AHRQ Comparative Effectiveness Review Surveillance Program

CER # 28:
Disease-Modifying Antirheumatic Drugs (DMARDs) in Children with Juvenile Idiopathic Arthritis (JIA)

Original release date: September 2011

Surveillance Report: February 2013

Key Findings:

- The conclusions for KQ1b (DMARDs vs conventionals improve radiological progression), KQ2b (comparative effects- DMARDs and radiological progression), KQ2c (comparative effects- DMARDs and symptoms), KQ2d (comparative effects- DMARDs and health status) are still considered valid
- The conclusions for KQ1a (DMARDs vs conventionals improve inflammation), KQ1c (DMARDs vs conventionals improve symptoms), KQ1d (DMARDS vs conventionals improve health status), are out of date, given additional data
- The conclusions for KQ2a (comparative effects- DMARDs and inflammation), KQ3a (adverse events- DMARDs), KQ3b (adverse events- DMARDs vs conventionals)are possibly out of date
- The conclusions for KQ4 (DMARDs and various categories of JIA) and KQ5 (outcome measures) are still considered valid but additional studies are available

Summary Decision

This CER's priority for updating is **High**

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Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project:

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Contents

Disease-Modifying Antirheumatic Drugs (DMARDs) in Children with Juvenile Idiopathic Arthritis (JIA)

1. Introduction

Comparative Effectiveness Review (CER) #28, Disease-Modifying Antirheumatic Drugs (DMARDs) in Children with Juvenile Idiopathic Arthritis (JIA) was released in September 2011.[1] It was therefore due for a surveillance assessment in March 2012. Resource constraints at the Surveillance Center delayed this until September 2012, and then late-breaking evidence delayed it until January, 2013.

2. Methods

2.1 Literature Searches

Using the search strategy employed for 2010-March 13, 2012. The search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and five specialty journals (Annals of the Rheumatic Diseases, Arthritis and Rheumatism, Clinical Rheumatology, Journal of Clinical Rheumatology, and Rheumatology). The specialty journals were those most highly represented among the references for the original report. This search resulted in 148 titles to review. Appendix A includes the search strategy.

2.2 Study selection

In general we used the same inclusion and exclusion criteria as the original CER.

2.3 Expert Opinion

We shared the conclusions of the original report with four experts in the field (including the original project leader, suggested field experts, original technical expert panel (TEP) members, and peer reviewers) for their assessment of the need to update the report and their recommendations of any relevant new studies. We heard back from the project lead and three subject matter experts completed the questionnaire matrix. Appendix C shows the questionnaire matrix that was sent to the experts.

2.4 Check for qualitative and quantitative signals

After abstracting the study conditions and findings for each new included study into an evidence table, we assessed whether the new findings provided a signal according to the Ottawa

Method and/or the RAND Method suggesting the need for an update. The criteria are listed in the table below.[2, 3]

	Ottawa Method
	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

2.5 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that included the key questions, the original conclusions, and the findings of the new literature search, the expert assessments, and any FDA reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the 4-category scheme described in the table above for the RAND Method.

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.

- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

3. Results

3.1 Search

The literature search identified 148 titles. After title and abstract review, we further reviewed the full text of 24 journal articles. The remaining 124 titles were rejected because they were editorials, letters, or did not include topics of interest. Seven further articles were reviewed at the suggestion of the experts.

Through literature searches and expert recommendations, 31 articles went on to full text review. Two articles were recently identified. Of these 8 were rejected because they did not answer a key question, were not related to DMARDs, or were reviews. Thus, 25 articles were abstracted into an evidence table (Appendix B).[4-28]

3.2 Expert Opinion

Overall, all three experts were in agreement that the key conclusions were up-to-date until 2 recent clinical trials[6, 22] were published that all 3 experts agreed provided additional information such that the priority for updating became 'high'. Regarding these 2 trials, in an editorial accompanying these studies[29], the editorialist writes that these studies represent dramatic examples of how advances in understanding the biology of inflammation have led to development of drugs such as the interleukin-1 inhibitor (canakinumab) and the interleukin-6 inhibitor (tocilizumab) which have revolutionized the treatment of systemic juvenile idiopathic

arthritis (JIA). The striking responsiveness to anti-interleuking-1 and anti-interleukin-6 points to an immunobiology of systemic JIA that is unique among the various JIA subsets. The agents tested in these trials have begun a new era in the treatment of systemic JIA and will likely illuminate further the mechanisms causing this disorder.

Given the additional input from our three experts, the priority of this assessment was changed to a “high”.

3.3 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts’ assessments, the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update, and qualitative signal.

