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Maternal Opioid Treatment: Human Experimental Research (MOTHER)—approach, issues and lessons learned

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ABSTRACT

Aims The Maternal Opioid Treatment: Human Experimental Research (MOTHER) project, an eight-site randomized, double-blind, double-dummy, flexible-dosing, parallel-group clinical trial is described. This study is the most current—and single most comprehensive—research effort to investigate the safety and efficacy of maternal and prenatal exposure to methadone and buprenorphine. **Methods** The MOTHER study design is outlined, and its basic features are presented. **Conclusions** At least seven important lessons have been learned from the MOTHER study: (i) an interdisciplinary focus improves the design and methods of a randomized clinical trial; (ii) multiple sites in a clinical trial present continuing challenges to the investigative team due to variations in recruitment, patient populations and hospital practices that, in turn, differentially impact recruitment rates, treatment compliance and attrition; (iii) study design and protocols must be flexible in order to meet the unforeseen demands of both research and clinical management; (iv) staff turnover needs to be addressed with a proactive focus on both hiring and training; (v) the implementation of a protocol for the treatment of a particular disorder may identify important ancillary clinical issues worthy of investigation; (vi) timely tracking of data in a multi-site trial is both demanding and unforgiving; and (vii) complex multi-site trials pose unanticipated challenges that complicate the choice of statistical methods, thereby placing added demands on investigators to effectively communicate their results.

Keywords Alcohol and other drug use, opioid dependence, pharmacological treatment, pregnancy.

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INTRODUCTION

The Maternal Opioid Treatment: Human Experimental Research (MOTHER) study [1] was a double-blind, double-dummy, randomized, stratified, flexible-dosing, parallel group clinical trial comparing methadone and buprenorphine. Its primary focus derived from a shared understanding of the outstanding issues faced when treating opioid-dependent pregnant women [2]. Its methods and procedures were based on extensive pilot research examining the safety and feasibility of studying these medications in pregnant women and their neonates

[3,4]. Implicit in the MOTHER design is the premise that effective study of available maintenance agonist treatments in opioid-dependent pregnant women would require a closely integrated, multi-site collaborative randomized clinical trial in order to recruit an adequately sized and diverse sample. The lead site, Johns Hopkins University, brought together seven other independently funded [National Institute on Drug Abuse (NIDA) regions of interest (ROIs)], geographically diverse sites (3 US urban sites, 2 US rural sites, 1 Canadian site and 1 European site) with experience in clinical trials, pregnancy and addiction to foster collaboration, address

clinical issues in opioid-dependent pregnant women and establish the infrastructure to conduct other medication trials in pregnant women.

The following sections describe the collective issues faced, the decisions made to address these issues and the lessons learned while conducting this trial. Specifically, we discuss issues regarding regulatory bodies, sample selection, screening, medication dosing, outcome selection, training and monitoring of the protocol and procedures, data collection and monitoring and statistical analysis.

FOOD AND DRUG ADMINISTRATION (FDA) REVIEW, INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL, DATA AND SAFETY MONITORING AND STUDY COORDINATION

As with any study of a new indication for a drug, an investigational new drug (IND) application submitted to the FDA was required. The lead-site Principal Investigator (PI) held an investigator-sponsored IND covering multiple sites to conduct a RCT with methadone and buprenorphine in opioid-dependent pregnant women. Each site ordered methadone from a local supplier and buprenorphine through NIDA. The lead-site PI, with NIDA's collaboration, maintained oversight and approval for the shipment of buprenorphine and placebo. Each study protocol was approved through the local site's respective IRB. Independent data and safety oversight was conducted by a Data and Safety Monitoring Board. The Center for Substance Abuse Research (CESAR) at the University of Maryland, College Park, was the coordinating center responsible for across-site randomization, data collection, coordination and protocol adherence monitoring.

