Evidence-based Practice Center Systematic Review Protocol

Project Title: *The Effectiveness of Disease-Modifying Antirheumatic Drugs (DMARDS) in Children With Juvenile Idiopathic Arthritis (JIA)*

I. Background and Objectives for the Systematic Review

Overview

Juvenile idiopathic arthritis (JIA), formerly known as juvenile rheumatoid arthritis, is the most common rheumatologic disease in childhood, with an overall prevalence of 70 to 400 per 100,000 children.[1] JIA is an important cause of chronic disease in childhood, with a prevalence similar to type 1 diabetes mellitus.[2] JIA consists of at least six categories with distinct yet overlapping clinical manifestations. These are:[3]

- Systemic arthritis: initial presentation includes fever, rash, and arthritis; one-quarter of children may have severe destructive joint disease.
- Oligoarthritis: affects up to four joints within the first 6 months of the illness; may be persistent (i.e., involving no more than four joints) or extended (i.e., involving more than four joints after the first 6 months of illness) and may be associated with uveitis.
- Polyarthritis: affects five or more joints during the first 6 months of disease; is subclassified as rheumatoid factor-negative and rheumatoid factor-positive disease, the latter of which may be associated with more destructive joint disease.
- Enthesitis-related arthritis: may be associated with uveitis.
- Psoriatic arthritis: may be associated with uveitis.
- Other: arthritis of unknown cause with symptoms for more than 6 weeks.

JIA can place a severe physical and psychological burden on affected children and be a major stressor to families. As with all chronic conditions in childhood, treatment may be enhanced by a multidisciplinary team to address these issues. There is no curative treatment for JIA. Until recently, treatment has focused on the use of non-steroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen) and intra-articular injections of corticosteroids[4] (see Table 1). Unfortunately, many patients will not respond to this first-line therapy.

Therapy with the so-called disease-modifying anti-rheumatic drugs (DMARDs) has become an increasingly important component of care. These drugs, which operate through a number of different mechanisms (see Table 2), share the common effect of limiting radiologic progression of disease.[4] Although these drugs can dramatically improve the disease course, no evidence-based guidelines exist regarding the management of JIA with DMARDs. There are many unanswered questions about the safety and effectiveness of these drugs, especially for their long-term use in children.

Controversy and Uncertainty

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A clear synthesis of the available evidence is needed to help clinicians provide care for children with JIA. This is especially important because there is a workforce shortage of pediatric rheumatologists,[5] leading to treatment of children by adult-focused rheumatologists who may be less familiar with the pediatric specific evidence. Understanding when to use a DMARD is especially challenging, because JIA is heterogeneous across the various subtypes. Furthermore, there are a large number of DMARDs that cannot simply be grouped by drug class. Failure with a drug in one particular class does not necessarily predict failure with another drug in the same class. Some children may even benefit from treatment with more than one DMARD at a time.

In order to assess the benefits or harms of any therapy, it is critical to have a comparison treatment. For many therapies, this is a placebo. However, for JIA the most appropriate comparator to judge the effectiveness of a DMARD or combination of DMARDs may be methotrexate. Methotrexate is a DMARD that has been found to be highly effective, and often is the first DMARD used in children with JIA.[6] Methotrexate has also been available for much longer then the other DMARDs, so there is greater clinical experience with the drug and the drug is relatively inexpensive.

Another critical component to evaluating the effect of therapies is the measurement of their impact. Evaluating changes in JIA disease status can be challenging. Most studies use the American College of Rheumatology (ACR)-30 scoring system, which evaluates the following domains: patient function, patient/parent assessment of well-being, physician assessment of overall disease activity, number of joints with active arthritis, number of joints with limited range of motion, and erythrocyte sedimentation rate (ESR). Improvement in any three of these domains by 30 percent and worsening in not more than one by 30 percent is considered to be improvement.[7] Other disease scoring systems have been developed (e.g., the Juvenile Arthritis Disease Activity Score [JADAS]).[8] The key informants identified three important concerns with existing scoring systems. First, these measures evaluate relative and not absolute changes in disease progression. However, standardized "absolute" measures may provide greater insight. Second, these instruments may not reflect the goals of treatment. For example, many providers would not consider a 30 percent improvement to be a clinically significant improvement. Even the ACR-70, which evaluates for a 70 percent improvement may not be enough since the goal of treatment is remission. Finally, some key informants who are clinicians noted that having an instrument that could be rapidly used in daily practice would be more helpful in assessing the impact of DMARDs. Regardless of the measure, it is important to be able to measure clinically meaningful responses to therapy and to assess for remission.

