Appendix A: Exact Search Strings

Search Strategies Used to Search MEDLINE® via PubMed – Last Search Date January 31, 2010

1. Key Questions 1, 2, 3, and 4

(("arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]) AND ((("abatacept"[Substance Name] OR "abatacept"[All Fields]) OR ("abatacept"[Substance Name] OR "abatacept"[All Fields] OR "orencia"[All Fields]) OR ("adalimumab"[Substance Name] OR "adalimumab"[All Fields]) OR ("interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "anakinra"[All Fields]) OR ("interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "kineret"[All Fields]) OR ("azathioprine"[MeSH Terms] OR "azathioprine"[All Fields]) OR ("azathioprine"[MeSH Terms] OR "azathioprine"[All Fields] OR "imuran"[All Fields]) OR ("canakinumab"[Substance Name] OR "canakinumab"[All Fields]) OR ilaris[All Fields] OR ("cyclosporine"[MeSH Terms] OR "cyclosporine"[All Fields] OR "cyclosporine a"[All Fields]) OR ("cyclosporine"[MeSH Terms] OR "cyclosporine"[All Fields] OR "neoral"[All Fields]) OR gengraf[All Fields] OR ("penicillamine"[MeSH Terms] OR "penicillamine"[All Fields] OR "d penicillamine"[All Fields]) OR Depen[All Fields] OR ("penicillamine"[MeSH Terms] OR "penicillamine"[All Fields] OR "cuprimine"[All Fields]) OR ("TNFR-Fc fusion protein"[Substance Name] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields]) OR ("TNFR-Fc fusion protein"[Substance Name] OR "TNFR-Fc fusion protein"[All Fields] OR "enbrel"[All Fields]) OR ("hydroxychloroquine"[MeSH Terms] OR "hydroxychloroquine"[All Fields]) OR ("hydroxychloroquine"[MeSH Terms] OR "hydroxychloroquine"[All Fields] OR "plaquenil"[All Fields]) OR ("infliximab"[Substance Name] OR "infliximab"[All Fields]) OR ("infliximab"[Substance Name] OR "infliximab"[All Fields] OR "remicade"[All Fields]) OR ("leflunomide"[Substance Name] OR "leflunomide"[All Fields]) OR ("immunoglobulins, intravenous"[MeSH Terms] OR ("immunoglobulins"[All Fields] AND "intravenous"[All Fields]) OR "intravenous immunoglobulins"[All Fields] OR "ivig"[All Fields]) OR carimune[All Fields] OR flebogamma[All Fields] OR ("Gamunex"[Substance Name] OR "Gamunex"[All Fields] OR "gamunex"[All Fields]) OR ("immunoglobulins, intravenous"[MeSH Terms] OR ("immunoglobulins"[All Fields] AND "intravenous"[All Fields]) OR "intravenous immunoglobulins"[All Fields] OR "gammagard"[All Fields]) OR ("immunoglobulins, intravenous"[MeSH Terms] OR ("immunoglobulins"[All Fields] AND "intravenous"[All Fields]) OR "intravenous immunoglobulins"[All Fields] OR "iveegam"[All Fields]) OR ("Octagam"[Substance Name] OR "Octagam"[All Fields] OR "octagam"[All Fields]) OR panglobulin[All Fields] OR polygam[All Fields] OR ("Privigen"[Substance Name] OR "Privigen"[All Fields] OR "privigen"[All Fields]) OR ("leflunomide"[Substance Name] OR "leflunomide"[All Fields] OR "arava"[All Fields]) OR ("methotrexate"[MeSH Terms] OR "methotrexate"[All Fields]) OR ("mycophenolate mofetil"[Substance Name] OR "mycophenolate mofetil"[All Fields]) OR ("mycophenolate mofetil"[Substance Name] OR "mycophenolate mofetil"[All Fields] OR "cellcept"[All Fields]) OR ("rilonacept"[Substance Name] OR "rilonacept"[All Fields]) OR arcalyst[All Fields] OR ("rituximab"[Substance Name] OR "rituximab"[All Fields]) OR ("rituximab"[Substance Name] OR "rituximab"[All Fields] OR "rituxan"[All Fields]) OR ("sulphasalazine"[All Fields] OR "sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields]) OR ("sulfasalazine"[MeSH Terms] OR "sulfasalazine"[All Fields] OR "azulfidine"[All Fields]) OR ("tacrolimus"[MeSH Terms] OR "tacrolimus"[All Fields]) OR ("tacrolimus"[MeSH Terms] OR "tacrolimus"[All Fields] OR "fk506"[All Fields]) OR ("tacrolimus"[MeSH Terms] OR "tacrolimus"[All Fields] OR "prograf"[All Fields]) OR ("thalidomide"[MeSH Terms] OR "thalidomide"[All Fields]) OR ("thalidomide"[MeSH Terms] OR "thalidomide"[All Fields] OR "thalomid"[All Fields]) OR ("sulfadiazine"[MeSH Terms] OR "sulfadiazine"[All Fields] OR "sulfazine"[All Fields]) OR ("tocilizumab"[Substance Name] OR "tocilizumab"[All Fields]) OR ("tocilizumab"[Substance Name] OR "tocilizumab"[All Fields] OR "actemra"[All Fields]) OR (disease-modifying[All Fields] AND ("antirheumatic agents"[MeSH Terms] OR ("antirheumatic"[All Fields] AND "agents"[All Fields]) OR "antirheumatic

agents"[All Fields] OR ("anti"[All Fields] AND "rheumatic"[All Fields] AND "drugs"[All Fields]) OR "anti rheumatic drugs"[All Fields] OR "antirheumatic agents"[Pharmacological Action])) OR dmards[All Fields]) OR (("betamethasone"[MeSH Terms] OR "betamethasone"[All Fields]) OR ("betamethasone"[MeSH Terms] OR "betamethasone"[All Fields] OR "celestone"[All Fields]) OR ("celecoxib"[Substance Name] OR "celecoxib"[All Fields]) OR ("celecoxib"[Substance Name] OR "celecoxib"[All Fields] OR "celebrex"[All Fields]) OR ("etodolac"[MeSH Terms] OR "etodolac"[All Fields]) OR ("etodolac"[MeSH Terms] OR "etodolac"[All Fields] OR "lodine"[All Fields]) OR ("triamcinolone"[MeSH Terms] OR "triamcinolone"[All Fields]) OR ("triamcinolone acetonide"[MeSH Terms] OR ("triamcinolone"[All Fields] AND "acetonide"[All Fields]) OR "triamcinolone acetonide"[All Fields] OR "kenalog"[All Fields]) OR ("triamcinolone hexacetonide"[Substance Name] OR "triamcinolone hexacetonide"[All Fields] OR "aristospan"[All Fields]) OR ("ibuprofen"[MeSH Terms] OR "ibuprofen"[All Fields]) OR advil[All Fields] OR ("ibuprofen"[MeSH Terms] OR "ibuprofen"[All Fields] OR "motrin"[All Fields]) OR ("indomethacin"[MeSH Terms] OR "indomethacin"[All Fields]) OR ("indomethacin"[MeSH Terms] OR "indomethacin"[All Fields] OR "indocin"[All Fields]) OR ("meloxicam"[Substance Name] OR "meloxicam"[All Fields]) OR ("meloxicam"[Substance Name] OR "meloxicam"[All Fields] OR "mobic"[All Fields]) OR ("naproxen"[MeSH Terms] OR "naproxen"[All Fields]) OR ("naproxen"[MeSH Terms] OR "naproxen"[All Fields] OR "naprosyn"[All Fields]) OR ("naproxen"[MeSH Terms] OR "naproxen"[All Fields] OR "aleve"[All Fields]) OR ("oxaprozin"[Substance Name] OR "oxaprozin"[All Fields]) OR ("oxaprozin"[Substance Name] OR "oxaprozin"[All Fields] OR "daypro"[All Fields]) OR ("tolmetin"[MeSH Terms] OR "tolmetin"[All Fields]) OR ("tolmetin"[MeSH Terms] OR "tolmetin"[All Fields] OR "tolectin"[All Fields]) OR ("anti-inflammatory agents, non-steroidal"[MeSH Terms] OR ("anti-inflammatory"[All Fields] AND "agents"[All Fields] AND "non-steroidal"[All Fields]) OR "non-steroidal anti-inflammatory agents"[All Fields] OR "nsaids"[All Fields] OR "anti-inflammatory agents, non-steroidal"[Pharmacological Action]) OR ("adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroids"[All Fields] OR "adrenal cortex hormones"[Pharmacological Action]))))) AND ("humans"[MeSH Terms] AND English[lang])

2. Key Question 5

(("ACR30"[All Fields] OR (American[All Fields] AND College[All Fields] AND ("rheumatology"[MeSH Terms] OR "rheumatology"[All Fields]) AND 30[All Fields]) OR (American[All Fields] AND College[All Fields] AND ("rheumatology"[MeSH Terms] OR "rheumatology"[All Fields]) AND Pediatric[All Fields]) OR (ACR[All Fields] AND Pediatric[All Fields])) OR ((("arthritis, juvenile rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "juvenile"[All Fields] AND "rheumatoid"[All Fields]) OR "juvenile rheumatoid arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND "arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]) AND ("humans"[MeSH Terms] AND English[lang])) AND (("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields]) OR ("health status"[MeSH Terms] OR ("health"[All Fields] AND "status"[All Fields]) OR "health status"[All Fields]) OR ("outcome assessment (health care)"[MeSH Terms] OR ("outcome"[All Fields] AND "assessment"[All Fields] AND "(health"[All Fields] AND "care)"[All Fields]) OR "outcome assessment (health care)"[All Fields] OR ("outcome"[All Fields] AND "assessment"[All Fields]) OR "outcome assessment"[All Fields]) OR "disability evaluation"[MeSH Terms] OR "severity of illness index"[MeSH Terms] OR "endpoint determination/methods"[Mesh Terms]))) AND (reliability[All Fields] OR ("reproducibility of results"[MeSH Terms] OR ("reproducibility"[All Fields] AND "results"[All Fields]) OR "reproducibility of results"[All Fields]) OR concordance[All Fields] OR ("sensitivity and specificity"[MeSH Terms] OR ("sensitivity"[All Fields] AND "specificity"[All Fields]) OR "sensitivity and specificity"[All Fields] OR "sensitivity"[All Fields]) OR ("sensitivity and specificity"[MeSH Terms] OR ("sensitivity"[All Fields] AND "specificity"[All Fields]) OR "sensitivity and specificity"[All Fields] OR "specificity"[All Fields]) OR ("roc curve"[MeSH Terms] OR ("roc"[All Fields] AND "curve"[All Fields]) OR "roc curve"[All Fields] OR ("receiver"[All Fields] AND "operating"[All Fields] AND "characteristic"[All Fields]) OR "receiver operating characteristic"[All Fields]) OR (response[All Fields] AND ("Change"[Journal] OR "change"[All Fields])) OR (sensitive[All Fields] AND ("Change"[Journal] OR "change"[All Fields])) OR (("sensitivity and specificity"[MeSH Terms] OR ("sensitivity"[All Fields] AND "specificity"[All Fields]) OR "sensitivity and specificity"[All Fields] OR "sensitivity"[All Fields]) AND ("Change"[Journal] OR "change"[All Fields])) OR responsiveness[All Fields] OR ("psychometrics"[MeSH Terms] OR "psychometrics"[All Fields]) OR

validity[All Fields] OR "Validation Studies as Topic"[Mesh] AND ("humans"[MeSH Terms] AND English[lang])) AND ("humans"[MeSH Terms] AND English[lang])

Appendix B: Screening Criteria

JIA – Abstract Screening Instructions

An abstract will be **included** if all of the following criteria apply for **RCTs**:

- The sample population has JIA according to the current ACR definition (KQ1-KQ5).
- Random allocation to the intervention or placebo/control groups (KQ1-KQ3).
- One or more DMARDs are evaluated (KQ1-KQ4).
- Outcome is change in one of the pre-specified intermediate or final outcomes and is assessed 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 or younger. If the study includes adults, at least 80% of the sample will be children or the outcomes must be reported separately for the child subgroup (KQ1-KQ5).
- Original data.

An abstract will be **excluded** if any of the following criteria apply for **RCTs:**

- Non-English language publication (KQ1-KQ5)

An abstract will be **included** if all of the following criteria apply for **Observational Studies**:

- The sample population has JIA according to the current ACR definition (KQ1-KQ5).
- One or more DMARDs are evaluated (KQ1-KQ4).
- Outcome is change in one of the pre-specified intermediate or long-term outcomes and is assessed 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 or younger. If the study includes adults, at least 80% of the sample will be children or the outcomes must be reported separately for the child subgroup (KQ1-KQ5)
- Outcomes are determined prospectively and are assessed using an acceptable standard (KQ1-KQ4).
- For studies of effectiveness, there must be a treatment comparator (KQ1-KQ4).
- Case-control studies, case series, and case reports are acceptable to assess for adverse events of DMARD treatment (KQ3).
- Cross-sectional studies are acceptable to evaluate clinical outcome measure tools (KQ5).

An abstract will be **excluded** if any of the following criteria apply for **Observational Studies:**

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

- Cross-sectional studies for the evaluation of the impact of treatment (KQ1-KQ4).

An abstract will be identified as a **review** if it is a relevant review article, meta-analysis, methods article, or cost-effectiveness analysis.

For each abstract, please mark either **"EX"** for **Exclude, "IN"** for **Include** or **"R"** for **Review.**

JIA – Full-text Screening Instructions/Exclusion Reasons
Key Questions 1-4

Key Questions 1-4 are as follows:

Key Question 1: In children with juvenile idiopathic arthritis (JIA), does treatment with disease-modifying anti-rheumatic drugs (DMARDs), compared to conventional treatment (defined as non-steroidal anti-inflammatory drugs [NSAIDs] or intra-articular corticosteroids, with or without methotrexate), improve laboratory measures of inflammation or radiological progression, symptoms (e.g., pain, symptom scores) or health status (e.g., functional ability, mortality)?

Key Question 2: In children with JIA, what are the comparative effects of various DMARDs on laboratory markers of inflammation or radiological progression, symptoms (e.g., pain, symptom scores), or health status (e.g., functional ability, mortality)?

Key Question 3: In children with JIA, does the rate and type of adverse events differ between the various DMARDs or between DMARDs and conventional treatment?

Key Question 4: How do the efficacy, effectiveness, safety, and adverse effects of treatment with DMARDs differ among the various categories of JIA?

General/introductory notes

- Key Question (KQ) 4 will draw on the entire body of evidence included for KQs 1-3; therefore, it does not have a separate set of inclusion/exclusion criteria.
- A wider range of study designs are acceptable for KQ 3 than for KQs 1-2, including case reports, non-comparative prospective studies, and retrospective studies. However, study duration must be ≥ 3 months (as for KQs 1-2).
- KQ 5 is very different from KQs 1-4 and has some distinctly different inclusion/exclusion criteria. A separate cheat sheet has been prepared for it.
- For all KQs, the study population may be drawn from primary or specialty care settings.
- For all KQs, the language of publication must be English.

1) Publication not peer-reviewed

For KQs 1-2:

- Publication must be peer-reviewed (excludes editorials, letters to the editor, etc.).

For KQ 3:

- Case reports published in non-peer-reviewed form (e.g., as letters) in academic journals are acceptable.
- Other types of studies must be peer-reviewed.

2) Population not JIA/JRA/JCA

For all KQs:

- The sample population must have juvenile idiopathic arthritis (JIA) according to the International League of Associations for Rheumatology (ILAR) criteria, or juvenile rheumatoid arthritis (JRA) according to the American College of Rheumatology (ACR) definition, or juvenile chronic arthritis (JCA) according to the European League Against Rheumatism (EULAR) criteria.
- Any subtype of JIA/JRA/JCA of any severity is acceptable.

