

## Evidence-based Practice Center Systematic Review Protocol

### Project Title: Nitrous Oxide for the Management of Labor Pain

Protocol Posting Date: May 11, 2011

Amendment Date(s) if applicable: August 1, 2011

(Amendments Details—see Section VII)

#### I. Background and Objectives for the Systematic Review

According to data from the Centers for Disease Control and Prevention (CDC), more than 4 million births occur in the United States each year; in 2007, there were 4,316,223 births.<sup>1</sup> The 2006 Listening to Mothers II survey found that 86 percent of responding women reported using one or more types of medication for pain relief; 76 percent used epidural or spinal analgesia/anesthesia, 22 percent received narcotics, 3 percent received general anesthesia, and 3 percent used nitrous oxide (likely an overestimate considering how few U.S. facilities offer this method as described later in this section). Although this survey is limited by reliance on women's self-reporting of analgesia use, it provides a general sense of the relative use of each method in the U.S.<sup>2</sup> A 2002 review of labor pain management strategies used in U.S. hospitals – stratified by number of yearly births and size of hospital – found that, among women who gave birth in 1997, from 21 to 50 percent received epidural analgesia, from 5 to 11 percent received combined spinal-epidural analgesia, from 40 to 56 received parenteral analgesia, and from 2 to 13 received paracervical or spinal analgesia.<sup>3</sup> In the same study, from 10 to 17 percent of women did not receive any form of analgesia<sup>3</sup>

Nitrous oxide is a commonly available option for labor pain relief in several countries outside the U.S. Rosen's 2002 systematic review on the topic cites evidence that nitrous oxide is used in the United Kingdom by approximately 50 to 75 percent of women and in Finland by approximately 60 percent of women.<sup>4</sup> In other studies, Irestedt found that 65 percent of women in Sweden received nitrous oxide for labor pain relief in 1991,<sup>5</sup> and a 1995 survey of hospitals in Ontario, Canada, found that nitrous oxide was available for labor pain analgesia in 75% of responding hospitals.<sup>6</sup> Nitrous oxide is also commonly used for labor analgesia in Australia and New Zealand.<sup>4</sup> The widespread use of nitrous oxide in other countries suggests it is an effective labor pain relief method.

Only three centers in the U.S. are known to currently provide nitrous oxide as an option for labor pain relief: the Birth Center at the University of California San Francisco (UCSF) Medical Center, the University of Washington Hospital in Seattle, and St. Joseph Regional Medical Center in Lewiston, Idaho. Bishop has briefly described the UCSF practices in "Administration of Nitrous Oxide in Labor: Expanding the Options for Women,"<sup>7</sup> including contraindications, preparation of the patient, and the documentation and competency requirements for midwives.

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The UCSF model uses a mixture of 50 percent nitrous oxide and 50 percent oxygen that is self-administered by the patient after initial instruction on use and potential side effects. No related publications or descriptions of the option used at the University of Washington Hospital or St. Joseph Regional Medical Center could be located in the literature.

Inhaled self-administered nitrous oxide in a 50/50 mix (e.g., Nitronox) is the most common method of nitrous oxide administration for labor pain relief described in the biomedical literature. Some literature addresses 50 vs. 70 percent concentrations of nitrous oxide in oxygen, and other literature addresses continuous vs. self-administered/intermittent administration. Alternatives/comparators to nitrous oxide include: epidural analgesia/anesthesia; systemic drugs such as opioids administered intravenously, intramuscularly, or orally; other inhalational agents such as sevoflurane and isoflurane; nonpharmacologic methods; and no pain relief.

Literature reporting on the use of nitrous oxide for the management of labor pain is sparse when compared to the use of other forms of analgesia/anesthesia. Initial searches of the PubMed database identified more than 600 studies. After the case reports and the nonoriginal research reports are eliminated, almost 500 studies remain. Currently, the Agency for Healthcare Research and Quality has no completed or in-progress products on the use of nitrous oxide. A search of [clinicaltrials.gov](http://clinicaltrials.gov) and the National Institutes of Health RePORTER database of funded research yielded no results, suggesting that nitrous oxide analgesia is not an active research topic.