Relevance

JIA is associated with significant morbidity and mortality. Affected individuals, their families, and clinicians are especially excited with the new DMARDs, which they believe may lead to more extensive resolution of symptoms for longer periods of time. Unfortunately, DMARDs are expensive and the risks of therapy are unclear. The disease experts we interviewed, including clinicians, a parent of a child with JIA, and a representative of a large health insurer, all underscored the need for a synthesis of the evidence to guide management. This is especially important because of workforce shortages in pediatric rheumatology. As a result, many adult-trained rheumatologists provide care for children. A clear summary of the

evidence would help these other health care providers in making evidence-based decisions and likely lead to overall improvements in outcomes for children with JIA. Both the parent and the payer who served as key informants identified the importance of an unbiased assessment of the evidence. The experts also endorsed synthesizing available data to identify missing gaps in the evidence and to set a future agenda in JIA clinical research.

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Table 1. Intra-articular corticosteroids and NSAIDs, JIA approval status, and samples of significant warnings from the drug product labels.

Generic Name	US Trade Name	Drug Type	Approved by the US Food and Drug Administration-for JIA	Warnings – Increased Risk
Betamethasone	Celestone	Intra-articular corticosteroid	Yes	Subcutaneous atrophy ; Cushing syndrome
Triamcinolone Acetonide	Kenolog	Intra-articular corticosteroid	Yes	Subcutaneous atrophy ; Cushing syndrome
Triamcinolone Hexacetonide	Aristospan	Intra-articular corticosteroid	No	Subcutaneous atrophy ; Cushing syndrome
Celecoxib	Celebrex	NSAID	Yes	Hepatotoxicity; nephrotoxicity; gastritis
Etodolac	Lodine	NSAID	No	Cardiovascular thrombotic events; gastritis
Ibuprofen	Motrin Advil	NSAID	Yes	Gastritis; hepatotoxicity; nephrotoxicity
Indomethacin	Indocin Indocin SR	NSAID	Yes	Headaches: gastritis; hepatotoxicity; nephrotoxicity
Meloxicam	Mobic	NSAID	Yes	Gastritis; hepatotoxicity; nephrotoxicity
Naproxen	Naprosyn Aleve	NSAID	Yes	Gastritis; hepatotoxicity; nephrotoxicity
Oxaprozin	Daypro	NSAID	Yes	Cardiovascular thrombotic events; gastritis
Tolmetin	Tolectin	NSAID	Yes	Gastritis; hepatotoxicity; nephrotoxicity

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Table 2. DMARDs, their mechanisms of action, JIA approval status, and samples of significant warnings from the drug product labels.

Generic Name	US Trade Name	Mechanism of Action	Approved by the US Food and Drug Administration for JIA	Warnings – Increased Risk
Abatacept	Orencia	Anti-CD28, T-cell costimulator antibodies; biologic	Yes	Infections
Adalimumab	Humira	TNF inhibitor; biologic	Yes	Infections; cancer
Anakinra	Kineret	IL-1 receptor antagonist; biologic	No	Infections
Canakinumab	Ilaris	IL-1 blocker; biologic	No	Vertigo
Etanercept	Enbrel	TNF inhibitor; biologic	Yes	Infections; cancer
Infliximab	Remicade	TNF inhibitor; biologic	No	Infections; cancer
IVIG	Baygam Carimune NF Flebogamma 5% DIF Gammar P Gamunex 10% Gammagard S/D Gammagard Liquid 10% Gammar P Iveegam EN Octagam 5% Panglobulin Polygam S/D Privigen 10% Vivaglobin	Interaction with activating Fc receptors; biologic	No	Hepatitis; acute renal failure; Venous thrombosis; aseptic meningitis
Rilonacept	Arcalyst	IL-1 blocker; biologic	No	Infection
Rituximab	Rituxan	Binds to CD20 antigen; biologic	No	Progressive multifocal leukoencephalopathy; severe skin reactions; infusion reactions
Tocilizumab	Actemra	IL-6 receptor antagonist; biologic	No	Infections; elevated lipid levels

Continued.

Table 2. Continued.

