

# Evidence-based Practice Center Systematic Review Protocol

## Project Title: Comparative Effectiveness of Treatments for Noncyclic Chronic Pelvic Pain in Women

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Amendment Date(s) if applicable: November 15, 2010, December 8, 2010, and February 4, 2011 (Amendment Details—see Section VII)

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

#### Background

Chronic pelvic pain (CPP) in women is a commonly occurring and poorly understood condition. Little consensus on the definition of the condition exists—the duration of pelvic pain noted in published studies varies from 3 to more than 6 months, and the location and pathology of the pain are largely unspecified.<sup>1</sup> The American College of Obstetrics and Gynecology (ACOG) defines CPP as “noncyclical pain of at least six months’ duration that appears in locations such as the pelvis, anterior abdominal wall, lower back, or buttocks, and that is serious enough to cause disability or lead to medical care.”<sup>2</sup> The causes of CPP are not well understood and may be associated with gynecologic (e.g., endometriosis) and nongynecologic (e.g., irritable bowel syndrome [IBS]) conditions. Diagnosis of an underlying cause is complicated because the pain is rarely associated with a single underlying disorder or contributing factor;<sup>3</sup> Howard outlined more than 60 diseases and conditions associated with CPP.<sup>3</sup> Frequently diagnosed etiologies include endometriosis, adhesions, IBS, and interstitial cystitis/painful bladder syndrome;<sup>2-3</sup> however, a definitive diagnosis is often not made. One retrospective study from the United Kingdom found that more than 25 percent of women with CPP never received a definitive diagnosis after nearly 4 years of followup.<sup>4</sup> A diagnosis of CPP is often ultimately dependent on surgery or other invasive procedures. A thorough patient evaluation, including pain history-taking and mapping, is a critical step in determining the potential etiology and an initial therapeutic course and in establishing a rapport between the clinician and patient.<sup>5,6</sup> Organizations such as the International Pelvic Pain Society have developed intake questionnaires to facilitate accurate history-taking.

Given the lack of established definitions for CPP, prevalence has been variously estimated. The prevalence of noncyclic pelvic pain (i.e., not occurring in concert with menstruation or in a temporal pattern) was estimated to range from 4.0 to 43.4 percent in a systematic review of worldwide prevalence.<sup>7</sup> Earlier prevalence estimates place the rate in the United States at 14.7%.<sup>8</sup> Annual costs of outpatient visits in the United States have been estimated at more than \$880 million,<sup>8</sup> and the condition carries a significant quality-of-life burden in terms of sexual functioning, depression, fatigue, and physical limitations and disability associated with pain.<sup>8-9</sup>

Treatment varies and is typically focused on ameliorating symptoms. Pharmacologic therapies include narcotic and non-narcotic analgesics, anticonvulsants, serotonin-reuptake inhibitors, and botulinum A toxin injections. Hormonal therapies include oral contraceptives, progestogens, and gonadotropin-releasing hormone agonists (GnRHs). Other medical therapies

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include aromatase inhibitors and combinations of pharmacologic and hormonal therapies. Surgical interventions, which may be performed laparoscopically or in open surgical procedures, include hysterectomy (with or without oophorectomy or salpingo-oophorectomy), uterosacral nerve ablation (UNA), presacral neurectomy, lysis of adhesions, and uterosacral ligament resection. Behavioral therapies include biofeedback, psychotherapy, cognitive behavioral therapy (CBT), and support groups. Among allied health approaches, physical therapy, dietary modification, and exercise therapy have been used to treat CPP. Complementary and alternative modalities include hypnosis, herbal medicine, massage, acupuncture, meditation, and stress-reduction techniques.

## Scan of the Literature

A significant body of literature reports on the treatment of CPP in women. Our initial searches of the PubMed database identified more than 3,000 papers published since 1980. After the case reports and the nonoriginal research studies were eliminated, more than 1,600 studies remained with an estimated 15 percent of these being relevant to CPP therapies in women. A wide variety of interventions are available in the medicosurgical, behavioral, allied health, and complementary medicine arenas that are aimed at treating CPP or underlying conditions such as endometriosis, dysmenorrhea, or adenomyosis; however, few randomized controlled trials (RCTs) have evaluated those interventions.

A recent Cochrane review of 14 RCTs of interventions for chronic pelvic pain (excluding studies of patients with primary diagnoses of dysmenorrhea, pelvic inflammatory disease [PID], IBS, or endometriosis) noted that the range of effective therapies for CPP is limited and that recommendations for their use are based largely on single studies.<sup>10</sup> A recent narrative review<sup>11</sup> similarly concluded that few treatment modalities have demonstrated benefit for relieving CPP symptoms. Evidence supports the use of oral medroxyprogesterone, injectable goserelin, adhesiolysis of severe adhesions, and a multidisciplinary treatment approach for patients without a specific diagnosis. Less supporting evidence is available for oral analgesics, combined oral contraceptive pills, GnRH agonists, intramuscular medroxyprogesterone, trigger point and botulinum A toxin injections, neuromodulative therapies, and hysterectomy.<sup>11</sup> ACOG guidelines from 2004 note good and consistent scientific evidence (level A) for using combined oral contraceptives and nonsteroidal anti-inflammatory drugs (NSAIDs) for dysmenorrheic pain; GnRH agonists for suspected and confirmed endometriosis- and IBS-associated pain; daily, high-dose progestins for pain associated with endometriosis and pelvic congestion syndrome; presacral neurectomy for centrally located dysmenorrhea; and the addition of psychotherapy to medical approaches.<sup>2</sup>