Most women in the U.S. use some type of medication for labor pain relief. However, the option of using nitrous oxide to relieve labor pain is limited by its lack of availability. With such prevalent use of nitrous oxide during labor in other countries and potential advantages of this pain relief method, such as being less expensive and invasive than widely used regional anesthesia, this review attempts to assess the effectiveness of nitrous oxide in managing labor pain and to identify the potential factors that may influence its availability and use within the U.S. Our key questions have been structured with this goal in mind. The primary outcomes for consideration, as identified by our Technical Expert Panel, include the comparative effectiveness of nitrous oxide for the management of labor pain, the influence of nitrous oxide on the satisfaction with the birth experience, the health system factors influencing its use within the U.S., and any adverse effects associated with this intervention. It is our intention to evaluate the relative effectiveness of nitrous oxide when compared with other pain relief methods, but this comparison is distinct from the assessment of the efficacy of nitrous oxide as a sole pain relief method and may not be adequately reported on in the biomedical literature. With the rate of cesarean birth continuing to rise—31.8 percent of all U.S. births reported in 2007<sup>1</sup>—it is also important to address whether the use of nitrous oxide during labor influences the route of birth in women initially intending a vaginal birth.

## II. The Key Questions

### Introduction

We conferred with key informants who are familiar with the current state of the literature, clinical applications, and status of the use of nitrous oxide for pain management during labor in

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the United States in developing the key questions and analytic framework. We held several discussions to accommodate the schedules of our key informants and TEP. The discussions began with introductions to the team, the topic, and the topic refinement and systematic review phases of the project. We explained the processes by which the topic was nominated. We distributed working drafts of the analytic framework and key questions prior to each discussion and solicited feedback on their utility, clarity, and relevance. Following these discussions, the questions and framework were posted to the AHRQ web site for public comment for approximately four weeks. Comments received on the posted key questions could also be used in framing the report even if they did not lead to specific changes of the key questions. Additional discussions with the TEP following the public comment phase were also critical in shaping the key questions.

One public comment of note called for the rewording of a proposed key question that read, “Where head-to-head comparisons are available, what is the effectiveness of nitrous oxide when compared with other methods of labor pain relief?” The term “pain relief” was replaced with “pain management”, as the term “relief” may imply total dissipation. This change will be made in all review materials. This question was deemed superfluous and subsequently removed after conferring with the internal team and TEP. The methods section of the review will note that head-to-head comparisons will be incorporated into each key question, as applicable.

The majority of comments received during the public comment phase were judgments regarding the effectiveness of nitrous oxide for the management of pain relief based on personal experiences. Several comments addressed the use of nitrous oxide in concert with other pain management methods and at different stages of labor. These issues are not specifically addressed in any key question but fall under KQ1, and reviewers will be cognizant of these issues. Several comments called for the addition of harms or outcomes to KQs 2 and 4, most notably potential harms associated with breast feeding. The outcomes listed are examples based on and not meant to be all inclusive.

Several comments provided issues to highlight in the discussion and future research sections, including methods of administration, type of equipment, and cost analyses.

### **Key Questions**

**KQ1.** What is the effectiveness of nitrous oxide when compared to other methods for the management of labor pain among women intending a vaginal birth?

**KQ2.** What is the comparative effectiveness of nitrous oxide on women’s satisfaction with their birth experience and pain management?

**KQ3.** What is the comparative effectiveness of nitrous oxide on the route of birth?

**KQ4.** What is the nature and frequency of adverse effects associated with the use of nitrous oxide for the management of labor pain, including but not limited to:

- Maternal adverse effects, such as nausea and vomiting, dreams, dizziness, unconsciousness, and postpartum complications.

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- Fetal/neonatal adverse effects, such as low Apgar scores and abnormal fetal cord blood gases.
- Childhood adverse effects, such as drug dependency and developmental complications.
- Adverse effects on health care providers and other individuals present for labor.

**KQ5.** What are the health system factors influencing the use of nitrous oxide for the management of labor pain, including but not limited to provider preferences, availability, setting, and resource utilization?

## **PICOTS**

### **Population(s)**

- Pregnant women in first and second stages of labor (up to birth), other attendees and health care providers, and the fetus/neonate.

### **Interventions**

- Nitrous oxide inhalation.

### **Comparators**

- No analgesic/anesthetic intervention, analgesia/anesthesia, other inhalational agents, and pharmacologic and nonpharmacologic pain relief methods.
  - Pharmacologic pain relief methods include, but are not limited to, epidural analgesia, paracervical block, pudendal block, and parenteral opioids.
  - Nonpharmacologic pain relief methods include, but are not limited to, acupuncture, aromatherapy, continuous labor support, heat and cold, hydrotherapy, hypnosis, movement and positioning, music and audioanalgesia, patterned breathing and relaxation, sterile water injections, touch and massage, and transcutaneous electrical nerve stimulation (TENS).

