing and enacting a plan to address key issues in response to the COVID-19 pandemic.

METHODS

The 11 PMC PCTs are unique in context, approach to pain management, timeline, and national organizational policies and guidance. By nature of being embedded within two geographically distributed health systems that serve similar populations but that have distinct practices, there is variation in the policies and cultures affecting postponement of care, suspension of face-to-face visits, suspension of elective procedures and surgery, and transitioning to use of virtual care. Military treatment facility policies are issued by DHA, while VHA policies are issued by a national central office and carried out by 21 regional Veterans Integrated Service Networks and 170 medical centers. Funding complexities that have arisen during the pandemic have been addressed and coordinated by the three PMC sponsors: the NIH, DoD, and VA, facilitated by Collaboratory leadership. The PMC PCTs vary in their size and complexity—their geographical distribution and federated approach to guidance complicate a simple and centralized characterization of the impact of COVID-19, due to influences by regional, state, and local impacts of the pandemic.

Beginning in January 2020, as the COVID-19 pandemic unfolded, we recognized the importance of tracking its effects across the 11 PCTs while using the PMC Work Groups as a vehicle for communication and documentation of effects of the pandemic. Particularly engaged were Work Groups focused on biostatistics and study design; phenotyping; stakeholder engagement and ethical and regulatory issues; availability of COVID-19 relevant data in electronic health records (EHRs); and implementation-science approaches for tracking COVID-19 impacts. Although the PMC is a large, mainly decentralized effort, our culture emphasizes the vitality of good communication; collaborative, congenial relationships (including defined mechanisms for conflict resolution); and cross-collaboratory standards, where feasible. We thus sought to harmonize COVID-19 tracking measures at the PMC^3 level, as we did for previous processes in place for participant phenotyping and PMC clinical-outcome measures. We tracked COVID-19 impacts across multiple domains and characterized the impact of COVID-19 on PCT operations. Specific domains that were tracked include intervention delivery, data collection, trial integrity, clinical outcomes, regulatory approval, study recruitment, and statistical analyses. PMC Work Group project managers updated the internal tracking measure as needed based upon formal and informal discussion with Work Group members and PCT investigators and with oversight from PMC^3 leadership. Frequent review and discussion involved members of the PCT investigative teams, the Coordinating Center, the Steering Committee, the MTFEC, and PMC sponsoring organizations.

It seems likely that patient-reported outcome data may be clouded by the effect of COVID-19 on pain as an experience and, thus, also affect mental health, substance use, and access to care. We, thus, decided collectively to capture patient experiences related to COVID-19 and coalesced a harmonized set of COVID-19 patient-reported measures to be used across all PCTs to facilitate later meta-analyses and cross-study comparisons of the impact of COVID-19. We developed questions to assess the impact of COVID-19 on an individual's psychosocial, functional, and financial status. We identified these factors as potential mediators influencing treatment effects noted in clinical research across the COVID-19 pandemic period. Although these data are applicable to pain-related outcomes, we structured our questions without direct attribution to pain status to allow for broad interpretation and application

Table 1 | Pragmatic clinical trials of the Pain Management Collaboratory with modifications in response to challenges by COVID-19 pandemic