## Summary

CPP is a common and broadly defined condition. When a definitive diagnosis of the etiology of CPP is achieved, it is largely made postoperatively, and multiple interventions are used empirically in clinical practice to manage potential etiologies and to treat pain symptoms. The condition is frequently complicated by comorbidities, including depression, anxiety, fibromyalgia, and other idiopathic pain disorders, and treatment must target symptoms across a spectrum of conditions. Existing literature cites a range of treatment options for women with CPP, many of which have not been tested in rigorous studies.

Key informants noted a critical need to understand how to prioritize treatment for women with noncyclic CPP or mixed cyclic/noncyclic CPP, particularly how to provide patients with

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balanced information about the probable outcomes given a specific course of treatment. Evidence about pathways of care and how to treat unresolved CPP once treatment avenues have been tried is largely lacking. Clearly there is a real need for synthesized research that evaluates the evidence base for various treatments and identifies gaps in the current literature that may drive the research agenda.

## FDA-Approved Treatments

While no surgical or nonsurgical treatments have been specifically approved for noncyclic CPP, multiple treatments have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of pain and other symptoms associated with noncyclic CPP; pharmacologic agents include analgesics, hormonal therapies, serotonin-reuptake inhibitors, anticonvulsants, antidepressants, aromatase inhibitors, neuromuscular blocking agents, and combination therapies. Selected specific agents are listed below (see PICOTS). Numerous surgical approaches have been advocated, including those that are preservative of the reproductive organs (i.e., lysis of adhesions, uterosacral nerve ablation, perineal injections) in addition to those that are excisional (i.e., hysterectomy, oophorectomy, and peritoneal excision). Other treatment categories include behavioral therapy, physical therapy, and integrative health measures.

## II. The Key Questions

### Introduction

For the purposes of this review, we will define noncyclic CPP as pain that has persisted for more than 3 months, is localized to the anatomic pelvis (lower abdomen below the umbilicus), and is of sufficient severity that it causes the patient to become functionally disabled or to seek medical care. This 3-month time frame concurs with published definitions of chronic pain,<sup>12-13</sup> including that of the International Association for the Study of Pain, which defines chronic pain as “current continuous or intermittent pain or discomfort which has persisted for more than three months, with recent or frequent seeking of treatment or use of analgesic medication.”<sup>13</sup>

We developed the key questions (KQs) for this review based on input from key informants and experts. The questions were posted to the Effective Health Care Program Web site for public comment for approximately 4 weeks. Comments received on the posted KQs will be used in framing the report.

The comments generally focused on the need to understand the association between the patient’s reproductive history (i.e., pregnancies, births, pelvic surgeries, etc.) and noncyclic CPP, including how that history may modify therapeutic choices. We will capture relevant patient factors as they are presented in the studies that meet our inclusion criteria to attempt to identify differences in outcomes based on medical history.

We explored the potential of developing a separate KQ to address patient history and its possible effects on noncyclic CPP with our Technical Expert Panel (TEP). We jointly agreed that our approach to such factors (capturing data when such factors are associated with outcomes) is sufficient and that a specific KQ addressing such factors is not necessary.

We also clarified the wording of KQ3 based on the public comments. Because one comment focused specifically on the need to understand surgical alternatives and outcomes for specific

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diagnoses, we clarified our intention to stratify our assessment of treatment effectiveness according to diagnosis when such information is available.

Additional public comments focused on the need to clarify that the comparative effectiveness review (CER) will address specific surgical and nonsurgical (e.g., herbal medicine) therapies. Our intention, therefore, is to include studies of any intervention used to manage noncyclic CPP if those studies meet our inclusion/exclusion criteria. The remaining public comments generally focused on etiology, diagnosis, treatment efficacy, and medical practice structures, topics that would be best addressed through original research or the development of practice guidelines, which could result from this review.

The KQs were further refined to:

- Articulate a discrete list of comorbidities of interest in KQ1
- Include dysmenorrhea as a comorbidity of interest in KQ1
- Clarify that KQ1 includes only women who have a diagnosis of noncyclic CPP
- Specify outcomes of interest in KQ2 and KQ4 in line with our discussion of outcomes in the PICOTS for the CER

The following KQs represent a synthesis of the input we received on the KQs and consensus among the research team.

## Key Questions

### Question 1

Among women who have been diagnosed with noncyclic/mixed cyclic and noncyclic CPP, what is the prevalence of the following comorbidities: dysmenorrhea, major depressive disorder, anxiety disorder, temporomandibular joint pain disorder, fibromyalgia, IBS, interstitial cystitis/painful bladder syndrome, complex regional pain syndrome, vulvodynia, functional abdominal pain syndrome, low back pain, headache, and sexual dysfunction?

