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Design considerations for point-of-care clinical trials comparing methadone and buprenorphine treatment for opioid dependence in pregnancy and for neonatal abstinence syndrome

Theresa Winhusen [a,*], Christine Wilder [a,b], Scott L. Wexelblatt [c,d], Jeffrey Theobald [a], Eric S. Hall [c], Daniel Lewis [a], James Van Hook [e], Michael Marcotte [f]

[a] Addiction Sciences Division, Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, 3131 Harvey Avenue, Cincinnati, OH 45229, USA
[b] Cincinnati Veterans Affairs Medical Center, 3200 Vine Street, Cincinnati, OH 45220, USA
[c] Perinatal Institute, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229, USA
[d] Department of Pediatrics, University of Cincinnati College of Medicine, 3235 Eden Avenue, Cincinnati, OH 45267-0555, USA
[e] Department of Obstetrics and Gynecology, University of Cincinnati College of Medicine, 231 Albert Sabin Way, PO Box 670526, Cincinnati, OH 45267-0526, USA
[f] Department of Obstetrics and Gynecology, Good Samaritan Hospital, 375 Dixmyth Ave, Cincinnati, OH 45220, USA

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ABSTRACT

Rationale: In recent years, the U.S. has experienced a significant increase in the prevalence of pregnant opioid-dependent women and of neonatal abstinence syndrome (NAS), which is caused by withdrawal from in-utero drug exposure. While methadone-maintenance currently is the standard of care for opioid dependence during pregnancy, research suggests that buprenorphine-maintenance may be associated with shorter infant hospital lengths of stay (LOS) relative to methadone-maintenance. There is no "gold standard" treatment for NAS but there is evidence that buprenorphine, relative to morphine or methadone, treatment may reduce LOS and length of treatment.

Design: Point-of-care clinical trial (POCCT) designs, maximizing external validity while reducing cost and complexity associated with classic randomized clinical trials, were selected for two planned trials to compare methadone to buprenorphine treatment for opioid dependence during pregnancy and for NAS. This paper describes design considerations for the *M*edication-assisted treatment for *O*pioid-dependent expecting *M*others (MOMs; estimated N = 370) and *I*nvestigation of *N*arcotics for *A*meliorating *N*eonatal abstinence syndrome on *T*ime in hospital (INFANTs; estimated N = 284) POCCTs, both of which are randomized, intent-to-treat, two-group trials. Outcomes would be obtained from participants' electronic health record at three participating hospitals. Additionally, a subset of infants in the INFANTs POCCT would be from mothers in the MOMs POCCT and, thus, potential interaction between medication treatment of mother and infant could be evaluated.

Conclusion: This pair of planned POCCTs would evaluate the comparative effectiveness of treatments for opioid dependence during pregnancy and for NAS. The results could have a significant impact on practice.

1. Introduction

The growing opioid-use epidemic in the U.S. [1] has been associated with a significant increase in the prevalence of

* Corresponding author: Tel.: +1 513 585 8292(office), +1 513 310 0442(cell); fax: +1 513 585 8278.
E-mail address: winhusen@carc.uc.edu (T. Winhusen).

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pregnant opioid-dependent women [2,3] and of neonatal abstinence syndrome (NAS) [4]. NAS is associated with adverse health effects for the infant [5–7] and with costly hospitalizations. In 2009, the average length of stay (LOS) for NAS was 16 days and the average cost of treatment was $53,400 [4], equaling over $3300 per day per infant. Both methadone and buprenorphine are clinically appropriate for maintenance therapy for opioid dependence during pregnancy and for treatment of NAS but comparative effectiveness trials evaluating these treatments are needed.

The gold standard for comparing two interventions is the randomized clinical trial (RCT) but such trials are often cost prohibitive and may not be representative of real-world patients and clinical practice [8]. Consequently, knowledge about the effectiveness of interventions in clinical settings often comes from observational studies, which, because they do not entail random assignment to interventions, are open to a number of biases and, thus, cannot be used to define evidence-based treatment. The point-of-care clinical trial (POCCT), or "clinically integrated randomized trial", is a third alternative which maintains the strength of random assignment while offering improved cost efficiency and ease of implementation within clinical practice [9–11]. In a POCCT, patients are randomly assigned to a treatment but standard clinical practice is followed otherwise, resulting in research studies which can answer certain comparative effectiveness research questions very efficiently.