Study name	PIs	Brief description of trial/intervention	Study modifications
Improving Veteran Access to Integrated Management of Back Pain (AIM-BACK)	S. George, S. N. Hastings	Comparison of the effectiveness of two low back pain care pathways designed to enhance access to nonpharmacological pain treatments according to the most recent guidelines and a biopsychosocial approach to care	• Delayed start of implementation phase recruitment, without protocol modification
Whole Health Team vs. Primary Care Group Education to Promote Non-Pharmacological Strategies to Improve Pain, Functioning, and Quality of Life in Veterans	K. Seal, W. Becker	Comparing a VA Whole Health Team (WHT) approach and Primary Care Group Education (adapted cognitive behavioral therapy for chronic pain [CBT-CP]) to Usual VA Primary Care (Control)	• Delayed start of implementation phase trial recruitment • Study protocol revision to convert active study interventions to telehealth following guidelines for usual primary care at each enrollment site
Chiropractic Care for Veterans, a Pragmatic Randomized Trial Addressing Dose Effects for Chronic Low Back Pain	C. Goertz, C. Long	Evaluating the impact of varying doses of standard chiropractic care and chronic pain management on clinical and health services outcomes and evaluating patient and clinician perceptions of nonspecific chiropractic treatment factors	• Delayed start of implementation phase recruitment without protocol modification
SMART Stepped Care Management for Low Back Pain in the Military Health System	J. Fritz, D. Rhon	Comparing the effectiveness and cost effectiveness of Stepped Care pain management options in a multiphase sequential, randomization trial	• Temporary suspension of recruitment during implementation phase with continued follow-up for enrolled participants
Cooperative Pain Education and Self-Management: Expanding Treatment for Real-world Access (COPES ExTRA)	A. Heapy	Comparing an interactive voice response (IVR) based form of CBT-CP versus in-person CBT-CP provided by clinicians previously trained through VA's evidence-based psychotherapy program	• Continued recruitment, with study revision • Modification of control arm from face-to-face CBT-CP to synchronous CBT-CP delivered face-to-face or via telehealth, compared to asynchronous IVR-based CBT-CP intervention
Engaging Veterans Seeking Service Connection Payments in Pain Treatment	M. Rosen, S. Martino	Testing the effectiveness and cost-effectiveness of Screening, Brief Intervention and Referral to Treatment for Pain Management (SBIRT-PM) as a mechanism of engaging veterans who apply for service connection compensation in a variety of nonpharmacological pain treatments	• Continued recruitment with study revision • Modified intervention to permit discussion of pandemic-related stressors and updated information about available virtual and self-help pain and substance use services accessible to veterans • Added a counseling visit to intervention as "booster" follow-up session • Included a COVID-19 questionnaire to identify how the pandemic affects participants' health, social determinants of health, and access to health care

(Continued)

Table 1 | Continued

Study name	PIs	Brief description of trial/intervention	Study modifications
APPROACH: Assessing Pain, Patient Reported Outcomes and Complementary and Integrative Health: A National Dissemination Project	S. Taylor, S. Zeliadt	Comparing the effectiveness of practitioner-delivered complementary and integrative health (CIH) combined with self-care CIH versus either practitioner-delivered or self-care among veterans with chronic musculoskeletal pain	• Slight protocol modification
Targeting Chronic Pain in Primary Care Settings Using Internal Behavioral Health Consultants	D. McGeary, J. Goodie	Examine the effectiveness of monthly booster sessions of brief CBT-CP delivered via telehealth media	• Continued follow-up for enrolled participants in pilot study • Modifying plans for implementation phase study to ensure that all aspects of research can be implemented virtually
Testing Two, Scalable, Veteran-Centric Mindfulness Based Interventions for Chronic Musculoskeletal Pain: A Pragmatic, Multisite Trial	D. Burgess	Comparing the effectiveness of a mobile application plus group mindfulness-based intervention to a mobile application-only mindfulness-based intervention as part of the Learning to Apply Mindfulness to Pain (LAMP) project	• Delayed start of implementation phase recruitment • Modification of intervention to virtual care delivery method using video-conferencing software
Ultrasound-Guided Percutaneous Peripheral Nerve Stimulation: A Non-Pharmacologic Alternative for the Treatment of Postoperative Pain	B. M. Ilfeld	Testing the feasibility and effectiveness of percutaneous peripheral nerve stimulation on postoperative analgesia, opioid requirements, physical and emotional functioning, development of chronic pain, and ongoing quality of life in patients undergoing ambulatory surgery	• Temporary suspension of pilot study recruitment without protocol modification due to suspension of nonemergent surgeries
Resolving the Burden of Low Back Pain in Military Service Members and Veterans: A Multi-Site Pragmatic Clinical Trial (RESOLVE Trial)	S. Farrokhi, C. Dearth, E. Russell Esposito	Evaluating the effectiveness of an active clinical practice guideline adherence strategy utilizing an education/audit/feedback model with specific training in psychologically informed physical therapy as compared to usual care	• Delayed start of pilot study recruitment • Exploring study protocol modification to account for telehealth visits