Site selection

A clear issue that impacted the study was the fact that the collaborating sites that contributed participants were located at hospitals that differed in terms of size and populations served, as well as in the size of the clinic site at which participants were recruited. Moreover, each site had its own treatment approach, and although all sites adhered to a common protocol there were differences in patient care across sites that led to differences in participant treatment. Because of the differences in hospital size and/or clinic site patient flow, each site was responsible for recruiting a differing number of participants. As noted below, the study inclusion and exclusion criteria were quite restrictive, and so a large number of potential participants were screened at each site in order to recruit the necessary number of participants [1]. Some sites were better positioned to recruit participants, given a

larger area population density and/or better clinic site patient flow, while other sites were at a relative disadvantage, regardless of the original intention that the sites be responsible for a differing number of participants. Furthermore, the task of meeting recruitment goals was complicated further by the inherent differences found in a broad cross-section of the US population represented by the six US sites (for one example, the six US clinic sites varied between expected 97% white and 15% white populations). As a result, the seven sites differed in ability to recruit the intended number of participants and to retain participants in treatment. Such problems—as occur inevitably with almost any multi-site trial—limited the ability to generalize the findings in unanticipated ways, as noted below.

Sample selection

In developing participant selection criteria, it was necessary to balance a patient sample with minimal confounding factors with a sample that allowed maximum generalizability. Therefore, participants were required to: (i) be 18–41 years of age, inclusive, based upon data showing increased obstetric risk outside this age range [5–7]; (ii) be currently opioid-dependent according to the E module of the Structured Clinical Interview for Diagnostic and Statistical Manual (DSM)-IV Axis I Disorders (SCID I; [8]) or have a history of opioid dependence and be at risk for relapse [9]; and (iii) provide an opioid-positive urine sample indicating current opioid use. A criterion addressing estimated gestational age (EGA) was also needed. The lower EGA limit of 13 weeks was selected originally in order to avoid possible physical teratogenic effects due to buprenorphine exposure in the first trimester or falsely attributing fetal problems to exposure to either medication. After a year of recruitment, the EGA was lowered to 6 weeks, with the requirement that a normal fetal heart beat was confirmed by sonogram and no vaginal bleeding was reported in the week prior to or at the time of enrollment. Six weeks' EGA was selected for several reasons, including the lack of substantive data to date [10] suggesting physical teratogenic effects of first-trimester buprenorphine exposure [10], the perceived need to evaluate the safety of early buprenorphine exposure, because buprenorphine exposure is occurring commonly in women in office-based buprenorphine treatment at the time they discover they are pregnant and the practical reason of providing treatment on demand. The upper EGA limit of 30 weeks was retained in order to allow study participants sufficient exposure to opioid maintenance treatment. The result of this change in inclusion criteria also augmented enrollment by 20%.

Potential participants were excluded if they: (i) had a medical condition making participation medically

hazardous [e.g. preterm labor, evidence of congenital fetal malformation, unstable cardiovascular system or HIV, due to possible interactions between buprenorphine or methadone and HIV medications]; (ii) had an acute severe psychiatric condition in need of immediate treatment or which represented an imminent risk to the woman herself or others; (iii) had pending legal action that could interfere with participation; (iv) had evidence of regular use of, abuse of or dependence on benzodiazepines or alcohol, because both produce withdrawal syndromes that are difficult to differentiate from opioid neonatal abstinence syndrome (NAS), may have teratogenic effects [11,12], potentially confounding the relationship between the medication effects and the outcome variables, and specific to benzodiazepines, can produce serious adverse drug interaction effects in combination with buprenorphine or methadone [13]; (v) had a multiple-fetus pregnancy, as multiple fetuses are associated with premature delivery, lower birth weight and smaller head circumference; and (vi) did not plan to deliver at the local site's hospital, because this hospital was the only one where the protocol was approved and nursing staff had been trained to administer the study-specific NAS assessment and NAS medication protocols; and (vii) non-English-speaking, or non-German-speaking at the European site.

MEDICAL SCREENING PROCEDURES

After obtaining written informed consent and admission to in-patient treatment, participants were provided with immediate-release morphine sulfate [3]. The morphine was administered four times daily in divided doses, with the total daily dose being guided by objective determination of clinical symptoms to ease the expected transition onto double-blind medication. Participants were administered a comprehensive screening battery of assessments that characterized each participant's pregnancy and fetal health, addiction severity, treatment history, medical and psychiatric status and HIV risk. Qualifying participants were randomized into a medication condition and started study medication. Non-qualifying participants were so informed and transferred to standard care (e.g. methadone maintenance).