### Question 2

Among women with noncyclic/mixed cyclic and noncyclic CPP, what is the effect of surgical interventions on pain status, functional status, satisfaction with care, and quality of life?

### Question 3

What is the evidence that surgical outcomes differ if the etiology of noncyclic/mixed cyclic and noncyclic CPP is identified after surgery?

### Question 4

Among women with noncyclic/mixed cyclic and noncyclic CPP, what is the effect of nonsurgical interventions on pain status, functional status, satisfaction with care, quality of life, and harms?

### Question 5

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What is the evidence for choosing one intervention over another to treat persistent or recurrent noncyclic/mixed cyclic and noncyclic CPP after an initial intervention fails to achieve target outcome(s)?

## PICOTS

### Population

- Adult women with noncyclic CPP or mixed cyclic/noncyclic CPP undergoing surgical or nonsurgical treatment (excluding studies of patients whose primary diagnoses include conditions other than CPP)

### Interventions

- Surgical interventions (via laparotomy or laparoscopy, and with or without oophorectomy and salpingo-oophorectomy) including:
  - Hysterectomy
  - Presacral neurectomy
  - Uterine suspension
  - Uterosacral nerve ablation (UNA)
  - Uterosacral ligament resection (ventrosuspension)
  - Lysis of adhesions
  - Ablation of endometrial implants
  - Resection of peritoneum (partial)
  - Diagnostic laparoscopy (only)
  - Venous blockage (via surgical approach or interventional radiology)
- Nonsurgical interventions including:
  - Medical therapies
    - Analgesics
      - *Non-narcotic agents* including nonsteroidal anti-inflammatory drugs (NSAIDs): acetaminophen/Tylenol<sup>®</sup>; pregabalin/Lyrica<sup>®</sup>; diclofenac/Cataflam<sup>®</sup>, Voltaren<sup>®</sup>, Zipsor<sup>®</sup>; celecoxib/Celebrex<sup>®</sup>; ibuprofen/Advil<sup>®</sup>, Motrin<sup>®</sup>; naproxen/Aleve<sup>®</sup>; indomethacin/Indocin<sup>®</sup>; ketorolac/Toradol<sup>®</sup>
      - *Narcotic agents* including opioids: fentanyl/Duragesic<sup>®</sup>; acetaminophen + codeine/Tylenol<sup>®</sup> with codeine; butorphanol/Stadol<sup>®</sup>; dihydrocodeine/Synalgos<sup>®</sup>; hydrocodone + ibuprofen/Reprexain<sup>®</sup>; hydromorphone/Dilaudid<sup>®</sup>; levorphanol/Levo-Dromoran<sup>®</sup>; meperidine/Demerol<sup>®</sup>; morphine + naltrexone/Embeda<sup>®</sup>; nalbuphine/Nubain<sup>®</sup>; oxycodone/OxyContin<sup>®</sup>, OxyIR<sup>®</sup>, Roxicodone<sup>®</sup>; oxycodone +

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acetaminophen/Endocet<sup>®</sup>, Percocet<sup>®</sup>, Roxicet<sup>®</sup>, Tylox<sup>®</sup>, Magnacet<sup>®</sup>, Primalev<sup>®</sup>; oxycodone + aspirin/Percodan<sup>®</sup>, Endodan<sup>®</sup>; oxycodone + ibuprofen/Combunox<sup>®</sup>; oxymorphone/Opana<sup>®</sup>; pentazocine/Talwin<sup>®</sup>; propoxyphene/Darvon<sup>®</sup>; tapentadol/Nucynta<sup>®</sup>; tramadol/Ryzolt<sup>®</sup>, Ultram<sup>®</sup>; hydrocodone/Vicodin<sup>®</sup>, Lortab<sup>®</sup>, Vicoprofen<sup>®</sup>