Notes/further guidance:

Criteria for Classification of JIA (ILAR = International League of Associations of for Rheumatology) from 1998

Note: All categories require age of onset prior to 16 yrs

JIA category	Definition	Exclusions
Systemic arthritis	Arthritis and fever plus one or more: 1. rash, 2. lymph node enlargement, 3. hepato or splenomegaly, 4. serositis	
Oligoarthritis	Arthritis of 1-4 joints in the first 6 mo,	Family history of psoriasis or HLA-B27 assoc. disease, RF+, HLA-B27+ males > 8 years, systemic arthritis
Persistent	< 5 joints during course,	
Extended	> 4 joints after 6 mo	
RF- polyarthritis	Arthritis of > 4 joints in the first 6 mo, RF-	RF+, systemic arthritis
RF+ polyarthritis	Arthritis of > 4 joints in the first 6 mo, RF +	RF-, systemic arthritis

JIA category	Definition	Exclusions
Psoriatic arthritis	Arthritis and psoriasis or arthritis and at least 2 of: (a) dactylitis, (b) nail abnormalities, (c) family history of psoriasis	RF+, systemic arthritis
Enthesitis related arthritis	Arthritis and enthesitis OR arthritis or enthesitis with at least 2 of: (a) sacroiliac tenderness and/or spinal pain, (b) HLA-B27, (c) family history of HLA-B27associated disease	Family history of psoriasis, systemic arthritis
Other arthritis	Children with JIA who do not fulfill criteria for any category or fulfill criteria for >1 category	

(Reference: Evaluation of the ILAR criteria for juvenile idiopathic arthritis. Krumrey-Langkammerer M, Häfner R.J Rheumatol. 2001 Nov;28(11):2544-7.)

Criteria for Classification of JRA (ACR = American College of Rheumatology) from 1976

Age of onset prior to 16 yrs
Arthritis (swelling, effusion, or presence of 2 or more of the following in one or more joints:

a. Limitation of range of motion
b. Tenderness or pain on range of motion
c. Increased heat

Duration of disease 6 weeks or longer
Onset type defined by type of disease in first 6 months:

a. Polyarticular: ≥ 5 inflamed joints
b. Oligoarticular (aka: pauciarticular): < 5 joints
c. Systemic onset: arthritis with characteristic fever

Exclusion of other forms of juvenile arthritis (psoriatic, spondyloarthopathy = juvenile ankylosing spondylitis, inflammatory bowel disease associated arthritis)

Criteria for Classification of JCA (EULAR = European League Against Rheumatism) from 1977

Age of onset prior to 16 yrs
Arthritis (swelling, effusion, or presence of 2 or more of the following in one or more joints):

a. Limitation of range of motion
b. Tenderness or pain on range of motion
c. Increased heat

Duration of disease 3 months or longer

Onset type defined by characteristics at presentation:

a. Polyarticular: ≥ 5 inflamed joints, Rheumatoid factor negative
b. Pauciarticular: < 5 joints
c. Systemic onset: arthritis with characteristic fever
d. Juvenile rheumatoid arthritis: ≥ 5 joints, rheumatoid factor positive
e. Juvenile ankylosing spondylitis
f. Juvenile psoriatic arthritis

3) Population not < 18 years

For all KQs:

- Study sample must consist of children 18 years or younger. If the study includes adults, at least 80% of the sample must be children, or outcomes must be reported separately for the 18 years or younger subgroup.

4) No acceptable DMARD intervention

For KQs 1-4:

- Study must include one of the DMARDs on our list (see table next page) either:
  - Alone;
  - In combination with another DMARD on our list; or
  - In combination with conventional treatment.

Included DMARDs (Table 2 from project protocol). List of DMARDs, their mechanism of action, FDA approval status for JIA, and examples of significant warnings from the drug product label.

Generic Name	US Trade Name	Mechanism of Action	FDA-approved 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,	Interaction with activating Fc receptors; biologic	No	Hepatitis; acute renal failure; venous thrombosis; aseptic

Generic Name	US Trade Name	Mechanism of Action	FDA-approved for JIA	Warnings – Increased Risk
	Gammar P, Gamunex 10%, Gammagard S/D, Gammagard Liquid 10%, Gammar P, Iveegam EN, Octagam 5%, Panglobulin, Polygam S/D, Privigen 10% Vivaglobin			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
Azathioprine	Azasan; Imuran	Purine Synthesis Inhibitor; non-biologic	No	Cancer; bone marrow suppression
Cyclosporine A	Neoral Gengraf	Inhibits calcineurin; non-biologic	No	Infections; nephrotoxicity; hepatotoxicity
D-Penicillamine	Depen; Cuprimine	Unknown (May lower IgM rheumatoid factor, depresses T-cell activity); non-biologic	No	Allergic reactions; Goodpasture's syndrome; hematologic toxicities; hepatotoxicity; myasthenia gravis
Hydroxy-chloroquine	Plaquenil	Not well understood, may reduce T-lymphocyte transformation and chemotaxis; non-biologic	No	Kidney damage; retinopathy
Leflunomide	Arava	Isoxazole immunomodulatory agent; non-biologic	No	Hepatotoxicity
Methotrexate	Methotrexate LPF	Unknown (anti-metabolite, inhibits dihydrofolic acid reductase); non-biologic	Yes	Hepatotoxicity; cancer
Mycophenolate mofetil	CellCept	Guanosine synthesis inhibitor; non-biologic	No	Cancer; bone marrow suppression
Sulfasalazine	Azulfidine Sulfazine	Unknown; non-biologic	Yes	Bone marrow suppression; hepatotoxicity; Stevens Johnson Syndrome
Tacrolimus (FK506)	Prograf	Reduces T-cell and IL-2 activity; non-biologic	No	Cancer; infection

Generic Name	US Trade Name	Mechanism of Action	FDA-approved for JIA	Warnings – Increased Risk
Thalidomide	Thalomid	Unknown; non-biologic	No	Birth defects; neuropathy

5) No acceptable comparator

***For KQ 1*, acceptable comparators are:**

- Conventional treatment, defined as "NSAIDs or intra-articular corticosteroids, with or without methotrexate" (see table below for acceptable NSAIDs and corticosteroids)

***For KQ 2*, acceptable comparators are:**

- Any other DMARD on our list (see table above) either:
  - Alone;
  - In combination with another DMARD on our list; or
  - In combination with conventional treatment (defined as above).

***For KQ 3*, acceptable comparators are:**

- None or any

Included NSAIDs and intra-articular corticosteroids (Table 1 from project protocol). List of intra-articular corticosteroids and NSAIDs FDA approval status for JIA, and examples of significant warnings from the drug product label.

Generic Name	US Trade Name	Drug Type	FDA-Approved 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;

Generic Name	US Trade Name	Drug Type	FDA-Approved for JIA	Warnings – Increased Risk
				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

6) Study not prospective

Relevant only to KQs 1-2:

- Any prospective comparative study is acceptable. Studies evaluating a prospective treatment group vs. a historical control group are also acceptable.

For KQ 3:

- Studies are not required to be prospective. For KQ3, any study design is acceptable (comparative or non-comparative, prospective or retrospective, any size [including case studies with n = 1]).

7) No outcome of interest

For KQs 1-2:

- Study must include at least one of the following intermediate or long-term outcomes:
  - Intermediate outcomes include:
    - Laboratory measures of inflammation
    - Active joint count
    - Number of joints with limited range of motion
    - Radiographic evidence of progression of disease
    - Global assessment of current status
  - Long-term outcomes include:
    - Pain control
    - Clinical remission
    - Quality of life
    - Growth
    - Development
    - Joint function
    - Functional Ability

        - Mortality

For KQ 3:

- Study must report adverse events
- We are especially (but not exclusively) interested in:
    - Mortality
    - Malignancy
    - Serious infection
    - Hepatitis
    - Bone marrow suppression
    - Nausea or vomiting
    - Risks to fetus or pregnant mother

8) Outcomes not measured using an objective standard

Relevant <u>only</u> to KQs 1-2:

- Outcomes must be measured using an objective standard

9) Study duration < 3 months

Relevant <u>only</u> to KQs 1-2:

- Study duration must be ≥ 3 months.

For KQ 3:

- Any study duration is acceptable.

JIA – Full-text Screening Instructions/Exclusion Reasons
Key Question 5

Key Question 5 is: What is the validity, reliability, responsiveness, and feasibility of the clinical outcomes measures for childhood JIA that are commonly used in clinical trials or within the clinical practice setting?

General/introductory notes

- For this and all other Key Questions (KQs), the study population may be drawn from primary or specialty care settings.

- For this and all other KQs, the language of publication must be English.

- For KQ 5 specifically:
  - Any treatment intervention/comparator is acceptable (including none).
  - Any study design is acceptable (including RCTs, non-randomized controlled trials, and observational studies [controlled or uncontrolled, cross-sectional or longitudinal]).
  - Any study duration is acceptable (study does not need to be ≥ 3 months).

1) Publication not peer-reviewed

- Publication must be peer-reviewed (excludes editorials, letters to the editor, etc.).

2) Population not JIA/JRA/JCA

For all KQs:

- The sample population must have juvenile idiopathic arthritis (JIA) according to the International League of Associations for Rheumatology (ILAR) criteria, or juvenile rheumatoid arthritis (JRA) according to the American College of Rheumatology (ACR) definition, or juvenile chronic arthritis (JCA) according to the European League Against Rheumatism (EULAR) criteria.
- Any subtype of JIA/JRA/JCA of any severity is acceptable.

Notes/further guidance:

Criteria for Classification of JIA (ILAR = International League of Associations of for Rheumatology) from 1998

Note: All categories require age of onset prior to 16 yrs

JIA category	Definition	Exclusions
Systemic arthritis	Arthritis and fever plus one or more: 1. rash, 2. lymph node enlargement, 3. hepato or splenomegaly, 4. serositis	
Oligoarthritis	Arthritis of 1-4 joints in the first 6 mo,	Family history of psoriasis or HLA-B27 assoc. disease, RF+, HLA-B27+ males > 8 years, systemic arthritis
Persistent	< 5 joints during course,	
Extended	> 4 joints after 6 mo	
RF- polyarthritis	Arthritis of > 4 joints in the first 6 mo, RF-	RF+, systemic arthritis
RF+ polyarthritis	Arthritis of > 4 joints in the first 6 mo, RF +	RF-, systemic arthritis
Psoriatic arthritis	Arthritis and psoriasis or arthritis and at least 2 of: (a) dactylitis, (b) nail abnormalities, (c) family history of psoriasis	RF+, systemic arthritis
Enthesitis related arthritis	Arthritis and enthesitis OR arthritis or enthesitis with at least 2 of: (a) sacroiliac tenderness and/or spinal pain, (b) HLA-B27, (c) family history of HLA-B27associated disease	Family history of psoriasis, systemic arthritis
Other arthritis	Children with JIA who do not fulfill criteria for any category or fulfill criteria for >1 category	

(Reference: Evaluation of the ILAR criteria for juvenile idiopathic arthritis. Krumrey-Langkammerer M, Häfner R.J Rheumatol. 2001 Nov;28(11):2544-7.)

Criteria for Classification of JRA (ACR = American College of Rheumatology) from 1976

Age of onset prior to 16 yrs
Arthritis (swelling, effusion, or presence of 2 or more of the following in one or more joints:

d. Limitation of range of motion
e. Tenderness or pain on range of motion
f. Increased heat

Duration of disease 6 weeks or longer
Onset type defined by type of disease in first 6 months:

d. Polyarticular: ≥ 5 inflamed joints
e. Oligoarticular (aka: pauciarticular): < 5 joints
f. Systemic onset: arthritis with characteristic fever

Exclusion of other forms of juvenile arthritis (psoriatic, spondyloarthopathy = juvenile ankylosing spondylitis, inflammatory bowel disease associated arthritis)

Criteria for Classification of JCA (EULAR = European League Against Rheumatism) from 1977

Age of onset prior to 16 yrs
Arthritis (swelling, effusion, or presence of 2 or more of the following in one or more joints):

d. Limitation of range of motion
e. Tenderness or pain on range of motion
f. Increased heat

Duration of disease 3 months or longer
Onset type defined by characteristics at presentation:

g. Polyarticular: ≥ 5 inflamed joints, Rheumatoid factor negative
h. Pauciarticular: < 5 joints
i. Systemic onset: arthritis with characteristic fever
j. Juvenile rheumatoid arthritis: ≥ 5 joints, rheumatoid factor positive
k. Juvenile ankylosing spondylitis
l. Juvenile psoriatic arthritis

3) Population not < 18 years

For all KQs:

- The study sample must consist of children 18 years or younger. If the study includes adults, at least 80% of the sample must be children, or outcomes must be reported separately for the 18 years or younger subgroup.

4) No clinical outcome measure (test) of interest

- Study must report at least one clinical outcome measure for childhood JIA that is commonly used in clinical trials or within the clinical practice setting.

Notes/further guidance:

The following list of specific measures/instruments was agreed on after discussions with the project's technical expert panel (TEP).

- Measures of disease activity:
  - Active joint count (AJC)
  - Physician global assessment of disease activity (PGA)

        - Parent/patient global assessment of well-being (PGW)
    - Measure of functional status/disability:
        - Childhood Health Assessment Questionnaire (CHAQ)
    - Measures of health-related quality of life:
        - Child Health Questionnaire (CHQ)
        - Pediatric Quality of Life Inventory (PedsQL) 4.0
        - Pediatric Quality of Life Inventory Rheumatology Module (PedsQL-RM)
    - Composite measures of response to therapy and developing definitions of disease status:
        - American College of Rheumatology Pediatric Response Criteria (ACR Pediatric 30)
        - A consensus-based definition of remission
        - Flare
        - Minimal disease activity (MDA)

5) No data reported on test performance

- Outcomes to be evaluated here are:
    - Validity of clinical outcomes measures
    - Reliability of clinical outcomes measures (inter- and intra-rater reliability, test-retest reliability)
    - Responsiveness of clinical outcomes measures (standardized response mean and responsiveness index).
    - Feasibility of clinical outcomes measures (specifically, time to administer).