RANDOMIZATION PROCEDURES

Patients were randomized within three stratification factors: (i) site; (ii) EGA (6 weeks and 0/7 days–18 weeks and 6/7 days; 19 weeks and 0/7–30 weeks and 6/7 days) to control for differences in duration of medication exposure; and (iii) cocaine use in the past 30 days (yes/no) to control for potential prenatal effects of polydrug exposure. Randomization assignment was communi-

cated from CESAR directly to the site's pharmacy. Eight sites provided screening data, while only seven sites contributed randomized data, because one site failed to randomize any participants.

INDUCTION AND MAINTENANCE DOSING ISSUES

Participants were inducted onto study medication in an inpatient setting. The first day's dose of double-blind study medication was based upon the total amount of morphine received in the preceding 24 hours before randomization. An individualized dosing schedule allowing for blinded dose unit increases or decreases based upon clinical response to medication was used to minimize possible bias resulting from over- or undermedication. This schedule also avoided potentially confounding comparisons between medications due to possible differences in dose adequacy that sometimes occur in set-dosing protocols [3,4]. Two issues needed adjustment during the study. First, the procedures for ensuring a comfortable transition onto double-blind medications were refined based on clinical experience (e.g. refining the timing of the second half of the first day's dosing administration to range from 30 minutes to 2 hours). Secondly, the doses and timing of 'extra' doses of double-blind medication during induction to maximize the comfort of all participants also needed adjustment based on the collective experiences of the sites.

Buprenorphine

Although Suboxone[®] (buprenorphine + naloxone) was created to reduce the abuse liability of Subutex[®] (buprenorphine alone) [14], Subutex[®] was selected for this trial for several reasons. First, as any medication has risks of potential teratogenic effects, pregnant women are advised to expose the fetus to as few exogenous compounds as possible. Secondly, a logical first step in the scientific process is to first examine the maternal, fetal and neonatal effects of buprenorphine alone before adding other medications into the milieu. Thirdly, animal data suggest that fetal naloxone exposure produces maternal and subsequently fetal hormonal changes [15,16]. We estimated that a flexible dose range of 2–32 mg of buprenorphine alone and sublingual tablets was equivalent to the methadone doses described below based on reported clinical trial data [17–19]. Increasing the doses beyond 32 mg may not increase the efficacy of the medication [19]. The sublingual buprenorphine and matched placebo tablets used in this study were supplied by Reckitt-Benckiser Inc. (Hull, UK). All participants always received seven tablets (three 8-mg size and four 2-mg size) to place under the tongue for 5 minutes or

until the tablets dissolved. Each tablet contained 2 or 8 mg buprenorphine or placebo (no active medication).

Methadone

A flexible dosing range of 20–140 mg methadone was used. This dose range was within the range typically used by all sites, and therefore provided a clinically meaningful standard for judging the effectiveness of adequate agonist treatment during pregnancy. The upper dose limit was chosen to maximize the likelihood that buprenorphine and methadone doses remain equivalent, especially as higher methadone levels would exceed the ceiling effects encountered with buprenorphine. Oral methadone concentrate was purchased by each site from a local supplier and diluted to provide the dose in a fixed volume (e.g. 40 ml; see [3,4] for additional details). All medications were dispensed through hospital pharmacies or community methadone clinics with Drug Enforcement Administration (DEA) licenses or other appropriate regulatory approvals.

COMPREHENSIVE SERVICES AND CONTINGENCY MANAGEMENT DURING THE STUDY

Ensuring that all sites had a comparable platform of comprehensive services to provide to patients was critical to maximizing the success of the study. All sites provided comprehensive care to participants, including access to individual and group substance addiction counseling, obstetric, medical and psychiatric care and a variety of other ancillary services (e.g. transportation).

Minimization of concomitant drug use was critical because other non-opioid drug use can cause or exacerbate NAS [11,12]. Contingency management (CM), a behavioral treatment approach in which patients earn monetary vouchers for providing drug-negative urine samples, has been demonstrated to reduce or eliminate drug use reliably (see [20] for review). A modified version of the highly efficacious CM schedule used by Jones *et al.* [4] that targeted abstinence from multiple classes of abused drugs was developed for the present study. The one modification made was the elimination of marijuana as a target drug due to concerns about being able to verify marijuana abstinence objectively under a frequent urinalysis testing schedule (thrice weekly), given the long half-life of this drug. Moreover, urine screening did not include tests for buprenorphine or methadone, so that research staff would not be able to determine which opioid agonist was being administered to a participant.

