The Odyssey of HOMER: Comparative Effectiveness Research on Medication for Opioid Use Disorder During the COVID-19 Pandemic

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ABSTRACT

The usual challenges of conducting primary care research, including randomized trials, have been exacerbated, and new ones identified, during the COVID-19 pandemic. HOMER (Home versus Office for Medication Enhanced Recovery; subsequently, Comparing Home, Office, and Telehealth Induction for Medication Enhanced Recovery) is a pragmatic, comparative-effectiveness research trial that aims to answer a key question from patients and clinicians: What is the best setting in which to start treatment with buprenorphine for opioid use disorder for this patient at this time? In this article, we describe the difficult journey to find the answer. The HOMER study began as a randomized trial comparing treatment outcomes in patients starting treatment with buprenorphine via induction at home (unobserved) vs in the office (observed, synchronous). The study aimed to enroll 1,000 participants from 100 diverse primary care practices associated with the State Networks of Colorado Ambulatory Practices and Partners and the American Academy of Family Physicians National Research Network. The research team faced unexpected challenges related to the COVID-19 pandemic and dramatic changes in the opioid epidemic. These challenges required changes to the study design, protocol, recruitment intensity, and funding conversations, as well as patience. As this is a participatory research study, we sought, documented, and responded to practice and patient requests for adaptations. Changes included adding a third study arm using telehealth induction (observed via telephone or video, synchronous) and switching to a comprehensive cohort design to answer meaningful patient-centered research questions. Using a narrative approach based on the Greek myth of Homer, we describe here the challenges and adaptations that have provided the opportunity for HOMER to thrive and find the way home. These clinical trial strategies may apply to other studies faced with similar cultural and extreme circumstances.

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"Passage home? Never. Surely, you're plotting something else, goddess, urging me—in a raft—to cross the ocean's mighty gulfs. So vast, so full of danger not even the deep-sea ships can make it through, swift as they are and buoyed up by the winds of Zeus himself."

– from *The Odyssey* by Homer[1]

INTRODUCTION

The usual challenges of conducting primary care research, including randomized trials, were exacerbated during the COVID-19 pandemic.[2,3] Research teams across the translational spectrum, from basic science to clinical research, faced obstacles in nearly every aspect of a study, including site and participant recruitment, protocols that required in-person assessment or treatment, related travel for participants as well as investigators, and the daily tasks of managing a research team through virtual communication.[4,5] Research studies suffered serious delays, and some reported full shutdown until pandemic restrictions were lifted.[6]

Researchers developed numerous methods to mitigate the negative impact of COVID-19 on their patients and their research.[7] After an initial decline in the number of studies in the United States, there was an overall increase in research, due to the enormous efforts to study COVID-19.[8] Research on other topics declined throughout the pandemic. Research institutions reacted to the pandemic by modifying current research, increasing virtual components of research among team members and study participants, and pivoting research toward COVID-19.[9-13]

Home versus Office for Medication Enhanced Recovery (HOMER) began as a pragmatic, comparative effectiveness research study comparing treatment outcomes in patients initiating long-term medication for opioid use disorder (OUD) in different settings. In prior work, the value of starting buprenorphine in the home vs the office was raised by practicing clinicians.[14] Although induction both in the office and at home are supported by evidence, there is a lack of evidence on which method might be better overall or which method might be better for specific patients based on individual characteristics and needs.[15-18] Conceived as a randomized trial between home or office induction of buprenorphine treatment, HOMER was funded by the Patient Centered Outcomes Research Institute (PCORI) with anticipated practice recruitment to begin July 2020. As the COVID-19 pandemic emerged and daily living evolved over the next 2½ years, the HOMER research team was confronted with myriad challenges. How could the team work together virtually? Without an in-person kick-off meeting, how might we best support practices for successful patient referrals to the study team? How might the unanticipated clinical model of virtual visits be incorporated into the research protocol? Here we describe our research journey—the major challenges, their immediate impact, and solutions identified, developed, and deployed to keep this primary care research study moving forward.

THE INITIAL PLAN

HOMER was a pragmatic, community-engaged, comparative-effectiveness research trial that aimed to answer a key question from patients and clinicians: What is the best setting in which to start treatment with buprenorphine for OUD for this patient at this time?[19] The study originally planned to randomize participants to begin treatment (ie, induction) using a home (unobserved) or an office-based (observed, synchronous) approach. Target enrollment was 1,000 patient participants from 100 diverse primary care practices associated with the State Networks of Colorado Ambulatory Practices and Partners and the American Academy of Family Physicians National Research Network.