Appendix C: Data Abstraction Forms

KQ 1-4 – Blank ET/data abstraction form

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
StudyID	**Geographical location:** **Study dates:** **Funding source:** **Setting:** **Study design:** RCT Nonrandomized comparative study Other **Intervention(s):** - DMARD name: - Dose: - Titration: - N: **Comparator(s):** **Were additional arthritis medications allowed?:** **If Yes to above, was this done:** Per protocol At discretion of clinician/investigator NR **Study duration:** **Primary outcome(s):**	**Number of patients:** - Screened for inclusion: - Eligible for inclusion: - Randomized: - Began treatment: - Completed treatment: - Withdrawals/losses to followup: **Age:** - Mean (SD): - Median: - Range: **Sex:** - Female: - Male: **Race/ethnicity:** **JIA diagnosis:** JRA JCA JIA Spondyloarthropathy Psoriatic arthritis Other (describe) **Baseline severity:** Active joint count: Duration of disease: Other (specify): NR **Percentage with uveitis:**	**1) Active joint count:** **2) Quality of life/functional status:** **3) Number of joints with limited range of motion:** **4) Global assessment of current status:** - Physician: - Patient/Parent: **5) Laboratory measures of inflammation:** - ESR: - Other: **6) Radiographic evidence of progression of disease:** **7) Pain control:** **8) Clinical remission:** **9) Flare of disease:** **10) Discontinuation of DMARD due to:** - Remission of disease: - Inefficacy: - Intolerance/AEs: **11) Mortality:** **12) Adverse events reported?:** Yes No	**Exclusion reasons (if appropriate):** **General comments:** **Quality assessment:** *Primary outcome:* - Overall rating: - Comments: *Adverse events:* - Overall rating: - Comments: **Applicability:** **This article is relevant to:** Question #_____

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Secondary outcome(s):	**Inclusion criteria:** **Exclusion criteria:**	**13) Other:**	

KQ 5 – Blank ET/data abstraction form

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
StudyID	**Geographical location:** **Setting:** Specialty clinic Other [specify] **Study design:** RCT Longitudinal non-RCT Cross-sectional Other [specify] **Study objective(s):** **Duration of followup:**	**Number of patients:** **Age:** - Mean (SD): - Median: - Range: **Sex:** - Female: - Male: **Race/ethnicity:** **JIA diagnosis:** JRA JCA JIA Spondyloarthropathy Psoriatic arthritis Other (describe) **Percentage with systemic JIA:** **Baseline severity:** Time since diagnosis: Active joint count: Other [specify]: NR	**Instrument(s) evaluated:** **Mode of administration:** Self-administered Interviewer-administered Other [specify]	**1) Reliability:** - Test-retest: - Kappa statistics: - Inter-rater: - Intra-rater: - Intra-class correlation: **2) Validity:** - Versus clinical outcomes: - Versus lab results: - Versus radiological results: - New instrument versus established instrument: **3) Other:** - Feasibility: NR [or report results] - Responsiveness: NR [or report results] - ROC curves: NR [or report results]	**Exclusion reasons (if appropriate):** **General comments:** **Quality assessment:**

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Inclusion criteria: **Exclusion criteria:**			

Appendix D: Evidence Tables – Main Literature Search

Evidence Table 1. Studies Relevant to Key Questions 1-4

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Brewer, Giannini, Kuzmina, et al., 1986 **#1181** **AND** **Van Kerchove, Giannini, and Lovell, 1988** **#1120**	**Geographical location:** US (13 centers; N = 65 patients); Soviet Union (5 centers; N = 97 patients) **Study dates:** NR **Funding source:** NIH Grant from Winthrop laboratories and funds from Merck Sharp Dohm Laboratories **Setting:** 18 pediatric rheumatology centers **Study design:** RCT **Intervention(s):** - DMARD name: PCN - Dose: 5 mg/kg/day - Titration: Increased at 2 months to 10 mg/kg/day - N = 54 - DMARD name: HCQ - Dose: 3 mg/kg/day - Titration: Increased at 2 months to 6mg/kg/day - N = 57 **Comparator(s):** Placebo (N = 51) **Were additional arthritis medications allowed?:** Yes: NSAIDs, antibiotics,	**Number of patients:** N = 162 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: NR - Began treatment: 162 - Completed treatment: 6 months = 143 (88%) 12 months = 123 (76%) - Withdrawals/losses to followup: NR **Age:** - Range: 18 months – 17 years - Mean 9.7 years **Sex:** - Female: 122 (75.3%) - Male: 40 (24.7%) **Race/ethnicity:** NR **JIA diagnosis:** JRA Polyarticular 142, pauciarticular 11, systemic 9 **Baseline severity:** Active joint count: PCN: 18 ± 13.5 HCQ: 18.6 ± 13.1 Placebo: 16.3 ± 10.6 Duration of disease: Mean 3.2 years ESR: PCN: 32 ± 23	**1) Active joint count:** Degree of change at 6 months: *Drug* / *Mean* / *Median* / *95% CI* PCN / -3.0 / -3 / -4.8 to -1.1 HCQ / -2.8 / -2 / -5 to - 0.7 PLA / -2.9 / -1.5 / -5.6 to 0.2 Degree of change at 12 months: *Drug* / *Mean* / *Median* / *95% CI* PCN / -3.7 / -3.5 / -5.6 to -1.9 HCQ / -6.7 / -4 / -9.4 to -4 PLA / -5.4 / -4.5 / -8 to -2.8 **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** Degree of change at 6 months: *Drug* / *Mean* / *Median* / *95% CI* PCN / -2.5 / -1 / -4.3 to -0.8 HCQ / -0.7 / -1 / -2.3 to 1 PLA / -3.8 / -2 / -6.2 to -1.3 Degree of change at 12 months: *Drug* / *Mean* / *Median* / *95% CI* PCN / -1.4 / -0.5 / -2.9 to -0.04 HCQ / -1.9 / -2 / -4.4 to 0.5 PLA / -3.4 / -3 / -5.8 to -0.9 **4) Global assessment of current status:** By physician: Number (%) much better / better / same / worse / much worse / NA 6 months:	**General comments:** Older medications, PCN not used any longer **Quality assessment:** *Primary outcome:* - Overall rating: Good *Adverse events:* - Overall rating: Fair - Comments: Listed by drug **Applicability:** Good

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	acetaminophen and codeine NSAIDs given per protocol – had to be steady dose, unchanged during study **Study duration:** 12 months **Primary outcome(s):** NR **Secondary outcome(s):** NR	HCQ: 28 ± 23 Placebo: 30 ± 21 **Percentage with uveitis:** NR **Inclusion criteria:** - Met the criteria for JRA established by the American Rheumatism Association or the criteria used in the Soviet Union and Eastern Europe - Presence of severe, clinically active. poorly controlled disease. - Age ≥18 months and ≤ 17 years **Exclusion criteria:** - Clinically important cardiac disorder or other severe or chronic disease - Pregnant or nursing women - Patients scheduled for surgery	PCN: 4(8) / 24(47) / 18(35) / 5(10) / 0 / 0 HCQ: 3(6) / 25(50) / 16(32) / 5(10) / 0 / 1(2) PLA: 6(14) / 15(36) / 17(41) / 2(5) / 1(2) / 1(2) 12 months: PCN: 9(21) / 15(35) / 12 (28) / 7(16) / 0 HCQ: 11(24) / 22(48) / 12(26) / 1(2) / 0 PLA: 7(21) / 11(32) / 14(41) / 2(6)0 By patient/parent: NR **5) Laboratory measures of inflammation:** ESR: Mean decrease (median) 12 months: PCN: 9.4 (4) HCQ: 10 (4) PLA: 10 (4) **6) Discontinuation of DMARD due to:** Remission of disease: NR Inefficacy (n [%]): PCN: 4(36) HCQ: 5(45) PLA: 4(24) Intolerance/AEs (n [%]): PCN: 2(18) HCQ: 3(27) PLA: 3(18) **7) Mortality:** NR **8) Adverse events reported?:** Yes - leucopenia, anemia **9) Other - Total sum of severity:** Degree of change at 6 months:	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

Drug	*Mean*	*Median*	*95% CI*
PCN	-23.5	-15	-34.7 to -12.3
HCQ	-15.4	-10	-23.9 to - 6.8
PLA	-12.7	-12.5	-24.8 to -0.6

Degree of change at 12 months:

Drug	*Mean*	*Median*	*95% CI*
PCN	-24.3	-17.5	-34.9 to -13.7
HCQ	-23.4	-14	-34.2 to - 12.6
PLA	-18.1	-16	-24.4 to -11.8

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Giannini, Brewer, Kuzmina, et al., 1992 **#1008**	**Geographical location:** 18 centers in the US and 5 in the Soviet Union **Study dates:** NR **Funding source:** FDA, NIH, National Arthritis Foundation, Children's Hospital Research Foundation, Lederle Laboratories **Setting:** Specialty centers **Study design:** RCT **Intervention(s):** - DMARD name: Methotrexate - Dose: Very low dose (5 mg/m^2/week) or low dose (10 mg/m^2/week) up to 15 mg/week max	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 127 - Began treatment: 127 - Completed treatment: 114 (for efficacy analysis); 108 completed the entire 6-month trial - Withdrawals/losses to followup: 19 discontinued therapy (see under "Results" for details); no reported loss to follow-up **Age:** - Mean (SD): 10.1 years - Median: NR - Range: 2.5 to 17.8 years **Sex:** - Female: 96 (76%) - Male: 31 (24%)	**1) Active joint count:** Very low dose: -5.2 Low dose: -7.2 Placebo: -5.2 p > 0.3 **2) Quality of life/functional status:** Composite index: Very low dose: 32% improved Low dose: 63% Placebo: 36% **3) Number of joints with limited range of motion:** Very low dose: -0.5 Low dose: -5.4 Placebo: -0.7 p = 0.04 **4) Global assessment of current status:** By physician:	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good - Comments: Well-conducted RCT *Adverse events:* - Overall rating: Good - Comments: Thorough explanation **Applicability:** Good

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- N: Planned for 30/group **Comparator(s):** Placebo **Were additional arthritis medications allowed?:** Yes: NSAIDs or prednisone Dose of these drugs had to be constant for at least 1 month before randomization and could not be changed **Study duration:** 6 months **Primary outcome(s):** - Physician's global assessment of the patient's response - Articular-severity score - Composite index **Secondary outcome(s):** - Number of joints with swelling - Pain on motion - Tenderness - Limitation of motion - Severity of condition - Duration of morning stiffness - Laboratory changes (hemogram and ESR)	**Race/ethnicity:** NR **JIA diagnosis:** JRA **Baseline severity:** Active joint count (n [SE]): Very low dose: 27 (2) Low dose: 21 (2) Placebo: 24 (2) Duration of disease: Mean 5.1 years Other (specify): Systemic in 32 (25%) **Percentage with uveitis:** NR **Inclusion criteria:** - Criteria for JRA of the ACR or the Soviet Union and Eastern Europe - 3 joints with active arthritis not adequately controlled by NSAIDs or second line agents - At least 18 months and less than 18 years of age **Exclusion criteria:** - Other clinically important severe or chronic disease - Girls who might become pregnant - Receipt of penicillamine, hydroxychloroquine, oral or parenteral gold, or intraarticular or long-acting parenteral steroids within 3 months before randomization	Low dose improved over placebo (p = 0.02) Very low dose not improved over placebo (p = 0.06) By patient/parent: NR – results "nearly identical with those of the physician's" **5) Laboratory measures of inflammation:** ESR: Very low dose: 7/28 with an elevated level had a normal value by the final visit Low dose: 13/28 with an elevated level had a normal value by the final visit Placebo: 8/27 with an elevated level had a normal value by the final visit **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** Remission of disease: NR Other reasons: Very low dose: 2 ineffectiveness of drug, 1 AE, 2 intercurrent illness Low dose: 2 AEs, 2 intercurrent illness, 2 "administrative," 1 noncompliance Placebo: 5 ineffectiveness of drug, 1 intercurrent illness, 1 "administrative" reasons **11) Mortality:** None **12) Adverse events reported?:**	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Previous receipt of methotrexate	Yes 8/40 with very low dose: 4 GI problems, 2 headache or dizziness, 2 inflammation of oral mucosa with headache and GI problems 6/47 with low dose: 3 GI problems, 1 ulceration of mucous membranes, 1 headache, 1 headache and abdominal problems 5/41 placebo: All GI problems 15 in very low dose, 15 in low dose, and 5 in placebo had abnormal lab results "judged to be clinically important" – most frequent were alterations in WBC differential, hematuria, and pyuria. Increased aminotransferase levels and anemia were most common with placebo.	
Giannini, Lovell, Silverman, et al., 1996 **#877**	**Geographical location:** 7 centers in US and Canada **Study dates:** Nov 1991-Nov 1994 **Funding source:** FDA, NIH, Immuno AG, Children's Hospital Research Foundation of Cincinnati, Schmidlapp Founation, IRCSS (Italian Research Hospital) **Setting:** Specialty **Study design:** RCT, blinded, with a run-in period between 3 and 6 months. RCT lasted 4 months and had an "escape" provision for those whose	**Number of patients:** N = 25 in the run-in phase, 19 in the blinded RCT - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 19 - Began treatment: 19 - Completed treatment: 12 completed, 6 "early escape" - Withdrawals/losses to followup: 1 **Age:** - Mean (SD): 10.9 (5.8) (n = 25 in the run-in period) - Median: NR - Range: 2 to 23 years **Sex:** - Female: 22 (88%)	**1) Active joint count:** In the RCT, -3% in IVIG group (n = 10), 30% increase in the placebo group (n = 9) **2) Quality of life/functional status:** 19/25 had "clinically important improvement" in the open label and entered the RCT During the RCT, 2/10 in the treatment group "escaped" to higher dosing based on clinically significant worsening. 5/9 in the placebo group escaped to treatment because of clinically significant worsening. **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** By physician:	**General comments:** Includes only subjects who responded to IVIG from the open-label trial – evaluates effectiveness based on lack of "escape" **Quality assessment:** *Primary outcome:* - Overall rating: Fair - Comments: No statistical inference testing; conflict of interest with funding source; main outcome not validated *Adverse events:* - Overall rating: Fair - Comments: No validated AE measure; potential conflict of interest with funding source

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	symptoms worsened. **Intervention(s):** - DMARD name: IVIG - Dose: 1.5-2.0 g/kg/infusion (100 g maximum) bimonthly - Titration: After 6 infusions, dose could be increased up to the maximum - N: 25 **Comparator(s):** Placebo **Were additional arthritis medications allowed?:** Yes - NSAIDs, "slow acting antirheumatic drugs (methotrexate, sulfasalazine, hyroxychloroquine), low dose prednisone (< 10 mg/day) **If Yes to above, was this done per protocol or at the discretion of study investigators:** NR **Study duration:** Run-in: 3 to 6 months RCT: 4 months **Primary outcome(s):** - "Clinically important benefit," defined as ≥ 25% improvement in at least 2 of the following: (a) total number of joints with active arthritis, (b) overall articular severity score, (c) physician's global assessment of overall disease activity - "Clinical important worsening,"	- Male: 3 (12%) **Race/ethnicity:** NR **JIA diagnosis:** All with poly-JRA Group A: Late onset (> 10 years) but short duration (< 3 years) Group B: ≥ 5 joints with active arthritis, disease before 8 years, short duration (< 3 years) Group C: Longer duration (> 5 years, substantial involvement (≥ 10 joints) **Baseline severity:** Active joint count: 26.7 (± 13.2) at run-in Duration of disease: 4.4 years (± 4.5) at run-in Other (specify): Overall articular severity score: 103 (± 60) Physician global assessment: 5.7 (± 2.0) JAFAR: 11.1 (± 6.5) Elevated ESR: 11/23 **Percentage with uveitis:** NR **Inclusion criteria:** Poly-JRA Between 2 and 23 years **Exclusion criteria:** - Known hypersensitivity to immunoglobulin - Leukopenia (WBC < 1500/mm^3)	In the RCT, -3% in physician global assessment in the IVIG group (n = 10), 91% increase in global assessment in the placebo group (n = 9) By patient/parent: NR **5) Laboratory measures of inflammation:** NR **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: NR **11) Mortality:** None **12) Adverse events reported?:** Yes – not broken down by treatment group In the open-label period, 3 patients, and in the RCT, 1 patient experienced AEs associated with the infusion process, namely headache, dizziness, nausea, vomiting, diarrhea, tachycardia, fatigue, and chills. AEs not associated with infusion: In the open-label period, 1 with joint pain, 1 with flare and worsening chronic iritis that required steroids, 1 with fever to 39.9 degrees C related to probable intercurrent	**Applicability:** Includes only subjects who responded to IVIG from the open-label study