NAS ASSESSMENT

Neonates were evaluated for NAS using a 28-item modified Finnegan Scale. Of these items, 19 are used for scoring

and medication decisions. The items include crying, sleeping, Moro reflex, disturbed tremors, undisturbed tremors, increased muscle tone, excoriation, generalized seizure, fever > 37.3, frequent yawning, sweating, nasal stuffiness, sneezing, tachypnea, poor feeding, vomiting (regurgitation), loose stools, failure to thrive and excessive irritability. The presence or absence of nine additional items from the scale published in Finnegan & Kaltenbach [21] were also collected. These items include myoclonic jerks, mottling, convulsions, fever > 38.4, respiration rate > 60/minute with retractions, nasal flaring, excessive sucking, projectile vomiting and watery stools. Collection of these additional items allowed for possible calculation of scores using the most recently published Finnegan scale [21]. Definitions of all NAS items were based on those developed by D'Apolito [22] and refined before data collection. A modified version of the medication initiation, maintenance and weaning protocol [4] was developed in consultation with neonatal and pediatric co-investigators at each site. This protocol defined the NAS score above which morphine was initiated, maintained, and below which it was weaned. In contrast to the medication protocol outlined by Finnegan & Kaltenbach [21], and based on collective concerns from the sites, if an infant's score was 13 or higher on the NAS scale morphine sulfate treatment was started immediately without later NAS re-scoring. Neonatal morphine dosing was symptom-based rather than weight-based.

While NAS observations were to continue until day 10 postpartum, the protocol allowed the location of NAS assessment to vary because the usual allowable length of hospital stay for neonates varied by site. Neonates treated for withdrawal continued to receive NAS assessment every 3–4 hours for the duration of their hospitalization. Neonates who did not receive medication to treat NAS or whose medication regimen ended before day 10 and were released from the hospital were assessed twice a day (with assessments separated by a minimum of 8 hours) until day 10. One baby was assessed for only 7 days, while three babies were assessed for only 9 days. All four babies were residing at home at the time. Mothers failed to return for assessment in three cases, while one baby was taken by child protective services, and timely arrangements could not be made with the foster parents to assess the baby.

PARTICIPANT TRACKING

All participants completed a participant tracking form at intake with periodic review. The form asked for the names, addresses and telephone numbers for three individuals (family members or friends) who typically knew of their whereabouts and whom we had permission to contact to locate them in the event that they failed to return for a scheduled appointment. In the event of a participant

failing to show for her daily medication visit or a scheduled appointment, outreach procedures included calling contacts, mailing letters, and in some cases actual staff visits to locations where participants resided.

TREATMENT FOR PARTICIPANTS WHO DISCONTINUED TREATMENT PREMATURELY

Any participant who left the study before delivery was returned to usual care that was available as a part of the site's comprehensive care treatment center.

REFERRAL FOLLOWING PARTICIPATION

All maternal participants were offered a choice of locally available treatment options (e.g. medication maintenance or detoxification) and that choice was implemented after 28 days postpartum. For participants being transitioned from blind medication onto either methadone or buprenorphine, across-site experience has resulted in general recommendations of starting the participants on low doses of maintenance medications and then adjusting doses based upon clinical response.

TREATMENT OUTCOME MEASURES

One of the decided strengths of the MOTHER study was the breadth and depth of maternal and neonatal data collection. MOTHER provided the single most comprehensive biopsychosocial assessment undertaken to date of the impact of illicit drug use during pregnancy on both the mother and neonate.

Neonatal outcomes

An in-depth assessment of neonatal outcomes was conducted. In addition to an assessment of neonatal abstinence signs (as described directly above), fetal assessments of growth and wellbeing, other physical birth parameters (weight, length and head circumference), cord pH, gestational age, congenital defects, medical complications, the peak, onset and duration of NAS and total amount of medication needed to treat NAS were collected. Several MOTHER sites also measured the neonatal neurobehavioral integrity using the NICU Network Neurobehavioral Scale (NNNS) [23].

