Evidence-based Practice Center Systematic Review Protocol

Treatments for Fibromyalgia in Adult Subgroups

I. Background and Objectives for the Systematic Review

Fibromyalgia is a chronic, diffuse musculoskeletal pain syndrome of unknown etiology that most commonly affects adults.[1] It is characterized by chronic widespread pain, abnormal pain processing/heightened pain sensitivity, chronic fatigue, sleep disorders, and emotional distress or depression.[1,2] Fibromyalgia has a negative impact on quality of life and productivity and is associated with varying degrees of functional disability, psychological distress, lost work time, and increased use of health care services when compared to unaffected individuals.[1, 3-5] Based on the narrower diagnostic criteria developed in 1990, fibromyalgia affects more than 5 million Americans,[6] with much higher prevalence in women compared with men (3.4% vs. 0.5%).[6,7] Although fibromyalgia can occur in children, it is typically diagnosed in middle age and the prevalence of fibromyalgia increases with age until age 65, then declines in women[1, 8] Most patients with fibromyalgia are middle-aged women; men are less likely to be diagnosed with fibromyalgia even if they meet diagnostic criteria.[9]

The diagnostic criteria for fibromyalgia have evolved.[10,11] Fibromyalgia diagnostic criteria were initially published in 1990 by the American College of Rheumatology (ACR) and required the palpation of myofascial "tender points" during physical examination by a physician and the presence of widespread pain for at least 3 months.[12] Two decades later, revised diagnostic criteria were published by the ACR that eliminated the tender point examination, but relied on physician-rated severity in two scales, the Widespread Pain Index and the Symptom Severity Scale, plus symptoms present for at least 3 months and the absence of another disorder that would account for the symptoms.[10,13] More recent modifications to the diagnostic criteria were published in 2011 that eliminated physician estimates of somatic symptom severity and replaced them with a patient-generated summary score derived from three self-reported symptom domains.[11] The goal of the 2011 modification was to obviate the need of an examiner in surveys of fibromyalgia patients and in clinical use.[11,14] The 2010 ACR preliminary criteria and the minor 2011 modification are currently utilized in practice by rheumatologists and generalists, and are considered interchangeable. However, these recent criteria capture a broader population of fibromyalgia patients than did the 1990 criteria which undoubtedly impacts prevalence estimates in more recent studies.[13,15,16] The 2010 and 2011 criteria are labeled *preliminary* because the current criteria are being vetted for use at the international level.

Since there is no known pathophysiologic mechanism associated with fibromyalgia and therefore, no specific laboratory, imaging, or objective diagnostic test for the syndrome,[17] there is great diagnostic variability among health care providers in the timing of a fibromyalgia diagnosis relative to other coexisting syndromes that have overlapping symptoms[6,9] and whether the diagnosis is made at all beyond diagnoses of other functional somatic syndromes.

There is no specific cure for fibromyalgia, but single or combined nonpharmacologic and pharmacologic treatments may mitigate symptoms and improve function in affected individuals.[1] Treatments are most often multifaceted and involve multidisciplinary approaches and providers. The general goals of treatment are to mitigate diffuse musculoskeletal pain, maximize physical

and cognitive function and optimize patient self-management and self-efficacy in dealing with fibromyalgia over time. Typical treatment components include comprehensive patient education (self-management, sleep hygiene, importance of exercise, etc.), the treatment of comorbid medical and mental health conditions, an exercise program, cognitive behavioral therapy and pharmaceutical therapy when indicated.[1,17] Complementary and alternative medicine approaches such as acupuncture, massage and many others are also commonly used.[17,18] Large-scale fibromyalgia clinics typically use multimodal treatment approaches, although many patients with fibromyalgia still receive uncoordinated care by seeking treatment from individual health care providers across multiple clinical settings.

Patients with fibromyalgia are highly heterogeneous and often have multiple coexisting conditions, syndromes, and symptoms that collectively impact outcomes and make successful patient diagnosis and management complex and challenging for providers.[1,6,9] The extent to which concomitant conditions are considered in determining treatments for fibromyalgia is unknown.

While numerous clinical trials suggest a mean benefit from treatments for a general population of fibromyalgia patients,[7,17] less is known about treatment effects within subgroups of fibromyalgia patients who typically present with complex symptoms in clinical settings and who often pose a treatment dilemma to providers. Patients with fibromyalgia can be grouped according to the number and type of coexisting syndromes or conditions, the severity of pain or impairment at baseline,[10] the presence of a mood or other mental health disorder, the primary complaint at baseline, or demographic or other related factors. The efficacy and comparative effectiveness of specific treatments that show mean benefits have not been well established for subgroups.

A large research team at McMaster University in Canada is currently undertaking a comprehensive systematic review of randomized clinical trials on interventions for fibromyalgia and related conditions in adults.[19] The McMaster review will examine all interventional randomized clinical trials to estimate the relative effectiveness of treatment approaches for fibromyalgia.[19]

This systematic review will complement the McMaster work by adding unique information on subgroup outcomes, and will include observational literature.

In determining which subgroups to address a priori, we consulted with a variety of experts. Certain subgroups of patients have a higher prevalence of fibromyalgia, are more complex or challenging to treat, or have historically unsatisfactory treatment outcomes.[6, 20] These include:

- Women: Women comprise the majority of fibromyalgia patients and most studies were conducted exclusively in women. More recent studies identified modest differences by sex in clinical features (pain sensitivity, tender point count, depression, sleep disturbance patterns, somatic symptoms, fatigue and pain duration), modes of treatment and patterns of health care service use[21-25] although findings differ by study size. However, little is known about differences in outcomes by gender for the same modes and intensities of treatment and which treatment modes best benefit males or females with fibromyalgia.
- Individuals with coexisting mental health conditions: Coexisting mental health disorders are particularly common in fibromyalgia patients, especially depression, anxiety and substance abuse.[26] Depression and/or anxiety occur in over one-third of fibromyalgia patients.[1,6,27] Traumatic or stressful events and post-traumatic stress disorder may trigger or exacerbate fibromyalgia.[1, 28] Simultaneous treatment of co-occurring mental health disorders has been advised especially in severe cases.[29]