- Hormonal therapies
  - *Contraceptives* including estrogen + progestin combinations: ethinyl estradiol + levonorgestrel/Alesse<sup>®</sup>, Nordette<sup>®</sup>, Seasonale<sup>®</sup>, Seasonique<sup>®</sup>, Triphasil<sup>®</sup>, Portia<sup>®</sup>, Jolessa<sup>®</sup>, Lessina<sup>®</sup>, Levora<sup>®</sup>; ethinyl estradiol + desogestrel/Ortho-Cept<sup>®</sup>, Apri<sup>®</sup>, Cyclessa<sup>®</sup>; ethinyl estradiol + drospirenone/Yasmin<sup>®</sup>, Yaz<sup>®</sup>; ethinyl estradiol + etonogestrel/NuvaRing<sup>®</sup>; ethinyl estradiol + norelgestromin/OrthoEvra<sup>®</sup>; ethinyl estradiol + norethindrone/Tri-Norinyl<sup>®</sup>, Junel<sup>®</sup>, Femhrt<sup>®</sup>, Ortho-Novum<sup>®</sup>, Ovcon<sup>®</sup>, Tilia<sup>®</sup>; ethinyl estradiol + norgestimate/Ortho-Cyclen<sup>®</sup>, Ortho-TriCyclen<sup>®</sup>; ethinyl estradiol + norgestrel/Lo Ovral<sup>®</sup>, Cryselle<sup>®</sup>; etonogestrel/Implanon<sup>®</sup>; levonorgestrel IUD/Mirena<sup>®</sup>; medroxyprogesterone/Depo-Provera<sup>®</sup>; norethindrone/Aygestin<sup>®</sup>, Camila<sup>®</sup>, Jolivette<sup>®</sup>; norethindrone + mestranol/Necon<sup>®</sup>, Norinyl<sup>®</sup>, Ortho-Novum<sup>®</sup>
  - *Progestogens* including medroxyprogesterone/Depo-Provera<sup>®</sup>, Provera<sup>®</sup>; norethindrone/Aygestin<sup>®</sup>, Camila<sup>®</sup>, Jolivette<sup>®</sup>, Ortho Micronor<sup>®</sup>
  - *GnRH agonists* (with or without add back estrogen therapy) including buserelin/Suprefact<sup>®</sup>; goserelin/Zoladex<sup>®</sup>; leuprolide/Lupron<sup>®</sup>; nafarelin/Synarel<sup>®</sup>
  - *Androgens* including danazol/Danocrine<sup>®</sup>
  - *Selective progesterone-receptor modulators* including mifepristone/Mifeprex<sup>®</sup>; ulipristal acetate/Ella<sup>®</sup>
  - *Selective estrogen-receptor modulators* including tibolone/Donna<sup>®</sup>, Librium<sup>®</sup>; ranitidine/Evista<sup>®</sup>; clomiphene/Clomid<sup>®</sup>; tamoxifen
- *Anticonvulsants* including gabapentin/Neurontin<sup>®</sup>; pregabalin/Lyrica<sup>®</sup>
- *Serotonin-reuptake inhibitors* including citalopram/Celexa<sup>®</sup>; escitalopram/Lexapro<sup>®</sup>; fluoxetine/Prozac<sup>®</sup>, Sarafem<sup>®</sup>, Selfemra<sup>®</sup>; fluvoxamine/Luvox<sup>®</sup>; olanzapine + fluoxetine/Symbyax<sup>®</sup>; paroxetine/Paxil<sup>®</sup>, Pexeva<sup>®</sup>; sertraline/Zoloft<sup>®</sup>
- *Tricyclic antidepressants* including amoxapine/Asendin<sup>®</sup>; desipramine/Norpramin<sup>®</sup>; nortriptyline/Pamelor<sup>®</sup>; protriptyline/Vivactil<sup>®</sup>;

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amitriptyline/Elavil<sup>®</sup>; clomipramine/Anafranil<sup>®</sup>; doxepin/Prudoxin<sup>®</sup>, Sinequan<sup>®</sup>, Zonalon<sup>®</sup>; imipramine/Tofranil<sup>®</sup>; trimipramine/Surmontil<sup>®</sup>

- Serotonin/norepinephrine-reuptake inhibitors including duloxetine/Cymbalta<sup>®</sup>; desvenlafaxine/Pristiq<sup>®</sup>; milnacipran/Savella<sup>®</sup>; venlafaxine/Effexor<sup>®</sup>
- *Anesthetics* (injectable) including lidocaine/Xylocaine<sup>®</sup>; bupivacaine/Marcaine<sup>®</sup>, Sensorcaine<sup>®</sup>
- *Aromatase inhibitors* including anastrozole/Arimidex<sup>®</sup>; letrozole/Femara<sup>®</sup>
- *Neuromuscular blocking agents* including onabotulinumtoxin A/Botox<sup>®</sup>; abobotulinumtoxinA/Dysport<sup>®</sup>
- *Combination therapies* (e.g., oral contraceptive + aromatase inhibitor)
- Behavioral interventions
  - Psychotherapy
  - Cognitive behavioral therapy
  - Counseling and support groups
- Physical therapy interventions
  - Physiotherapy
  - Biofeedback
  - Exercise therapy
- Complementary and alternative interventions
  - Dietary restrictions (e.g., low oxalate diet)
  - Dietary additions (e.g., probiotics)
  - Massage
  - Acupuncture
  - Transcutaneous electrical nerve stimulation (TENS), electrical stimulation
  - Herbal medicine
  - Magnetic field therapy

Note: Cointerventions include any surgical or nonsurgical modality received along with the primary treatment.

## Comparators

- Surgical compared with nonsurgical approaches
- Nonsurgical approach compared with nonsurgical approach
- Surgical approach compared with surgical approach

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- Combination approaches (surgical and nonsurgical approaches combined) compared with other approaches

## Outcomes and adverse events

- Primary outcomes
  1. Pain status
    - a. Reduction in pain
      - i) At least 50 percent reduction
      - ii) At least 30 percent reduction
      - iii) Proportion below 30/100 mm (no worse than mild pain)
      - iv) Patient's global impression (very much improved)
    - b. Recurrence of pain
      - i) Percent of patients with recurrence at a selected interval
      - ii) Interval between resolution of pain and recurrence of pain
    - c. Subsequent intervention for the unresolved or worsening pain (if reported within a longitudinal study)
  2. Functional status (resolution/improvement of functioning)
    - a. Measured with the same instrument before and after the intervention is received and in the intervention group and the comparator group
    - b. Activities of daily living
    - c. Sexual functioning (if this was affected by the pain)
- Secondary outcomes
  1. Patient satisfaction with pain management
  2. Quality of life
  3. Harms and adverse events
    - a. Withdrawal because of an adverse event
    - b. Serious adverse events
    - c. Death (including suicide)