Because the results of the Fischer *et al.* study [24] were not available when the MOTHER grant proposal was submitted, five primary outcome measures were selected for examination based on the findings of Jones *et al.*'s [4] study, given their importance to the health and wellbeing of the child and the cost of this illness to society: (i) peak

NAS score; (ii) number of neonates requiring treatment for NAS; (iii) amount of medication needed to treat NAS; (iv) head circumference; and (v) length of hospital stay. Jones *et al.*'s [4] findings, as well as preliminary results reported in the literature, led to the global hypothesis that buprenorphine would produce a superior outcome for all five variables.

Maternal outcomes

Both objective [urine and breath (alcohol only)] and self-reported drug use from the Addiction Severity Index (ASI) [25] were collected from the expectant mothers at study entry. Repeated monthly ASI administration allowed for the assessment of changes in psychosocial functioning throughout the course of pregnancy, and the extent to which differences in these changes might be related to methadone or buprenorphine treatment. Moreover, starting at 9 weeks EGA, blood samples were also taken every 4 weeks in order to provide information about the extent of change of hematology, blood chemistry, hepatitis B and C, liver enzymes and HIV values. Detailed maternal care information, including number of obstetric visits, concomitant medications prescribed and weight gain, as well as the course of and complications during pregnancy, labor and delivery, and the postpartum period, provided critical evidence to characterize the course of treatment of this population and how this course might differ as a function of the two study medications. Finally, the adequacy of each study medication, side effects and adverse events during the study were captured with brief self-report questionnaires that were developed as part of the Jones *et al.* [4] study.

TRAINING OF CLINICAL RESEARCH STAFF IN ADMINISTRATION OF MEASURES

To produce reliable and valid clinical observations based on the interviewers' judgments, standardized clinical instruments were used. Clinical research personnel were trained on administration of the ASI, SCID-E and the NAS. There were three overlapping but distinct aspects to the training and periodic evaluation of raters: (i) training to criterion (i.e. interviewer/rater achieves the standard of agreement with the scores provided by the gold-standard experts); (ii) assessment of concordance with a 'gold standard' expert (i.e. periodic evaluation of the agreement between scores of expert staff and each interviewer/scorer based on viewing the same set of videos, to identify and correct any drift); and (iii) collection of inter-rater reliability data (i.e. episodic collection of ratings from both the site's expert and the interviewer/scorer on a subset of the sample, which allowed for the assessment of both consistency and agreement among the raters).

DATA MANAGEMENT AND QUALITY CONTROL

With limited exceptions, data were submitted to CESAR using a paper document capture and processing methodology. This allowed the CESAR coordinating center staff to process data using a procedure that, at the time MOTHER began data collection, could be considered state-of-the-art. Forms were submitted by fax transmission, and were scanned electronically for completeness and consistency at the time of submission and reviewed subsequently by CESAR staff.

Statistical analysis

The basic statistical model that undergirded the MOTHER study design was a simple one—namely, a two-arm trial. However, there was also the need to control for a site effect, which was conceptualized originally as a random effect in the model (in order to increase the potential generalizability of the findings). Moreover, the MOTHER grant proposal had used Bonferroni's principle to set $\alpha = 0.01$ ($0.05/5$) for each of the five primary outcome measures (see Neonatal outcomes, above). In addition, the intensive maternal, fetal and neonatal assessment effort yielded a relatively large number of secondary outcome measures, for which Bonferroni's principle was then utilized for several different sets of these secondary outcomes (with $\alpha = 0.003125$, for example). Finally, the distributional properties of the various outcome measures required the use of not only ordinary least-squares analysis of variance models, but also Poisson regression and logistic regression methods.

SUMMARY OF LESSONS LEARNED

The following discussion highlights seven important lessons learned from the development and implementation of MOTHER in the areas of design, methodology, sampling, training and medication. (i) Studying the maternal and fetal/neonatal safety and efficacy of opioid agonist medications in opioid-dependent pregnant women prompted rich, interdisciplinary discussions among experts from behavioral sciences, internal and family medicine, psychiatry, obstetrics and gynecology, neonatology, pediatrics and nursing, each providing unique information and perspective within a multi-center collaborative trial. This collective knowledge improved the design and methods of the study significantly. Moreover, it was not feasible to conduct work of such complexity without the smooth integration and collaboration of all the disciplines that are involved ultimately in a woman's pregnancy, delivery and postnatal care of both mother and child. (ii) Multiple sites in a clinical trial present continuing demands on investigators due