- Individuals with high fibromyalgia symptom severity (Fibromyalgia Impact Questionnaire (FIQ) 59-100)[30]: Patients with high FIQ scores report greater functional limitations, higher overall impairment and greater symptoms, making them a challenging group of patients to treat and manage over time. Typical treatments may be less effective[31] or not feasible in this group of individuals and treatments require adaptation to severity.[29, 32]
- Older adults: Older adults typically have higher medical comorbidity burden than younger and middle-aged adults in the absence of fibromyalgia. More frequent and more severe medical comorbidities in older adults may increase the likelihood of adverse effects, drug interactions and altered drug tolerance from pharmaceutical therapies for fibromyalgia, increasing the risk for falls, fractures and other injuries from standard modes of treatment. Although recent information shows less impact of fibromyalgia on HRQoL in older women[33] and less fibromyalgia symptomatology in older compared with middle-age adults,[34] feasible modes of treatment and outcomes may vary in this subgroup.
- Obese adults: Higher rates of obesity and overweight are reported in patients with fibromyalgia, and severe obesity is associated with greater fibromyalgia symptoms and lower quality of life.[35]
- Persons with multiple medical comorbidities:[22]
  - Concurrent rheumatic disease: rheumatoid arthritis (RA), lupus (SLE), ankylosing spondylitis (AS) etc., including osteoarthritis (OA): At least one-third of patients with rheumatic conditions also have fibromyalgia. [1,36]
  - Other comorbidities.
- Persons with other significant chronic pain conditions:
  - Migraine or tension headaches are present in more than half of patients.[1,6,27]
  - Functional somatic syndromes (e.g., irritable bowel syndrome, chronic fatigue syndrome, temporomandibular joint dysfunction, low back pain and others) are associated with having fibromyalgia.[1,17]
  - The presence of other functional somatic syndromes with fibromyalgia complicates treatment and compromises outcomes.[37]
- Individuals with longer duration of fibromyalgia symptoms: Longer duration of fibromyalgia symptoms is associated with poorer outcomes. Initial assessment values are predictive of longer term outcomes in fibromyalgia patients seen in rheumatology centers.[38]

The extent to which the literature addresses these important patient subgroups identified by baseline characteristics, demographics or comorbid medical and mental health issues is unknown. Yet these patient groups are of greatest interest to clinicians. We will also be open to including other subgroups identified in the review.

The goal of treatment for select subgroups of fibromyalgia patients is to balance the benefits and harms of treatment within each specific subgroup. The extent to which adverse effects from treatments, especially pharmaceuticals are more common, more severe or otherwise different within specific subgroups of fibromyalgia patients is unknown and will therefore be included in this review.

II. The Key Questions

The draft key questions were posted for public comment on AHRQ's Effective Health Care Web site from October 25, 2013 through November 14, 2013. Comments about the key

questions, analytic framework and PICOTS were received from a large professional organization, several physicians and a few consumers and anonymous individuals. The comments were largely requests for text clarification of terms used in the PICOTS or analytic framework, although the following suggestions were made and incorporated into the revised key questions below:

1) We added improvement of symptoms to the final outcomes.
2) We specified gender as an additional pre-specified subgroup.
3) We added sleep quality as a final health outcome.

Key Questions

Question 1:

What are the efficacy and comparative effectiveness of treatments for fibromyalgia in specific adult subpopulations?

- Women and men
- Individuals with coexisting mental health conditions
- Individuals with high fibromyalgia symptom severity (FIQ 59-100)
- Older adults
- Obese adults
- Persons with multiple medical comorbidities
  - Concurrent rheumatic disease: rheumatoid arthritis (RA), lupus (SLE), ankylosing spondylitis (AS) etc., including osteoarthritis (OA)
  - Other comorbidities
- Persons with other significant chronic pain conditions (e.g. low back pain, headache, irritable bowel syndrome (IBS), etc.)
- Individuals with longer duration of fibromyalgia symptoms

Question 2:

What are the harms of treatments for fibromyalgia in specific adult subpopulations?

- Women and men
- Individuals with coexisting mental health conditions
- Individuals with high fibromyalgia symptom severity (FIQ 59-100)
- Older adults
- Obese adults
- Persons with multiple medical comorbidities
  - Concurrent rheumatic disease: rheumatoid arthritis (RA), lupus (SLE), ankylosing spondylitis (AS) etc., including osteoarthritis (OA)
  - Other comorbidities
- Persons with other significant chronic pain conditions (e.g. low back pain, headache, irritable bowel syndrome (IBS), etc.)
- Individuals with longer duration of fibromyalgia symptoms

The subgroups in key questions 1 and 2 were identified from expert informant input and the initial literature scan. Additional subgroups may be found during our review. We will analyze the

above-listed subgroups during this review and will include other subgroups as they are identified (such as smokers, Worker's Compensation, etc.).

The PICOTS Framework (Population, Intervention, Comparator, Outcomes, Timing, Setting):

Population

Subgroups of adults with fibromyalgia:

- By sex
- Individuals with coexisting mental health conditions
- Persons with high symptom severity (e.g., Fibromyalgia Impact Questionnaire scores 59-100 indicating a severe effect[39] or a related scale (such as the ACR Symptom Severity Scale[10])
- Older individuals (age 65 and older)
- Obese individuals (baseline body mass index of 30 or higher)
- Persons with multiple medical comorbidities
  - Concurrent rheumatic disease: rheumatoid arthritis (RA), lupus (SLE), ankylosing spondylitis (AS) etc., including osteoarthritis (OA)
  - Other comorbidities
- Persons with other significant chronic pain conditions (e.g. low back pain, headache, irritable bowel syndrome (IBS), etc.)
- Individuals with longer duration of fibromyalgia symptoms

Interventions

Pharmacologic treatments that are FDA-approved for use in the United States for fibromyalgia or other conditions (off-label use for fibromyalgia) will be included. Nonpharmacologic interventions that are or were available for use in the U.S. will be included.