## Timing

- Short-term outcomes will be those that occur within 12 weeks

## Setting

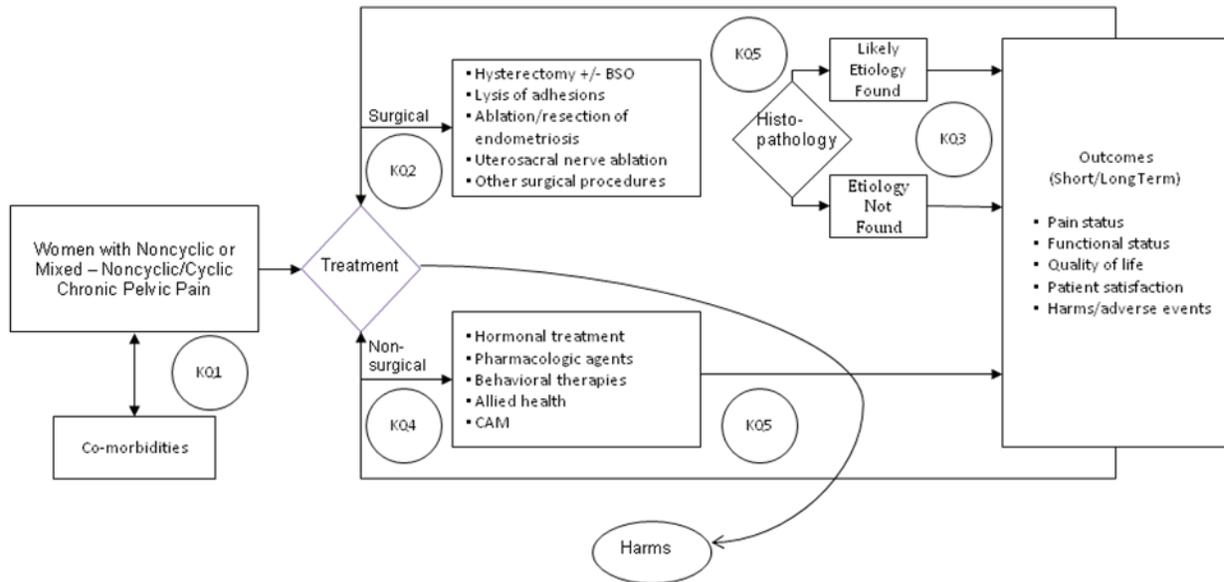
- Settings include any clinical setting

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### III. Analytic Framework

**Figure 1: Analytic Framework for Therapies for Women With Noncyclic Chronic Pelvic Pain\***



**Alternate Text**

This figure illustrates how women with chronic noncyclic or mixed cyclic/noncyclic pelvic pain enter into treatment choices. Treatment choices include surgical or nonsurgical approaches and may lead to outcomes including changes in patient satisfaction, quality of life, need for pain medication, unresolved pelvic pain, or harms/adverse effects. In addition, outcomes may vary by diagnosis in those patients receiving a confirmed diagnosis for the etiology of their chronic pelvic pain.

\*We refined this framework after the public posting of the key questions (KQs) to concur with frameworks included in recent CERs prepared for the Agency for Healthcare Research and Quality (AHRQ). Specifically, we removed contextual factors that may affect therapeutic choices or outcomes (e.g., provider training, socioeconomic status, health literacy, etc.) and will discuss such factors in the text of the CER.

Abbreviations: BSO = bilateral salpingo-oophorectomy; CAM = complementary and alternative medicine

### IV. Methods

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

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

As an inclusion criterion, we set the cut-off level for the study size of RCTs and prospective studies at a minimum of 50 participants. We considered the following factors in choosing this study size:

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- **Prevalence:** varies by population; to maximize acceptable study size, we will use 100 percent.
- **Loss to followup:** varies by study; to maximize acceptable sample size, we will assume 0 percent.
- **Type I error, alpha level, or p value:** we will set at a standard of 5 percent.
- **Clinical effect size anticipated or clinically relevant:** 30 percent minimum; 50 percent is a better benchmark (for reduction of pain outcome with a validated measure).
- **Placebo effect:** known to be from 30 to 50 percent in chronic pain studies.
- **Desired statistical power level:** set at a standard of 0.80.
- **Statistic:** use the two-tailed z-test and the t-test for sample size.
- **Sample size:** for an RCT with 2 groups, with 100 percent meeting the diagnostic criteria for CPP, with 0 percent lost to followup.
- **Null hypothesis of effect size of 50 percent:** need 64 subjects per study group; a total sample size of 128 would be the smallest acceptable.
- **Null hypothesis of effect size of 30 percent:** need 176 subjects per group; a total sample size of 352 would be the smallest acceptable.