This study was reviewed and approved by the Colorado Multiple Institutional Review Board (IRB). Participating practices ceded human subjects oversight to the board or completed human subjects review and approval at their own institution. HOMER is registered at ClinicalTrials.gov (NCT04664062, last update: August 11, 2022).

THE JOURNEY

The study team collected field notes during recruitment and follow-up communication with practices. As barriers and challenges were identified, several brief survey questionnaires were sent to practice staff and clinicians about study participant recruitment and how the practice was doing in general and specifically with this research study. Field notes and survey results were discussed at weekly HOMER team meetings and with our clinician and patient advisory groups. As a research study using a participatory approach, the study team engaged community partners, practices, and patients to adapt its strategies and study design to answer meaningful patient-centered research questions. We describe these challenges as they came up chronologically and how each was addressed and how they led to failure, success, or occasionally, additional challenges. Table 1 describes the specific events, challenges, and our approaches to overcoming the challenges throughout the study.

OBSTACLES ALONG THE WAY

COVID-19 Pandemic

The COVID-19 pandemic had a major impact on study design that occurred early in the study journey. COVID-19 was declared a worldwide pandemic in March 2020, just as the study was finalizing the funding from PCORI. Practices rapidly converted to virtual telehealth visits, and some practices greatly reduced in-person office visits. When the grant proposal was written, telehealth induction was much less common and not included in the study design. Patients using a telehealth induction protocol to initiate medication for OUD as the pandemic emerged therefore were not eligible to participate in HOMER. This ineligibility greatly affected practice and patient recruitment.

The research team, including community advisors, considered the options: include only practices that could offer in-person visits, change the design from a randomized trial to a cohort study, add a third study arm, or shut down and hope for rapid resolution of the pandemic. After much discussion, the decision was made to add a third arm to the randomized trial, a telehealth induction arm. This change required modifying the study design and the statistical analysis. Over the next 4 months, in collaboration with the PCORI project officer and team, HOMER became a 3-arm randomized trial of office (in-person, synchronous) vs home (unobserved, asynchronous) vs telehealth (virtual, observed, synchronous) induction for starting buprenorphine for long-term treatment of OUD. The trial name was updated accordingly: Comparing Home, Office, and Telehealth Induction for Medication Enhanced Recovery.

Practice recruitment and orientation plans were also substantially altered as a result of COVID-19. During our initial application, more than 60 practices had expressed interest in participation, so the expectation was that we could easily reach the target of 100 participating practices. The original plan therefore was to recruit all 100 practices in the first 6 months and hold an in-person project kick-off orientation meeting for all participating practices and research team members in January 2021. This kick-off would provide protocol and data collection training, cover study participant eligibility and recruitment plans, offer networking between primary care practices that offer buprenorphine for OUD, and generate excitement and energy.

Table 1. The Odyssey of HOMER—Mitigation and Change in a Comparative Effectiveness Trial