- Pharmacologic
  - Antidepressants (e.g., tricyclic antidepressants such as amitriptyline; serotonin-norepinephrine reuptake inhibitors such as duloxetine and milnacipran; selective serotonin-reuptake inhibitors such as fluoxetine)
  - Antiepileptics (such as pregabalin or gabapentin)
  - Non-opioid analgesics
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Opioid analgesics
  - Skeletal muscle relaxants (such as tizanidine or cyclobenzaprine)
  - Other off-label: nabilone (synthetic cannabinoid), sodium oxybate
- Psychological
  - Cognitive behavioral therapy
  - Other
- Physical
  - Passive
    - Massage therapy
    - Acupuncture

        - Chiropractic
        - Modalities: ultrasound, heat, electrical muscle stimulation, etc.
        - Other (such as magnets)
    - Active
        - Exercise: supervised or independent (aerobic, strength training, stretching, water/therapeutic pool, Yoga)
    - Multimodal physical
        - Combinations of active and/or passive physical interventions
- Multicomponent
    - Various combinations of multiple intervention categories (such as pharmacologic + psychological + physical interventions simultaneously or in coordination)
- Lifestyle modifications
    - Dietary improvements, smoking cessation, sleep hygiene, etc.
- Other therapies
    - Mind-body therapies: meditation, hypnosis, tai chi, visualization
    - Other (such as transcranial direct current stimulation)
    - Nutraceuticals (such as coenzyme Q10, omega-3 fatty acids, algae)

Comparators

All the interventions listed above compared with one another, alone or in combination, placebo, or usual care.

Outcomes

Final health outcomes: KQ 1 and some potential measures of each outcome:

- Overall pain (Visual Analog Scale (VAS)[40], Brief Pain Inventory[41], McGill Pain Questionnaire[42])
- Symptom improvement: (such as Fibromyalgia Impact Questionnaire (FIQ)[43], Revised FIQ (FIQR)[44], Patient Global Impression of Change (PGI-C)[45], Patient Global Impression of Improvement (PGI-I)[45])
- Function (physical, emotional): (such as the FIQ, FIQR subscales)
- Participation (work, social activities): (FIQ, FIQR subscales[30, 46])
- Health-related quality of life (such as the SF-36[47])
- Fatigue: (such as the Multidimensional Assessment of Fatigue (MAF)[48])
- Sleep quality: (such as the Medical Outcomes Study (MOS) Sleep Scale[49])

Adverse effects or harms of intervention(s): KQ 2

- Drug-related side effects (such as dizziness, nausea, fatigue, dry mouth, weight gain, difficulty concentrating, hypertension, thoughts of suicide, peripheral edema, anxiety, tachycardia, constipation, etc.)
- Adverse effects from non-pharmaceutical treatments (such as muscle aches, minor injuries or falls during or after exercise; soreness or aches from passive physical treatments such as massage, etc.)

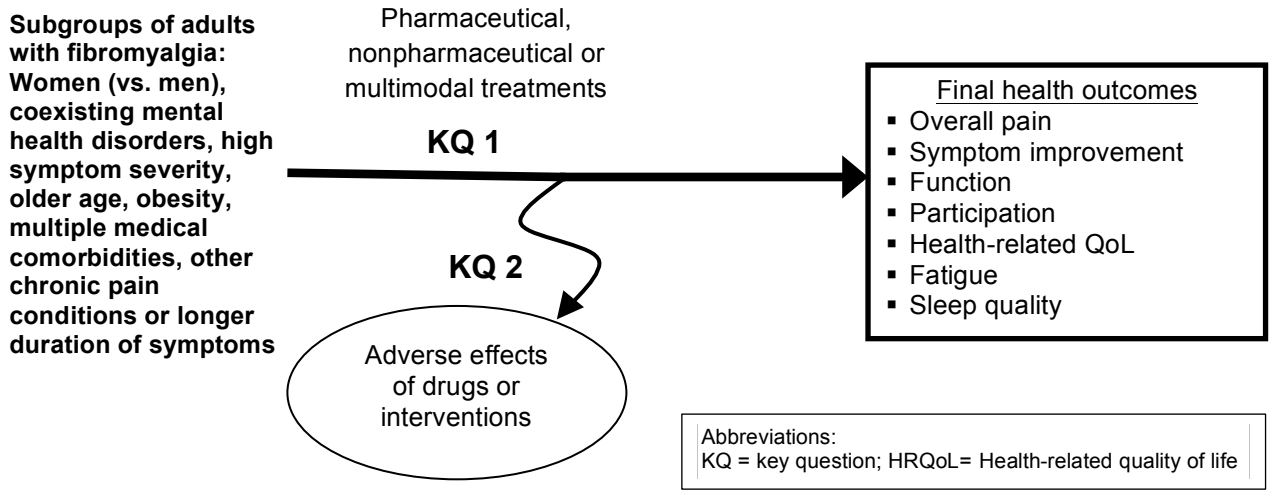
Timing

Duration of follow-up: minimum of 3 months. Since fibromyalgia is a chronic condition, outcomes improvements over time are more salient to patients and clinicians than temporary treatment effects.

Setting
Any non-inpatient (nonhospital) setting

III. Analytic Framework

Figure 1. Analytic framework for Treatments for Fibromyalgia in Adult Subgroups



IV. Methods

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

Studies for this comparative effectiveness review of fibromyalgia treatments in adult subgroups will be included or excluded based on the PICOTS framework outlined in Section II above, and the study-specific inclusion criteria described in Table 1 below.

Table 1. Study inclusion criteria

Category	Criteria for Study Inclusion
Target population	• Enrolled adults (age 18 and older) with fibromyalgia in studies that tested the effectiveness of treatments for fibromyalgia and reported outcomes in at least one of the adult subgroups of interest as identified in the PICOTS above. • Enrolled patients who met either the 1990[12] or 2010[10] revised fibromyalgia diagnostic criteria from ACR, or the Yunus criteria for fibrositis[51] (or similar) for studies published from 1985-1990. • We will not exclude other subgroups, if found, in the literature.
Interventions	• Pharmacologic treatments that are FDA-approved for use in the United States for fibromyalgia or other conditions (off-label use for fibromyalgia) will be included. Nonpharmacologic interventions that are or were available for use in the US will be included.
Study designs	• Randomized clinical trials (RCTs), nonrandomized controlled trials, and prospective or retrospective cohort studies will be included. Observational studies without control groups will be excluded. Cohort studies must include

	appropriate analytic techniques to address bias, such as propensity scores, instrumental variables, or multivariate analysis.
Time of publication	• English language studies published from 1985 forward will be included. The initial ACR diagnostic criteria were published in 1990 using clinical data that was collected starting in 1986.[12] Revised diagnostic criteria were released in 2010 that may capture a slightly broader sample of patients.[10,50] Pre-1990 studies may have used the Yunus criteria for fibrositis.[51]
Language of publication	• English language publications will be included because that literature best represents interventions available in the United States. However, we will not limit our search so that potential language bias can be assessed
Study quality	• All studies that meet the inclusion criteria will be screened for eligibility • Studies that do not adequately report study information to allow the abstraction of outcomes for the subgroups of adults identified in the key questions or have indeterminate numerators and denominators for outcomes and adverse event rates at follow-up time points will be excluded.