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	defined as ≥ 25% worse in 2/3 above **Secondary outcome(s):** Juvenile Arthritis Functional Assessment Report (JAFAR)	- Thrombocytopenia (platelets < 100,000/mm^3) - Significant renal or hepatic disease - IgA deficiency - Malignancy - Chronic infection - Immunized with a live virus in past 2 weeks - Pregnancy	illness **13) Other:** Mean time to failure during the RCT in the placebo group was 2.5 months (range 1.8 to 3.2 months) In the RCT, 10% increase in JAFAR in the IVIG group (n = 8), 59% increase in the placebo group (n = 7) – sample size smaller because subjects with JAFAR = 0 at baseline were excluded	
Hoza, Kadlecova, Nemcova, et al., 1991 **#1048**	**Geographical location:** Prague, Czechoslovakia **Study dates:** NR **Funding source:** NR **Setting:** Hospital **Study design:** RCT **Intervention(s):** - DMARD name: Sulfasalazine (SSZ) - Dose: 20-30 mg/kg/day - N: 21 **Comparator(s):** - DMARD name: Chloroquin (DLG) - Dose: 3 to 4 mg/kg/day - N: 18 **Were additional arthritis medications allowed?:** Yes: NSAIDs, prednisone	**Number of patients:** N = 39 - Screened for inclusion: - Eligible for inclusion: 39 - Randomized: SSZ, 21; DLG, 18 - Began treatment: 39 - Completed treatment: 34 - Withdrawals/losses to followup: 5 withdrawals **Age:** NR **Sex:** - Female: 26 (66.7%) - Male: 13 (33.3%) **Race/ethnicity:** NR **JIA diagnosis:** *SSZ:* Poly: 11 Oligo: 8 Systemic: 2 *DLG:* Poly: 12	**1) Number of criteria:** At time 0/6 months: SSZ: 7/6 DLG: 4/3 **2) Number of affected joints:** At time 0/6 months: SSZ: 6/5 DLG: 4/3 **3) AM stiffness (minutes)** At time 0/6 months: SSZ: 29/20 DLG: 37/21 **4) Pain score** At time 0/6 months: SSZ: 5/4 DLG: 5/3 **5) Global assessment of current status:** Improved/no effect/worse SSZ: - Physician: 9/9/3 - Patient: 10/7/3 - Parent: 7/11/3	**General comments:** - Not controlled, not blinded - Poor description of population **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Fair/poor - Comments: Poor description of patients; unclear if blinded; some outcomes validated, others not; short study duration *Adverse events:* Overall rating: Poor - Comments: Not characterized by patient or treatment received; no n/% given **Applicability:** - Unclear population in terms of age and disease severity - Study outside US - Not blinded

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	NR whether these were added per protocol or at the discretion of clinician/investigator **Study duration:** 6 months **Primary outcome(s):** - Number of JCA criteria - Number of affected joints - Duration of morning stiffness - Pain score - ESR - Functional capacity - Parent/patient and physician global - Improvement (= when 5 of 6 indices reported improved) **Secondary outcome(s):** NR	Oligo: 5 Systemic: 1 **Baseline severity:** NR Percentage with uveitis: NR **Inclusion criteria:** Pauci or polyarticular JCA **Exclusion criteria:** NR	DLG: - Physician: 8/3/7 - Patient: 7/5/3 - Parent: 8/5/5 **5) Laboratory measures of inflammation:** - ESR at time 0/6 months: SSZ : 52.7/36.3 DLG: 41.2/28.9 **6) Discontinuation of DMARD due to:** NR **7) Mortality:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: SSZ, 4; DLG, 1 **11) Mortality:** 0 **12) Adverse events reported?:** Yes SSZ: 4 (19%) discontinued due to AEs DLG: 1 (5%)	
Ilowite, Porras, Reiff, et al., 2009 **#62**	**Geographical location:** 17 sites in USA, Canada, Australia, New Zealand, and Costa Rica **Study dates:** July 2000 to February 2004 **Funding source:** Amgen, Inc.	**Number of patients:** N = 86 in run-in phase, 50 in blinded RCT phase, 30 in extension phase - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 50 - Began treatment: 50 - Completed treatment: 31 - Withdrawals/losses to followup	**1) Active joint count:** NR **2) Quality of life/functional status:** CHAQ change at week 28: Anakinra: -0.25 Placebo: 0.13 P value NR **3) Number of joints with limited range of**	**General comments:** - Primary outcome changed from efficacy to safety because of low enrollment - Baseline CHAQ and ESR values NR **Quality assessment:** *Primary efficacy outcome:*

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Setting: NR **Study design:** RCT, blinded, placebo-controlled, multicenter, with a 12-week, open-label, run-in period; 16-week, blinded RCT phase; and a 12-month open-label extension period Patients who experienced disease flare during the blinded phase were given the option to switch arms (and remain blinded) **Intervention(s):** - DMARD name: Anakinra - Dose: 1.0 mg/kg/day (max dose 100 mg/day) by daily injection - Titration: NA - N: 86 in run-in phase, 25 in RCT phase (plus 25 who received placebo), and 29 who completed open-label extension phase **Comparator(s):** Placebo (N = 25) **Were additional arthritis medications allowed?:** Yes: NR whether these were added per protocol or at the discretion of study investigators **Study duration:** 12-week run-in phase 16-week blinded phase 12-month extension phase	during blinded phase: 19/50 (38%; Anakinra N = 6 [4 for disease flare], placebo N = 13 [10 for disease flare]) Note: Reasons for withdrawal from blinded phase NR **Age:** - Mean (SD): 12 (SD NR) - Range: 3 to 17 **Sex:** - Female: 63 (73%) - Male: 23 (27%) **Race/ethnicity:** White: 46 (53%) Black: 5 (6%) Hispanic: 29 (34%) American Indian/Alaskan native: 3 (3%) Asian: 1 (1%) Other: 2 (2%) **JIA diagnosis:** JRA Onset: Anakinra N (%) / Placebo N (%) - Polyarticular 14 (56) / 19 (76) - Systemic 9 (36) / 2 (8) - Pauciarticular 2 (8) / 4 (16) **Baseline severity:** NR **Percentage with uveitis:** NR **Inclusion criteria:** - Presenting with polyarticular-course JRA, independent of onset	**motion:** NR **4) Global assessment of current status:** - Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation:** - ESR change at week 28: Anakinra: -2.21 Placebo: 13.73 P value NR **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** By week 28: Anakinra N (%) / Placebo N (%) - Polyarticular 2 (14) / 8 (42) - Systemic 2 (22) / 1 (50) - Pauciarticular 0 / 1 (25) P = 0.11 "Time to disease flare was greater in patients receiving anakinra, nearly reaching statistical significance (p = 0.057)." **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: 27/86 patients (31%) in open-label run-in phase withdrew because of nonresponse - Intolerance/AEs: 4/86 patients (5%) in open-label run -n phase withdrew because of AEs	- Overall rating: Poor - Comments: Not powered for efficacy; insufficient reporting of randomization and concealment; no validated AE measure; conflict of interest with funding source, run-in phase *Adverse events:* - Overall rating: Fair - Comments: Insufficient reporting of randomization and concealment; no validated AE measure; conflict of interest with funding source **Applicability:** Outcomes measured; differential dropout rates (12% vs. 26%)

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Primary outcome(s): Safety, as defined by the incident of treatment-emergent AEs and lab values Assessments done at baseline, week 2, week 4, and every 4 weeks thereafter in blinded phase, then every 3 months in extension phase up to 12 months **Secondary outcome(s):** Response, defined as ≥ 30% improvement in any 3 of 6 JRA core set criteria variables, including: - Physician global assessment of disease activity; - Patient/parent assessment of disease activity; - CHAQ; - Number of joints with active arthritis; - Number of joints with limited range of motion; - ESR. Also assessed: - Proportion of patients with disease flares in the blinded phase; - Time to disease flare; - Changes in the JRA core components at week 28; - Pharmacokinetics.	- Required to have ≥ 5 swollen joints due to active arthritis (not bony overgrowth) and 3 joints with limitation of motion at screening and day 1 visit - Age between 2 and 17 years - Minimum weight of 10 kg - On a stable dose of MTX for 6 weeks before study entry and not receiving biologic therapy within 4 weeks of initiating study drug - Negative pregnancy test of childbearing potential **Exclusion criteria:** - Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal - Creatinine > 1.5 times the upper limit of normal - WBC < 2.0 x 10^9/L - Neutrophil count < 1.5x10^9/L - Platelet count < 150x10^9/L - Receiving treatment with a DMARD other than MTX - Receiving intraarticular or systemic corticosteroid injections within 4 weeks before study entry - Clinically significant systemic disease (such as hepatic, renal, neurological, endocrine, cardiac, gastrointestinal [except NSAID-induced GI problems]) - Hematological disease - Presence of symptoms of systemic disease, such as intermittent fever, rash, hepatosplenomegaly, or pericarditis within 24 weeks of the first dose of anakinra	Reasons for withdrawal from blinded phase NR **11) Mortality:** None **12) Adverse events reported?:** Yes **13) Other:** Responders: Anakinra (%) / Placebo (%) - Polyarticular: 53 / NR - Systemic 73 / NR - Pauciarticular 67 / NR	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Kvien, Hoyeraal, and Sanstad, 1985 **#1207**	**Geographical location:** Oslo, Norway **Study dates:** 1979 to 1983 **Funding source:** Norsk Hydro Research Foundation for Rheumatology, Norwegian Women Public Health Association, Astra Syntex Research Foundation at Oslo Sanitersforening Rheumatism Hospital and the Norwegian Medicinal Depot **Setting:** NR **Study design:** RCT **Intervention(s):** - DMARD name: Hydroxychloroquine (HC)-Ercoquin - Dose: 5 mg/kg daily, rounded upwards to nearest 25 mg and given twice per day - Titration: Given 9 months then withdrawn - N: 25 - DMARD name: Gold sodium thiomalate (GSTM) - Myocrisin - Dose: 0.7 mg/kg by weekly injection - Titration: After total of 14mg/kg (20 weeks), 0.7mg/kg given monthly through week 50 - N: 23	**Number of patients:** N = 72 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 72 - Began treatment: 72 - Completed treatment: 44 - Withdrawals/losses to followup: 28 **Age:** - Median: 10.8 years - Range: 3.6 to 15.9 years **Sex:** - Female: 47 (65.3%) - Male: 25 (34.7%) **Race/ethnicity:** NR **JIA diagnosis:** JRA (pauciarticular or polyarticular) **Baseline severity:** Active joint count: 7-9 Duration of disease: Median 16 months (range, 3 to 164) Other: Radiographic erosions or severe growth disturbances in ≥ 1 joint, n = 9 **Percentage with uveitis:** "Chronic iridocyclitis," n = 11 **Inclusion criteria:** - Fulfillment of the diagnostic criteria of JRA - Present pauciarticular or polyarticular disease type - Between 2 and 16 yrs old	**1) Active joint count:** Baseline (BL) median and median change values at 12, 24, and 50 weeks: Drug | BL | 12 wk | 24 wk | 50 wk HC | 9 | -1 | -2 | -4 GSTM | 7 | -1 | -2 | -5 PEN | 8.5 | -2 | -2 | -2.5 P = NS **2) Quality of life/functional status:** "Functional capacity" reported as a 1-20 graphic rating scale – see "Global assessment of current status," below **3) Number of joints with limited range of motion:** Baseline (BL) median and median change values at 12, 24, and 50 weeks: Drug | BL | 12 wk | 24 wk | 50 wk HC | 3 | 0 | 0 | 0 GSTM | 3 | 0 | -1 | 0 PEN | 4 | 0 | -1 | -2 P = NS **4) Global assessment of current status:** By physician (1-20 scale, 20 maximum activity): Baseline (BL) median and median change values at 12, 24, and 50 weeks: Drug | BL | 12 wk | 24 wk | 50 wk HC | 11 | -2 | -2.5 | -8 GSTM | 12 | -3 | -5 | -9 PEN | 12 | -2 | -4 | -7.5 P = NS By physician: HVM ≥ 50% improvement by physician's overall assessment at 12, 24,	**General comments:** None **Quality assessment:** *Primary outcome:* - Overall rating: Poor - Comments: Allocation concealment not specified; important baseline differences; unclear if outcomes assessed blind to intervention; outcomes not well described *Adverse events:* - Overall rating: Poor - Comments: Allocation concealment not specified; important baseline differences; unclear if outcomes assessed blind to intervention; outcomes not well described **Applicability:** Non-USA

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- DMARD name: D-Penicillamine (Pen)- Distamin - Dose: Rounded to nearest 25 mg and given twice per day - Titration: 2.5mg/kg weeks 1-4; 5 mg/kg weeks 5-8; 7.5 mg/kg weeks 9-12; 10 mg/kg after week 12 to week 50 - N: 24 **Comparator(s):** Three DMARDs compared, no placebo **Were additional arthritis medications allowed?:** Yes: NSAIDs, preferred to be kept constant; acetaminophen as needed **Study duration:** 50 weeks **Primary outcome(s):** Not stated; outcomes measured at 12, 24, and 50 weeks **Secondary outcome(s):** - Joint counts - Articular indices - Physicians' overall assessment - Goniometric measurements - Various functional tests - Ophthalmological examinations - ESR and other laboratory measures	- Active disease with indication for use of slow-acting antirheumatic drugs (SAARD), that is, progressive disease with reversible disease manifestations without sufficient effect of NSAID **Exclusion criteria:** - Contraindication for use of either hydroxychloroquine, gold sodium thiomalate, or D-penicillamine - Secondary amyloidosis - Present systemic disease type - Use of either systemic corticosteroids, immunoregulatory drugs, or SAARD during the 6 months prior to the study, or local corticosteroid injections or joint surgery during the preceding 2 months	and 50 weeks Drug | 12 wk | 24 wk | 50 wk HC | 4/25 | 9/24 | 12/17 GSTM | 6/19 | 8/19 | 10/15 PEN | 0/23 | 8/19 | 8/12 P = NS By patient/parent: NR **5) Laboratory measures of inflammation:** - ESR: Baseline (BL) median and median change values at 12, 24, and 50 weeks: Drug | BL | 12 wk | 24 wk | 50 wk HC | 28 | -4 | -9.5 | -12 GSTM | 27 | -7 | -10 | -11 PEN | 20 | -7 | -6 | -8 P = NS **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** Pain on movement – Baseline (BL) median and median change values at 12, 24, and 50 weeks: Drug | BL | 12 wk | 24 wk | 50 wk HC | 6 | -1 | 0 | -1 GSTM | 4.5 | -1 | -1 | -2 PEN | 7 | -3 | -2 | -2 P = NS **8) Clinical remission:** NR **9) Flare of disease:** Withdrawals by week 50 due to disease exacerbation HC: 1	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			GSTM: 0 PEN: 2 **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: HC, 6; GSTM, 4; PEN, 4 - Intolerance/AEs: HC, 0; GSTM, 3; PEN, 6 **11) Mortality:** NR **12) Adverse events reported?:** Yes Number of AEs reported (HC / GSTM / PEN): Dermatitis: 1 / 2 / 1 Stomatitis: 0 / 1 / 0 GI upset: 1 / 0 / 4 Taste disturbances: 0 / 0 / 2 Proteinuria: 0 / 2 / 1 Eosinophilia: 0 / 3 / 0 Thrombocytopenia: 0 / 0 / 3 Antibodies to native DNA: 0 / 0 / 1 Other: 0 / 2 / 4 Withdrawals due to AEs: HC: 0 GSTM: 3 PEN: 6	
Kvien, Hoyeraal, and Sandstad, 1986 **#1188**	**Geographical location:** Oslo, Norway **Study dates:** 1979-83 **Funding source:** Norsk Hydro Research Foundation for Rheumatology, Norwegian Women Public Health Association, Astra Syntex Research Foundation at Oslo	**Number of patients:** N = 32 (AZA N = 17; PL N = 15) - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 32 - Began treatment: 32 - Completed treatment: NR - Withdrawals/losses to followup: 8 – follow-up rates: Week 8: 15/17 AZA; 15/15 PL Week 16: 13/17 AZA; 11/15 PL	**1) Active joint count:** Baseline (BL) median and median change values at 8 and 16 weeks: Drug | BL | 8 wk | 16 wk AZA | 17 | -5 | -7 PL | 31 | 1 | -1 P = 0.45 **2) Quality of life/functional status:** Baseline (BL) median and median change	**General comments:** Reference 15 in the published report has more information on outcomes assessment **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Fair - Comments: Allocation concealment not stated; small sample with some potentially