Table 1. Summary Table

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Key Question 1: In children with JIA, does treatment with DMARDs, compared to conventional treatment:				
Key Question 1a: Improve laboratory measures of inflammation?				
Trials of DMARDs usually report changes in laboratory measures of inflammation (e.g., ESR—erthrocyte sedimentation rate). However, ESR is inconsistently associated with treatment. This conclusion is based on 14 studies of 1,060 subjects. Strength of Evidence: Low	There were two new studies.[6, 22] The first contained an RCT that evaluated canakinumab treatment. It found that, at baseline, the median CRP was 137.0 (71.2-194.9) in the placebo group and 141.3 (88.0-270.0) in the canakinumab group. At the end of trial 1, 90% of the placebo patients had discontinued. The median CRP of the treated patients was 12.0 (3.3-76.6).[22] A study of tocilizumab found improvement in measures of inflammation including CRP and ESR. The CRP was elevated in 92% of those on placebo at baseline and was 94% after 12 weeks. In the treatment group, it went from 96% to 1%.[6] The ESR was 54.1 mm/hr for those on placebo at baseline and 59.8 after 12 weeks. In the treatment group, the ESR was 57.6 at baseline and 4.4 after 12 weeks.[6, 22]	No new data	All 3 experts stated that two additional trials[6, 22] have important findings. One expert expressed that they show that both tocilizumab and canakinumab are extremely effective in improving inflammatory markers in systemic JIA, but they need to be broken out from studies of drugs in other forms of JIA. One expert suggested two new articles[5, 7] as additional new evidence.	The conclusions are out of date
Key Question 1b: Improve radiological progression?				
Insufficient data are available to evaluate the impact of DMARDs on radiological progression. Only one cohort study of 63 subjects reported data on radiological progression. Strength of Evidence: Insufficient	One new case report[20] found MTX led to systemic repair of bone erosion in a 15 year old female.	No new data	All 3 experts thought the conclusions were still valid. One expert noted that there were only anecdotal reports, no prospective studies	The conclusions are still valid

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Among children who have responded to a biologic DMARD, randomized discontinuation trials show that continued treatment for from 4 months to 2 years decreases the risk of having a flare (RR 0.46, 95% CI 0.36 to 0.60). This conclusion is based on four studies of 322 subjects. Among the nonbiologic DMARDs, there is some evidence that methotrexate is superior to conventional therapy and oral corticosteroids, based on two randomized trials of 215 subjects. Strength of Evidence: Moderate	One RCT[26] of 364 patients on MTX found that, in patients with JIA in remission, a 12 month vs 6 month withdrawal of MTX did not reduce the relapse rate. One RCT of canakinumab measured the patient's global assessment of patient's overall well-being and found a median of 63.0 (45.0-81.0) at baseline decreasing to 6.5 (0.0-26.0) in those treated with canakinumab. 90% of patients on placebo discontinued the treatment.[22] A study of tocilizumab found 80% of treated patients had >70% improvement, up to 52 weeks.[6]	No new data	One expert noted that there was no good data about when ok to stop biologics, the findings of one study[26], that MTX studies are fraught with dose/ route issues that could greatly affect the results, and was not sure what was meant by 'conventional therapy'. All 3 experts agreed that two additional trials[6, 22] have important findings. One expert expressed that they show that both tocilizumab and canakinumab are extremely effective in improving inflammatory markers in systemic JIA, but they need to be broken out from studies of drugs in other forms of JIA. One expert listed two new studies[5, 7]	The conclusions are out of date, with five additional studies available
Key Question 1d: Improve health status?				

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Changes in health status were reported in 12 studies involving 927 subjects. Health status improved inconsistently with treatment with DMARDs. Strength of Evidence: Low	There were 14 new studies, 3 studies including 74 patients on anakinra[9, 15, 24] which showed effectiveness, 3 studies including 490 patients on etanercept[10, 14, 19] with inconsistent results, 1 study including 72 patients on etanercept or adalimumab[8] that found them to be effective, safe and well-tolerated; 1 study including 55 patients on rituximab[18] that found improvement in those with severe JIA, refractory to several prior agents. 2 studies including 107 patients on canakinumab[22, 24] found efficacy. 1 study including 190 patients on abatacept[23] that found improvements in HRQOL; 2 studies including 131 patients on tocilizumab[6, 11] which showed early and sustained efficacy and tolerability for treating intractable polyarticular JIA.	No new data	All 3 experts agreed that two additional trials[6, 22] have important findings. One expert expressed that they show that both tocilizumab and canakinumab caused improved CHAQ in systemic JIA, but they need to be broken out from studies of drugs in other forms of JIA. One expert suggested one study[23] and another expert suggested two studies[5, 7] as additional new evidence.	The conclusions are out of date given the five new studies available
Key Question 2: In children with JIA, what are the comparative effects of DMARDs on:				
Key Question 2a: Laboratory measures of inflammation?				

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Trials of DMARDs usually report changes in laboratory measures of inflammation (e.g., ESR—erthrocyte sedimentation rate). However, ESR is inconsistently associated with treatment. This is based on 4 RCTs of 448 subjects and 1 cohort study of 72 subjects. Strength of Evidence: Low	No new studies of ESR alone	No new data	All 3 experts thought the conclusions were still valid. One expert suggested two new studies[5, 7] as additional new evidence. These demonstrate marked improvement in ESR	The conclusions are possibly out of date given data from these two new studies
Key Question 2b: Radiological progression?				
No study addressed radiologic progression. Strength of Evidence: Insufficient	No new studies	No new data	All 3 experts thought the conclusions were still valid.	The conclusions are still valid
Key Question 2c: Symptoms?				
The nonbiologic DMARDs that were compared directly (penicillamine vs. hydroxychloroquine, sulfasalazine vs. hydroxychloroquine, and leflunomide vs. methotrexate) had similar efficacy. Changes in symptoms between the treatment arms were not measured with significant precision to detect a difference. This is based on 4 RCTs of 448 subjects and 1 cohort study of 72 subjects. One poor-quality RCT of 94 subjects found that etanercept was similar to infliximab. Strength of Evidence: Low	No new studies	No new data	All 3 experts thought the conclusions were still valid. One expert suggested two new studies[5, 7] as additional new evidence	The conclusions are still valid
Key Question 2d: Health status?				