KQ = key question; RCT = randomized controlled trial

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

Bibliographic database searches will be used to identify systematic reviews, randomized controlled trials, and observational studies published from 1985 to the present on treatments for adults with fibromyalgia. Relevant bibliographic databases for this topic include Ovid MEDLINE®, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Ovid PsychINFO, and AMED (Allied and Complementary Medicine).

Our preliminary MEDLINE search strategy through November 2013 is in Appendix 1. An experienced librarian in the Minnesota EPC developed the MEDLINE search strategy; the search will be modified for other databases. The search strategies will be peer reviewed by an independent biomedical librarian. The search strategy employs relevant Medical Subject Headings (MeSH®) and natural language terms to identify two related fibromyalgia concepts, fibromyalgia and myofascial pain syndrome, and specific filters to identify study designs. Bibliographic database searches will be supplemented with backward citation searches of highly relevant systematic reviews. We will update the literature searches while the draft report is under public and peer review.

Two independent investigators will review titles and abstracts of bibliographic database search results to identify studies that examined interventions for fibromyalgia. Citations determined potentially eligible by either investigator will undergo full text screening for potential subgroup reporting. Two independent investigators will screen full text to determine if all inclusion criteria are met and to determine if subgroup outcomes are reported. Differences in screening decisions will be resolved by consultation between investigators and a third investigator.

We will conduct additional grey literature searches to identify relevant completed and ongoing studies. Relevant grey literature resources include trial registries and the U.S. Food and Drug Administration databases. Grey literature search results will be used to identify studies, outcomes, and analyses not reported in the published literature to assess publication and reporting bias. We will search ClinicalTrials.gov and the International Controlled Trials Registry Platform (ICTRP) for studies that specify a fibromyalgia subgroup analysis in their study protocol. We will also review Scientific Information Packets sent by manufacturers for relevant pharmaceuticals and interventions.

C. Data Abstraction and Data Management

One investigator trained in research methodology will extract relevant study, population, risk of bias, and outcomes data. Initial data abstraction will be quality checked by a second trained investigator. Data fields to be extracted will be determined based upon the proposed summary analysis. These fields will include author, year of publication; setting, subject inclusion and exclusion criteria, subgroup, intervention(s) and control characteristics (intervention delivery, timing, frequency, duration), follow-up duration, participant baseline demographics, comorbidities; fibromyalgia diagnostic and severity criteria, descriptions and results of primary outcomes and adverse effects, and study funding source. Data will be entered into Excel spreadsheets by one trained investigator and checked for accuracy by a second.

D. Assessment of Methodological Risk of Bias of Individual Studies

Sound study design, conduct, and reporting are especially important in fibromyalgia studies due to the heterogeneity of patients and the generally small to medium purported effects of pharmaceuticals[52] and other available treatments.[7] The risk of bias of eligible studies will be assessed by two independent investigators using instruments specific to each study design. Two independent investigators will consult to reconcile any discrepancies in overall risk of bias assessments. When agreement cannot be reached through consultation between the two reviewers, a third investigator will be consulted to reconcile the summary judgment.

For randomized clinical trials (RCTs), we will assess the risk of bias using a modified Cochrane Risk of Bias tool.[53] The seven domains of the tool are sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias (i.e., problems not covered by other domains). Additional items will be developed to assess potential risk-of-bias not addressed by the Cochrane tool. Outcomes measurement issues inherent in the psychometric properties of the questionnaires used to measure outcomes and assessment methods used to detect change in those questionnaire results will be specifically evaluated for detection bias. Additional items may be necessary to evaluate potential risk-of-bias associated with treatment definition and implementation (treatment fidelity) for nonpharmacologic treatments.

We will include additional items to assess the credibility of subgroup analysis of individual RCTs based on Sun et al.[54] These guidelines include: if the subgroup variable was measured at baseline, if the subgroup hypothesis was a priori, if the study included only a small number of subgroup hypotheses, if the interaction test suggest a low likelihood of chance explanation, among other contextual issues.[54]

Overall summary risk of bias assessments for each study will be classified as low, moderate, or high based upon the collective risk of bias inherent in each domain and confidence that the results are believable given the study's limitations.[55] Elements contributing to a low risk of bias assessment include whether a study used a random sequence generation, concealed allocation of treatment assignments, blinded outcomes assessors, demonstrated treatment fidelity, had minimal to modest missing outcomes data or balanced missing data across groups with similar reasons for missing data across groups, and credible subgroup analysis methods. [53] High risk of bias elements include nonrandom sequence generation, lack of blinding of outcomes assessors when the outcome was likely to be affected by the lack of blinding, or had high and/or differential losses to follow-up across treatment groups when missing outcomes data may have been related to real outcomes. Moderate risk of bias will be assigned to studies that are challenged across

several of the domains but the study was blinded or, if blinding was not possible, outcome assessors were blinded to treatment assignment. The potential for placebo effects in fibromyalgia treatments is high, thus special weight is given to the blinding domain.

We developed an instrument to assess risk of bias for observational studies using the RTI Observational Studies Risk of Bias and Precision Item Bank[56] (Appendix 2) because concerns about selection bias and blinding make the use of observational studies debatable in comparative effectiveness reviews. We selected items most relevant in assessing risk of bias from observational studies of fibromyalgia and to foster consistency with the risk-of-bias instrument for randomized controlled trials.[53] Bias issues common to observational studies involve the nonrandom selection of subjects, the completeness and validity of the recording of baseline patient information, attrition, and the ascertainment of outcomes. Items included from the RTI Item Bank address participant selection, group membership, efforts to address selection bias, identification of baseline effect modifiers and confounders, and appropriateness of analytic methods for observational studies. The overall summary risk-of-bias assessments for each individual study will be classified as low, moderate, or high based on the collective risk of bias inherent in each outcome domain and confidence that the results are believable given the study's limitations (Appendix 2). Similar to risk of bias for RCTs, the overall summary risk of bias will be weighted towards low for studies that demonstrate comparability across groups. Moderate risk of bias may be assigned to large cohort studies with a sample size for adequate power to detect differences, moderate to large effect sizes, and strong evidence of attempting to control for plausible confounders.