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Sanitetsforening Rheumatism Hospital, Norwegian Medicinal Depot and Norma and Leon Hess' Foundation for Support of Rheumatological Research at Olslo Sanitetsforening Rheumatism Hospital **Setting:** NR **Study design:** RCT **Intervention(s):** - DMARD name: Azathioprine (AZA) -Imuran - Dose: 2.5 mg/kg rounded to nearest 12.5 mg, given daily - Titration: NA - N: 17 **Comparator(s):** - Matching Placebo (PL) - N: 15 **Were additional arthritis medications allowed?:** Prednisolone, preferably 0.2 mg/kg at trial start; reduced in 5-8 steps until withdrawal by study end; NSAIDS, preferably maintained at stable dose **Study duration:** 16 weeks **Primary outcome(s):** Not specified **Secondary outcome(s):** Multiple disease activity measures	**Age:** Median (range): AZA: 10.2 years (2.4-14.8) Placebo: 9.5 years (4.1-15.0) **Sex:** - Female: AZA 12 (70.6%) Placebo 10 (66.7%) - Male: AZA 5 (29.4%) Placebo 5 (33.3%) **Race/ethnicity:** NR **JIA diagnosis:** JRA **Baseline severity:** Active joint count: 17 AZA; 31 PL Duration of disease: 31 months AZA (range 4-139); 21 months PL (range 3-110) Other (specify): Severe radiographic abnormalities: 8 AZA, 7 PL **Percentage with uveitis:** Chronic iridocyclitis: AZA n = 5; PL n = 3 **Inclusion criteria:** - Required therapy with immunomodulatory drugs - Disease was active and progressive (with severe systemic features and/or with severe articular involvement progressing towards irreversible	values at 8 and 16 weeks: Drug | BL | 8 wk | 16 wk AZA | 5 | -2 | -4 PL | 6 | 0 | 0 P < 0.01 **3) Number of joints with limited range of motion:** Baseline (BL) median and median change values at 8 and 16 weeks: Drug | BL | 8 wk | 16 wk AZA | 9 | -1 | -1 PL | 16 | 1 | -2 P = 0.51 **4) Global assessment of current status:** - By physician (1-20 scale, 20 maximum activity): Baseline (BL) median and median change values at 8 and 16 weeks: Drug | BL | 8 wk | 16 wk AZA | 13 | -3 | -5 PL | 16 | 1 | -2 P = 0.12 - By patient ("subjective total assessment, 1-20, 20 maximum activity"): Baseline (BL) median and median changes at 8 and 16 weeks: Drug | BL | 8 wk | 16 wk AZA | 5 | -1 | -2 PL | 6 | 1 | 0 P = 0.02 - By patient – HVM "subjective total assessment improved by ≥ 50%:	important baseline differences and significant dropouts *Adverse events:* - Overall rating: Fair - Comments: No details on AE assessments **Applicability:** Not U.S.A.

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		joint abnormalities) - Insufficient response to previous adequate therapy with slow acting antirheumatic drugs for 6 months for patients with pauci- and polyarticular disease type - Systemic disease patients were included if their responses to previous therapy with corticosteroids were insufficient **Exclusion criteria:** - Previous use of azathioprine or other immunomodulatory drugs - Evidence of concomitant infectious, hematological, or hepatic disease, or other disorders contraindicating use of immunomodulatory drugs - Probably insufficient cooperation and local followup - Joint surgery or corticosteroid injections (both local or systemic) during a period of 2 months before the study - Alterations of the dose of NSAID or corticosteroid during the 7 days before the study - Lack of assent/consent from the patient/parent to take part in the study	AZA: 6/15 week 8; 8/13 week 16 PL: 1/15 week 8; 1/11 week 16 P = 0.01 **5) Laboratory measures of inflammation:** - ESR: Patients with ≥ 50% improvement AZA: 3/15 week 8; 4/13 week 16 PL: 3/15 week 8; 2/11 week 16 P = 0.36 - ESR: Patients with ≥ 25% improvement AZA: 8/15 week 8; 4/13 week 16 PL: 4/15 week 8; 4/11 week 16 P = 0.41 **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** - Pain on movement (1-20, 20 maximum activity): Baseline median and median changes at 8 and 16 weeks: Drug | BL | 8 wk | 16 wk AZA | 3 | -1 | -2 PL | 7 | 0 | -1 P = 0.10 **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy (exacerbation): 1 AZA; 2 PL - Intolerance/AEs: 3 AZA; 0 PL **11) Mortality:** NR **12) Adverse events reported?:** Yes	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Lahdenne, Vahasalo, and Honkanen, 2003 **#530**	**Geographical location:** Finland **Study dates:** NR **Funding source:** NR **Setting:** NR **Study design:** Nonrandomized comparative study **Intervention(s):** - DMARD name: Infliximab or etanercept - Dose: Infliximab 3-4 mg/kg IV at weeks 0, 2, 6, and then 4- to 8-week intervals; etancercept (0.4 mg/kg) subcutaneously twice/week - Titration: NR - N: 24 (14 infliximab, 10 etanercept) **Comparator(s):** Open-label comparison to other DMARD **Were additional arthritis medications allowed?:** Yes: One or more of methotrexate, prednisolone, cyclosporine A, sulfasalazine, hydroxylchloroquine, intraarticular corticosteroid injections, NSAIDs NR whether these were added per protocol or at the discretion of study investigators	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: NA - Began treatment: 24 - Completed treatment: 18 - Withdrawals/losses to followup: Etancerpt (1 noncompliance – switched to infliximab), infliximab (5 noncompliance or adverse events) **Age:** - Mean (SD): 10.2 (NR) - Median: NR - Range: 3.3-16.3 years **Sex:** - Female: NR - Male: NR **Race/ethnicity:** NR **JIA diagnosis:** Polyarticular JIA **Baseline severity:** Active joint count: Etanercept: 10 (5-19) Infliximab: 13 (6-21) Duration of disease: At least 1 year **Percentage with uveitis:** NR **Inclusion criteria:** Refractory to standard treatment for 1 year **Exclusion criteria:** NR	**1) Active joint count:** Etanercept: -9.5 (95% CI -19 to -3) Infliximab: -11.5 (95% CI -17 to -7.5) P = 0.74 **2) Quality of life/functional status:** CHAQ: Etanercept -0.81 (95% CI -1.44 to -0.19) Infliximab: -0.31 (95%CI -0.75 to -0.25) P = 0.12 **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** - Physician: Etanercept: -29 (95% CI -52 to -14.5) Infliximab: -35 (95% CI -50.5 to -23.5) P = 0.65 - Patient/Parent: Etanercept: -24.5 (95% CI-50.5 to -7.0) Infliximab: -27.5 (95%CI -47.5 to -12) P = 0.81 ACR Paediatric 50: Etancercept: 3 mo (90%), 6 mo (89%), 12 mo (89%) Infliximab: 3 mo(67%) , 6 mo (83%), 12 mo (78%) ACR Paediatric 75: Etancercept: 3 mo (60%), 6 mo (78%), 12 mo (67%) Infliximab: 3 mo(50%) , 6 mo (58%), 12 mo (67%) **5) Laboratory measures of inflammation:** - ESR: Etancercept: -28.5 (95% CI -51.5 to -15)	**General comments:** - Drug switching makes it hard to interpret the effect of the drugs individually - Not much reported on the subjects **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Poor - Comments: No funding source reported, assessment not masked *Adverse events:* - Overall rating: Fair - Comments: No validated AE measure, no funding source reported **Applicability:** Outcomes measured prospectively

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Study duration: 12 months **Primary outcome(s):** ACR Paediatric 50 and 75 **Secondary outcome(s):** Components of the ACR Paediatric instrument (ESR, number of active joints, number of swollen joints, parent/patient global assessment, doctor's global assessment, and CHAQ)		Infliximab: -25 (95%CI: -36 to -15) P = 0.37 **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: 0 - Inefficacy: NR - Intolerance/AEs: 3 in the infliximab group – infusion reaction with chest pain, dyspnea and urticaria which could not be controlled by slowing infusion or premedication 1 in infiximab group – possible macrophage activation syndrome 1 in infliximab group – alopecia 3 in the infliximab group switched to etanercept, which was tolerated **11) Mortality:** None **12) Adverse events reported?:** Yes	
Lovell, Giannini, Reiff, et al., 2000 **#721** **AND**	**Geographical location:** Multiple sites in US and Canada **Study dates:** NR **Funding source:** Supported by Immunex Corporation, Seattle, which provided the study drug and grants to investigational	**Number of patients:** N = 69 - Screened for inclusion: NR - Eligible for inclusion: NR - Enrolled in lead-in phase: 69 - Completed lead-in phase: 64 - Enrolled in RCT phase: 51 - Began treatment: 51 - Completed treatment: 40 - Withdrawals/losses to followup:	**1) Active joint count:** Placebo N = 26 / Etanercept N = 25 Baseline: 27.0 / 32.0 3 mo: 37.5 / 13.0 7 mo: 13.0 / 7.0 **2) Quality of life/functional status:** CHAQ score:	**General comments:** - Well designed, executed, and reported study - Some potential for conflict of interest **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Lovell, Giannini, Reiff, et al., 2003 **#547**	sites; by the Children's Hospital Foundation of Cincinnati; and by grants from the National Institutes of Health (AR42632 and AR44059-P60 MAMDC). **Setting:** NR **Study design:** RCT, multicenter, double-blind, with open-label lead-in and RCT phases (Lovell et al. #721) and ongoing open-label extension phase with 58 patients (Lovell et al. #547) **Intervention(s):** - DMARD name: Etanercept - Dose: 0.4 mg/kg (up to 25 mg) subcutaneously twice weekly, until disease flare occurred or 4 months elapsed - N: 25 **Comparator(s):** Placebo - N: 26 **Were additional arthritis medications allowed?:** Yes: - MTX was discontinued 14 days and other DMARDs 28 days before start of treatment with etanercept - Intraarticular and soft-tissue corticosteroid injections not permitted during or for 1 month prior to the trial - Stable doses of NSAIDs or low doses of corticosteroids	Lead-in phase: 5/69 (1 AE, 2 withdrew consent, 2 lack of response) RCT phase, etanercept: 6/25 (24%) withdrew because of disease flare RCT phase, placebo: 18/26 (69%) withdrew because of disease flare, and 1 because of parental withdrew consent - Enrolled in open-label extension phase: 58 - Included in analysis of extension phase: 48 - Withdrawals from extension phase: 10 (suboptimal response 7; lost to followup 1; AEs 1; remission 1) **Age:** - Mean (SD): 10.5 (SD NR) - Range: 4-17 years **Sex:** - Female: 43 (62%) - Male: 26 (38) **Race/ethnicity:** White: 52 (75%) Black: 6 (9%) Hispanic: 9 (13%) Other: 2 (3%) **JIA diagnosis:** JRA Lead-in phase, n (%): - Pauciarticular: 7 (10) - Polyarticular: 40 (58) - Systemic: 22 (32)	Placebo N = 26 / Etanercept N = 25 Baseline 1.3 / 1.6 3 mo 0.4 / 0.9 7 mo 1.2 / 0.8 Lead-in phase: 37% median improvement in scores seen for all patients RCT phase: 54% mean improvement in etanercept vs. no change in placebo group (p = 0.01) **3) Number of joints with limited range of motion:** Placebo N = 26 / Etanercept N = 25 Baseline 6.5 / 8.0 3 mo 1.0 / 2.0 7 mo 4.5 / 1.0 **4) Global assessment of current status:** Physician's global assessment of disease severity: Placebo N = 26 / Etanercept N = 25 Baseline 6 / 7 3 mo 1 / 2 7 mo 5 / 2 Patient's or parent's global assessment of overall well-being: Placebo N = 26 / Etanercept N = 25 Baseline 5 / 5 3 mo 1 / 2 7 mo 5 / 3 **5) Laboratory measures of inflammation:**	*Adverse events:* - Overall rating: Good **Applicability:** No significant issues

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	permitted, at discretion of clinician - Pain meds allowed except during the 12 hours before joint assessment **Study duration:** Lead-in phase: 3 months RCT phase: 4 months **Primary outcome(s):** Number of patients with disease flare, defined as worsening of ≥ 30% in 3 of 6 response variables, with improvement of ≥ 30% in no more than 1 variable **Secondary outcome(s):** Assessments at screening, baseline, day 15, and at the end of each month, with final safety assessment 30 days after discontinuation of study drug	RCT phase, n (%): - Pauciarticular: 3 (6) - Polyarticular: 31 (61) - Systemic: 14 (56) **Baseline severity:** Active joint count: 28 Duration of disease: 5.9 years **Percentage with uveitis:** NR **Inclusion criteria:** - 4-17 years of age - Polyarticular JRA - Had active disease despite treatment with NSAIDs and with methotrexate at doses of at least 10 mg per square meter of body-surface area per week - Had normal or nearly normal platelet, white-cell, and neutrophil counts, hepatic amino-transferase levels, and results of renal-function tests **Exclusion criteria:** - Pregnant or lactating females (girls with childbearing potential were required to use contraception throughout the study) - Major concurrent medical conditions	- ESR: Placebo N = 26 / Etanercept N = 25 Baseline: 27 / 41 3 mo: 12 / 15 7 mo: 30 / 18 - CRP: Placebo N = 26 / Etanercept N = 25 Baseline: 1.8 / 3.5 3 mo: 0.3 / 0.2 7 mo: 3.5 / 0.4 "In the double-blind study as compared with the end of the open-label study, a significant proportion of patients who received placebo had shifts from normal levels of CRP and ESR to above-normal values (p ≤ 0.03 for each variable)." **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** - Visual analog scale (0 = best, 10 = worst): Placebo N = 26 / Etanercept N = 25 Baseline: 3.5 / 3.5 3 mo: 0.3 / 1.3 7 mo: 3.5 / 1.5 **8) Clinical remission:** NR **9) Flare of disease:** RCT phase: Placebo: 21 (81%) Etanercept: 7 (28%) P = 0.003	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			Rates of flare remained consistently and significantly lower in the etanercept group (p < 0.001) after adjustment for the effects of baseline characteristics. Median time to flare was > 116 days in the etanercept group, and 28 days in the placebo group (p < 0.001). **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: 2/69 (3%) in lead-in phase - Intolerance/AEs: 1/69 (2%) in lead-in phase **11) Mortality:** None **12) Adverse events reported?:** Yes **13) Other:** Definition of improvement: 30% improvement from baseline on ≥ 3 of 6 core variables, with 30% worsening on no more than 1 variable 51/69 (74%) met the definition of improvement at the end of the lead-in phase. 44 (64%) and 25 (36%) met ACR Pedi 50 and ACR Pedi 70 response criteria, respectively At the end of the RCT phase, 18 patients (72%) in the etanercept group and 6 patients (23%) in the placebo group met ACR Pedi 50 criteria for response	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Lovell, Ruperto, Goodman, et al., 2008 **#100**	**Geographical location:** Multiple centers in US, Italy, France, Czech Republic, Belgium, Germany, and the Slovak Republic **Study dates:** Lead-in and RCT phases, Sep 2002 to Jan 2005; ongoing extension phase **Funding source:** Supported by a research grant from Abbott Laboratories **Setting:** NR **Study design:** RCT, double-blind, placebo-controlled, multicenter, medication-withdrawal study, with lead-in, RCT, and extension phases Random allocation, stratified by MTX use (never received MTX vs. discontinued MTX > 2 weeks before) Patients achieving ACR Pedi 30 response at 16 weeks of the lead-in phase entered RCT phase **Intervention(s):** - DMARD name: Adalimumab - Dose: Based on body-surface area during first part of extension phase; in later part, fixed dose given (20 mg for patients weighing < 30 kg, and 40 mg for	**Number of patients:** N = 171 (85 on MTX, 86 not on MTX) - Screened for inclusion: 196 - Eligible for inclusion: 171 - Open-label lead-in phase: 171 (85 on MTX, 86 not on MTX) - Completed lead-in phase: 160 (83 on MTX, 77 not on MTX) - Began treatment in RCT phase: 133 (75 on MTX, 58 not on MTX) - Completed RCT phase: 128 (71 on MTX, 57 not on MTX) - Entered extension phase: 128 - Withdrawals/losses to followup: Before RCT phase: 38 During RCT phase: 5 **Age:** - Mean (SD): MTX: 11.4 (3.3) No MTX: 11.1 (3.8) - Range: 4-17 years **Sex:** - Female: MTX: 68 (80%) No MTX: 67 (78%) - Male: MTX: 17 (20%) No MTX: 19 (22%) **Race/ethnicity:** White: MTX: 81 (95%) No MTX: 76 (88%) Black: MTX: 0 (0%) No MTX: 3 (3%) Other:	**1) Active joint count:** NR **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** - Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation:** - ESR: NR - Other: CPR measured but NR **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** Defined as > 30% worsening in ≥ 3 of 6 core criteria for JRA and improvement of ≥ 30% in no more than 1 criteria No. of disease flares during RCT phase: Sub-group | Placebo | Adalim | P value MTX | 24/37 (65%) | 14/38 (37%) | 0.02 No MTX | 20/28 (71%) | 13/30 (43%) | 0.03 **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: NR	**General comments:** - Very well designed, executed, and reported study - Potential for conflict of interest, given the funding source and the authors' relationships with industry - Allocation concealment not specified **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good *Adverse events:* - Overall rating: Good **Applicability:** No significant issues