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
The nonbiologic DMARDs that were compared directly (penicillamine vs. hydroxychloroquine sulfasalazine vs. hydroxychloroquine, and leflunomide vs. methotrexate) had similar efficacy. Changes in health status between the treatment arms were not measured with significant precision to detect a difference. This is based on 4 RCTs of 448 subjects and 1 cohort study of 72 subjects. One poor quality RCT of 94 subjects found that etanercept was similar to infliximab. Strength of Evidence: Low	No new studies	No new data	All three experts thought the conclusions were still valid. One expert suggested two new studies [5, 7] as additional new evidence	The conclusions are still valid
Key Question 3: In children with JIA, do the rate and type of adverse events differ between:				
Key Question 3a: The various DMARDs?				

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Three RCTs directly compared two DMARDs; two compared penicillamine to hydroxychloroquine, and one compared leflunomide to methotrexate. The rate and type of adverse events did not differ between treatment groups in these studies. High variability across studies in the ascertainment and reporting of adverse events preclude valid comparisons of the rate and type of adverse events among the various DMARDs. Recently published studies of adverse event reporting databases provide indirect evidence that suggests a possible relationship between cancer and exposure to tumor necrosis factor blockers. Strength of Evidence: Insufficient	There were no studies comparing DMARDs. However there were 4 that examined AEs among DMARDs. There were 3 cases of scleritis associated with etanercept[8], national JIA registries of Netherlands, Germany, Finland, Denmark and Italy from a registry, found 13/1651 cases of IBD in JIA patients using etanercept.[27] A German registry found 5 cases of malignancy in 1560 JIA patients exposed to tnf-ihibitors.[10] A cohort of national Medicaid of 7812 children with and without JIA found children with JIA have an increased rate of incident malignany. Treatment, including tnf inhibitors did not appear to be significantly associated wth development of malignancy.[5]	There were 3 alerts: one alert regarding potential hepatic dysfunction and hepatic failure with adalimumab, one regarding potential acute febrile neutrophilic dermatosis (Sweet's syndrome) with azathioprine, and , one regarding potential hypogammaglobulinemia with rituximab. Information provided by Genentech advised of potential serious infections, gastrointestinal perforations, hypersensitivity reactions, including anaphylaxis, demyelinating disorders and risk of malignancies with	All three experts thought the conclusions were still valid. However, one expert cited that data were very poor and suggested one new article which did not fit our inclusion criteria. 2 experts suggested one new article[22]	The conclusions are possibly out of date. There is one additional study available and signals for AEs need follow-up

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Key Question 3b: DMARDs and conventional treatment with or without methotrexate?				
No RCT directly compared a DMARD to conventional treatment. Thirteen trials directly compared a DMARD to placebo. The rate and type of adverse events were generally similar between intervention and placebo groups, with the notable exceptions of infliximab plus methotrexate being associated with more serious adverse events (32% vs. 5% over differing lengths of followup), and methotrexate being associated with higher rates of laboratory abnormalities (35% vs. 13%). Strength of Evidence: Insufficient	There were 3 applicable studies: One RCT compared MTX +etanercept +prednisolone vs MTX+placebo. No difference in AEs or remission.[5] An RCT of infliximab +MTX, MTX alone or combo of MTX+ sulfasalazine+ hydroxychloroquine found that infliximab+MTX was superior to the combination and strikingly superior to MTX alone.[7] An open observational study of etanercept with or without MTX or corticosteroids (or both) found that, among other factors, concomitant treatment with MTX seemed to independently increase the chance for achieving remission.[11]	No new data	Two experts thought the conclusions were still valid. One expert suggested two new articles[5, 7] as additional new evidence. One expert was not sure.	The conclusions are possibly out of date given there are 3 additional studies which possibly could change the strength of the evidence evaluation

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Key Question 4: How do the efficacy, effectiveness, safety, and adverse effects of treatment with DMARDs differ among the various categories of JIA?				
Only one study—an RCT of methotrexate versus placebo in which each group could also receive oral corticosteroids, intra-articular corticosteroids, and NSAIDs—evaluated efficacy by JIA category. No difference was found among those with extended oligoarticular JIA (n = 43) and systemic JIA (n = 45). We did not identify any studies that provide reliable information on the comparative safety or rates or types of adverse events among the various categories of JIA. Strength of Evidence: Insufficient	There were 2 studies looking at TNF-blocking agents in 2 categories of JIA. They were drawn from the same cohort and found that in 22 patients with enthesitis-related arthritis, TNF-blockers seemed effective and safe however a sustained disease-free state could not be achieved and none discontinued the agents successfully.[12] In 18 patients with juvenile psoriatic arthritis, TNF blockers seemed effective in treating arthritis but arthritis flared after treatment discontinuation and psoriatic skin lesions did not respond well, with 4 patients developing de novo psoriasis.[13] There was one RCT of abatacept in patients with psoriatic arthritis that found that 10mg/kg of abatacept led to significant improvements over other doses of abatacept or placebo.	No new data	All 3 experts thought the conclusions were still valid.1 expert listed additional new evidence including- JIA Rx document[5, 7, 9, 15, 18, 22, 24-26]	The conclusions are still valid, with additional studies available
Key Question 5: What is the validity, reliability, responsiveness, and feasibility of the clinical outcome measures for childhood JIA that are commonly used in clinical trials or within the clinical practice setting?				