of this measure to other areas of clinical research. The harmonized outcome assessment was adopted broadly across nearly all PCTs, with individual frequency of data collection and use determined by each PCT's data collection strategy. Development of this intentionally concise set of measures (one page) was guided by past, well-defined processes, surveys, and instruments developed by the NIH Disaster Research Response Program for use in anticipation of, during, or following a natural disaster [14]. These included the COVID-19-relevant Behavioral and Social Science domains for clinical or population research and COVID-19-related measurement protocols currently in use as part of the PhenX Toolkit.

RESULTS

The rapidly evolving pandemic brought heightened focus of frequent PMC Work Group discussions, which unearthed both immediate and longer-term issues related to effects of the pandemic on the management of chronic pain and our ability to test and deliver integrated care solutions to individuals in at-risk military and veteran populations. As social isolation imposed by the pandemic raises the risk for substance use and addiction and probably exacerbates existing mental health conditions [15], the PMC's focus on nonpharmacological therapies takes on a new level of urgency. Because pain is a complex, multidimensional personal and social experience, it is especially important to consider potential impacts of changes in socially relevant phenotyping variables, such as employment, income, emotional, and mental health, on PCT research participants. This focus resonates with growing interest and prioritization of attention to social determinants of health by the U.S. Department of Health and Human Services [16]. Herein, we report initial findings that reveal an array of actual and potential impacts of the COVID-19 pandemic on PCT operations and outcomes. When necessary and/or appropriate, PCTs made protocol changes, as guided by the regulatory board and sponsoring organization direction and as-needed consultations with PMC biostatisticians. Effects varied widely: Some PCTs experienced little to no effect, whereas others were forced to temporarily suspend research activities (Table 1).

Effects on delivery of interventions

The PMC PCTs are testing a range of pain management interventions that have been affected by the COVID-19 pandemic in both anticipated and unanticipated ways. Nonurgent and nonemergent face-to-face care, including surgeries, have been postponed in accordance with federal/state guidelines and facility-level directives during the COVID-19 pandemic. As a result, trials involving peri-operative interventions or interventions highly dependent on in-person, hands-on care—such as chiropractic care and physical therapy—became temporarily unavailable or at least greatly disrupted. The increasing availability and use of virtual care, which was already a priority for both DHA and VHA, has accelerated out of necessity given the rapid unfolding of the pandemic and is having a range of effects on the availability and method of delivery of pain management approaches. A shift to all-virtual care for interventions with a history of virtual delivery (such as psychological approaches) and for interventions where robust telehealth approaches had not been established (such as chiropractic care and physical therapy) may affect scientific rigor. Geographic variability across these health systems may affect the availability and use of virtual care based upon differences in the robustness of pre-COVID-19 telehealth implementation and social-distancing timelines among states: a potential mediator of treatment effectiveness being tracked centrally by the PMC. As one example, in a PMC study assessing technology-assisted care delivery, the digitalization of usual-care processes resulted in fewer differences between the treatment and control conditions than when the trial was proposed. The Cooperative Pain Education and Self-management: Expanding Treatment for Real-world Access (COPES ExTRA) study was originally designed to compare the effectiveness of an interactive voice-response based cognitive behavioral therapy (CBT) pain self-management intervention (COPES) with in-person CBT, for reducing pain and improving function for veterans with chronic pain [17]. However, in the context of COVID-19, in-person CBT is now being delivered virtually, over the phone and by videoconference. Thus, one key potential advantage of COPES (the ability to participate in treatment from home relative to in-person CBT) is no longer relevant, although other differences remain. The asynchronous nature of COPES may render it a lower burden treatment because patients can participate at their convenience, not only during business hours but also with reduced treatment-session time. The trial will examine asynchronous delivery of COPES without real-time contact with a therapist to synchronous CBT for chronic pain delivered by a therapist over the phone or via videoconferencing.