Therefore, a conservative lower limit for sample size can be set at 50, to account for potential meta-analyses aggregating smaller trials at sufficient power to produce a confidence interval that excludes 1.

We will limit the review to studies published between 1990 and the present because laparoscopic techniques were used more frequently and were reported more extensively in the 1990s; the 1990 time frame is also contemporaneous with the introduction of medications, such as serotonin-reuptake inhibitors, used to treat noncyclic CPP. We will also exclude those studies primarily focused on common comorbidities of noncyclic CPP including IBS and painful bladder syndrome, as well as those focused on pain (i.e., primarily on cancer pain or pain during pregnancy). Given a lack of translation resources, we will also focus the review on studies published in English.

In addition, for KQ1 we will include only studies that report the selected comorbidities and include at least 100 participants.

To ensure that harms/adverse events data that may be presented in descriptive studies are included, we will include case series with  $\geq 100$  participants (adult women with noncyclic CPP) and report nonsurgical harms data. We will also extract data on nonsurgical harms from papers included in the review.

We reviewed these criteria with the TEP and used their feedback to clarify our approach to the harms analyses. We will extract data on nonsurgical harms from studies included in the review. We will supplement harms data—especially surgical harms data, which are well-reported in published syntheses and overview materials—with harms data reported in relevant published systematic reviews. We also used feedback from the TEP to correct an inconsistency between our discussion of outcome measures and our requirement that validated outcome measures be used as an inclusion/exclusion criterion. We will now require that studies include at least one outcome measure (regardless of validation) for an outcome detailed in our PICOTS (pain status, functional status, harms).

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**Table 1: Inclusion/Exclusion Criteria**

Category	Criteria
Study population	Adult women ( $\geq 18$ years of age) with noncyclic or mixed cyclic/noncyclic chronic pelvic pain (CPP) undergoing surgical or nonsurgical treatment
Time period	1990–present
Publication languages	English only
Admissible evidence (study design and other criteria)	<p><u>Admissible designs</u></p> <ul style="list-style-type: none"> <li>• Controlled trials, prospective trials with historical controls, prospective cohort studies with <math>N \geq 50</math></li> <li>• Case series with <math>N \geq 100</math> and harms or prevalence data relevant to the KQs</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>• Patient populations must include adult women (<math>\geq 18</math> years of age) being treated for noncyclic CPP; studies with a primary focus on coexisting conditions (vulvodynia, IBS, etc.) or on cancer pain or pregnancy-related pain will be excluded</li> <li>• Studies must include at least one measure of an outcome listed in the PICOTS</li> <li>• Studies must address one or more of the following for noncyclic CPP: <ul style="list-style-type: none"> <li>○ Treatment modality aimed at modifying noncyclic CPP symptoms</li> <li>○ Short- and long-term outcomes (including harms) related to treatment for symptoms of noncyclic CPP</li> </ul> </li> <li>• Studies must include extractable data on relevant outcomes</li> <li>• Sample sizes must be appropriate for the study question addressed in the paper</li> <li>• Studies addressing KQ1 must include subjects who have been diagnosed with a comorbid condition by using at least one validated tool for that condition (exception: no validated tool exists for the condition or existed at the time the study was published)</li> </ul>

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

**Searching the Literature.** To ensure comprehensive retrieval of relevant studies of therapies for women with noncyclic CPP, we will use four key databases: the PubMed medical literature database, the PsycINFO psychology and psychiatry database, the Cumulative Index of Nursing and Allied Health Literature (CINAHL), and the EMBASE Drugs & Pharmacology database. The search strategies for each of these databases will focus specifically on terms related to noncyclic CPP and its treatment, including key words, subject headings, and a combination of subject headings and/or key words (e.g., pelvic pain, endometriosis, therapy, therapeutics, etc.).

During our reviews of abstracts and full-text articles, we will update the literature search quarterly by adding relevant studies as needed. We will also update the search when the draft report is submitted and add relevant studies as needed while the draft report is undergoing peer review. We will also incorporate studies that meet our inclusion criteria or are relevant as background material that may be identified by both public and peer reviewers.

We will carry out hand searches of the reference lists of recent systematic reviews or meta-analyses of noncyclic CPP in women; the investigative team will also scan the reference lists of articles that are subjected to the full-text review for studies that potentially could meet our inclusion criteria.

**Searching for Grey Literature and Regulatory Information.** Approaches for managing pelvic pain often include initial treatment with widely used drugs such as ibuprofen and oral contraceptives to attempt to elucidate an underlying cause. Broad searches for grey literature and regulatory information on such commonly used drugs would likely return little relevant material.