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Most of the studies examining the psychometric properties of the instrumentsused in JIA were fair-quality cross-sectional or longitudinal nonrandomized controlled trials. No one instrument or outcomes measure appeared superior in measuring disease activity or functional status. The current response criteria of the ACR Pediatric 30, a composite measure that includes articular indices, functional status, laboratory measure, and global assessments, takes into account the various measures most commonly used. However, the responsiveness of several of these measures, including functional status and parent/patient global assessment, are poor to moderate, and they may not adequately reflect changes in disease state. Furthermore, given that the ACR Pediatric 30 is a relative measure of disease activity, the impact of JIA category on percent improvement is unclear, as certain instruments, such as the CHAQ, appear to have differential responsiveness depending on extent of disease at baseline. The ACR Pediatric 30 is also a relative measure of disease activity and not a measure of current disease state. Strength of Evidence: Insufficient	No new studies	none	All three experts thought the conclusions were still valid.	The conclusions are still valid.

Legend: AEs=Adverse Events; ESR=Erythrocyte Sedimentation Rate; MTX=Methotrexate; RCT=Randomized Controlled Trial; JIA=Juvenile Idiopathic Arthritis; HRQOL= Health-Related Quality of Life; ESR= Erythrocyte sedimentation rate; IBD=inflammatory bowel disease; TNF= Tumor Necrosis Factor

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Appendices

Appendix A: Search Methodology

Appendix B: Evidence Table

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2010-3/13/2012

LANGUAGE:
English

SEARCH STRATEGY:
arthritis, juvenile rheumatoid OR "juvenile rheumatoid arthritis" OR "juvenile ideopathic arthritis" OR "juvenile chronic arthritis"

LIMITED TO THE FOLLOWING JOURNALS:
Annals Of Internal Medicine
BMJ
JAMA
Lancet
New England Journal Of Medicine

Annals of the Rheumatic Diseases
Arthritis and Rheumatism
Clinical Rheumatology
Journal of Clinical Rheumatology
Rheumatology

NUMBER OF RESULTS: 148

Appendix B. Evidence Table

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Key Question 1: In children with JIA, does treatment with DMARDs, compared to conventional treatment:						
Key Question 1a: Improve laboratory measures of inflammation?						
De Benedetti, 2012[6]	RCT, double blind tocilizumab vs placebo, with open-label extension for all patients	112	2-17 yo with systemic JIA >6 months and inadequate responses to NSAIDS and glucocorticoids	Absence of fever and improvement of 30% or more on 3/6 variables of ACR core set, with no >1 variable worsening >30%	Every 2 weeks x 12 weeks	Measures of inflammation included CRP and ESR. The CRP was elevated in 92% of those on placebo at baseline and was 94% after 12 weeks. In the treatment group, it went from 96% to 1%. The ESR was 54.1 mm/hr for those on placebo at baseline and 59.8 after 12 weeks. In the treatment group, the ESR was 57.6 at baseline and 4.4 after 12 weeks
Ruperto, 2012[22]	RCT, Trial 1- 1 dose of canakinumab vs placebo Trial 2- open label treatment with canakinumab	84	Age 2-19, systemic JIA and active systemic features	Improvement of 30% or more in at least 3/6 core criteria for JIA, worsening >30% in no more than 1 criteria and resolution of fever.	Trial 1- single dose Trial 2- 32 weeks	Measures of inflammation included CRP. At baseline of trial 1, the median CRP was 137.0 (71.2-194.9) in the placebo group and 141.3 (88.0-270.0) in the canakinumab group. At the end of trial 1, 90% of the placebo patients had discontinued. The median CRP of the treated patients was 12.0 (3.3-76.6)
Key Question 1b: Improve radiological progression?						

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Nakatani, 2011[13]	Case report, methotrexate	1	Rheumatoid factor positive polyarthritis-type JIA	Symptom changes, disease progression	1 and 1/2 years	Clinical remission was achieved within 10 months after the start of MTX and systemic repair of bone erosion was noted 8 months after remission
Key Question 1c: Improve symptoms?						
De Benedetti, 2012[6]	RCT, double blind tocilizumab vs placebo, with open-label extension for all patients	112	2-17 yo with systemic JIA >6 months and inadequate responses to NSAIDS and glucocorticoids	Absence of fever and improvement of 30% or more on 3/6 variables of ACR core set, with no >1 variable worsening >30%	Every 2 weeks x 12 weeks	12 weeks- 64/75 (85%) of tocilizumab group vs 9/37 (24%) placebo [P<0.001]. 52 weeks- 80% of tociluzumab patients had >70% improvement with no fever, including 59% w. 90% improvement. 48% had 0 joints with active arthritis, 52% discontinued glucocorticoids
Ruperto, 2012[22]	RCT, Trial 1- 1 dose of canakinumab vs placebo Trial 2- open label treatment with canakinumab	84	Age 2-19, systemic JIA and active systemic features	Improvement of 30% or more in at least 3/6 core criteria for JIA, worsening >30% in no more than 1 criteria and resolution of fever.	Trial 1- single dose Trial 2- 32 weeks	In trial one, the patient's global assessment of patient's overall well-being was a median of 63.0 (45.0-81.0) at baseline decreasing to 6.5 (0.0-26.0) in those treated with canakinumab. 90% of patients on placebo discontinued the treatment.
Key Question 1d: Improve health status?						