### **Outcomes**

Primary outcomes:

1. Pain reduction.
2. Satisfaction with pain management.
3. Satisfaction with birth experience.
4. Long-term maternal, child, and occupational health outcomes.

Other outcomes:

- Labor and intermediate outcomes
  - Pain.
  - Coping.
  - Labor progress.
  - Satisfaction with pain management.
  - Satisfaction with birth experience.
  - Availability and timeliness.

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- Cointerventions associated with the use of nitrous oxide or other pain management methods.
- Birth and long-term outcomes
  - Maternal outcomes, including but not limited to route of birth and postpartum complications.
  - Child outcomes, including but not limited to Apgar scores, fetal cord blood gases, neurobehavioral outcomes, and drug dependency.
  - Health care provider outcomes (occupational health) from exposure.
  - Maternal satisfaction with pain management.
  - Maternal satisfaction with birth experience.
- Adverse effects, including but not limited to:
  - Maternal adverse effects, such as nausea and vomiting, dreams, dizziness, and unconsciousness.
  - Fetal/neonatal adverse effects, such as drug dependency.
  - Childhood adverse effects, such as drug dependency and developmental complications.
  - Individuals present for labor adverse effects.
  - Health care provider adverse effects (occupational health).

### **Timing**

- Intermediate outcomes will include associated labor outcomes.
- Long-term outcomes will include associated birth outcomes.
- There will be no restriction on duration of follow-up.

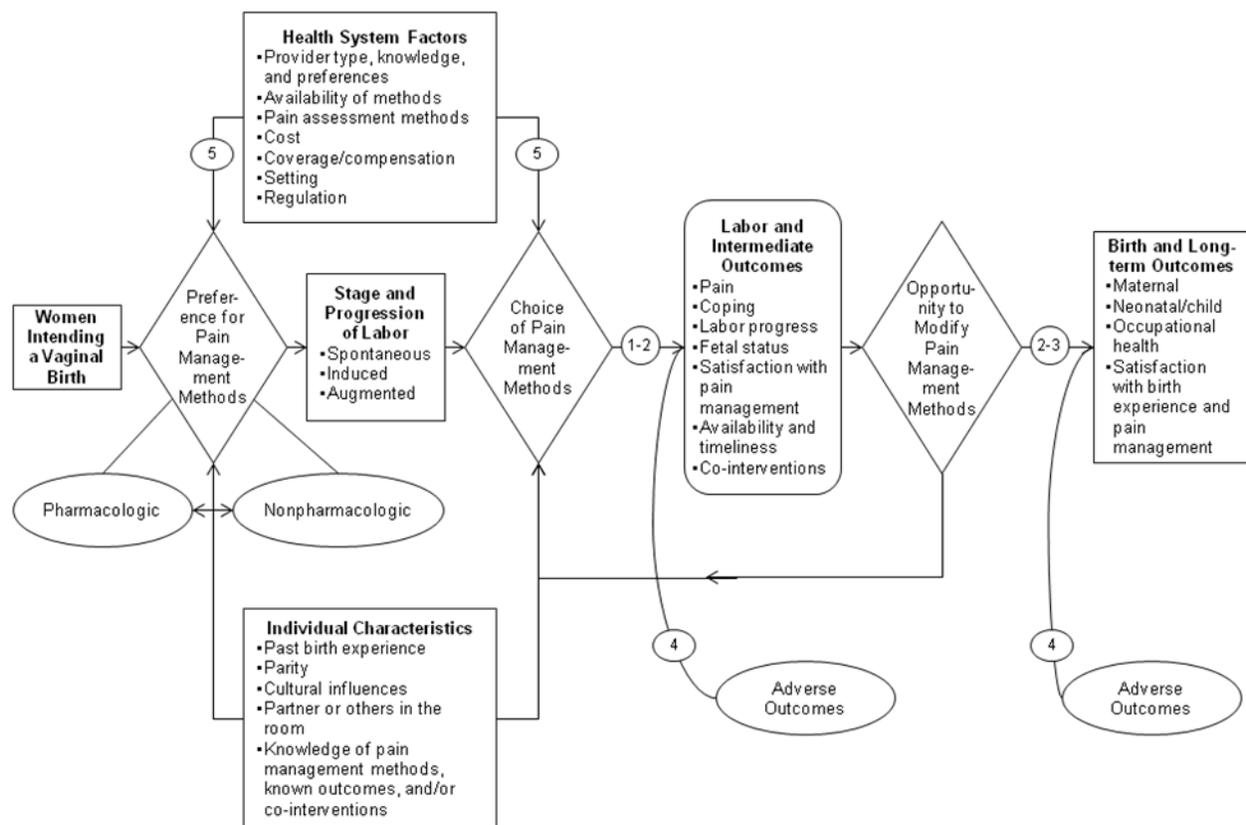
### **Setting**

- All birth settings will be considered, including hospital, birth center, and home.