What Happened?	How Did It Impact the Study?	What Did We Do?
COVID-19 declared a worldwide pandemic	• Original plan for a large, in-person kick-off meeting cancelled • Original plan for in-person practice recruitment and training cancelled • Rapid decline in in-person clinical visits • Practices struggling with revenue and financial survival unable to take on new or additional work	• Delayed patient recruitment 4 months • Extended practice and patient recruitment window • Rather than 1 initial kick-off, offered flexible start "windows," initially in waves of multiple practices and then eventually single practice starts • Allowed more practice types, not just single-specialty primary care practices
Rapid expansion and reliance on telehealth	• Practices stressed with need to rapidly deploy telehealth • Given the 2-arm randomized study design comparing home and office induction, patients starting treatment with a telehealth induction protocol were ineligible and could not participate	• Expanded the original 2-arm study design (home vs office) to a 3-arm study design (home vs office vs telehealth) • Conducted extensive conversations with funder and project officer; changed total number of participants (new power calculation: 1,200 participants for 3 arms)
Fewer prescriptions for opioids, so fewer potential patients with OUD in the practice	• Decreased opportunity to identify patients in the practice who might have OUD • More difficult to identify OUD • Low patient enrollment	• Created comprehensive patient recruitment materials • Created practice materials (website template, portal templates, EHR "dot phrases," EHR search terms, medication and refill messages) • Created other materials (newspaper articles, outreach to community organizations)
Rapid increase in fentanyl analogues in community	• Fewer patients seeking refills on prescription opioids • Increased overdose deaths • Increase in new and emerging drugs combined with opioids	• Disseminated community messages, newspaper articles with local clinician quotes • Conducted clinical education for practices • Provided additional training on MOUD treatment protocols • Included "microdosing" and bridge dosing protocols
COVID-19 waves alpha, delta, omicron	• Clinician burnout leading to a decline in participation • Practice burnout leading to withdrawal from study or decline in participation • Low practice engagement • Low rate of practice survey completions	• Attended to "care and feeding" of practices • Instituted more robust communication and engagement; offered regular newsletters, regular optional "drop-in" video calls • Tailored practice feedback reports • Offered survey completion incentives • Developed a StoryMap[a] • Conducted in-person and virtual site visits • Gave out practice care packages
Patient or clinician preference for induction method	• Patients who were unwilling to be randomized to induction method (home, office, telehealth), or whose clinician chose the method, were not eligible to participate	• Modified the study design • Converted to the comprehensive cohort study design with parallel enrollment into a randomized component and a nonrandomized, patient preference component
Ongoing primary care struggles of low payment, COVID, consolidation, shrinking workforce, and work overload	• Clinician burnout • Practice burnout	• Increased frequency of contact with practices—practice support • Conducted ongoing practice recruitment • Modified (lowered) enrollment goals • Extended patient enrollment 9 months
"Fourth wave" of opioid epidemic: multiple drug use with cocaine, benzodiazepines, methamphetamine, xylazine	• Patients were less likely to present for care • Practices struggled with treatment options other than buprenorphine because patients had more than just opioid dependence, affecting patient care and also eligibility for the study	• Conducted regular educational webinars for clinicians and practice staff • Focused on buprenorphine for OUD, referral to additional services for other drug use

EHR = electronic health record; HOMER = Home versus Office for Medication Enhanced Recovery; MOUD = medication for opioid use disorder; OUD = opioid use disorder.

[a] StoryMaps offer an engaging multimedia format to disseminate research findings, study stories, and participant voices. We used ArcGIS StoryMaps, an app within the ArcGIS system (Esri), to organize audio/visual content into a StoryMap.

During this critical practice recruitment period in 2020, practices were overwhelmed. In recruitment communications, they expressed exhaustion as they struggled to remain viable. Some practices were inundated with COVID-19 cases. Some clinicians were redeployed to the emergency department or hospital to care for patients with COVID-19. Practices with fewer in-person office visits were forced to limit their hours and lay off staff. Some visits could be handled virtually, and most practices were able to receive clinical revenue for telehealth visits. As has been documented elsewhere, the work to rapidly convert to telehealth and manage COVID-19 in addition to all the usual care was simply exhausting.[20]

As the COVID pandemic grew, adding anything to practices' workload was out of the question, and practice recruitment ground to a halt. Although a small group of early adopter practices completed the necessary paperwork to participate, many practices that had expressed interest were preoccupied by the challenges resulting from COVID-19. Some were difficult to reach by telephone or e-mail, while others withdrew their interest temporarily or permanently. The option of holding the in-person kick-off meeting was eliminated, and our team reconsidered recruitment efforts, hoping for some relief from the pandemic toward the end of 2020 into early 2021.

Practice recruitment resumed in earnest when the COVID-19 vaccination rollout began in April 2021. As clinicians and patients could return to the office, practices began considering participation once again. The team called for an "all hands on deck" effort to reach as many practices as possible quickly. E-mails, telephone calls, visits, and informational video sessions were scheduled. An initial group of 30 practices was ready to start. Several other practices were interested but unable to start in the spring because of COVID-19–related competing demands. Starting all practices at the same time was not going to work. In response, we transitioned to a wave approach of practice initiation throughout 2021 rather than a single initial kick-off. Virtual orientations were held with groups of practices in waves to train practices in all aspects of the research study. Each group was offered multiple online training times to accommodate practice, staff, and clinician schedules. Because of slow recruitment, we regularly scheduled orientations even when only a single practice could attend.