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	patients weighing ≥ 30 kg) During lead-in phase: 24 mg/m^2 (up to 40 mg) subcutaneously every other week for 16 weeks - Titration: As above - N: 68 **Comparator(s):** Placebo - N: 65 **Were additional arthritis medications allowed?:** Yes: - Patients taking MTX were at a stable dose of at least 10 mg/m^2/week for 3 months and continued through lead-in and RCT phases - NSAIDs, low-dose corticosteroids, or pain meds given at the discretion of clinician/investigator **Study duration:** 16-week open-label lead-in phase, 32-week RCT withdrawal phase, and ongoing open-label extension phase **Primary outcome(s):** Percentage of patients not receiving MTX who had a disease flare during the RCT phase **Secondary outcome(s):** - ACR Pedi 30, 50, 70, 90, and 100 responses - Safety evaluated on basis of physical exams, lab results, vital	MTX: 4 (5%) No MTX: 7 (8%) **JIA diagnosis:** JRA, polyarticular **Baseline severity:** Active joint count: - MTX: 15.0 - No MTX: 19.4 Duration of disease, in years: - MTX, placebo: 4.0 - MTX, adalimumab: 4.3 - No MTX, placebo: 2.9 - No MTX, adalimumab: 3.6 **Percentage with uveitis:** NR **Inclusion criteria:** - Age 4-17 years - Polyarticular JRA with active disease - Inadequate response to NSAIDs - Either previously treated with MTX or had AEs or no response to MTX **Exclusion criteria:** - Hematologic, hepatic, or renal abnormalities - Ongoing infection or recent severe infection - Recently vaccinated - Previously treated with IVIG, cytotoxic agents, investigational agents, DMARDs other than MTX, or corticosteroids administered IV, IM, or	During lead-in phase, 1/85 patients (1%) in the MTX stratum and 2/86 (2%) in the no MTX stratum withdrew because of an AE, and 5/85 (6%) in the no MTX stratum withdrew because of lack of efficacy During the RCT phase, 1/133 (1%) withdrew consent, and 4/133 (3%) withdrew for other reasons **11) Mortality:** None **12) Adverse events reported?:** Yes **13) Other:** ACR 30: "The patients improved according to all levels of ACR Pedi response during the open-label lead-in phase." "More patients treated with adalimumab than patients treated with placebo had ACR Pedi 30, 50, 70, or 90 responses in both the methotrexate stratum and the stratum not receiving MTX." "During the open-label extension phase, ACR Pedi responses were sustained during 2 years of treatment. After 104 weeks of treatment, 40% of patients had an ACR Pedi 100 response."	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	signs, and AEs	intraarticular		
Opper-mann and Mobius, 1994 **#937**	**Geographical location:** Cottbus, Germany **Study dates:** NR **Funding source:** NR **Setting:** NR **Study design:** Nonrandomized comparative study **Intervention(s):** - DMARD name: Alphaglobulin (AG) - Dose: 400 mg IG/kg daily x 5 days; repeated 3 days each month for 6-8 months - Titration: None - N: 8 **Comparator(s):** - DMARD name: Methylprednisolone (MP) - Dose: 30 mg/kg (max 1.0 g/pulse) x 3 days; pulses repeated monthly for 6-8 months - Titration: None - N: 12 **Were additional arthritis medications allowed?:** Yes: - NSAIDS continued - Methotrexate 10 mg/m^2/week - Glucocorticosteroids ≤ 0.2 mg/kg body weight/day – given on alternate days	**Number of patients:** N = 20 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: NA - Began treatment: 20 - Completed treatment: NR - Withdrawals/losses to followup: NR **Age:** - Range: 2-15 years **Sex:** NR **Race/ethnicity:** NR **JIA diagnosis:** JCA **Baseline severity:** Active joint count: NR Duration of disease: NR **Percentage with uveitis:** NR **Inclusion criteria:** PJCA or SJCA, characterized by high inflammatory activity of the rheumatic process **Exclusion criteria:** NR	**1) Active joint count:** NR **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** - Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation: (Estimated from graph)** - ESR: MP: Baseline 59, 6 months 21 AG: Baseline 61, 6 months 24 **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: NR **11) Mortality:** NR **12) Adverse events reported?:** No	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Poor - Comments: Open-label, nonrandomized, analyses not adjusted for baseline differences, patients not adequately described *Adverse events:* - Overall rating: NA - Comments: AEs not reported **Applicability:** Not USA

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Study duration: Unclear, likely 6-8 months **Primary outcome(s):** NR **Secondary outcome(s):** ESR, CD4, CD8 counts			
Prieur, Piussan, Manigne, et al., 1985 **#1212**	**Geographical location:** France **Study dates:** NR **Funding source:** Supported by Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés **Setting:** Outpatient or 3 specialized centers **Study design:** RCT, double-blind **Intervention(s):** - DMARD name: D-penicillamine - Dose: 5 mg/kg/day x 2months - Titration: Increased to 10 mg/kg/day x 4 months - N: 38 **Comparator(s):** Placebo; N = 36 **Were additional arthritis medications allowed?:** Yes: Pyridoxine hydrochloride 10 mg/kg/day **Study duration:** 6 months	**Number of patients:** N = 74 (DP 38, placebo 36) - Screened for inclusion: NR - Eligible for inclusion: 74 - Randomized: 74 - Began treatment: 74 - Completed treatment: 55 - Withdrawals/losses to followup: 12 (4/8) Analysis complete on 70 (2 misdiagnosed not included) **Age:** - Mean (SD): DP: 8.2 (3.9) Placebo: 9.8 (3.9) - Range: 3-18 years **Sex:** - Female: 51 (68.9%) - Male: 23 (31.1%) **Race/ethnicity:** NR **JIA diagnosis:** Polyarticular JCA or pauciarticular JCA (but with polyarticular course) or systemic onset JCA	**1) Morning stiffness (minutes, mean [SD]):** Drug / Time 0 / Final DPN / 47.5 (36.2) / 26.8 (38.7) Placebo / 48.2 (32.5) / 37.2 (43.8) **2) Number of painful joints (mean [SD]):** Drug / Time 0 / Final DPN / 6.3 (5.5) / 3.3 (3.8) Placebo / 7.6 (5.3) / 5.5 (5.5) **3) Number of inflamed joints (mean [SD]):** Drug / Time 0 / Final DPN / 5.2 (5.2) / 2.5 (3.4) Placebo / 2.6 (2.7) / 1.7 (2.1) **4) Number of stiff joints (mean [SD]):** Drug / Time 0 / Final DPN / 11.7 (9.0) / 8.5 (7.9) Placebo / 10.6 (7.5) / 11.1 (9.2) **5)Severity of pain (mean [SD]):** Drug / Time 0 / Final	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Fair - Comments: Outcome measures not validated, patients in placebo group may have had worse disease *Adverse events:* - Overall rating: Good **Applicability:** Outdated medication

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Primary outcome(s): - Functional Steinbrocker class - Duration morning stiffness (minutes) - Number of painful joints - Number of inflamed joints - Number of stiff joints - Sum of severity of pain - Sum of severity of inflammation - Sum of severity of stiffness - Consumption of steroids and --- - ASA - ESR	**Baseline severity:** Number of inflamed joints: DPN: 10.5 (± 6.5) Placebo: 13.9(± 19.1) Duration of disease: DPN: 3.1 (± 2.3) Placebo: 4.2 (±3.3) **Percentage with uveitis:** NR **Inclusion criteria:** - Met previously established diagnostic criteria - At least 2 of the following inflammatory criteria: erythrocyte sedimentation rate (ESR) > 25 mm/hour, serum fibrinogen > 400 mg/dL, and elevation (> 2 SD) of IgG, IgA, or IgM **Exclusion criteria:** - Persistence of systemic extraarticular symptoms (mainly spiking fever) during the previous 6 months - Arthritic involvement of < 4 joints - Use of NSAIDs not authorized for pediatric use in France - Systemic corticosteroid therapy > 0.5 mg/kg/day of prednisone or the equivalent -Use of SAARD during the previous 3 months - Any modification of treatment (including physiotherapy) during the past month - Presence of renal, blood, or hepatic disorders during the previous 6 months	DPN 7.2 (5.8) 3.6 (4.2) Placebo 8.3 (6.6) 6.5 (6.3) **6) Functional class 3-4 (time 0/final):** DPN: 9/4 Placebo: 6/6 **7) Remissions (time final):** DPN: 7 Placebo: 4 **8) ESR (mean [SD]):** Drug / Time 0 / Final DPN / 49 (32) / 31 (26) Placebo / 41 (26) / 33 (23) **9) Physician/parent/patient assessment** Not completed by all **10) Discontinuation of DMARD due to:** - Remission of disease: 0 - Inefficacy: 1 - Intolerance/AEs: 2 **11) Mortality:** NR **12) Adverse events reported?:** Yes Cytopenia (1) Rash/mouth ulcers (1)	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- History of penicillin allergy		
Riddle, Ryser, Morton ,et al., 2006 **#313**	**Geographical location:** Dallas, Texas **Study dates:** NR **Funding source:** NR **Setting:** Hospital specializing in pediatric rheumatological conditions **Study design:** Nonrandomized comparative study **Intervention(s):** - DMARD name: Methotrexate (MTX) - Dose: NR - Titration: NR - N: 20 **Comparator(s):** - NSAID, dose not specified, n = 22 - Methylprednisolone (MP) IV at time 1 and 4 months later; dose not specified, n = 20 **Were additional arthritis medications allowed?:** NR **Study duration:** 4 months **Primary outcome(s):** - Pediatric Quality of Life Inventory (PedsQL), version 4.0 -Generic Core Scales	**Number of patients:** N = 57 - Screened for inclusion: NR - Eligible for inclusion: 63 - Randomized: NA - Began treatment: 63 - Completed treatment: 57 - Withdrawals/losses to followup: **Age:** - Mean (SD): 8.1 (4.8) **Sex:** - Female: 44 (77.2%) - Male: 13 (22.8%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Baseline severity:** - Active joint count: Mean of 2.8 to 8.6 across groups - Duration of disease: NR **Percentage with uveitis:** NR **Inclusion criteria:** - Diagnosis of JIA - Beginning new medication treatment – NSAIDs, MTX, or steroids - Age 1-18 years **Exclusion criteria:** - Presence of any other major illness or disability, as determined by the pediatric	**1) Active joint count:** Baseline and 4-month mean (SD): NSAID: 2.8 (2.6), 2.0 (2.2) MTX: 8.1 (8.9), 4.1 (5.2) MP: 8.6 (7.3), 1.5 (2.5) F (2, 35) = 5.62, p = 0.008, MP greater percent improvement than other two treatments **2) Quality of life/functional status:** - Generic PedsQL Total Score (Parent report) – Baseline and 4-month mean (SD): NSAID: 76.1 (16.8), 77.5 (17.5) MTX: 69.7 (13.3), 74.7 (15.0) MP: 44.9 (19.4), 72.0 (18.9) Time*Medication F(10, 58) = 2.36, p = 0.02; MP greater percent improvement than other two treatments - Rheumatology PedsQL Total Score (Parent Report) – Baseline and 4-month mean (SD): NSAID: 70.8 (23.5), 75.7 (20.5) MTX: 60.3 (16.9), 71.9 (14.7) MP: 45.9 (19.2), 74.2 (20.1) Time*Medication F(10, 52) = 2.86, p = 0.007; MP greater percent improvement than other two treatments **3) Number of joints with limited range of motion:** Baseline and 4-month mean (SD): NSAID: 3.7 (8.0), 3.1 (7.3) MTX: 7.9 (8.5), 4.3 (6.4) MP: 9.5 (9.3), 3.5 (6.9) **4) Global assessment of current status:**	**General comments:** Patient reports of HRQOL also given **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Poor - Comments: Confounding by indication; analysis adjusts only for baseline scores and not other potential confounders; outcomes not assessed blind to treatment condition; patients not blind to treatment assignment *Adverse events:* - Overall rating: Fair - Comments: Outcomes not assessed blind to treatment condition; patients not blind to treatment assignment **Applicability:** Poor