### III. Analytic Framework

Several comments were received during the public comment phase and TEP discussions that addressed issues with the analytic framework. The term “pain relief” was replaced with “pain management”, as the term “relief” may imply total dissipation. “Provider knowledge” and “Pain assessment methods” were added to the Health System Factors box. “Knowledge of pain management methods” and “Parity” were added to the Individual Characteristic box, and “Past experience” was clarified to read “Past birth experience”.

**Figure 1. Analytic framework for nitrous oxide for the management of labor pain**



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## IV. Methods

### A. Criteria for Inclusion/Exclusion of Studies in the Review

Table 1 lists inclusion/exclusion criteria developed based on our understanding of the literature developed during the topic refinement phase, input from content experts, and established principles of methodological quality.

We set a cut-off level for study size for inclusion in the review at a minimum of 20 participants. We determined this level based on considering the state of the literature and the general lack of larger studies. We will also focus the review on studies published in English; included studies may include non-U.S. populations but must be published in English. In the opinion of the team of clinical experts participating in the review, the majority of research is published in English, regardless of the country of origin or native language of the researchers.

**Table 1: Inclusion/Exclusion Criteria**

Category	Criteria
Study population	Pregnant women in first and second stages of labor (up to birth), other attendees and health care providers, and the fetus/neonate
Time period	No limit
Publication languages	English only
Admissible evidence (study design and other criteria)	<p><u>Admissible designs</u></p> <ul style="list-style-type: none"> <li>• Study size <math>\geq</math> 20 pregnant women in labor OR addresses harms or occupational exposures</li> </ul> <p><u>Other criteria</u></p> <ul style="list-style-type: none"> <li>• Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results</li> <li>• Studies with mixed patient populations must include <math>\geq</math> 20 pregnant women in labor or provide extractable information addressing harms or occupational outcomes</li> <li>• Studies must include at least one outcome measure of an outcome listed in the PICOTS</li> <li>• Relevant outcomes must be extractable from data presented in the papers</li> </ul>

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## **B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions**

***Search the Literature.*** To ensure comprehensive retrieval of relevant research into the use of nitrous oxide for pain relief in women in labor, our approach to the literature will include three key databases: the PubMed medical literature database, the Cumulative Index of Nursing and Allied Health Literature (CINAHL), and the EMBASE Drugs & Pharmacology database. Search strategies in each of these databases will focus specifically on terms related to nitrous oxide and pregnancy/labor, including keywords and subject terms representing nitrous oxide and labor and excluding non-English materials, literature related to non-human subjects, and publications not resulting from some form of clinical trial (e.g. reviews, letters, commentaries, and others).

We will update the search quarterly during the abstract and full-text review stages, adding relevant references to the pool of articles under consideration as needed. We will also update the search upon submission of the draft report and add relevant references as needed while the draft report is undergoing review. We will also incorporate references meeting our inclusion criteria or of particular relevance for background sections that may be brought forward by public/peer reviewers.

We will employ additional searches of the reference lists of recent existing systematic reviews or meta-analyses of nitrous oxide for labor pain relief; the investigative team will also scan the reference lists of articles undergoing full text review for citations potentially meeting inclusion criteria.

***Search for Grey Literature and Regulatory Information.*** The use of nitrous oxide to reduce labor pain involves regulated gas and medical equipment, and may be subject to varying state and federal regulations. Our approach to searching for regulatory information will include a search of FDA sources to identify any relevant materials; based on preliminary searches at topic triage, we do not expect this search to provide much additional guidance. State laws governing possession or use of nitrous oxide primarily seek to restrict the buying and selling of the product by non-medical personnel and to restrict access to those older than 18 years of age; an exhaustive search of state laws is therefore unlikely to provide guidance with regard to the use of nitrous oxide for labor pain.

We will conduct a broad search for grey literature relevant to the topic, including meeting abstracts and reports. We will also seek suggestions from the TEP with regards to additional potential sources of grey literature. We will incorporate relevant information from grey literature searches into the review as appropriate (i.e. for assessing publication bias or selective outcomes reporting).