We consulted the TEP to determine which studies of drugs or devices would be likely to provide relevant information about harms or other outcomes. The TEP advised us to prioritize our search by focusing on hormonal therapies (e.g., Provera<sup>®</sup>, Lupron<sup>®</sup>, Mirena<sup>®</sup>) that are commonly used to treat noncyclic CPP and have a number of known side effects. Our research team also thought it important to search for other drugs (e.g., aromatase inhibitors) that are beginning to be used to treat women with noncyclic CPP. Based on this input, we will request additional information on the following:

- Medroxyprogesterone/Depo-Provera<sup>®</sup>, Provera<sup>®</sup>
- GnRH agonists (with or without add-back estrogen therapy) including busarelin/Suprefact<sup>®</sup>, goserelin/Zoladex<sup>®</sup>, leuprolide/Lupron<sup>®</sup>, and nafarelin/Synarel<sup>®</sup>
- Selective progesterone receptor modulators including mifepristone/Mifeprex<sup>®</sup> and ulipristal acetate/Ella<sup>®</sup>
- Selective estrogen receptor modulators including tibolone/Donna<sup>®</sup>, Librium<sup>®</sup>; ranitidine/Evista<sup>®</sup>; clomiphene/Clomid<sup>®</sup>; and tamoxifen
- Aromatase inhibitors including anastrozole/Arimidex<sup>®</sup>, and letrozole/Femara<sup>®</sup>
- TENS, electrical stimulation

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We will incorporate relevant information from searches of the grey literature into the review as appropriate.

**Developing Data-Collection Forms.** We will develop data-collection forms for the abstract review, the full-text review, and data extraction. The forms used for the abstract review will contain questions about the primary exclusion and inclusion criteria. The forms used for the full-text review are more detailed and are intended to assist in a) identifying studies that meet inclusion criteria and b) initially sorting the studies according to the KQs. Finally, data-extraction forms will collect those data necessary to create evidence tables and perform data synthesis. We anticipate that these data will include operational definitions of CPP and those patient history factors (as discussed on page 3) associated with our outcomes of interest.

Before data collection, we will develop lists of potential confounders and effect modifiers (e.g., simultaneous therapies/synergistic effects, comorbidities/coexisting conditions, sociocultural context, etc.) and expected outcomes for the data-extraction form that will be informed by our clinical expertise. The form also will include a field in which to report the funding source of a study.

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 beginning each stage of data extraction. We expect that the data-collection forms will undergo several revisions after these tests are completed.

**Initial Review of Abstracts.** We will review all the titles and abstracts identified through our searches against our inclusion/exclusion criteria. Each abstract will be reviewed by at least two 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-text articles and review them against the inclusion/exclusion criteria.

## C. Data Extraction and Data Management

**Retrieving and Reviewing Articles.** We will retrieve and review all articles that meet our predetermined inclusion/exclusion criteria or for which we have insufficient information to make a decision about eligibility. Each article will be reviewed by at least two members of the investigative team. When differences between the reviewers arise, we will err on the side of inclusion.

**Deciding Which Outcomes Are To Be Extracted.** Outcomes, including nonsurgical harms, will be extracted a priori. We will identify critical outcomes related to pain management based on our clinical expertise, our initial scan of the literature, and our abstract review. We have elected not to extract surgical harms data because these data, which would be garnered from selected pain intervention studies, would not adequately capture all harms related to the surgical interventions.

Across the breadth of clinical presentations and clinical research there is not an established set of validated outcome measures for noncyclic CPP. Therefore, we will not restrict this review to validated outcome measures. Rather, we will evaluate and describe selected outcome measures reported for individual studies and provide those data in a transparent way. For the quality assessment of an individual study, we will consider the established validity of the outcome measure(s) as one factor when assessing the outcome reporting bias.

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The ideal outcome measure has the following attributes: 1) appropriate content and conceptual model; 2) reliability; 3) validity; 4) responsiveness; 5) interpretability; 6) precise scores; 7) acceptability to both respondent and administrator; 8) burden to respondent; 9) feasibility of administration; 10) availability and equivalence of alternate forms and methods of administration (e.g., self-report, interview); and 11) availability and equivalence of versions for different cultures and in different languages.<sup>14</sup>

In evaluating the outcome measures, the greatest weight is usually given to validity, reliability, responsiveness, appropriateness of content, and participant burden.<sup>14</sup> Reliability, validity, and responsiveness can be condition- or context-specific and are not invariant properties of a measure.<sup>14</sup> For the purpose of this review, we will consider outcome measures to be in two categories:

1. Validated Outcome Measures:

- a. A Core Outcome Measure for chronic pain recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)<sup>14</sup>
- b. An outcome measure described as validated by an authoritative professional clinical organization (reference provided within the index study)
- c. An outcome measure described as validated by the authors of the index study, with a linked reference to the validation study and appraisal of the validation study by two reviewers confirms that its validity is established

2. Other Outcome Measures:

- a. An outcome measure described as validated by the authors of the index study, without a linked reference that provides an authoritative statement from an independent professional clinical organization or a validation study but is not a Core Outcome Measure as described above in 1a
- b. An outcome measure that is not described as validated by the authors of the index study and is not a Core Outcome Measure as described above in 1a

For studies that meet the conditions of 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 those data-extraction forms against the original articles for quality control. Differences in data coding between the abstractor and the reviewer will be resolved by consensus.

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<sup>®</sup> (Thomson Reuters, New York, NY) bibliographic database so that we can later compile a listing of excluded articles and the reasons for such exclusions.

**Monitoring 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 data extraction, its status in the review and data-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.).