Once signed up to participate, practices were assigned a "study buddy" from our research team and received monthly check-in calls. Potential patient participants were referred by the practice to our research team for enrollment. Each patient participant was entered into a secure participant tracker for the practice to use as a clinical tool and study data collection reminder. Monthly check-ins offered a time to answer questions the practice had about the study, understand how patient referral was going, assess support they may need in completing study activities, give reminders about outstanding survey questionnaires or data collection tools, and fill in any information that was missing from the practice's participant tracker. Each practice contact was documented in field notes, which were reviewed and summarized by study team members with qualitative analysis expertise and discussed at research team meetings.

Through early 2022, a total of 170 practice members from 69 practices had completed orientation (Table 2). However, IRB decisions and approvals delayed several trained practices' referral activities. A lack of patient referrals over 9 or more months led some practices to cease referral efforts. With the number of practices "activated" (trained, IRB approved, and committed) changing over time, additional practices were recruited, and orientation was conducted with individual practices through November 2023. Figure 1 depicts enrolled vs activated practices.

Induction Preference

A second major change to the HOMER study design related to induction preference. In accordance with our study protocol, practices referred patients who were beginning or scheduled to begin treatment to our study team for recruitment via a HOMER telephone line that was monitored during business hours. Initial study participant referral efforts included numerous materials for practices and clinicians. Practices were provided with a comprehensive packet that included flyers, eligibility checklists, talking points, and instructions for referral to the study team. The patient-facing materials were available in English and Spanish. As documented in their regular check-in field notes, "study buddies" began hearing from practices that, in some cases, the patient or the clinician had a preference for how the patient started buprenorphine. Some patients raised a concern about randomization to what they perceived as a less favorable study arm. A review of field notes revealed that many practices were not referring potential study participants because they were not willing to undergo randomization. To better understand and quantify the impact of this preference, we administered a brief practice

Table 2. HOMER Study Practice Group Orientations

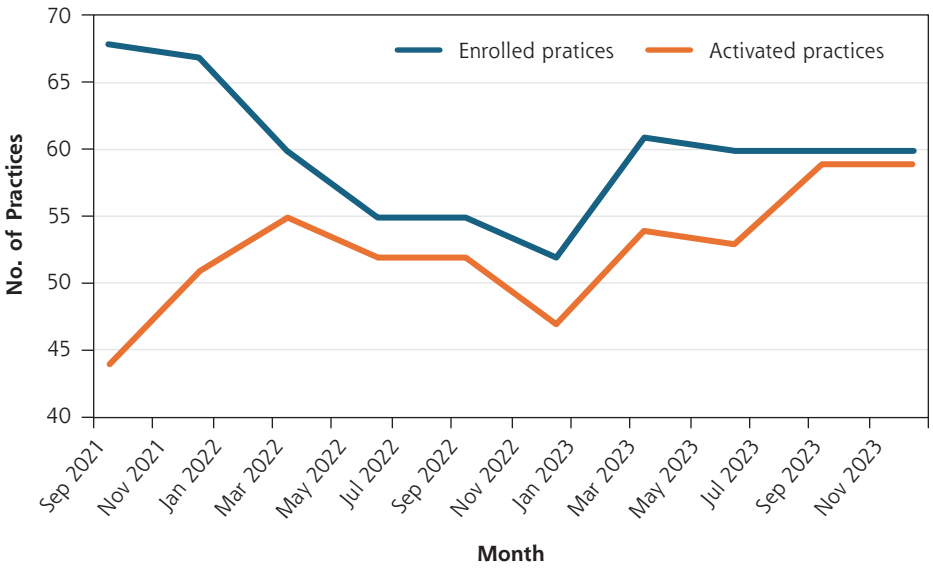
Practice Orientation Wave	Dates	No. of Practices	No. of Practice Staff
1	April 28 and May 5, 2021	30	85
2	July 8 and 14, 2021	18	41
3	September 2 and 8, 2021	14	31
4	November 9, 11, and 19, 2021	5	7
5	February 16, 2022	2	6
Total		69	170

HOMER = Home versus Office for Medication Enhanced Recovery.

survey, in which 48% of practices reported their patients had a strong preference for one induction method over the others. The survey also estimated that during a 3-month period, 130 patients were not referred for enrollment because of the requirement for randomization.