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Sevcic, 2011[25]	Cohort, open observational study of etanercept and adalimumab(if failed to respond to etanercept)	72	JIA, <18 years old, failed to respond or did not tolerate MTX	Disease activity	1 year	All disease activity parameters improved significantly in first 3 months. After 3 months 88% achieved ACR Pedi 30. After 12 months, 76% did.

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Quartier, 2011[21]	RCT, anakinra vs placebo	24	Systemic- onset JIA	Response, defined by ACR Pedi 30, resolution of systemic symptoms and decrease of at least 50% of both C-reactive protein and ESR	12 months	At month 1, there were 9 responders (8/12 receiving anakinra and 1 receiving placebo (p=0.003). At M2, 10 patients in placebo group switched to anakinra and 9 became responders.
Prince, 2011[20]	Cohort, parents and data from the arthritis and biologicals in children-register	49	JIA, failed to respond or did not tolerate MTX	Cost and treatment success	27 months	Utility was 0.53 before start of etanercept, according to HUI3. After 27 months, increased to 0.78. Also all JIA core set response variables improved significantly over 27 months of etanercept treatment

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Otten, 2011[15]	Cohort, open observational study of etanercept	262	JIA	Response to etanercept and association between baseline factors and response	7 years	At 15 months, 85 patients (32%) were excellent responders, 92 (36%) intermediate responders, and 85 (32%) poor responders. An excellent response was associated with lower baseline disability score (range, 0-3 points; OR 0.49; 95% CI 0.33-0.74), fewer DMARDS used prior to etanercept (adjusted OR per DMARD 0.64; 95% CI 0.43-0.95), younger age at onset (adj OR per year increase, 0.92; 95% CI 0.84-0.99). A poor response was associated with systemic JIA (adj OR systemic vs nonsystemic categories, 2.92; 95% CI1.26-6.80), female (adj OR f vs m 2.16; 95% CI, 1.12-4.18). At 15 months, 119 patients experienced 1 or> infectious, noninfectious, or serious adverse events and 61 patients discontinued etanercept

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Alexeeva, 2011[4]	Case series of rituximab	55	JIA, refractory to infliximib and standard immunosuppressive therapy	ACR Pedi 30 response at week 24	96 weeks	At week 24, ACR Pedi 30, 50, and 70 responses were achieved by 98%, 50%, and 40%. By week 96, ACR Pedi 30, 50, and 70 responses were achieved by 98%, 93%, and 93% of 25 patients. Remission was recorded in 25% after 24 weeks, 52% after 48 weeks, 75% after 72 weeks, and 98% after 96 weeks of rituximab. 52% of patients achieved remission of arthritis by week 48.

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Otten, 2010[18]	Cohort, ongoing multicenter observational study of all Dutch patients with JIA using etanercept	179	JIA patients who failed to meet response criteria after 3 months of etanercept treatment	Evaluate response	15 months	34 patients did not respond after 3 months, of which 20 continued etanercept and 11 achieved response thereafter. Of these 11, 91% showed ACRpedi50 and 73% showed ACRpedi70 response. 36% achieved inactive disease at 15 months

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Ruperto, 2012[24]	Open-label controlled trial of canakinumab at 0.5mg/kg, 1.5 mg/kg or 4.5mg/kg	26	Children with JIA and active systemic features	Assess dosing, preliminary safety and efficacy of canakinumab	5 months	By day 15, 15/25 (60%) had achieved an adapted ACR Pedi50, with 4 of them achieving inactive disease status. 11/13 patients were able to maintain their response throughout the study. In 8/11 responders who had been receiving steroids at baseline, the steroid dosage was decreased and 4 of them were able to discontinue steroids. Therapy was generally well tolerated and few patients experienced injection-site reactions.

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Ruperto, 2010[23]	RCT, abatacept or placebo (+MTX)	190	Active polyarticular course JIA and an inadequate response/ intolerance to >/= 1 DMARD	HRQOL	10 months	During the open-label period (A) there were substantial improvements across all of the CHQ domains (greatest improvement in pain/discomfort) and the Physical (8.3 units) and the psychosocial summary scores (4.3 units) with abatacept. At the end of the 6 month withdrawal period (B) abatacept-treated subjects had greater improvements vs placebo in all domains (except behavior) and both summary scores, with similar improvements in pain and sleep. In period A, 2.6 days /month and 2.3 parents; usual activity days/month were gained. In period B there were 1.9 vs 0.9 {P=0.033} and 0.2 vs -1.3 {P=0.109} school days/ month and parents' usual activity days/month respectively, in abatacept vs placebo

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Hedrich, 2011[9]	Cohort, reviewed charts of all systemic onset JIA patients from 2005-2010	4	Systemic- onset JIA with first-line anakinra-treatment	Efficacy and safety	Up to 50 months	2 patients responded to anakinra mono-therapy, 2 required corticosteroids. Normalized body temperature and absence of evanescent rashes were achieved after a median of 4 days. No AEs other than local injection site inflammation.

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Imagawa, 2012[11]	Case series, open-label study of tocilizumab q 4 weeks	19	JIA, intractable to conventional methotrexate therapy	Safety and efficacy	Initial study (to week 12) and then an extension study (at least 48 weeks)	ACR Pedi 30,50,70 and 90 response rates respectively were 94.7%, 94.7%,57.9% and 10.5% at week 12 and 100%, 94.1%, 88.2%, 64.7% at week 48. Mean disease activity score remained below the remission level (2.6) from week 24. One discontinued because ACR Pedi 50 was insufficient and one developed antibodies to tocilizumab. Adverse events were generally mild, and the four serious adverse events resolved spontaneously or with treatment.