Risk of bias assessment for observational studies that pooled patient-level data from randomized clinical trials will be given special consideration. Risk of bias of pooled analyses will depend in part on the risk of bias of the inputs (RCTs) and the risk of bias in how the pooled analysis was conducted and reported. The risk of bias of the individual RCTs that comprise each pooled analysis will be assessed per the Cochrane tool as described above.[53,54] The additional risk of bias in how the pooled analysis was conducted will be assessed using the critical appraisal by Fisher et al.[57] of the principal methods for pooling individual-level RCT data to determine treatment-covariate interactions in the literature. Only within-trial patient-level interactions will be considered as across-trial information has a higher risk of bias.[57]

E. Data Synthesis

We will summarize the results into evidence tables and synthesize evidence by the type of study (RCT, observational, pooled RCT) for each unique population, comparison, and outcome combination within specific follow-up time periods. Because of the high probability of placebo effects in fibromyalgia treatments, if subgroup analysis is available through an RCT or pooled RCT literature for a given subgroup-treatment-outcome comparison, observational literature with high risk of bias will not be included in the analytic set for that comparison. We will conduct a brief qualitative sensitivity analysis of the excluded observational literature for differences in findings.

We will emphasize patient-centered outcomes in the evidence synthesis. Pain, fatigue, function, and quality of life will serve as primary outcomes for the review. We plan to pool data from multiple studies if we find two or more studies for the same subgroup-treatment-outcome comparison. The commonly used FIQ and FIQR tools assess the same domains and have comparable scoring characteristics that will potentially allow for pooling. Standardized mean differences will be calculated for different measures of the same outcome. We will categorize

treatment effects from the studies by the clinical importance of differences. Results will be stratified by the fibromyalgia diagnostic criteria (1990, 2010, other) used for study inclusion.

We will assess the heterogeneity among clinical, methodological and PICOTS elements to determine the appropriateness of pooling data.[58] Pooling criteria will include the same definitions of the fibromyalgia interventions and the outcomes for similar subgroups.[56] If pooling is possible, we will pool by study design; RCT and observational studies will not be combined. When a quantitative analysis is not appropriate or possible due to lack of comparable studies for given subgroup-treatment-outcome combination, qualitative synthesis will be conducted. Our preliminary examination of the literature suggests that study heterogeneity will allow only minimal opportunity for pooling; if this proves to be the case, a qualitative synthesis will be conducted for those subgroup-treatment-outcome combinations.

F. Grading the Strength of Evidence (SOE) for Individual Comparisons and Outcomes

The overall strength of evidence for select clinical outcomes within each comparison will be evaluated based on four domains: (1) study limitations (internal validity); (2) directness (single, direct link between the intervention and outcome); (3) consistency (similarity of effect direction and size); and (4) precision (degree of certainty around an estimate) with the study limitations domain having considerable importance.[59] A fifth domain, reporting bias, will be assessed when the strength of evidence is moderate or high based on the first four domains.[56] Study limitations will be rated as low, moderate or high according to study design and conduct. Consistency will be rated as consistent, inconsistent, or unknown/not applicable (e.g., single study). Directness will be rated as either direct or indirect. Precision will be rated as precise or imprecise. Other factors that may be considered in assessing strength of evidence include dose-response relationship, the presence of confounders, and strength of association. Deficiencies in the five domains will lower the strength of evidence grade.[59] We will require the existence of at least two moderate studies to assign a low strength of evidence rather than considering it to be insufficient. We will require at least one good study (low risk of bias) for moderate strength of evidence and two good studies (low risk of bias) for high strength of evidence. In addition, to be considered moderate or higher, intervention-outcome pairs need a positive response on two out of the three domains other than risk of bias. Based on these factors, the possible SOE grades are:[59]

- **High.** Very confident that the estimate of effect lies close to the true effect. Few or no deficiencies in body of evidence; findings believed to be stable.
- **Moderate.** Moderately confident that the estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings likely to be stable but some doubt.
- **Low.** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence necessary before concluding that findings are stable or that estimate of effect is close to true effect.
- **Insufficient.** No evidence, unable to estimate and effect, or no confidence in estimate of effect. No evidence is available or the body of evidence precludes judgment.

G. Assessing Applicability

Applicability of studies will be determined according to the PICOTS framework. Study characteristics that may affect applicability include, but are not limited to, changes in the diagnostic criteria over time (1990 versus 2010), narrow inclusion criteria or patient and intervention characteristics different than those described by population studies of fibromyalgia

interventions. Adults in clinical trials of fibromyalgia treatments may be higher functioning and/or less impaired than the fibromyalgia patient population as a whole. For the subgroup analyses we have planned, this would not limit applicability but would rather limit the number of studies that we find with adequate subgroup inclusion and reporting.