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The Project Coordinator will also monitor the progress of reviews. During the review phase of the study, the Project Coordinator will report to the Methods and Content Leads on a weekly basis the number of abstracts and articles out for review, will contact the reviewers to determine their progress and to collect completed reviews, and will 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 e-mail to communicate any concerns or questions that arise during the course of the reviews.

A spreadsheet for recording study characteristics 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

**Assessing Study Quality.** The quality of individual studies will be assessed by using specific assessment tools for each type of study. For RCTs, the fundamental domains will include: adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, and freedom from selective reporting bias.

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

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; disagreements will be resolved through discussion or third-party adjudication as needed. We will record quality assessments in tables, summarizing for each study.

## E. Data Synthesis

**Preparing Evidence Tables.** We will enter data into evidence tables by using predetermined abbreviations and acronyms consistently across all entries. The dimensions (i.e., areas of special focus, or the columns) of each evidence table may vary by KQ 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., RCT, prospective observational study, etc).

## F. Grading the Evidence for Each Key Question

**Assessing the Strength of Evidence.** We will also utilize explicit criteria for rating the overall strength of the collective evidence on each KQ into qualitative categories (e.g., low, moderate, high, insufficient). We will use established concepts of the quantity of evidence (e.g.,

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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 as appropriate for each of the main KQs and any subquestions related to specific outcomes.

The strength of evidence evaluation will be that stipulated in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*,<sup>15</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 that addressed the KQ 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).<sup>16</sup> 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; disagreements will be resolved as needed through discussion or third-party adjudication. We will record strength of evidence assessments in tables, summarizing for each outcome.

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## VI. Definition of Terms

For the purposes of this review, we will define CPP as pain that has persisted for more than 3 months, is localized to the anatomic pelvis (lower abdomen below the umbilicus), and is of sufficient severity that it causes the patient to become functionally disabled or to seek medical care. This 3-month time frame concurs with published definitions of chronic pain,<sup>12-13</sup> including that of the International Association for the Study of Pain, which defines chronic pain as “current continuous or intermittent pain or discomfort which has persisted for more than three months, with recent or frequent seeking of treatment or use of analgesic medication.”<sup>13</sup>

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## VII. Summary of Protocol Amendments

**Table 2. Summary of protocol amendments**

<b>Date</b>	<b>Section</b>	<b>Protocol Deviation</b>	<b>Rationale</b>
November 15, 2010	Methods / Table 1	Clarification of approach to studies with participants with unclear pain status—for those studies that do not report data for women with cyclic and noncyclic pelvic pain separately, we will require that the study population include at least 80 percent of participants with noncyclic pain.	Many studies of CPP do not clearly differentiate between women with cyclic chronic pelvic pain (e.g., dysmenorrhea) and noncyclic pain in reporting baseline measures and outcomes. Studies may report the number of women with noncyclic pain at baseline, but followup results combine data for women with cyclic and noncyclic pain. Because the current review is focused on noncyclic pain, we will retain those studies whose populations are composed of at least 80 percent of women with noncyclic pain. We will note in our discussion of these studies that the results apply to the whole population and should be considered in that light.
November 15, 2010	Methods / Table 1	Clarification of approach to studies with participants who are less than 18 years of age—for those studies that include subjects who are younger than 18 years but do not report data separately for women older than 18 years, we will require that the study population include at least 80 percent of participants older than 18 years.	Our review protocol limits the study population to women over the age of 18 years. Some studies (~9) include subjects who are younger than 18 years of age. There is empirical evidence that chronic noncyclic abdominal and pelvic pain in teenagers may have a different etiologic profile than noncyclic CPP in adults. If a study does not specify the percentage of the study population who are younger than 18 years, we will attempt to calculate the likely percentage and range, by interpolating from the mean age and age range data and other data provided. We will note in our discussion of these studies that the results apply to the whole study population and should be considered in that light.

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**Table 2. Summary of protocol amendments (continued)**

<b>Date</b>	<b>Section</b>	<b>Protocol Deviation</b>	<b>Rationale</b>
December 8, 2010	Methods / Table 1	Clarification of approach to studies including male participants—for those studies that include both male and female participants, we will require that the study population include at least 80 percent female participants.	Our review protocol limits the study population to women over the age of 18 years. Some studies (~2) include male participants. If a study population is composed of at least 80 percent women, we will retain the study and extract data on female participants only where possible. When extracting data on female subjects only is not possible, we will note in our discussion of these studies that the results apply to the whole study population and should be considered in that light.
February 4, 2011	Title	Alignment of title and scope of review.	We have focused this CER on women with noncyclic (i.e., not tied to any temporal associations) CPP based on input from our key informants and technical experts. To ensure that title of the review accurately matches its focus, we will change the CER title to “Comparative Effectiveness of Therapies for Women With Noncyclic Chronic Pelvic Pain.”

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**NOTE: The following protocol elements are standard procedures for all protocols.**

### **VIII. Review of Key Questions**

For Comparative Effectiveness reviews (CERs) the key questions were posted for public comment and finalized after review of the comments. For other systematic reviews,

### **IX. Technical Expert Panel (TEP)**

A TEP panel is 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. The TEP provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

### **X. Peer Review (*Standard Language*)**

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research, National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. 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.

It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.