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Foell, 2010[7]	RCT, continue methotrexate 6 months or 12 months after disease remission	364	JIA, with clinical remission	relapse rate in the 2 treatment groups	3 years	98/183 (56.7%) of the 6 month group relapsed within 24 months, while 94/181 (55.6%) of the 12 month group did. (OR 1.02, 95% CI, 0.83-1.27; P=0.86). The median relapse-free interval after inclusion was 21.0 months in group 1 and 23.0 months in group 2. (HR 1.07, 95% CI 0.82-1.41; P=0.61). MRP8/14 levels during remission were significantly higher in patients who subsequently developed flares (median, 715 [IQR, 320-1110] ng/mL compared with patients maintaining stable remission (400 [IQR, 220-800] ng/mL; P=0.003). Low MRP8/14 levels indicated a low risk of flares within the next 3 months, AU receiver operating characteristic C, 0.76; 95% CI, 0.62-0.90

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Ruperto, 2012[22]	RCT, Trial 1- 1 dose of canakinumab vs placebo Trial 2- open label treatment with canakinumab	84	Age 2-19, systemic JIA and active systemic features	Improvement of 30% or more in at least 3/6 core criteria for JIA, worsening >30% in no more than 1 criteria and resolution of fever.	Trial 1- single dose Trial 2- 32 weeks	Trial 1- 36/43 (84%) in canakinumab group had adapted JIA ACR 30 response vs 4/41 (10%) in placebo [P<0.001]. Trial 2- 74% of canakinumab group had no flare vs 25% in placebo group [HR 0.36; P=0.03]

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
De Benedetti, 2012[6]	RCT, double blind tocilizumab vs placebo, with open-label extension for all patients	112	2-17 yo with systemic JIA >6 months and inadequate responses to NSAIDS and glucocorticoids	Absence of fever and improvement of 30% or more on 3/6 variables of ACR core set, with no >1 variable worsening >30%	Every 2 weeks x 12 weeks	12 weeks- 64/75 (85%) of tocilizumab group vs 9/37 (24%) placebo [P<0.001]. 52 weeks- 80% of tociluzumab patients had >70% improvement with no fever, including 59% w. 90% improvement. 48% had 0 joints with active arthritis, 52% discontinued glucocorticoids. AEs during double blind phase included 159 events w/ tocilizumab vs 38 w/ placebo including 60 infections (2 serious) vs 15, combined phases included 39 serious AEs (0.25/patient year) including 18 (0.11/patient year) serious infections, 19 with neutropenia, 21 with aminotransferase levels > 2.5 upper limit of normal range

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Nigrovic, 2011[14]	Cohort, medical records from international multicenter series +/- corticosteroids, +/- additional DMARDs	46	System JIA receiving anakinra as part of initial DMARD	Safety and efficacy of anakinra as 1st-line therapy for systemic JIA	Up to 55 months, median 14.5 months	Fever and rash resolved within 1 month in >95%. C-reactive protein and ferritin normalized within this interval in >80%. Active arthritis persisted at 1 month in 39%, at 3 months in 27%, at > 6 months in 11%. Approximately 60% of patients, including 8/10 receiving anakinra monotherapy, attained a clinical response without escalation of therapy. Partial responders were younger at onset (median 5.2 years vs 10.2 years; P=0.004). AE's included bacterial infection in 2 patients and hepatitis in 1
Key Question 2: In children with JIA, what are the comparative effects of DMARDs on:						
Key Question 2a: Laboratory measures of inflammation?						
No new evidence	No new evidence	No new evidence	No new evidence	No new evidence	No new evidence	No new evidence
Key Question 2b: Radiological progression?						

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
No new evidence	No new evidence	No new evidence	No new evidence	No new evidence	No new evidence	No new evidence
Key Question 2c: Symptoms?						
No new evidence	No new evidence	No new evidence	No new evidence	No new evidence	No new evidence	No new evidence
Key Question 2d: Health status?						
No new evidence	No new evidence	No new evidence	No new evidence	No new evidence	No new evidence	No new evidence
Key Question 3: In children with JIA, do the rate and type of adverse events differ between:						
Key Question 3a: The various DMARDs?						
Gaujoux-Viala, 2011[8]	Case series of scleritis associated with etanercept use for RA	3 cases	3 patients with seropositive RA	NA	7-28 months	3 patients developed scleritis 7-28 months after initiation of etanercept. Ocular inflammation went into remission of etanercept and no relapses were observed

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
van Dijken, 2011[27]	Cohort- national JIA registries of Netherlands, Germany, Finland, Denmark and Italy were searched for JIA and IBD	1651 JIA patients in registry	Patients with JIA using etanercept	IBD cases	9 years	13 cases of IBD in JIA patients using etanercept were identified (362 per 100,000 patient-years, 43 x higher than the general pediatric population. Median time of onset was 6 years and 10 months. Time between start of etanercept and IBD was 9 days to 4.5 years

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Horneff, 2011[10]	Cohort, German JIA biologics registry	1260	JIA exposed to TNF inhibitors	Cases with malignancy	9 years	5 cases of malignancies were documented. 1 of each non-Hodgkin's lymphoma, Hodgkin's lymphoma, thyroid carcinoma, yolk sac carcinoma and cervical dysplasia.