V. References

1. Centers for Disease Control and Prevention. Fibromyalgia. In: Centers for Disease Control and Prevention, editor; 2012.
2. Goldenberg D, Schur P, Romain P. Clinical manifestations and diagnosis of fibromyalgia in adults. UpToDate: Wolters Kluwer; 2013.
3. Howard KJ, Mayer TG, Neblett R, et al. Fibromyalgia syndrome in chronic disabling occupational musculoskeletal disorders: prevalence, risk factors, and posttreatment outcomes. J Occup Environ Med. 2010 Dec;52(12):1186-91. PMID 21124244.
4. Kleinman N, Harnett J, Melkonian A, et al. Burden of fibromyalgia and comparisons with osteoarthritis in the workforce. J Occup Environ Med. 2009 Dec;51(12):1384-93. PMID 19952796.
5. McDonald M, DiBonaventura M, Ullman S. Musculoskeletal pain in the workforce: the effects of back, arthritis, and fibromyalgia pain on quality of life and work productivity. J Occup Environ Med. 2011 Jul;53(7):765-70. PMID 21685799.
6. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum. 2008 Jan;58(1):26-35. PMID 18163497.
7. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. JAMA. 2004 Nov 17;292(19):2388-95. PMID 15547167.
8. Haviland MG, Banta JE, Przekop P. Fibromyalgia: prevalence, course, and co-morbidities in hospitalized patients in the United States, 1999-2007. Clinical & Experimental Rheumatology. 2011 Nov-Dec;29(6 Suppl 69):S79-87. PMID 22243553.
9. Vincent A, Lahr BD, Wolfe F, et al. Prevalence of fibromyalgia: a population-based study in Olmsted County, Minnesota, utilizing the Rochester Epidemiology Project. Arthritis care & research. 2013 May;65(5):786-92. PMID 23203795.
10. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis care & research. 2010 May;62(5):600-10. PMID 20461783.
11. Wolfe F, Clauw DJ, Fitzcharles MA, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol. 2011 Jun;38(6):1113-22. PMID 21285161.
12. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis & Rheumatism. 1990;33(2):160-72.
13. Hauser W, Wolfe F. Diagnosis and diagnostic tests for fibromyalgia (syndrome). Reumatismo. 2012;64(4):194-205. PMID 23024964.
14. Fitzcharles MA, Shir Y, Ablin JN, et al. Classification and Clinical Diagnosis of Fibromyalgia Syndrome: Recommendations of Recent Evidence-Based Interdisciplinary Guidelines. Evid Based Complement Alternat Med. 2013;2013:528952. PMID 24379886.
15. Hauser W, Jung E, Erbsloh-Moller B, et al. Validation of the Fibromyalgia Survey Questionnaire within a cross-sectional survey. PLoS ONE [Electronic Resource]. 2012;7(5):e37504. PMID 22662163.

16. Kim SM, Lee SH, Kim HR. Applying the ACR Preliminary Diagnostic Criteria in the Diagnosis and Assessment of Fibromyalgia. Korean J Pain. 2012 Jul;25(3):173-82. PMID 22787548.
17. Goldenberg D, Schur P, Romain P. Initial treatment of fibromyalgia in adults. UpToDate: Wolters Kluwer; 2013.
18. Terhorst L, Schneider MJ, Kim KH, et al. Complementary and alternative medicine in the treatment of pain in fibromyalgia: a systematic review of randomized controlled trials. Journal of Manipulative & Physiological Therapeutics. 2011 Sep;34(7):483-96. PMID 21875523.
19. Busse JW, Ebrahim S, Connell G, et al. Systematic review and network meta-analysis of interventions for fibromyalgia: a protocol. Systems Review. 2013;2:18. PMID 23497523.
20. Fitzcharles MA, Ste-Marie PA, Gamsa A, et al. Opioid use, misuse, and abuse in patients labeled as fibromyalgia. Am J Med. 2011 Oct;124(10):955-60. PMID 21962316.
21. Hauser W, Kuhn-Becker H, von Wilmoswky H, et al. Demographic and clinical features of patients with fibromyalgia syndrome of different settings: a gender comparison. Gender Medicine. 2011 Apr;8(2):116-25. PMID 21536230.
22. Wolfe F, Anderson J, Harkness D, et al. A prospective, longitudinal, multicenter study of service utilization and costs in fibromyalgia. Arthritis & Rheumatism. 1997 Sep;40(9):1560-70. PMID 9324009.
23. Weimer MB, Macey TA, Nicolaidis C, et al. Sex Differences in the Medical Care of VA Patients with Chronic Non-Cancer Pain. Pain Med. 2013 Dec;14(12):1839-47. PMID 23802846.
24. Castro-Sanchez AM, Mataran-Penarrocha GA, Lopez-Rodriguez MM, et al. Gender differences in pain severity, disability, depression, and widespread pressure pain sensitivity in patients with fibromyalgia syndrome without comorbid conditions. Pain Med. 2012 Dec;13(12):1639-47. PMID 23171037.
25. Aparicio VA, Ortega FB, Carbonell-Baeza A, et al. Are there gender differences in quality of life and symptomatology between fibromyalgia patients? Am J Mens Health. 2012 Jul;6(4):314-9. PMID 22494975.
26. Epstein SA, Kay G, Clauw D, et al. Psychiatric disorders in patients with fibromyalgia. A multicenter investigation. Psychosomatics. 1999 Jan-Feb;40(1):57-63. PMID 9989122.
27. Arnold LM, Leon T, Whalen E, et al. Relationships among pain and depressive and anxiety symptoms in clinical trials of pregabalin in fibromyalgia. Psychosomatics. 2010 Nov-Dec;51(6):489-97. PMID 21051680.
28. Smith HS, Harris R, Clauw D. Fibromyalgia: an afferent processing disorder leading to a complex pain generalized syndrome. Pain Physician. 2011 Mar-Apr;14(2):E217-45. PMID 21412381.
29. Hauser W, Burgmer M, Kollner V, et al. [Fibromyalgia syndrome as a psychosomatic disorder - diagnosis and therapy according to current evidence-based guidelines]. Z Psychosom Med Psychother. 2013;59(2):132-52. PMID 23775553.
30. Bennett RM, Bushmakin AG, Cappelleri JC, et al. Minimal clinically important difference in the fibromyalgia impact questionnaire. J Rheumatol. 2009 Jun;36(6):1304-11. PMID 19369473.
31. Wasserman RA, Brummett CM, Goesling J, et al. Characteristics of chronic pain patients who take opioids and persistently report high pain intensity. Reg Anesth Pain Med. 2014 Jan-Feb;39(1):13-7. PMID 24310048.