Effects on outcomes

Anticipated reductions in clinical encounters due to the suspension of many face-to-face interventions and rapid transition to telehealth interventions may result in missing phenotyping and outcome data in participant EHRs, complicating analyses. One PMC PCT, the SMART Stepped Care Management for Low Back Pain in Military Health Systems, employs a sequential, multiple-assignment, randomized trial (SMART) design, an adaptive approach of the VA Stepped Care Model [18], adopted as the standard of care in DHA as well. In this study, the intervention components have been affected very differently

by the pandemic based upon changes to delivery media—ranging from a minimal impact in a remotely delivered lifestyle intervention to a major impact on face-to-face physical therapy. From a research perspective, we can expect potential alterations in the strength of treatment effects based on changes in delivery media, as well as individuals' preference to talk about issues related to COVID-19 rather than pain management during CBT. From the perspective of research participants, these shifts might be positive (e.g., reducing cost and travel barriers) or negative (e.g., decreased access to care from poor connectivity and insufficient digital literacy).

Effects on regulatory approvals and ethical issues

Like other groups conducting clinical, community-, and population-based research studies, PMC PCTs have the responsibility to remain in timely and open communication with their institutional review boards and sponsoring agencies. In the current environment, it remains important that PCTs document and make formal requests for project modifications as detailed by federal regulations for research with human subjects (21 CFR 56.108(a)(4), 45 CFR 46.108(a)(3)(iii)). For those PCTs experiencing a shift to virtual care, additional regulations affect both care delivery and data collection, including the use of approved delivery media. Such considerations were done in close contact with PCT investigators, sponsoring organizations and their program officers, relevant staff from institutional review boards and data-safety monitoring boards, PMC[3] leadership, and Work Groups. Ethical issues arise related to research participants' capacity to be informed, with changes in consent processes involving the use of sophisticated virtual processes (e.g., receiving/sending encrypted email and smartphone screen capture of informed consent documents) and changes in delivery media from internally hosted applications to third-party software applications. These tasks and modifications may make it difficult for some study participants to fully comprehend informed consent materials.

Effects on participant recruitment

Realities of the pandemic period noted above are likely to lead to changes in participant recruitment. These effects may include increased interest in participating in the PMC PCTs as a function of limited availability of some pain interventions due to restrictions from the pandemic. A characteristic feature of the PMC is that all the PCTs are embedded within federated data systems consisting of linked EHRs. Decreases in the frequency of clinical encounters that result in missing EHR data may dampen recruitment efforts since many of the PCTs rely on EHR data as a means of determining eligibility, as well as secondary outcomes and endpoints. Some PCTs are seeing increases in stakeholder engagement due to streamlined communication channels and sponsor interest in maintaining care in the pandemic. For example, VHA has expressed particular interest in supporting virtual psychotherapy for veterans with pain. It is unclear whether these effects on outcomes, and others as-yet not observed, will be temporary or long lasting.

Effects on sample size and analysis

The pandemic has introduced difficult methodological issues that affect the assessment and inferences about treatment effectiveness. One major challenge is changes in the delivery of interventions, which affect treatment fidelity, require changes in study designs (e.g., SMART, discussed above) along with sample size reconsiderations, and introduce temporal changes in the assessment of treatment effectiveness. Other challenges include assessing moderating and mediating effects of COVID-19 and its impact on the fidelity of interventions, particularly usual care, for which data available may differ from prepandemic times of measurement. There are no simple solutions to these problems. New frameworks and innovative solutions are needed to address these methodological challenges. To address some of these problems, the Food and Drug Administration has recently issued a recommendation document titled "Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency" [19]. The guidance document proposes trial mitigation and analysis strategies to address the impact of COVID-19. Although this is a guidance document for industry, some of the strategies could be useful for trials studying nonpharmacological interventions for pain.

DISCUSSION

Disruptions to research can be brought on by a range of unpredictable events due to severe weather events or other emergencies. But long-lasting, systemic interference on a broad scale has made the COVID-19 pandemic unique. In addition to imparting substantial health impacts and loss of life, the crisis is forcing us to adjust norms and even responsibilities. Our health care system has prioritized attention to contending with the still poorly understood behavior and effects of COVID-19, leaving many health conditions undermanaged, by necessity, through altered standards of care, as well as reduced routine health services.