Generic Name	US Trade Name	Mechanism of Action	Approved by the US Food and Drug Administration for JIA	Warnings – Increased Risk
Azathioprine	Azasan Imuran	Purine synthesis inhibitor; nonbiologic	No	Cancer; bone marrow suppression
Cyclosporine A	Neoral Gengraf	Inhibits calcineurin; nonbiologic	No	Infections; nephrotoxicity; hepatotoxicity
D-Penicillamine	Depen Cuprimine	Unknown (may lower IgM rheumatoid factor; depresses T-cell activity); nonbiologic	No	Allergic reactions; Goodpasture's syndrome; hematologic toxicities; hepatotoxicity; myasthenia gravis
Hydroxy-chloroquine	Plaquenil	Not well understood (may reduce T-lymphocyte transformation and chemotaxis); nonbiologic	No	Kidney damage; retinopathy
Leflunomide	Arava	Isoxazole immunomodulatory agent; nonbiologic	No	Hepatotoxicity
Methotrexate	Methotrexate LPF	Unknown (antimetabolite; inhibits dihydrofolic acid reductase); nonbiologic	Yes	Hepatotoxicity; cancer
Mycophenolate mofetil	CellCept	Guanosine synthesis inhibitor; nonbiologic	No	Cancer; bone marrow suppression
Sulfasalazine	Azulfidine sulfazine	Unknown; nonbiologic	Yes	Bone marrow suppression; hepatotoxicity; Stevens Johnson syndrome
Tacrolimus (FK506)	Prograf	Reduces T-cell and IL-2 activity; nonbiologic	No	Cancer; infection
Thalidomide	Thalomid	Unknown; nonbiologic	No	Birth defects; neuropathy

II. The Key Questions

The key questions for this review were developed after a topic-refinement process that included a preliminary review of the medical literature and two teleconferences with experts and key stakeholders in JIA. The following is a summary of the comments we received based on the JIA Topic Refinement posting and the resulting modifications in this document.

- *The trade name of tocilizumab, Actemra, was not listed in the table of DMARDs.*

  This has been corrected.

- *Adalimunab is now approved for JIA in children.*

  This has been corrected.

- *Clarify that corticosteroids refers to intra-articular corticosteroids.*

  This has been corrected.

- *Categorize DMARDs into biologic versus nonbiologic DMARDs.*

  This has been added to the table. However, this classification system does not necessarily predict the effectiveness of treatment. Therefore, the analyses will not be based on this classification system alone.

- *Methotrexate is a DMARD.*

  Methotrexate is the most commonly used DMARD for childhood JIA. In our preliminary review of the literature, we found that methotrexate is rapidly becoming a component of the "traditional" therapy of intra-articular corticosteroids and NSAIDs. In our analyses, it is likely that we will need to compare other DMARDs to therapy that includes methotrexate.

In addition, the Technical Expert Panel (TEP) recommended the addition of specific NSAIDs and DMARDs that were not initially included.

The following is a list of the revised key questions based on the comments received about the JIA Topic Refinement posting:

Key Questions	**KQ 1:**	In children with JIA, does treatment with disease-modifying antirheumatic drugs (DMARDs), when compared to conventional treatment (i.e., NSAIDs or corticosteroids) with or without methotrexate, improve laboratory measures of inflammation or radiologically evident disease progression, symptoms (e.g., pain, symptom scores), or health status (e.g., functional ability, mortality)?
	KQ 2:	In children with JIA, what are the comparative effects of DMARDs on laboratory markers of inflammation or radiologically evident progression of disease, symptoms (e.g., pain, symptom scores), or health status (e.g., functional ability, mortality)?
	KQ 3:	In children with JIA, does the rate and type of adverse events differ between the various DMARDs or between DMARDs and conventional treatment with or without methotrexate?
	KQ 4:	How do the efficacy, effectiveness, safety, and adverse effects of treatment with DMARDs differ among the various subtypes of JIA?
	KQ 5:	What is the validity, reliability, responsiveness, and feasibility of the clinical outcomes measures for JIA that are commonly used in clinical trials or within the clinical practice setting?

- **Population(s):**

  KQ1-KQ5
  - We will include children (i.e., those 18 years of age and younger) with any subtype of JIA of any severity.

- **Interventions:**

  KQ1-KQ4
  - The interventions will include any DMARD (see Table 2) alone or in any combination.

  KQ5
  - The ACR-30 and other high-priority instruments will be used to assess clinical outcomes or remission of JIA, regardless of treatment.

- **Comparators:**

  KQ1-KQ4
  - The comparators will include either traditional therapy (NSAIDs with or without the intra-articular corticosteroids listed in Table 1) or traditional therapy with methotrexate. Methotrexate is the DMARD most commonly used to treat children with JIA. When possible, we will also compare DMARDs against each

other as active comparators.