32. Nijs J, Roussel N, Van Oosterwijck J, et al. Fear of movement and avoidance behaviour toward physical activity in chronic-fatigue syndrome and fibromyalgia: state of the art and implications for clinical practice. Clin Rheumatol. 2013 Aug;32(8):1121-9. PMID 23639990.
33. Campos RP, Vazquez MI. The impact of Fibromyalgia on health-related quality of life in patients according to age. Rheumatol Int. 2013 Jun;33(6):1419-24. PMID 23152088.
34. Shillam CR, Dupree Jones K, Miller L. Fibromyalgia symptoms, physical function, and comorbidity in middle-aged and older adults. Nurs Res. 2011 Sep-Oct;60(5):309-17. PMID 21873914.
35. Kim CH, Luedtke CA, Vincent A, et al. Association of body mass index with symptom severity and quality of life in patients with fibromyalgia. Arthritis care & research. 2012 Feb;64(2):222-8. PMID 21972124.
36. Zammurrad S, Munir W, Farooqi A. Disease activity score in rheumatoid arthritis with or without secondary fibromyalgia. J Coll Physicians Surg Pak. 2013 Jun;23(6):413-7. PMID 23763802.
37. Mourao AF, Blyth FM, Branco JC. Generalised musculoskeletal pain syndromes. Best Pract Res Clin Rheumatol. 2010 Dec;24(6):829-40. PMID 21665129.
38. Wolfe F, Anderson J, Harkness D, et al. Health status and disease severity in fibromyalgia: results of a six-center longitudinal study. Arthritis & Rheumatism. 1997 Sep;40(9):1571-9. PMID 9324010.
39. Schaefer C, Chandran A, Hufstader M, et al. The comparative burden of mild, moderate and severe fibromyalgia: results from a cross-sectional survey in the United States. Health Qual Life Outcomes. 2011;9:71. PMID 21859448.
40. McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. Psychol Med. 1988 Nov;18(4):1007-19. PMID 3078045.
41. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994 Mar;23(2):129-38. PMID 8080219.
42. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain. 1975 Sep;1(3):277-99. PMID 1235985.
43. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol. 1991 May;18(5):728-33. PMID 1865419.
44. Bennett RM, Friend R, Jones KD, et al. The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. Arthritis Res Ther. 2009;11(4):R120. PMID 19664287.
45. Guy W. ECDEU assessment manual for psychopharmacology, revised. Rockville, MD: US Department of Health, Education and Welfare publication (ADM). National Institute of Mental Health. 1976.
46. Bennett R. The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses. Clin Exp Rheumatol. 2005 Sep-Oct;23(5 Suppl 39):S154-62. PMID 16273800.
47. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun;30(6):473-83. PMID 1593914.
48. Belza BL. Comparison of self-reported fatigue in rheumatoid arthritis and controls. J Rheumatol. 1995 Apr;22(4):639-43. PMID 7791155.

49. Hays RD, Martin SA, Sesti AM, et al. Psychometric properties of the Medical Outcomes Study Sleep measure. Sleep Med. 2005 Jan;6(1):41-4. PMID 15680294.
50. Oncu J, Iliser R, Kuran B. Do new diagnostic criteria for fibromyalgia provide treatment opportunity to those previously untreated? Journal of Back and Musculoskeletal Rehabilitation. 2013;26(4):437-43. PMID 2013624582.
51. Yunus M, Masi AT, Calabro JJ, et al. Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls. Seminars in Arthritis & Rheumatism. 1981 Aug;11(1):151-71. PMID 6944796.
52. Hauser W, Bartram C, Bartram-Wunn E, et al. Adverse events attributable to nocebo in randomized controlled drug trials in fibromyalgia syndrome and painful diabetic peripheral neuropathy: systematic review. Clinical Journal of Pain. 2012 Jun;28(5):437-51. PMID 22336767.
53. Higgins JPT, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions: Version 5.1.0. London: The Cochrane Collaboration; March 2011. Available at http://www.cochrane-handbook.org.
54. Sun X, Briel M, Walter SD, et al. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ. 2010;340:c117. PMID 20354011.
55. Higgins JPT, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions: Version 5.1.0. The Cochrane Collaboration; 2011.
56. Viswanathan M, Berkman ND. Development of the RTI item bank on risk of bias and precision of observational studies. Journal of Clinical Epidemiology. 2011.
57. Fisher DJ, Copas AJ, Tierney JF, et al. A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners. J Clin Epidemiol. 2011 Sep;64(9):949-67. PMID 21411280.
58. Fu R, Gartlehner G, Grant M, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. Journal of Clinical Epidemiology. 2011 Nov;64(11):1187-97. PMID 21477993.
59. Berkman ND, Lohr KN, Ansari M, et al. Grading the strength of a body of evidence when assessing health care interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Rockville, MD: November 2013. http://www.effectivehealthcare.ahrq.gov/ehc/products/457/1752/methods-guidance-grading-evidence-131118.pdf

VI. Definition of Terms

Not applicable

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

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, 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.

X. Technical Experts

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodologic 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.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest which cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHSA 290-20-12000161 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix 1: Search Strategy: MEDLINE®

Database: Ovid MEDLINE(R) <1946 to November Week 2 2013> Search Strategy:

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1 meta analysis as topic/ (14174)
2 meta-analy$.tw. (58094)
3 metaanaly$.tw. (1283)
4 meta-analysis/ (51865)
5 (systematic adj (review$1 or overview$1)).tw. (47251)
6 exp Review Literature as Topic/ (7718)
7 or/1-6 (115989)
8 cochrane.ab. (33481)
9 embase.ab. (29939)
10 (psychlit or psyclit).ab. (1190)
11 (psychinfor or psycinfo).ab. (8325)
12 or/8-11 (48550)
13 reference list$.ab. (11704)
14 bibliograph$.ab. (11806)
15 hand search.ab. (876)
16 relevant journals.ab. (904)
17 manual search$.ab. (2248)
18 or/13-17 (25683)
19 selection criteria.ab. (26165)
20 data extraction.ab. (10119)
21 19 or 20 (33811)
22 review/ (1921415)
23 21 and 22 (26055)
24 comment/ (537610)
25 letter/ (807565)
26 editorial/ (337037)
27 animal/ (5506319)
28 human/ (13689930)
29 27 not (28 and 27) (3970292)
30 or/24-26,29 (5167730)
31 7 or 12 or 18 or 23 (144954)
32 31 not 30 (135948)
33 randomized controlled trials as topic/ (102691)
34 randomized controlled trial/ (390224)
35 random allocation/ (81795)
36 double blind method/ (131905)
37 single blind method/ (19625)
38 clinical trial/ (504861)
39 clinical trial, phase i.pt. (16220)
40 clinical trial, phase ii.pt. (26918)
41 clinical trial, phase iii.pt. (10181)
42 clinical trial, phase iv.pt. (997)
43 controlled clinical trial.pt. (89925)