COVID-19 has added fuel to already raging fires—the opioid epidemic and chronic pain, which remain major public health challenges. As a group, people living with chronic pain have the largest global morbidity measured by years lived in disability [20]. Chronic pain especially affects veterans, military service members, and their families [21] whose livelihoods have collided with the opioid epidemic in various ways, including

increased risk for opioid-use disorder. Inadequate recognition of chronic pain as a complex multifactorial experience with frequent comorbidities has resulted in many people receiving suboptimal treatment for years-long episodes of discomfort, disability, and psychological distress. This is even though nonpharmacological approaches have been shown to be effective for managing chronic pain [22]. Unfortunately, the COVID-19 pandemic has disrupted pain patients' routine medical office visits, elective pain intervention procedures, physical therapy, chiropractic care, and medication trials, putting these individuals at risk.

The PMC's pragmatic research program is being conducted within large, integrated health systems that provide care to millions of veterans and military service members. As such, our work that is embedded within this large ecosystem has implications for helping substantial numbers of people disabled by the burdens of chronic pain. As the COVID-19 pandemic hit, we have taken concrete steps to ensure rigor in our ongoing work to implement effective strategies for managing chronic pain while paying close attention to minimizing the burden on research participants, investigators, and clinical care teams. Similar actions can be reapplied in the case of future disruptions to research activities.

A benefit of pragmatic approaches is their characteristic ability to "learn" within actual health environments through a bidirectional model of research and practice that involves diverse, real-world populations (e.g., relaxed eligibility criteria) and, often, community-based providers. PCTs test the efficacy of interventions in real-world contexts, and the approach can also be used to compare effects across health care settings. The COVID-19 pandemic forced changes in the delivery of pain management interventions and will likely alter treatment effects. Through the use of harmonized instruments and surveys, we are capturing these changes and plan to monitor the impact on research practices, as well as on health outcomes over time. However, health care remains a very fluid environment due to the novelty of COVID-19 and, thus, we cannot assess when a "new normal" will arrive.

Shifts in care delivery emergent during the COVID-19 pandemic (e.g., virtual care) may offer some benefit through increased access to care, but it is likely that a greater, less sanguine impact will be the deepening of care disparities. Many people living with chronic pain share features of those hardest hit by COVID-19: low socioeconomic status, underlying health conditions, low health literacy, and limited access to health care. The digital divide may also likely contribute to undertreatment of at-risk populations due to lack of access to high-speed Internet, as well as lacking knowledge and familiarity with online tools and treatment modalities [23]. Thus, we are considering these issues as potential confounders to PCT findings in a changed environment of research and care. We are also considering pros and cons of virtual care platforms that offer high security (e.g., VA Video Link), ease of use (Zoom), or asynchronous delivery (interactive voice response via telephone).

Regional differences elicited by state-to-state variation in actions and policies amid the COVID-19 pandemic will have effects on both the conduct and outcomes of PMC PCTs that have multiple sites. We are preparing for additional, potentially multiple waves of COVID-19 across the nation over the coming months, should they emerge. Our actions now will guide those efforts, including recognizing and embracing permanent or temporary changes to consent procedures and wider adoption of virtual therapies in routine clinical care.

We are fortunate that pragmatic research approaches, flexible by design, offer opportunities to capture changes and to understand their effects on chronic pain and other health indicators. We are especially concerned, however, about the potential increased harm to people living with chronic pain and believe that our research to identify and implement effective, low-risk treatment is especially timely. Analyses of patient-reported measures over time will inform potential relationships between chronic pain, mental health, and various socioeconomic stressors common among Americans during the COVID-19 pandemic.

We hope that our forthcoming data from the 11 PCTs will inform future use of interventions to manage chronic pain and provide relief to millions of people caught within several crises at once. These findings should also help us understand interrelationship(s) of pandemic stressors and comorbidity on pain as a complex, multimodal experience.

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Compliance with Ethical Standards

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