KQ5

- Any measure that can establish psychometric properties.

- **Outcomes for each question**

  KQ1-KQ4

  - Primary outcomes: Improvement in intermediate or long-term outcomes. The intermediate outcomes include laboratory measures of inflammation, active joint count, number of joints with limited range of motion, radiographic evidence of the progression of disease, or global assessment of current status. The long-term outcomes include pain control, clinical remission, quality of life, growth, development, joint function, functional ability, and mortality.
  - Secondary outcomes: None.
  - Adverse events: These are specific to the interventions being examined (see Table 2). Specifically, we will examine mortality, malignancy, serious infection, hepatitis, bone marrow suppression, nausea or vomiting, and risks to fetus or pregnant mother. Because of the known risks associated with DMARDs, we anticipate our findings will focus on significant infections and the development of cancer.

  KQ5

  - Primary Outcomes: Inter-rater and intra-rater reliability, test-retest reliability, responsiveness (standardized response mean and responsiveness index), and time to administer.

- **Timing:**

  KQ1-KQ4

  - All studies must be at least 3 months in duration.

  KQ5

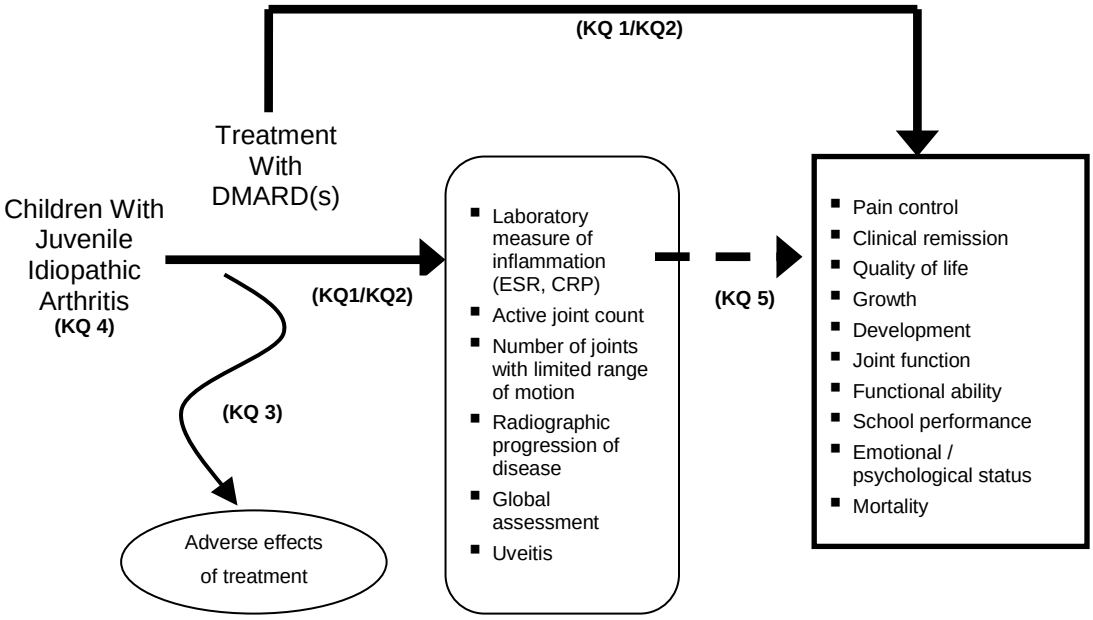
  - Cross-sectional studies or longitudinal studies of any duration.

- **Settings:**

  KQ1-KQ5

  - Data will come from specialty medical settings, either from pediatric or adult rheumatology clinics.

III. Analytic Framework



This figure depicts the key questions within the context of the PICOTS described in the previous section. In general, the figure illustrates how treatment of JIA in children with DMARDs versus intra-articular corticosteroids and NSAIDs may result in intermediate outcomes (e.g., changes in laboratory measures of inflammation, changes in the active joint count, or radiologically evident progression of disease) and/or long-term outcomes (e.g., clinical remission, changes in quality of life, changes in growth, and changes in development). In addition, adverse events may occur at any point after the treatment is received.

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IV. Methods

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

General criteria used to identify eligible articles are described below for randomized controlled trials (RCTs) and observational studies. Because JIA is rare, assembling a large sample size is challenging. Therefore, we will not restrict studies based on sample size alone. Depending on the specific factors or interventions being examined, additional criteria may apply.