44 randomized controlled trial.pt. (390224)
45 multicenter study.pt. (182851)
46 clinical trial.pt. (504861)
47 exp Clinical trials as topic/ (296596)
48 or/33-46 (959756)
49 (clinical adj trial$).tw. (211765)
50 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (129589)
51 placebos/ (33783)
52 placebo$.tw. (161799)
53 randomly allocated.tw. (16078)
54 (allocated adj2 random$).tw. (18581)
55 49 or 50 or 51 or 52 or 53 or 54 (418203)
56 48 or 55 (1126654)
57 case report.tw. (184302)
58 case report.tw. (184302)
59 letter/ (807565)
60 historical article/ (300466)
61 57 or 58 or 59 or 60 (1281048)
62 56 not 61 (1102751)
63 exp cohort studies/ (1371088)
64 cohort$.tw. (263920)
65 controlled clinical trial.pt. (89925)
66 epidemiologic methods/ (30994)
67 limit 66 to yr=1971-1983 (5365)
68 63 or 64 or 65 or 67 (1546297)
69 exp case-control study/ (666622)
70 (case$ and control$).tw. (314550)
71 69 or 70 (892406)
72 exp Fibromyalgia/ (6360)
73 fibromyalgia.ti,ab. (6304)
74 myofascial pain syndrome*.ti,ab. (387)
75 32 or 62 or 68 or 71 (2692964)
76 72 or 73 or 74 (7791)
77 75 and 76 (2584)
78 limit 77 to "all adult (19 plus years)" (1910)
79 limit 78 to "all child (0 to 18 years)" (309)
80 77 not 79 (2275)
81 78 or 80 (2584)

Appendix 2: Instrument to Assess Risk of Bias for Observational Studies using the RTI Observational Studies Risk of Bias and Precision Item Bank

Treatments for Fibromyalgia in Adult Subgroups
Risk of Bias Assessment for Observational Studies

Author _____ ***Year*** _____ PMID _____ **Reviewer** _____

Question	Response	Criteria	Justification
	Internal Validity		
1. Study design: prospective, retrospective or mixed?	Prospective ☐	Outcome had not occurred when study was initiated; information was collected over time	
	Mixed ☐	One group was studied prospectively; other(s) retrospectively	
	Retrospective ☐	Analyzed data from past records, claims	
2. Were inclusion/exclusion criteria clearly stated?	Yes ☐	Clearly stated	
	Partially ☐	Some, but not all criteria stated or some not clearly stated.	
	No ☐	Unclear	
3. Were baseline characteristics measured using valid and reliable measures and are they equivalent in both groups?	Yes ☐	Valid measures, groups ~equivalent	
	No ☐	Non-validated measures or non-equivalent groups	
	Uncertain ☐	Could not be ascertained	
4. Were important variables known to impact the outcome(s) assessed at baseline?	Yes ☐	Yes, most or all known factors were assessed	
	No ☐	Critical factors are missing	
	Uncertain ☐		
5. Is the level of detail describing the intervention adequate?	Yes ☐	Intervention sufficiently described	
	Partially ☐	Some of the above features.	
	No ☐	Intervention poorly described	
6. Is the selection of the comparison group appropriate?	Yes ☐	Other fibromyalgia patients with similar patient characteristics, severity and comorbid features	
7. Was the impact of a concurrent intervention or an unintended exposure that might bias results isolated?	Yes ☐	By inclusion criteria, protocol or other means	
	Partially ☐	Some were isolated, others were not	
	No ☐	Important concurrent interventions were not isolated or prohibited	
8. Were there attempts to balance the allocation across groups? (e.g. stratification, matching or propensity scores)	Yes ☐	(*If yes, what method was used?)*	
	No ☐		
	Uncertain ☐	Could not be ascertained	

9. Were outcomes assessors blinded?	Yes	☐	Who assessed outcomes?	
	No	☐		
	Uncertain	☐	Not reported	
10. Were outcomes assessed using valid and reliable measures, and used consistently across all study participants?	Yes	☐	Measures were valid and reliable (i.e. objective measure, validated scale/tool); consistent across groups	
	Partially	☐	Some of the above features	
	No	☐	None of the above features	
	Uncertain	☐	Could not be ascertained.	
11. Was length of follow-up the same for all groups?	Yes	☐		
	No	☐		
	Uncertain	☐	Could not be ascertained	
12. Did attrition result in differences in group characteristics between baseline and follow-up?	Yes	☐	*(If yes, for which follow-up period(s)?)*	
	No	☐		
	Uncertain	☐	Could not be ascertained	
13. If dissimilar baseline characteristics, does the analysis control for baseline differences between groups?	Yes	☐	What method?	
	No	☐		
	Uncertain	☐	Could not be ascertained	
14. Were confounding and/or effect modifying variables assessed using valid and reliable measures across all study participants?	Yes	☐		
	No	☐		
	Uncertain	☐	Could not be ascertained (i.e. retrospective designs where eligible at baseline could not be determined)	
	NA	☐	No confounders or effect modifiers included in the study.	
15. Were important confounding and effect modifying variables taken into account in design and/or analysis? (e.g. matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment)	Yes	☐		
	Partially	☐	Some variables taken into account or adjustment achieved to some extent.	
	No	☐	Not accounted for or not identified.	
	Uncertain	☐	Could not be ascertained	
16. Are statistical methods used to assess the primary outcome appropriate to the	Yes	☐	Statistical techniques used must be appropriate to the data.	
	Partially	☐		
	No	☐		

data?	Uncertain	☐	Could not be ascertained	
17. Is there suggestion of selective outcome reporting?	Yes	☐		
	No	☐	Not all prespecified outcomes reported, subscales not prespecified reported, outcomes reported incompletely	
	Uncertain	☐	Could not be ascertained	
18. Was the funding source identified?	No	☐		
	Yes	☐	Who provided funding?	
	Uncertain	☐		
Overall Assessment				
Overall Risk of Bias assessment	Low	☐	Results are believable taking study limitations into consideration	
	Moderate	☐	Results are probably believable taking study limitations into consideration	
	High	☐	Results are uncertain taking study limitations into consideration	