Still, several characteristics of the POCCT design currently limit the clinical questions it can answer. First, an important, but potentially problematic, feature of a POCCT is the use of the electronic health record (EHR) system to randomize participants and to collect treatment outcomes. For a POCCT evaluating insulin therapies, Fiore and colleagues utilized the Veterans Affairs (VA) Healthcare System, which, unlike many EHRs, has the functionality required to conduct a POCCT [9]. The utilization of an EHR to collect data has significant advantages in terms of cost and in selecting outcomes of clinical importance but is also limiting in that outcomes are restricted to the data elements obtained in standard practice. Fiore and colleagues considered a number of primary outcomes but ultimately selected hospital length of stay (LOS) as the primary outcome because it has both important clinical and cost implications [9]. Second, a POCCT can only be used to compare interventions that are clinically acceptable and that are equipoise, at least from the patient's stand-point, in the potential effectiveness of the intervention as well as the cost of the intervention to the patient. Fiore and colleagues are conducting their POCCT in the VA Healthcare System, which covers the cost of the clinical interventions, something that is often missing from other practice settings. The present paper describes the design of a pair of planned POCCTs, one in opioid-dependent pregnant women and one in infants with NAS, which will be conducted using the Epic (Epic Systems Corporation, Verona, Wisconsin) EHR system at three hospitals.

2. Research background and design

2.1. Research background

The present study entails the completion of two related POCCTs (see Fig. 1). As noted in Section 1 Introduction, the POCCT design limits the potential outcomes to data elements collected in standard clinical care. Consistent with the selection of hospital LOS for the primary outcome by Fiore and colleagues for their trial [9], we selected hospital LOS for the infant, which has both important clinical and cost implications, as the primary outcome for the present POCCTs. The present section provides a literature review on the impact of methadone vs. buprenorphine during pregnancy, and for NAS, on treatment outcomes with a particular focus on infant hospital LOS.

2.1.1. Methadone vs. buprenorphine for opioid dependence during pregnancy

While methadone-maintenance remains the standard of care for opioid dependence during pregnancy, research suggests that buprenorphine-maintenance in the mother is associated with shorter infant hospital LOS relative to methadone-maintenance. In two small-scale, double-blind, double-dummy controlled RCTs, one trial found a short infant LOS (5 days) for both methadone and buprenorphine [12] while the other revealed that infant mean LOS was significantly less for buprenorphine-maintained women [13]. The MOTHER study, a large randomized double-blind, double-dummy controlled multi-site clinical trial, revealed that infant LOS was significantly less for buprenorphine-maintained women than for methadone-maintained women (a decrease of 43% in LOS) but that treatment dropout was greater for buprenorphine-maintained (33%) than for methadone-maintained (18%) women [14]. This differential drop-out rate may have been related to issues with buprenorphine induction, with 29% of buprenorphine-arm drop-outs occurring on the first study day [3]. As noted by the investigators, MOTHER was a tightly controlled efficacy study that maximized internal validity at the expense of external validity [15] suggesting that effectiveness trials are still needed [2,15,16]. Based on a review of the research literature, the American College of Obstetricians and Gynecologists (ACOG) Committee on Health Care for Underserved Women and the American Society of Addiction Medicine published an opinion in 2012 that opioid-dependent pregnant women should not be tapered off opioids but, rather, should be treated with methadone or buprenorphine [17]. Thus, at present, both methadone and buprenorphine are considered clinically appropriate treatments for opioid dependence during pregnancy, making POCCT an appropriate mechanism to compare the two treatments.

2.1.2. Methadone vs. buprenorphine for NAS

NAS, characterized by central nervous system hyperexcitability and autonomic instability, results when a newborn withdraws from in-utero drug exposure. NAS is most strongly associated with prenatal exposure to opioids with 55% to 94% of infants exposed to opioids in-utero reported to develop withdrawal signs [4,18–20]. Signs of neonatal drug withdrawal often begin within 24 h of birth for heroin-exposed newborns, from 24–72 h for methadone-exposed newborns [21], and from 24–96 h for buprenorphine-exposed newborns [22]. The severity and duration of withdrawal are affected by the type and extent of drug exposure [23,24], tobacco use during pregnancy [25], and the use of maternal breast milk after delivery [26,27]. There are no evidence-based standard treatment protocols for NAS [2,28,29].