With so many patients declining randomization and therefore referral to the study recruitment, we realized a major modification would be needed to answer our research questions. The study biostatistician and analyst researched and evaluated parallel cohort designs in the literature. On the basis of our study purpose and patient referral protocol, we selected and received approval from PCORI to change the underlying research design from a 3-arm randomized comparative effectiveness study to a comprehensive cohort design study.[21-23] Potential participants were asked if they would accept randomization. If yes, they were randomized to 1 of the 3 arms. If no, they were enrolled into their preferred buprenorphine induction method (Figure 2). This change reflected the participatory approach to HOMER and was widely applauded by the participating practices. Further, it presented additional research questions, including investigating differences by participants' willingness to be randomized, treatment outcome differences between randomized and nonrandomized participants, and patient and practice characteristics associated with long-term treatment success among all arms of the study.

Figure 1. Enrolled vs activated practices in the HOMER study (September 2021-November 2023).



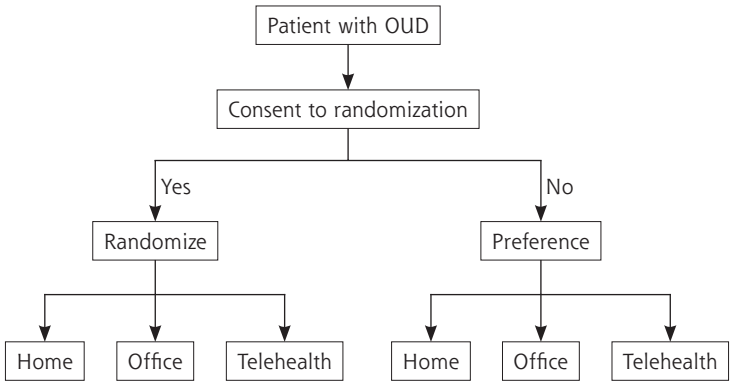
HOMER = Home versus Office for Medication Enhanced Recovery.

"Microdosing" With Buprenorphine

As fentanyl analogues became widespread throughout the United States,[24] concern about induction and precipitated withdrawal grew. The practice of "microdosing" buprenorphine[25,26] provides a bridge of low-level and more tolerable withdrawal from the full opioid agonist (typically fentanyl) to the partial opioid agonist (buprenorphine). Initially, clinicians and our research team viewed this low-dose buprenorphine regimen as a wholly different induction method. Patients using a low-dose medication regimen were not enrolled. Through multiple discussions with our team and medical consultants in 2022, however, it became clear that low-dose buprenorphine was simply a specific dosing regimen used by clinicians to varying degrees regardless of whether the induction was done in the office or at home. As a study about induction for long-term treatment of OUD, low-dose buprenorphine was accepted as one of many dosing regimens available to practices. Although the term *microdosing* was commonly used during HOMER's early days, the term is a misnomer, as bridge dosing regimens do not use "micro" doses of buprenorphine. *Low-dose* and *bridge dosing* became preferred terms.

Patients with OUD obtain buprenorphine through many means. Many patients with OUD have previously used buprenorphine on occasion for withdrawal management. Questions arose over whether patients who use buprenorphine occasionally for withdrawal management were eligible for the study. Buprenorphine is not synonymous with induction for long-term treatment of OUD. Buprenorphine is an effective short-term management approach for withdrawal from full-agonist opioids. Understanding that buprenorphine is both an acute treatment for opioid withdrawal and a long-term

Figure 2. Comprehensive cohort study design in HOMER.



HOMER = Home versus Office for Medication Enhanced Recovery; OUD = opioid use disorder.

treatment for OUD helped sort out study eligibility. Namely, a few doses of buprenorphine from family, friends, drug dealers, or even the emergency department[27] as acute withdrawal treatment did not exclude potential participants from joining the HOMER study, which focuses on use of buprenorphine as part of a formal induction to long-term treatment for OUD. This allowance enabled practices to continue to refer patients who had received a dose or 2 of buprenorphine in the emergency department or from other sources.

Mixed Drug Use

The concept of a "fourth wave" of the opioid crisis that includes mixed drug use with opioids, cocaine, methamphetamines, and nonopioid sedatives such as xylazine arose during our study.[28] Our clinician and patient collaborators described the devastating effect of these combined drug products. We provided additional educational webinars on mixed OUD and identification of newer drugs. Because the stimulants and nonopioid sedatives have no approved medication treatment, with guidance from our advisory groups, we continued to focus on the OUD treatment, encouraging practices to treat OUD and help their patients address the other drug use through ongoing relationship, drug counseling, and referral to local drug treatment and rehabilitation services.