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- Rheumatology Module, version 3.0 **Secondary outcome(s):** - Adverse effects - Joint counts - ESR - Global assessment	rheumatologist - Lack of proficiency in the English language prohibiting the administration of study questionnaires	- Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation:** ESR – Baseline and 4-month mean (SD): NSAID: 22.6 (22.7), 22.1 (21.3) MTX: 40.2 (30.6), 27.7 (23.4) MP: 77.3 (32.3), 19.3 (18.8) F (2, 35) = 12.3, p = 0.001, MP greater percent improvement than other two treatments **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** Reported only as a subscale of Rheumatology PedsQL **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: NR **11) Mortality:** NR **12) Adverse events reported?:** Yes	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Ruperto, Lovell, Cuttica, et al., 2007 **#188**	**Geographical location:** 34 sites in North America (9), South America (3), and Europe (22) **Study dates:** Oct 2001 to Apr 2004 **Funding source:** Centocor, Inc. **Setting:** NR **Study design:** RCT, Phase III, international, multicenter, double-blind, placebo-controlled, with double-blind all active treatment extension **Interventions:** DMARD name: Infliximab plus methotrexate Dose: 3 mg/kg Titration: None N: 60 **Comparator:** Placebo + methotrexate for 14 weeks, followed by Inliximab 6 mg/kg plus MTX in weeks 14-52 N: 62 **Were additional arthritis medications allowed:** Yes: Methotrexate 10-15 mg/m^2/week oral or parenteral; other drugs (NSAIDs, opioids, corticosteroids) given at the discretion of the clinician/investigator	**Number of patients:** N = 122 - Screened for inclusion: NR - Eligible for inclusion: 122 - Randomized: 122 - Began treatment: 122 - Completed treatment: 109 - Withdrawals/losses to followup: 13 (11%) **Age:** Mean (SD): 6 mg/kg: 11.0 (±4.0) 3 mg/kg: 11.3 (±4.0) Range: ≥ 4 to < 18 **Sex:** Female: 6 mg/kg: 49(79.0%) 3 mg/kg: 53(88.3%) Male: 6 mg/kg: 13 (21.0%) 3 mg/kg: 7 (11.7%) **Race/ethnicity:** White: 6mg/kg: 53(88.3%) 3 mg/kg: 50(83.3%) Other: 6 mg/kg: 9 (11.7%) 3 mg/kg: 10 (16.7%) **JIA diagnosis:** JRA Systemic onset: 6 mg/kg: 8 (13.1%) 3 mg/kg: 11 (18.3%) Pauciarticular onset, then polyarticular:	**1) Active joint count:** "At week 14, the number of joints with active arthritis differed significantly between patients in the infliximab 3 mg/kg group and those in the placebo group (p = 0.016), whereas there were no significant differences for the other core set variables." **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** - Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation:** - ESR: NR - Other: NR **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** 0 active joints at 52 weeks: Infliximab 3mg/kg: 26/59 (44.1%) Placebo then Infliximab 6 mg/kg: 25/58 (43.1%) **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: 9 patients infliximab, 1 placebo + MTX	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Fair - Comments: Results inconsistently, incompletely, and inadequately reported *Adverse events:* - Overall rating: Fair Comments: Results inconsistently, incompletely, and inadequately reported **Applicability:** Good

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Study duration: 52 weeks **Primary outcome:** Proportion meeting ACR Pedi 30 criteria at week 14 **Secondary outcome:** - Improvement > 50% and > 70% on Pedi 50 and Pedi 70 - At week 52, number of joints with active disease	6 mg/kg: 15 (24.6%) 3 mg/kg: 13 (21.7%) Polyarticular: 6 mg/kg: 38 (62.3%) 3 mg/kg: 36 (60%) **Baseline severity:** Duration of disease (mean years ± SD): 6 mg/kg: 3.6 (± 3.4) 3 mg/kg: 4.2 (±3.6) Active joint count (mean ± SD): 6 mg/kg: 18.5 (± 11.5) 3 mg/kg: 19.5 (± 12.3) Rheumatoid factor + (n [%]): 6 mg/kg: 14 (23.7%) 3 mg/kg: 13 (21.7%) **Percentage with uveitis:** 0% **Inclusion criteria:** - Age ≥ 4 years and < 18 years - JRA - Suboptimal response to MTX after ≥ 3 months - ≥ 5 active joints - No active systemic symptoms **Exclusion criteria:** - Active uveitis - Serious infection, including tuberculosis - Malignancy - Prior treatment with TNF inhibitor	**11) Mortality:** 2 deaths (1 placebo + MTX, 1 Infliximab) **12) Adverse events reported?:** Yes **13) Other:** ACR30 (primary study outcome) Week 14: Infliximab 3 mg/kg: 37/58 (63.8%) Placebo + MTX: 29/59 (49.2%) Week 52 (all patients): Pedi 50: 78/112 (69.9%) Pedi 70: 58/112 (51.8%) No significant differences between study groups "By the end of the study, following crossover of placebo-treated patients to infliximab 6 mg/kg, improvement in the JRA core set components was comparable between the treatment groups."	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Ruperto, Lovell, Quartier, et al., 2008 **#102**	**Geographical location:** Europe, Latin America, USA **Study dates:** Feb 2004-June 2006 **Funding source:** Bristol-Myers Squibb **Setting:** Pediatric rheumatology centers **Study design:** Open-label run-in followed by RCT **Intervention(s):** Open label: Abatacept 10mg/kg (max 1000 mg) on days 1, 15, 29, 57, and 85 of the 4-month open-label period Subjects who met ACR-Ped 30 were randomized to abatacept or placebo Abatacept 10mg/kg in 28-day intervals for 6 months or until a flare **Comparator(s):** Placebo (for RCT) **Were additional arthritis medications allowed?:** Methotrexate (if stable on it), folinic or folic acid, stable oral corticosteroids (10 mg/day or 0.2 mg/kg/day, whichever less), NSAIDs or analgesics for pain	**Number of patients:** - Screened for inclusion: 214 - Eligible for inclusion: 190, of whom 170 enrolled in open-label trial - Randomized: 123 (based on response in open-label trial) - Began treatment: 122 - Completed treatment: 42 discontinued because treatment not effective - Withdrawals/losses to followup: 1 withdrew consent; 80 completed all visits in the 6-month double-blind period **Age:** Mean (SD) for the double-blind period: Abatacept (n = 60): 12.6(3) Placebo (n = 62): 12.0 (3) Overall age range: 6-17 years **Sex:** For the double-blind period Abatacept: - Female: 72% - Male: 28% Placebo: - Female: 73% - Male: 27% **Race/ethnicity:** For the double-blind period Abatacept: - White: 77% - Black: 8% - Other: 15% Placebo:	**1) Active joint count:** At the end of the RCT (mean [SD]): Abatacept: 4.4 (7.0) Placebo: 6.0 (5.8) P = 0.02 **2) Quality of life/functional status:** CHAQ (mean [SD]): Abatacept: 0.8 (0.9) Placebo: 0.7 (0.6) P = 0.04 **3) Number of joints with limited range of motion (mean [SD]):** Abatacept: 8.8 (12.8) Placebo: 8.6 (12.0) P = 0.01 **4) Global assessment of current status:** By physician (mean [SD]): Abatacept: 14.7 (18.9) Placebo: 12.5 (12.5) P < 0.01 By patient/parent (mean [SD]): Abatacept: 17.9 (22.2) Placebo: 23.9 (21.6) P = 0.70 **5) Laboratory measures of inflammation:** ESR (mean [SD]): Abatacept: 25.1 (26.4) Placebo: 30.7 (30.1) P = 0.96 C-reactive protein (mean [SD]): Abatacept: 0.16 (0.25) Placebo: 0.29 (0.54) P = 0.03	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good - Comments: Potential funding conflict *Adverse events:* - Overall rating: Good - Comments: Potential funding conflict **Applicability:** Good

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	control **Study duration:** 4 months (open-label), then 6 months (RCT); study also reports a 5-year open-label followup after the RCT component **Primary outcome(s):** Time to flare (30% or more in at least 3 of 6 core variables, with at least 30% improvement in no more than 1 variable) **Secondary outcome(s):** ACR Pediatric 30, 50, 70, and 90	- White: 79% - Black: 7% - Other: 15% **JIA diagnosis:** JIA **Baseline severity:** For the double-blind period (mean [SD]): Active joint count: Abatacept: 18.2 (11.5) Placebo: 14.7 (12.8) Duration of disease: Abatacept: 3.8 (3.7) years Placebo: 3.9 (3.5) years CHAQ disability index: Abatacept: 1.3 (0.7) Placebo: 1.2 (0.8) Parent global assessment: Abatacept: 41.8 (22.5) Placebo: 39.9 (24.7) ESR: Abatacept: 31.4 (27.7) Placebo: 30.8 (26.9) **Percentage with uveitis:** None **Inclusion criteria:** - 6-17 years - JIA - At least 5 active joints - Active disease (at least 2 active joints and 2 joints with limited ROM) - Inadequate response to or intolerance to at least one DMARD (including etanercept,	**6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** Inactive disease in 30% of abatacept vs. 11% controls (p = 0.02) **9) Flare of disease:** By ACR Pediatric 30 criteria, after 6 months of RCT or time of flare for those who did not complete, 82% in the abatacept improved compared with 69% in the placebo (p = 0.17) By ACR Ped 50, 77% in abatacept improved, compared with 52% in controls (p < 0.01) By ACR Ped 70, 53% in abatacept improved, compared with 31% placebo (p = 0.02) By ACR Ped 90, 40% in abatacept improved, compared with 16% in placebo (p < 0.01) **10) Discontinuation of DMARD due to:** - Remission of disease: None during RCT - Inefficacy: 10 - Intolerance/AEs: None during RCT **11) Mortality:** None **12) Adverse events reported?:** Yes During the run-in: 25 headache (13%), 19 nausea (10%), 17 cough (9%), 17 diarrhea	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		infliximbab, adalimumab) **Exclusion criteria:** - Active uveitis - Major concurrent medical conditions - Pregnant or lactating - No live vaccine within 3 months of the first dose of study medication - Intraarticular injections 4 weeks before enrollment or throughout the trial	(9%), 14 upper respiratory tract infection (7%), 12 fever (6%), 8 infusional AEs During the RCT: No serious AEs for those with abatacept	
Silverman, Cawkwell, Lovell, et al., 1994 **#914**	**Geographical location:** US **Study dates:** NR **Funding source:** Baxter HealthCare, American Red Cross, Children's Hospital Research Foundation of Cincinnati, The Arthritis Foundation **Setting:** 9 sites in the US **Study design:** RCT **Intervention(s):** - DMARD name: IVIG - Dose: 1.5 g/kg, max 75 g every 2 weeks for the first 2 months then monthly for an additional 4 months - Titration: NR - N: 14 **Comparator(s):**	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 31 - Began treatment: NR - Completed treatment: 15 - Withdrawals/losses to followup: 1 dropout in placebo group, 1 placebo who did not meet eligibility criteria, 6 in each group because treatment insufficient, 1 in placebo for logistical reasons, 1 due to AE (noninfectious hepatitis) **Age:** IVIG - Mean (SD): 8.85 (1.3) - Median: 8.32 Placebo - Mean (SD): 9.07 (1.2) - Median: 8.53 **Sex:**	**1a) Active joint count (mean change [SE], median):** IVIG: 3 (5), -2 Placebo: 1.5 (3.6), -1 **1b) Overall severity (mean change [SE], median):** IVIG: 21.4 (26.5), -5.5 Placebo: 5.1 (18.9), -18 **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** By physician: 50% of the IVIG and 27% of the placebo improved (p > 0.3) By patient/parent: NR **5) Laboratory measures of inflammation:** NR **6) Radiographic evidence of progression**	**General comments:** - Small sample size led to heterogeneity - High dropout rate (50%) **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Poor. - Comments: Method not described or validated; small sample size *Adverse events:* - Overall rating: Poor - Comments: Rating was used to assign likelihood that the AE was related to IVIG; no AE data reported for the placebo group **Applicability:** Poor (small sample size)

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Placebo N: 17 **Were additional arthritis medications allowed?:** Yes: - No more than 2 NSAIDs and up to 2 SAARDs – NR whether these were given per protocol or at the discretion of the clinician/ investigator; - Corticosteroids: 2 arms, either no steroids or steroid tapering, given per protocol **Study duration:** 6 months **Primary outcome(s):** Physician's global assessment **Secondary outcome(s):** - Joint count - Hemoglobin - Albumin - Platelet count - ESR	IVIG - Female: 5 - Male: 9 Placebo - Female: 7 - Male: 10 **Race/ethnicity:** NR **JIA diagnosis:** Systemic JRA **Baseline severity:** Active joint count: IVIG: 11.8 (3.2) Placebo: 16.8 (3.5) Duration of disease: IVIG: 1.55 (0.8) years Placebo: 1.89 (0.5) years Sum of severity scores for swelling, pain on motion, tenderness, and limitation of motion: IVIG: 48.1 (11.1) Placebo: 78.5 (17.4) **Percentage with uveitis:** NR **Inclusion criteria:** - Active, refractory systemic JRA, - At least 1 day of fever of 38.5 or greater within 30 days before enrollment - At least 1 of the following: Hb < 10.5 g/dL, albumin < 35 mg/dL, ESR > 20 mm/h, platelet count > 450,000 - Active articular disease	**of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: None - Inefficacy: 6 in each group - Intolerance/AEs: 1 (IVIG) **11) Mortality:** None **12) Adverse events reported?:** Yes 4 patients in IVIG group had 10 AEs, of which 6 were considered probably or possibly treatment-related. 9/10 were chills, fever, emesis, or headache; 1 was hepatitis. Most AEs were infusion-related.	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Exclusion criteria: Intraarticular steroids		
Silverman, Mouy, Spiegel, et al., 2005 **#383**	**Geographical location:** Multinational **Study dates:** NR **Funding source:** Sanofi-Aventis **Setting:** NR **Study design:** RCT **Intervention(s):** - DMARD name: Oral leflunomide - Dose: if < 20 kg, 100 mg loading x 1 day and then 10 mg every other day; if 20-40 kg, 100 mg loading x 2 days, then 10 mg daily; if > 40 kg, loading 100 mg x 3 days, then 20 mg daily **Comparator(s):** Oral methotrexate 0.5 mg/kg/week (max 25 mg), and placebo **Were additional arthritis medications allowed?:** Yes: Folic acid or folinic acid (everyone), NSAIDs, prednisone (in unchanged), up to 2 doses of intraarticular corticosteroid – all given at the discretion of the clinician/investigator **Study duration:**	**Number of patients:** - Screened for inclusion: 103 - Eligible for inclusion: 94 - Randomized: 94 - Began treatment: 47 in each group - Completed treatment: 86 completed 16-week study and 54 completed 48-week extension - Withdrawals/losses to followup: For the 16-week study, 3 in the methotrexate group withdrew (1 AE, 1 lack of efficacy, 1 lost), 5 in the leflunomide group withdrew (3 AEs, 1 lack of efficacy, 1 declined to take drug). For the extension, in the methotrexate group, 7 did not enroll (3 at nonparticipating site, 2 for lack of efficacy, 2 declined consent). In the leflunomide group, 9 did not enroll (4 at nonparticpating site, 4 lack of efficacy, 1 declined consent). **Age:** Leflunomide: - Mean (SD): 10.1 (4.0) - Median: 11 - Range: 3-17 Methotrexate: - Mean (SD): 10.2 (3.8) - Median: 11 - Range: 3-17	**1) Active joint count:** At 16 weeks: -8.1 in leflunomide group versus -8.9 in methotrexate group (NS) **2) Quality of life/functional status:** At 16 weeks: ACR Pedi 30 responses were 68% in leflunomide and 89% in methotrexate (p = 0.02) Median time to ACR Pedi 30 response was 52 days in leflunomide and 56 days in methotrexate group ACR Pedi 50 responses were 60% in leflunomide and 77% in methotrexate (p = 0.1) ACR Pedi 70 responses were 43% in leflunomide and 60% in methotrexate (p = 0.14) Mean percent improvement index -44.41 for leflunomide and -52.87 for methotrexate (p = 0.18) CHAQ: -0.44 in leflunomide group and -0.39 in methotrexate group Similar findings described for the extension **3) Number of joints with limited range of motion:** -5.2 in leflunomide group vs. -5.3 in methotrexate group (NS)	**General comments:** Lacks placebo group **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good - Comments: Percent improvement index lacks validation *Adverse events:* - Overall rating: Good **Applicability:** Good