## **C. Data Extraction and Data Management**

***Develop Data Collection Forms.*** We will develop data collection forms for abstract review, full text review and data extraction. Abstract review forms will contain questions about primary exclusion/inclusion criteria. Full text review forms are somewhat more detailed and intended to assist in a) identifying studies that meet inclusion criteria and b) conducting an initial sort of

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studies into appropriate key questions. Finally, data extraction forms will collect those data necessary for evidence tables and synthesis.

Prior to data collection, we will develop, informed by clinical expertise, lists of potential confounders and effect modifiers (e.g., simultaneous therapies/synergistic effects, comorbidities/co-existing conditions, socio-cultural context, etc.) and expected outcomes for the data extraction form.

After reviewing a sample of relevant articles, the Methods and Content Leads will design the data collection forms and test them on multiple articles before initiating each stage of data extraction. We expect that the data collection forms will undergo several revisions based upon these tests.

***Initial Review of Abstracts.*** We will review all titles and abstracts identified through searches against our inclusion/exclusion criteria. Each abstract will be reviewed by at least 2 members of the investigative team. When differences between the reviewers arise, we will err on the side of inclusion. For studies without adequate information to make the determination, we will retrieve the full articles and review them against the inclusion/exclusion criteria.

***Retrieve and Review Articles.*** We will retrieve and review all articles meeting our predetermined inclusion/exclusion criteria or for which we have insufficient information to make a determination. Each article will be reviewed by at least 2 members of the investigative team. When differences between the reviewers arise, we will err on the side of inclusion.

***Determine Outcomes to Extract.*** Outcomes to extract have been identified *a priori*. Critical outcomes related to nitrous oxide use are based on clinical expertise and our initial scan of the literature and abstract review. Primary outcomes include pain reduction and satisfaction with pain management and birth experience. Outcomes related labor will be classified as intermediate, and include the primary outcomes as well as additional outcomes such as availability of nitrous oxide, timeliness of administration, and cointerventions associated with nitrous oxide. Outcomes related to birth will be classified as long-term, and include the primary outcomes as well as route of birth, postpartum complications, Apgar scores, and occupational health and provider outcomes from exposure. Maternal, fetal/neonatal, individuals present for labor, and provider and occupational health adverse effects of nitrous oxide exposure will also be extracted.

The feasibility of extracting outcomes is dependent on the quality of available literature. The proposed outcomes to extract have been determined by our internal team and TEP. Outcomes to extract may change based on the review of full-text articles meeting the inclusion criteria, at which point a protocol amendment will be completed if necessary.

For the studies meeting the second-round assessment, the abstractors will extract key data and study quality elements from the article(s) and enter them into evidence tables. The Methods and Content Leads and content experts will review extraction forms against the original articles for quality control. Differences between the abstractor and the reviewer will be resolved by consensus.

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We will develop a simple categorization scheme for coding the reasons that articles, at the stage of full review, are not finally included in the report. The abstractor will note the reason for exclusion on the article cover page. We will then record that code in an EndNote® database, our bibliography software, so that we can later compile a listing of excluded articles and the reasons for such exclusions.

**Monitor Study Reviews.** As reviews are conducted, the Project Coordinator and Administrative Support staff will track the status of each article. The Project Coordinator will maintain a master list of all the retrieved articles that indicates who was assigned the initial review and extraction, its status in the review and extraction process, the results of the review (e.g., whether it was selected for a full review or the reason why it was not, the date the initial review and extraction were completed, etc.).

The Project Coordinator will also monitor the progress of reviews. Weekly during the review phase of the study, the Project Coordinator will report the number of abstracts and articles out for review to the Methods and Content Leads, contact reviewers to determine progress and collect completed reviews, and assess each evidence table entries for completeness. Twice a month, the project staff will meet to discuss the results and progress to date; review cases that have been particularly difficult to classify, abstract, interpret or adjudicate; and address any questions the review team may have. In addition, all abstractors and other project team members will routinely use email to communicate any concerns or questions arising during the course of the reviews.

A study characteristics spreadsheet will be developed by the Project Coordinator and Administrative Support staff to aid the Content Lead, Content Experts, and Investigators in compiling abstracted data. These spreadsheets will allow each author to count key data points, such as study location, study type, and number of study participants.

#### **D. Assessment of Methodological Quality of Individual Studies**

**Assess Study Quality.** Quality assessment of individual studies will be performed using specific assessment tools for the type of study. For randomized controlled trials, the fundamental domains will include: adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, and free of selective reporting bias.