NEARLY HOME—LESSONS LEARNED

Although our journey is not yet over, many lessons have emerged from the HOMER study. The strategies used to work through the challenges our research team faced can inform, and perhaps even inspire, other researchers conducting research in a world with COVID-19 (Table 3). As a research study that grew out of listening to the stories of those receiving and providing care to patients with OUD, this work continued to be about more than just answering our research question. In this case, helping people who struggle with OUD was our Ithaca, our destination. Relationships mattered. Supporting the research staff through regular meetings, routine and special communications, and constant encouragement helped maintain a sense of teamwork. The care and feeding of practices, listening, learning, adapting, and incorporating their suggestions kept them engaged. Listening to patient and clinical advisors, and asking about their experience, opinion, and expertise helped ground the work in lived personal and clinical experience. Flexibility, seasoned by participatory engagement, ensured relevance. Perseverance, even in the midst of a pandemic, prevailed. The path changed, but the destination was fixed. The COVID-19 pandemic, the changes in OUD, and the emergence of fentanyl analogues challenged the team and investigators. Keeping the destination clear in our minds helped us navigate through the troubles.

As a research study guided by participatory values, HOMER listened to our practices, clinicians, patients, and community advisors. Frequent contact with practices through regular telephone calls provided bidirectional communication, timely feedback, and opportunity for adaptation. Brief surveys and review of field notes provided evidence beyond anecdotes. Regular community advisory meetings to discuss recruitment issues, survey results, and field note findings ensured a patient-centered approach. Regularly providing the PCORI team with what we were learning ensured they were able to support the collaborative nature of HOMER. Most practices leaned in and adapted along with us, often seeking and sharing creative ways to identify and refer patients.

Although evidence-based practice needs practice-based evidence,[29] engaging practices and patients in methodologic decisions is crucial to ensure relevance and acceptability. Randomized controlled trials may be an essential component of the pathway from discovery to practice implementation. Our practice-based study partners felt, however, that the randomized trial was not necessarily compatible with patient-centered care. Clinical focus on shared decision making, as described by the participating clinicians, relied heavily on patient preference for induction method. As a result, many patients declined randomization, severely limiting early enrollment. Research models such as the comprehensive cohort design that include parallel studies on randomized and nonrandomized participants deserve consideration. For HOMER, this design not only increased participation but also opened our research aims to include investigating how different induction methods might affect care in real-world settings. Flexibility and openness to alternative research methods requires constant listening, team training, and a supportive funder. Without practices, practice-based research cannot succeed. We have been fortunate to work with practices that stuck with us, learned new ways of doing research and using medication for OUD, and taught us a few things about clinical priorities and practice-based research. HOMER worked because everyone was committed to improving patients' health.

Table 3. Lessons: What We Will Be More Intentional About Next Time

Domain	Lesson
Destination	Keeping our focus on the most important element—helping patients with opioid use disorder—as we were reminded by our patient and community advisory groups
Relationship	Attending to the care and feeding of our research team, participating practices, and advisory groups
Listening	Listening to patients, study participants, clinicians, practice staff, advisory groups, research team, community, media
Flexibility	Balancing changes to the protocol with scientific rigor and fidelity to the research plan with a focus on the destination
Communication	Ensuring bidirectional dialog among research staff, practices, patients and study participants, advisory groups; proactive and responsive

Although we initially named our study HOMER to remind us of the lifelong struggle toward a destination often associated with OUD, in the midst of our research study, HOMER became an apt name to reflect the challenges that arose from the COVID-19 pandemic as well as cultural changes in the substance use and treatment world. The study itself became a journey fraught with internal and external obstacles, barriers, and changes, all contributing to the odyssey of HOMER.

As of January 2024, HOMER had enrolled nearly 300 study participants. Practices are still participating despite the challenges outlined above. Participant recruitment has ended, and our energy is focused on follow-up data collection, analysis, and dissemination. We are thankful to the many practices and clinicians who were committed to this study and the care of their patients with OUD. Practice-based research may be fraught with challenges, but the journey is one of service, learning, camaraderie, and shared commitment.

Read or post commentaries in response to this article.

Key words: opioid use disorder; buprenorphine; primary care; practice-based research; vulnerable populations; participatory research; clinical trials as topic; health services; COVID-19; pandemics

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