to differences in recruitment goals, patient populations and hospital practices that, in turn, differentially impact recruitment rates, treatment compliance and attrition. (iii) Study designs and protocols must be sufficiently flexible to incorporate new knowledge and respond to new and often unforeseen clinical challenges related to use of the study medication and barriers in sample selection and recruitment. (iv) Staff turnover in a multi-center trial is constant and reinforces the need for ensuring that systems are in place not only for training of initial staff but training of replacement staff. (v) Administering double-blind medication to pregnant patients provided an opportunity to review and develop protocols for management of other clinical issues that may be impacted by the study medications, including medication induction, pain management and co-occurring. Moreover, the involvement of multiple levels of clinical care and responsibility necessitated continued communication and collaborative management of ongoing clinical challenges in this particularly vulnerable patient population. (vi) Although fax submission of data from the sites significantly eased the burden of data entry and management, it did little to ease what then became the major burden of data management—tracking of timely data submission. Relieving the coordinating center staff from spending significant staff time on data management and quality control did not ensure that the data were, in fact, submitted by each of the sites in a timely way. Thus, time was spent by both the sites and coordinating center staff in determining why a measure was not administered (e.g. participant terminated participation in the study, procedural error). Although real-time web-based data entry and tracking will address part of this problem in future research, it does not resolve it completely. (vii) The statistical analyses were complicated, and therefore placed an added demand on the investigators to effectively communicate the results. Because the number of participants recruited fell short of the intended number, and the number of participants recruited by each site varied widely, it was not possible to include site as a random effect in the statistical model as was intended initially. Rather, several of the sites had to be combined to form conceptual groupings (US urban versus US rural versus European), and so site was then treated as a fixed effect in the statistical model. Moreover, the Data Safety and Monitoring Board requested an interim analysis that resulted in a recalculation of the final α based on the O'Brien–Fleming spending function, such that α was set to 0.0091 for each primary outcome measure for the end-of-trial analyses. This use of non-traditional and differing α levels based on multiple applications of Bonferroni's principle places increased demands on the reader. (viii) Finally, in order to discount possible alternative explanations for the findings due to the effects of a

confounding variable or variables, there was the need to conduct the analyses of all the outcome measures, both primary and secondary, using a relatively large set of possible 'third variables' (none of which had any impact on the conclusions based on the initial set of analyses).

As with all research, the MOTHER study has limitations. The exclusion criteria were numerous, yet they yielded a sample in which the effects of the opioid agonist medications could be isolated and examined. Moreover, the care provided the participants as part of the protocol easily exceeded usual care. In addition, the choice of a conservative α level protected against Type 1 error at the expense of the ability to detect a small effect. These three aspects of the protocol combined to maximize internal validity at the expense of external validity. As a result, the extent to which the findings generalize to the larger population of opioid-dependent pregnant women awaits further research. Finally, despite efforts to develop an induction protocol that would comfortably transition participants onto double-blind medication, results suggest that this goal might not have been achieved, especially among buprenorphine-treated participants. None the less, a multi-center trial design provided a mechanism for acquiring a large amount of data that has moved and will continue to move this underserved population of opioid-dependent pregnant women to the forefront of both treatment service delivery and medication advances, and will provide an innovative research structure from which to launch treatment studies that could benefit future generations of mothers and children.

Clinical trial registration

The clinical trial was registered with ClinicalTrials.gov (Identifier: NCT00271219; title: RCT Comparing Methadone and Buprenorphine in Pregnant Women).

Declarations of interest

MOTHER Study

All MOTHER grants are from the National Institute on Drug Abuse (NIDA) unless noted otherwise: Brown University, R01 DA 015778; Johns Hopkins University, R01 DA 015764; Medical University of Vienna, R01 DA 018417; Thomas Jefferson University, R01 DA 015738; University of Toronto, R01 DA 015741; University of Vermont, R01 DA 018410 and M01 RR 109; Vanderbilt University, R01 DA 017513 and M01 RR 00095, and Wayne State University, R01 DA 15832.

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All other authors declare no competing financial interests.

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Present Paper

No additional declarations of interest.

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