Inclusion criteria for RCTs:

- Sample population has JIA according to the International League of Associations for Rheumatology criteria or juvenile rheumatoid arthritis according to the American College of Rheumatology definition (KQ1-KQ5).
- Random allocation to the intervention or the placebo/control groups (KQ1-KQ3).
- One or more DMARDs are evaluated (KQ1-KQ4).
- Outcome is change in one of the prespecified intermediate or final outcomes and is assessed by using an acceptable standard (KQ1, KQ2).
- Study duration is at least 3 months (KQ1-KQ4). [Rationale: We expect that response to a particular treatment will take at least 3 months to be realized.]
- Population may be from primary or specialty care settings (KQ1-KQ5). [Rationale: JIA is most likely to be managed by specialists. Therefore, it is unlikely that studies will come from a primary care setting.]
- Sample consists of children 18 years of age or younger. If the study includes adults, at least 80 percent of the sample will be children or the outcomes must be reported separately for the child subgroup (KQ1-KQ5).

Exclusion criteria for RCTs:

- Non-English language publication (KQ1-KQ5).

Inclusion criteria for observational studies:

- Sample population has JIA according to the International League of Associations for Rheumatology criteria or juvenile rheumatoid arthritis according to the American College of Rheumatology definition (KQ1-KQ5).
- One or more DMARDs are evaluated (KQ1-KQ4).
- Outcome is change in one of the prespecified intermediate or long-term outcomes and is assessed by using an acceptable standard (KQ1, KQ2).
- Study duration is at least 3 months (KQ1-KQ4).

- Population may be from primary or specialty care settings (KQ1-KQ5).
- Sample consists of children 18 years of age or younger. If the study includes adults, at least 80 percent of the sample will be children or the outcomes must be reported separately for the child subgroup (KQ1-KQ5).
- Outcomes are determined a priori and are assessed by using an acceptable standard (KQ1-KQ4).
- For studies of effectiveness, there must be a treatment comparator (KQ1-KQ4).
- Case control studies are acceptable to assess for adverse events of DMARD treatment (KQ3, KQ4).
- Cross-sectional studies are acceptable to evaluate clinical outcome measure tools (KQ5).

Use of gray literature

We will only include data from articles that have undergone peer-review. Research letters published in peer-reviewed journals usually undergo only minimal peer-review. We will provide a narrative overview of information available from research letters that provide information on adverse events associated with DMARDs in the treatment of JIA or JRA (depending on the diagnosis criteria) or that provide information about DMARD therapy for which few data are otherwise available (i.e., uveitis). We will not include research letters in any quantitative assessment (i.e., meta-analysis).

We will review the quarterly data files from the United States Food and Drug Administration Adverse Event Reporting System (AERS) from July 2008 to June 2009 for adverse events related to JIA treatment with DMARDs. These findings will be described qualitatively.

We will also search abstracts presented at key meetings to identify publications in press (see next section for search strategy). However, specific findings from abstracts will not be included in the review.

Exclusion criteria for observational studies:

- Non-English language publication (KQ1-KQ5).
- Cross-sectional studies for the evaluation of the impact of treatment (KQ1-KQ4).

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

We plan to conduct a primary review of the literature by systematically searching, reviewing, and analyzing the scientific evidence for each key question. To identify articles relevant to each question, we will begin by searching MEDLINE (via PubMed), EMBASE, the Cochrane Library, and the Cochrane Central Trials Registry. We will further evaluate the bibliographies of included primary studies and any systematic or nonsystematic reviews that are

identified. To assure completeness, search strategies will be developed in consultation with the TEP.

Using prespecified inclusion/exclusion criteria, titles/abstracts will be reviewed by two reviewers for potential relevance to the key questions. Articles included by either reviewer will undergo full-text screening. At the full-text screening stage, two independent reviewers must agree on a final inclusion/exclusion decision. Articles meeting eligibility criteria will be included for data abstraction.

After the draft report is submitted, we will conduct an updated literature search covering the interval since the original search was completed. These studies, along with any studies identified in the peer-review process, will be reviewed to determine if they meet study eligibility criteria.

We will search abstracts from two major scientific meetings—that is, the annual meetings of the European League Against Rheumatism and the American College of Rheumatology—from the previous 2 years. We will contact the authors to identify in-press articles in press that would meet the criteria for inclusion in this review.