For observational studies we will assess three broad perspectives: (1) the selection of the study groups; (2) the comparability of the groups; and (3) the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. For example, for a cohort study, the fundamental criteria will include: representativeness of cohort, selection of nonexposed cohort, ascertainment of exposure, outcome of interest, comparability of cohorts, assessment of outcome, adequate duration of follow-up, and adequate follow-up of cohort. Other sources of bias would include baseline imbalances, source of funding, early stopping for benefit, and appropriateness of crossover design.

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Decision rules regarding detailed use of the quality assessment tools will be specified *a priori* by the review team. Two senior staff will independently perform quality assessment of the included studies with disagreements resolved through discussion or third party adjudication, as needed. We will record quality assessments in tables, summarizing for each study.

## E. Data Synthesis

**Prepare Evidence Tables.** We will enter data into evidence tables, using predetermined abbreviations and acronyms and otherwise attending to consistency across entries from the outset. The dimensions (i.e., areas of special focus, or the columns) of each evidence table may vary by key question as appropriate, but the tables will contain some common elements, such as author, year of publication, study location (e.g., country, city, state) and time period, population description, sample size, and study type (e.g., randomized controlled trial, prospective observational study, etc).

## F. Grading the Evidence for Each Key Question

**Assess the Strength of Evidence.** We will also utilize explicit criteria for rating the overall strength of the collective evidence on each key question into qualitative categories (e.g., low, moderate, high, insufficient). We will use established concepts of the quantity of evidence (e.g., numbers of studies, aggregate ending sample sizes), the quality of evidence (from the quality ratings on individual articles), and the coherence or consistency of findings across similar and dissimilar studies and in comparison to known or theoretically sound ideas of clinical or behavioral knowledge. We will make these judgments for each of the main key questions and any subquestions related to specific outcomes, as appropriate.

The strength of evidence evaluation will be that stipulated in the EPC Methods Guide<sup>8</sup>, which emphasizes the following four major domains: risk of bias (low, medium, high), consistency (inconsistency not present, inconsistency present, unknown or not applicable), directness (direct, indirect), and precision (precise, imprecise). Risk of bias is derived from the quality assessment of the individual studies which addressed that Key Question and specific outcome under consideration. Each key outcome on each comparison of interest will be given an overall evidence grade based on the ratings for the individual domains.

The overall strength of evidence will be graded as “high” (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of effect); “moderate” (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate); “low” (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of effect and is likely to change the estimate); or “insufficient” (indicating that evidence is either unavailable or does not permit estimation of an effect). When no studies are available for an outcome or comparison of interest, the evidence will be graded as insufficient.

Two senior staff will independently grade the body of evidence, with disagreements resolved through discussion or third party adjudication, as needed. We will record strength of evidence assessments in tables, summarizing for each outcome.

## G. Assessing Applicability

Our team will assess the applicability of findings reported in the included literature to the general population of pregnant women in labor by determining the population, comparator, timing and setting in each study and developing an overview of these elements. This will be done to account

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for any factors limiting the ability to apply the intervention to other populations or other settings, such as inadequate description of the intervention or failure to report critical data. We will also review potential modifiers of effect of treatment, which may include different age groups, race, parity, availability of other pain management methods, and setting of care.

## V. References

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## VI. Definition of Terms – if applicable

NA

## VII. Summary of Protocol Amendments

August 1, 2011

Section	Protocol Amendment	Rationale
Methods / Section D	Updated the quality assessment approach to utilize established tools. The Cochrane Collaboration's risk of bias tool will be utilized	The decision to employ established quality rating tools was based on several factors, most notably the fact that these measures are repeatable and can be employed across all reviews, versus developing quality scoring methods on

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	to assess the quality of randomized controlled trials. The Newcastle-Ottawa scale will be utilized to assess the quality of nonrandomized and observational studies.	a per-project basis. We believe the use of repeatable methods will improve confidence in methods for assessing risk of bias and improve internal consistency in methods across systematic reviews as a field.
Methods / Section A	Clarified the N > 20 inclusion criterion to specify that studies must include twenty women using nitrous oxide during labor and reporting outcomes, not just twenty women total.	This decision was reached after determining that a meta-analysis would not be possible based on the state of the literature. In the absence of meta-analysis, each study must stand alone. To do so, studies must be adequately powered to confirm effects, which is not possible with less than 20 participants.

### VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

### IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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## **X. Technical Experts**

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## **XI. Peer Reviewers**

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.