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Beukelman, 2012 [5]	Cohort of national Medicaid of children with and without JIA	7,812	Children with JIA	Incidence of malignancy	5 years	The standardized incidence ratio (SIR) for children with JIA vs without JIA, was 4.4 (95% CI 1.8-9.0) for probable and highly probable malignancies. For those taking MTX without tnf inhibitor use, the SIR was 3.9 (95% CI 0.4-14). Following any use of tnf inhibitors, no probable or highly probable malignancies were identified (SIR 0 95% CI 0-9.7)
Key Question 3b: DMARDs and conventional treatment with or without methotrexate?						

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Wallace, 2011[28]	RCT of etanercept+methotrexate (MTX)+prednisolone (arm 1) vs methotrexate (arm 2)	85	Rheumatoid factor positive or negative polyarticular juvenile idiopathic arthritis (poly-JIA) of <12 months duration	Clinical inactive disease (CID) at 6 months	12 months	At 6 months, 40% of patients in Arm 1 and 23% of patients in Arm 2 had achieved CID (x2=2.91;p=0.088). After 12 months, 9 patients in Arm 1 and 3 in Arm 2 achieved clinical remission (p=0.0534)
Tynjala, 2011[26]	RCT of infliximab+ MTX (TNF) vs MTX+sulfasalazine+ hydroxychloroquine (COMBO) vs MTX alone	60	DMARD naive, recent-onset polyarticular JIA, aged 4-15 years	ACR Pedi 75 improvement	54 weeks	ACR Pedi 75 was achieved in 100% of patients receiving TNF; 65% on COMBO (95% CI 44%-86%); and 50% on MTX (95% CI 28-72%) (p<0.0001). 68% on TNF achieved inactive disease (95% CI 47%-89%); 40% on COMBO (95% CI 22-63%); and 25% on MTX (95% CI 6-44%) (P0.002). Those on TNF spent a mean 26 weeks with inactive disease (95%CI 18-34) longer than those on COMBO (13 weeks, 95% CI 6-20) or MTX (6 weeks, 95% CI 2-10)

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Papsdorf, 2011[19]	Cohort, open observational study of etanercept +/- MTX or corticosteroids (or both)	787	JIA patients	Identify contributing factors associated with inactive disease (ID) and clinical remission	100 months	47.6% of patients reached criteria for ID and 26.6% achieved remission. For both, significant influence of shorter disease duration (P<0.001 and P<0.001), a weekly dosage of at least 0.8 mg/kg (P=0.02), lower active joint counts (P=0.001) and lower childhood HAQ score (P<0.001 and P=0.004) at baseline was found. Concomitant administration of MTX raised the relative chance, especially in patients with seronegative polyarthritis (OR 2.0; P=0.03)
Key Question 4: How do the efficacy, effectiveness, safety, and adverse effects of treatment with DMARDs differ among the various categories of JIA?						
Otten, 2011[17]	Cohort, observational register patients taking etanercept, adalimumab, infliximab	22	Children with enthesitis-related arthritis (ERA)	Evaluate effectiveness and safety	51 months	ID was achieved in 7/22 (32%) after 3 months of treatment, 5/13 (38%) after 15 months, 5/8 (63%) after 27 months. No serious AEs occurred

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Otten, 2011[16]	Cohort, observational register patients taking etanercept or adalimumab	18	Children with juvenile psoriatic arthritis	Evaluate effectiveness	39 months	83% achieved ACR30 response after 3 months of treatment, increasing to 100% after 15 months. 67% reached ID after 39 months. No patients discontinued for inefficacy.
Mease, 2011[12]	RCT, abatacept (ab) 3 mg/kg, 10mg/kg or 30/10 mg/kg or placebo	170	Psoriatic arthritis who had previously taken DMARDs	Safety and efficacy of abatacept in patients with psoriatic arthritis	6 month	Patients achieving an ACR20 response were 19%-placebo, 33% ab 3mg, 48% ab10mg, 42% ab30/10. Compared to placebo, improvements were significantly higher for ab 10 (P=0.006) and 30/10 (P=0.022), but not for ab 3 (P=0.121). All ab regimens led to improved MRI, HAQ and SF-36 scores, with 10mg/kg showing the greatest improvements. Improvements in TL and PASI scores were observed in all ab arms; a response according to the investigator's global assessment was seen only with ab 3. Safety profiles were similar
Key Question 5: What is the validity, reliability, responsiveness, and feasibility of the clinical outcome measures for childhood JIA that are commonly used in clinical trials or within the clinical practice setting?						

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
No new evidence	No new evidence	No new evidence	No new evidence	No new evidence	No new evidence	No new evidence

Legend: AEs=Adverse Events; ESR=Erythrocyte Sedimentation Rate; MTX=Methotrexate; RCT=Randomized Controlled Trial; JIA=Juvenile Idiopathic Arthritis; HRQOL= Health-Related Quality of Life; ESR= Erythrocyte sedimentation rate; IBD=inflammatory bowel disease; TNF= Tumor Necrosis Factor

Appendix C. Questionnaire Matrix

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

Title: Disease-Modifying Antirheumatic Drugs (DMARDs) in Children with Juvenile Idiopathic Arthritis (JIA)