C. Data Abstraction and Data Management

Data from published reports will be abstracted into evidence tables by one reviewer and over-read by a second reviewer. Data elements include descriptors to assess applicability, quality elements, intervention/exposure details, and outcomes. Disagreements will be resolved by consensus or by obtaining a third reviewer's opinion when consensus cannot be reached. Key characteristics will include age, gender, JIA subtype, severity, study treatment, and outcomes as described previously. All results will be tracked in an Endnote database.

D. Assessment of Methodological Quality of Individual Studies

We will develop separate criteria for assessing the methodological quality of RCTs and observational studies. Quality assessment will be performed, in the first instance, by the person abstracting or evaluating the included article; this initial assessment will then be over-read by a second reviewer. Disagreements will be resolved between the two reviewers or when needed by arbitration from a third reviewer.

For RCTs, we will use the key criteria described in the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews,[9] adapted to this specific topic. These criteria are: adequacy of randomization and allocation concealment; the comparability of groups at baseline; blinding; the completeness of followup and differential loss to followup; whether or not incomplete data were addressed appropriately; the validity of outcome measures; and conflict of interest.

To assess individual observational studies, we will adapt a basic set of quality criteria used in previous AHRQ evidence reports.[10,11] These criteria concern the methods used to select the cohort, the adequacy of the sample size, the methods used to ascertain exposure status and outcomes, the adequacy and completeness of followup, and the appropriateness of the analytic methods used. Abstractors will be instructed to assign a rating of "yes," "partially," "no," or "can't tell" to each item and provide a brief rationale for their decisions. We will not attempt to assign a summary quality score (A, B, C or Good, Fair, Poor) to individual RCTs or

observational studies. First, there is no evidence that the use of any particular quality scoring system has a substantial impact on the results of systematic reviews.[12] Second, our experience has been that it is more helpful to identify consistent and specific quality issues that affect the majority of the literature (concerning, e.g., sample size, analytic methods, or ascertainment bias) in order to guide future research, rather than relying on a global quality score.

E. Data Synthesis

We will summarize the primary literature by abstracting relevant continuous and categorical data. We will then determine the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depends on the volume of relevant literature, conceptual homogeneity of the studies, and completeness of the results reporting.

Data synthesis will be stratified by intervention and study population (e.g., age, JIA subtype). We anticipate that studies may report dichotomous outcomes (e.g., global assessment of improvement) and continuous outcomes (e.g., change in ACR-30). We will adapt the classification approach used by Angevaren et al.[13] to categorize instruments into measures addressing the same construct. We will use the weighted mean difference when studies use the same outcome scale; otherwise, standardized mean differences will be used. Preplanned sensitivity analyses include: study quality, including the quality of the measurement of exposure to the factor; thoroughness of adjustment for potential confounders; and patient characteristics, such as age, gender, and JIA subtype.

Data synthesis for observational studies is more challenging. Initially, data will be synthesized qualitatively with a particular focus on design issues that may lead to systematic bias. Design issues, including confounding, will be examined as a source for heterogeneous results. If feasible, results will be synthesized quantitatively.

F. Grading the Evidence for Each Key Question

The strength of evidence for each key question will be assessed using the approach described in the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews.[9] In brief, this approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains are to be used when appropriate: coherence, dose-response association, impact of plausible residual confounders, strength of association (magnitude of effect), and publication bias. These domains will be considered qualitatively and a summary rating will be assigned after discussion by two reviewers as "high," "moderate," or "low" strength of evidence. In some cases, high, moderate, or low ratings will be impossible or imprudent to make. In these situations, a grade of "insufficient" will be assigned.

V. References

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VI. Definition of Terms

ACR	American College of Rheumatology
AHRQ	Agency for Healthcare Research and Quality
CERs	Comparative Effectiveness Reviews
CRP	C-Reactive Protein
DMARDs	Disease-Modifying Antirheumatic Drugs
EPC	Evidence-based Practice Center
IgM	Immunoglobulin M
IL-1	Interleukin 1
IL-6	Interleukin 6
JIA	Juvenile Idiopathic Arthritis
NSAIDs	Nonsteroidal Antiinflammatory Drugs
PICOTS	Population(s), Interventions, Comparators, Outcomes, Timing, Settings
RCTs	Randomized Controlled Trials
TEP	Technical Expert Panel
TNF	Tumor Necrosis Factor

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.

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, key questions submitted by partners are reviewed and refined as needed by the EPC and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

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 healthy 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

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.

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