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 1: In children with JIA, does treatment with DMARDs, compared to conventional treatment:			
Key Question 1a: Improve laboratory measures of inflammation?			
Trials of DMARDs usually report changes in laboratory measures of inflammation (e.g., ESR—erthrocyte sedimentation rate). However, ESR is inconsistently associated with treatment. This conclusion is based on 14 studies of 1,060 subjects. Strength of Evidence: Low	☐	New Evidence:	☐
Key Question 1b: Improve radiological progression?			
Insufficient data are available to evaluate the impact of DMARDs on radiological progression. Only one cohort study of 63 subjects reported data on radiological progression.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Strength of Evidence: Insufficient			
Key Question 1c: Improve symptoms?			
Among children who have responded to a biologic DMARD, randomized discontinuation trials show that continued treatment for from 4 months to 2 years decreases the risk of having a flare (RR 0.46, 95% CI 0.36 to 0.60). This conclusion is based on four studies of 322 subjects. Among the nonbiologic DMARDs, there is some evidence that methotrexate is superior to conventional therapy and oral corticosteroids, based on two randomized trials of 215 subjects. Strength of Evidence: Moderate	☐	New Evidence:	☐
Key Question 1d: Improve health status?			
Changes in health status were reported in 12 studies involving 927 subjects. Health status improved inconsistently with treatment with DMARDs. Strength of Evidence: Low	☐	New Evidence:	☐
Key Question 2: In children with JIA, what are the comparative effects of DMARDs on:			
Key Question 2a: Laboratory measures of inflammation?			
Trials of DMARDs usually report changes in laboratory measures of inflammation (e.g.,		New Evidence:	

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
ESR—erthrocyte sedimentation rate). However, ESR is inconsistently associated with treatment. This is based on 4 RCTs of 448 subjects and 1 cohort study of 72 subjects. Strength of Evidence: Low	☐		☐
Key Question 2b: Radiological progression?			
No study addressed radiologic progression. Strength of Evidence: Insufficient	☐	New Evidence:	☐
Key Question 2c: Symptoms?			
The nonbiologic DMARDs that were compared directly (penicillamine vs. hydroxychloroquine, sulfasalazine vs. hydroxychloroquine, and leflunomide vs. methotrexate) had similar efficacy. Changes in symptoms between the treatment arms were not measured with significant precision to detect a difference. This is based on 4 RCTs of 448 subjects and 1 cohort study of 72 subjects. One poor-quality RCT of 94 subjects found that etanercept was similar to infliximab. Strength of Evidence: Low	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 2d: Health status?			
The nonbiologic DMARDs that were compared directly (penicillamine vs. hydroxychloroquine sulfasalazine vs. hydroxychloroquine, and leflunomide vs. methotrexate) had similar efficacy. Changes in health status between the treatment arms were not measured with significant precision to detect a difference. This is based on 4 RCTs of 448 subjects and 1 cohort study of 72 subjects. One poor quality RCT of 94 subjects found that etanercept was similar to infliximab. Strength of Evidence: Low	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 3: In children with JIA, do the rate and type of adverse events differ between:			
Key Question 3a: The various DMARDs?			
Three RCTs directly compared two DMARDs; two compared penicillamine to hydroxychloroquine, and one compared leflunomide to methotrexate. The rate and type of adverse events did not differ between treatment groups in these studies. High variability across studies in the ascertainment and reporting of adverse events preclude valid comparisons of the rate and type of adverse events among the various DMARDs. Recently published studies of adverse event reporting databases provide indirect evidence that suggests a possible relationship between cancer and exposure to tumor necrosis factor blockers. Strength of Evidence: Insufficient	☐	New Evidence:	☐
Key Question 3b: DMARDs and conventional treatment with or without methotrexate?			
No RCT directly compared a DMARD to conventional treatment. Thirteen trials directly compared a DMARD to placebo. The rate and type of adverse events were generally similar between intervention and placebo groups, with the notable exceptions of infliximab plus methotrexate being associated with more serious adverse events (32% vs. 5% over differing lengths of followup), and methotrexate being associated	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
with higher rates of laboratory abnormalities (35% vs. 13%). Strength of Evidence: Insufficient			
Key Question 4: How do the efficacy, effectiveness, safety, and adverse effects of treatment with DMARDs differ among the various categories of JIA?			
Only one study—an RCT of methotrexate versus placebo in which each group could also receive oral corticosteroids, intra-articular corticosteroids, and NSAIDs—evaluated efficacy by JIA category. No difference was found among those with extended oligoarticular JIA (n = 43) and systemic JIA (n = 45). We did not identify any studies that provide reliable information on the comparative safety or rates or types of adverse events among the various categories of JIA. Strength of Evidence: Insufficient	☐	New Evidence:	☐
Key Question 5: What is the validity, reliability, responsiveness, and feasibility of the clinical outcome measures for childhood JIA that are commonly used in clinical trials or within the clinical practice setting?			
Most of the studies examining the psychometric properties of the instrumentsused in JIA were fair-quality cross-sectional or longitudinal nonrandomized controlled trials. No one instrument or outcomes measure appeared superior in measuring disease activity or functional status. The current response criteria of the ACR Pediatric 30, a composite measure that includes articular indices, functional status, laboratory measure, and	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
global assessments, takes into account the various measures most commonly used. However, the responsiveness of several of these measures, including functional status and parent/patient global assessment, are poor to moderate, and they may not adequately reflect changes in disease state. Furthermore, given that the ACR Pediatric 30 is a relative measure of disease activity, the impact of JIA category on percent improvement is unclear, as certain instruments, such as the CHAQ, appear to have differential responsiveness depending on extent of disease at baseline. The ACR Pediatric 30 is also a relative measure of disease activity and not a measure of current disease state. Strength of Evidence: Insufficient			
Are there new data that could inform the key questions that might not be addressed in the conclusions?			