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	16 weeks with an optional 32-week extension **Primary outcome(s):** - ACR Pedi 30 - Percent Improvement Index (mean of the percent changes from baseline in each core set of disease activity measures, with negative values indicating improvement and positive values set to 0 indicating no improvement) **Secondary outcome(s):** - Rates of ACR Pedi 50 and ACR Pedi 70 responses - Time to an ACR Pedi 30 response - Area under the curve analyses - Mean changes in the core set of disease activity measures and - C-reactive protein concentrations	**Sex:** Leflunomide: - Female: 75% - Male: 26% Methotrexate: - Female: 72% - Male: 28% **Race/ethnicity:** Leflunomide: - White: 87% - Black: 2% - Asian: 2% - Other: 9% Methotrexate: - White: 74% - Black: 4% - Asian: 0% - Other: 21% **JIA diagnosis:** JRA **Baseline severity:** Active joint count: - Leflunomide: 14.4 (7.9) - Methotrexate: 14.0 (9.9) Duration of disease: - Leflunomide: 1.69 (3.21) - Methotrexate: 1.37 (1.97) ESR: - Leflunomide: 30.8 (18.2) - Methotrexate: 34.5 (21.7) **Percentage with uveitis:** NR **Inclusion criteria:**	**4) Global assessment of current status:** Change at 16 weeks: By physician: Leflunomide -31.5, methotrexate -32.1 (overlapping 95% CIs) By patient/parent: Leflunomide -15.9 methotrexate -22.0 **5) Laboratory measures of inflammation:** ESR: Decrease in leflunomide group -6.5; decrease in methotrexate group -7.2 (non-significant) C-reactive protein: decreased -3.9 in leflunomide group vs. -11.4 in methotrexate group (p = 0.04) **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: 1 in methotrexate group and 1 in leflunomide group during the first 16 weeks; 2 in the methotrexate group during the extension; 4 in the leflunomide group during the extension - Intolerance/AEs: 1 in the methotrexate group during the first 16 weeks, 3 in the leflunomide group during the first 16 weeks **11) Mortality:** None **12) Adverse events reported?:** Yes	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Active polyarticular disease - Not received methotrexate or leflunomide - Sexually active female patients negative serum pregnancy studies throughout the study **Exclusion criteria:** - ACR Functional class IV disease - Active systemic symptoms within 4 weeks before entry - Persistent or severe infection within 3 months before entry - Inflammatory disease other then JRA or a history of such a disease	In the first 16 weeks leading to withdrawal: 1 methotrexate = LFT abnormalities 1 leflunomide = LFT abnormalities 1 leflunomide = parapsoriasis 1 leflunomide = Crohn's disease (not thought to be related) Other serious AEs Leflunomide: 1 with suspected salmonellosis None in the methotrexate group	
Smith, Thompson, Whitcup, et al., 2005 **#400**	**Geographical location:** Bethesda, MD **Study dates:** Sep 17,1999-Sep 28, 2001 (enrollment) **Funding source:** Immunex Corp **Setting:** NIH **Study design:** 1year duration – 2 phases: 1st phase: RCT, double-blind 2nd phase: Single arm, open-label Randomized 2:1 etanercept/placebo **Interventions:** DMARD name: Etanercept	**Number of patients:** N = 12 - Screened for inclusion: 24 - Eligible for inclusion: 12 - Randomized: 12 (7 to DMARD, 5 to placebo) - Began treatment: 12 - Completed treatment: 12 - Withdrawals/losses to followup: 0 **Age:** Mean (SD): 11 Median: 11 Range: 6-15 years **Sex:** Female: 9 (75%) Male: 3 (25%) **Race/ethnicity:** Hispanic: 4 (33.3%)	**1) Active joint count:** NR **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** - Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation:** NR **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR	**General comments:** - Uveitis patients only - Pilot study **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Fair - Comments: Small sample size; potential conflict from sponsor *Adverse events:* Fair - Comments: Small sample size; potential conflict from sponsor **Applicability:** All uveitis patients; only ophthalmic outcomes

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Dose: 0.4mg/kg twice weekly N: 7 **Comparator:** Placebo N: 5 **Were additional arthritis medications allowed:** Yes, if stable MTX and prednisone and at the discretion of the clinician/investigator **Study Duration:** 1 year **Primary outcome:** Ophthalmic outcomes: - Reduction of anterior chamber cells to 0 or trace while using steroids < 3x/day - 50% reduction in number or dose of other anti-inflammatory medication **Secondary outcomes:** - 10-letter change in best corrected visual acuity - 2-step change in anterior chamber cell count, vitreous haze, or anterior chamber cells - Presence of cystoid macular edema	Black: 1 (8.3%) White: 6 (50%) Pacific Islander: 1 (8.3%) **JIA diagnosis:** JRA **Baseline severity:** NR **Percentage with uveitis:** 100% **Inclusion criteria:** - 2-18 years of age - ACR criteria for JRA - Active uveitis - No change in arthritis meds for at least 8 weeks prior **Exclusion criteria:** - Media opacities - Periocular injections of steroids within 2 months - DMARD therapy except MTX or prednisone - Spondylarthropathy/enthesitis	**9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: 1 - Intolerance/AE: 0 **11) Mortality:** None **12) Adverse events reported?:** Yes **13) Ophthalmic outcomes:** Successful outcome: 6 months DMARD: 6/12 12 months DMARD: 4/7 6 months placebo: 2/5 Failures: 6 months DMARD: 1/12 12 months DMARD: 1/7 6 months placebo: 1/5	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Van Rossum, Fiselier, Franssen, et al., 1998 **#798**	**Geographical location:** 7 pediatric rheumatology centers in The Netherlands **Study dates:** Aug 1992 – Dec 1994 **Funding source:** NR **Setting:** Pediatric rheumatology centers **Study design:** RCT **Intervention(s):** - DMARD name: Sulfasalazine (SSZ) - Dose: 50 mg/kg/day in 2 doses; max 2000 mg/day - Titration: ¼ total dose, increased weekly by ¼'s until target dose reached. Dose could be modified to highest dose tolerated, but no less than 50% of initial prescribed dose. - N: 35 **Comparator(s):** Placebo, N = 34 **Were additional arthritis medications allowed?:** Yes - NSAIDS continued in type and dose - Corticosteroids (oral or intraarticular) and other DMARDS not permitted - Other therapy considered necessary for patient's welfare	**Number of patients:** N = 69 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 69 - Began treatment: 69 - Completed treatment: 52 - Withdrawals/losses to followup: 17 (1 excluded postrandomization, not eligible) **Age:** - Mean (SD): SSZ: 8.4 (4.4) Placebo 9.7 (3.6) - Range: SSZ: 2.5-17.6 Placebo: 2.5-15.1 **Sex:** - Female: SSZ: 23 (66%) Placebo: 23 (68%) - Male: SSZ: 12 (34%) Placebo: 11 (32%) **Race/ethnicity:** NR **JIA diagnosis:** JCA **Baseline severity:** Active joint count (median [range]): 5 (2-11) SSZ; 7 (3-12) PL **Percentage with uveitis:** NR **Inclusion criteria:** - Met EULAR criteria for	**1) Active joint count:** Mean (SEM) change (uncertain if this is baseline to 24 weeks or incorporates all assessments): SSZ: -5.54 (1.16) PL: -0.78 (1.22) P = 0.005 **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** Mean (SEM) change (uncertain if this is baseline to 24 weeks or incorporates all assessments): SSZ: -2.49 (1.12) PL: -1.97 (0.80) P = 0.64 **4) Global assessment of current status:** Mean (SEM) change (uncertain if this is baseline to 24 weeks or incorporates all assessments): By physician: SSZ: -1.95 (0.18) PL: -0.99 (0.19) P = 0.0002 By patient: SSZ: -0.92 (0.18) PL: -0.24 (0.18) P = 0.008 By parent: SSZ: -0.98 (0.14) PL: -0.44 (0.16) P = 0.010 **5) Laboratory measures of inflammation:**	**General comments:** Pain scores not reported, but number of painful joints reported **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good *Adverse events:* - Overall rating: Good **Applicability:** Non-USA

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	allowed at the discretion of the clinician/investigator **Study duration:** 24 weeks **Primary outcome(s):** Response, defined as ≥ 2 grade improvement in joint swelling severity score or score of 0 in ≥ 50% of joints involved at baseline and, if applicable, development of disease activity in ≤ 10% of the other joints, with the restriction that the number of deteriorated joints had to be ≤ 50% of the number of improved joints **Secondary outcome(s):** - Overall articular severity score (sum of swelling, tenderness/pain and limitation of movement scores) - Patient's general impression of disease activity (1-5) - Parent's general impression of disease activity (1-5) - Physician's general impression of disease activity (0-5) - ESR, C-reactive protein - Radiological evaluation	oligoarticular- or polyarticular-onset JCA - Age between 2-18 years, with onset of JCA before age 16 - At least 1 joint with active arthritis (defined as the presence of swelling or limitation of motion, with either pain on movement or tenderness) - An insufficient response to NSAID therapy at an optimal dosage for at least 3 months and, if applicable, to intraarticular corticosteroid injections - Intraarticular corticosteroid injections were not permitted 8 weeks prior to the start of the study - There was a 4-week washout period for DMARDs **Exclusion criteria:** - Previous treatment with SSZ - Known hypersensitivity to sulfa preparations or salicylates - Known glucose-6-phosphate dehydrogenase deficiency or porphyria - Leukopenia < $3.0a10^9$/L or granulopenia < $1.0x10^9$/L or thrombocytopenia < $100x10^9$/L - Liver transaminase levels more than twice the upper limit of normal - Renal impairment, defined as creatinine clearance < 90 mL/minute/$1.73m^2$ (determined as an elevated serum creatinine level more than 2 SD above the mean value for age)	ESR (mm/hour): SSZ: -0.74 (0.07) PL: -0.04 (0.08) P < 0.0001 - Other: CRP given **6) Radiographic evidence of progression of disease:** Mean number of improved joints: SSZ: 0.71 (range, 0-3) PL: 0.53 (range 0-3) P = NS **7) Pain control:** NR **8) Clinical remission ("response"):** Can be estimated from graph at multiple time points. At 24 weeks: SSZ: 69% (9% SEM) PL: 45% (9% SEM) No significant difference for oligoarticular- and polyarticular-onset patients. Pavia criteria for improvement: SSZ: 44% (9% SEM) PL: 21% (8% SEM) **9) Flare of disease:** NR **10) Discontinuation of DNRMARD due to:** - Remission of disease: NR - Inefficacy: 3 (all PL) - Intolerance/AEs: 10 (all on SSZ) **11) Mortality:** NR **12) Adverse events reported?:** Yes	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Unwillingness or inability of parent/children to adhere to the protocol - Females who might become pregnant and if sexually active, not practicing effective birth control	**13) Medication compliance:** > 80% for 83% of subjects	
Woo, Southwood, Prieur, et al., 2000 **#693**	**Geographical location:** UK and France **Study dates:** NR **Funding source:** Supported by Arthritis Research Campaign grant WO-120; MTX and placebo tablets provided by Lederle Laboratories **Setting:** NR **Study design:** RCT, double-blind, cross-over design **Intervention(s):** - DMARD name: Methotrexate - Dose: 15 mg/m^2 PO weekly - Titration: increase to 20 mg/m^2 after 2 months if no improvements in global - N: Goal 44 per group; actual 43 and 45 **Comparator(s):** Placebo **Were additional arthritis medications allowed?:** Yes: Prednisolone, steroid injections,	**Number of patients:** N = 88 - Screened for inclusion: NR - Eligible for inclusion: 88 - Randomized: 88 - Began treatment: 88 - Completed treatment: 79 - Withdrawals/losses to followup: 9 (7 from systemic group, 2 from EOA = extended oligoarticular arthritis) **Age:** - Mean ± SD (range): EOA: Male: 7.4 ± 3.0 (5.0-11.7) Female: 8.53 ± 3.43 (3.3-15.5) Systemic: Male: 8.5 ± 3.3 (3.7-14.1) Female: 8.0 ± 4.25 (2.5-15.7) **Sex (male):** EOA: 5 (12%) Systemic: 22 (49%) **Race/ethnicity:** NR **JIA diagnosis:** JIA: extended oligoarticular and systemic **Baseline severity:**	**1) Global assessment of current status:** When analyzed separately, no statistically significant differences between MTX and placebo; when combined, statistically significant improvement with MTX *Assessment by physician:* MTX (EOA/systemic): Very active: 28%/28%, -23/-15 Mildly active: 21/28%, +50/+43 Placebo (EOA/systemic) Very active: 24%/33%, -6/-14 Mildly active: 32/23%, +11/+10 P < 0.001 *Assessment by parent:* MTX (EOA/systemic): Very active: 29%/26%, -22/-15 Mildly active: 19/32%, +50/+35 Placebo (EOA/systemic): Very active: 29%/30%, -14/-19 Mildly active: 27/32%, +11/+4 P < 0.001 *Assessment by patient:* MTX (EOA/systemic): Very active: 28%/31%, -18/-24 Mildly active: 13/41%, +39/+28	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good - Comments: Cross-over with adequate washout; validated outcomes *Adverse events:* - Overall rating: Good **Applicability:** - Study outside US- may be more homogeneous population - Long duration of disease at baseline (average 3-4.4 years)

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	and NSAIDs NR whether these were added per protocol or at the discretion of clinician/investigator **Study duration:** 12 months (4 months treatment, 2 months washout, 4 months treatment, 2 months washout) **Primary outcome(s):** - > 30% improvement in 3 or more core variables and > 30% worsening in no more than 1 Core clinical variables: Physician global, parent/child global, number of joints with active disease, range of joint motion For systemics, 8 core measures were: Rash; fever; cervical, axillary, ingunial lymphadenopathy; hepatomegaly; splenomegaly; pericarditis **Secondary outcome(s):** - Steroid dose - For systemics, presence of systemic features	Active arthritis in past 3 months: EOA: 45 (100%) Systemic: 43 (96%) Duration of disease (months): EOA: 53.8 (4-132) Systemic: 33.7 (4-116) **Percentage with uveitis:** NR **Inclusion criteria:** - Under 16 years of age - Fulfilled the ILAR/WHO criteria for systemic or extended oligoarticular arthritis **Exclusion criteria:** NR	Placebo (EOA/systemic) Very active: 26%/31%, -13/-17 Mildly active: 29/24%, +11/10 *Systemic core features (outcome = systemic score of 0):* MTX (start/end): 32%/61% Placebo (start/end): 27%/45% **2) Limited joint range:** Treatment effect (mean [SEM]): EOM: 4.47 (3.67) Systemic: 2.57 (6.68) **3) Limited joint score:** Treatment effect (mean [SEM]): EOA: -3.0 (1.8) Systemic: -3.3 (3.5) **4) Laboratory measures of inflammation:** ESR (baseline mean [SD], treatment effect mean [SEM]): EOA: 49 (28), -16.6 (3.6) Systemic: 57 (31), -12.4 (6.5) C-reactive protein (baseline mean, treatment effect mean [SEM]): EOA: 2.7, -45% (-27%) Systemic: 6.9, -29%(-51%) **5) Steroid dose (mg/day, baseline mean [SD], treatment effect mean [SEM]):** EOM: 1.2 (2.4), -0.012 (0.012) Systemic: 11.6 (6.5), -0.55 (0.92) **6) Overall clinical improvement (MTX/placebo)** EOA: 48/18 Systemic: 25/16	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			7) Discontinuation of DMARD due to: - Inefficacy: 6 systemic, 1 EOA - Intolerance/AEs: 1 systemic, 1 EOA **8) Mortality:** NR **9) Adverse events reported?:** Yes	
Yokota, Imagawa, Mori, et al., 2008 **#138**	**Geographical location:** Japan **Study dates:** NR **Funding source:** Chugai Pharmaceuticals supplied study medication and was responsible for data processing and management, statistical analysis, and reporting of serious adverse events **Setting:** 8 university hospitals and children's hospitals in Japan **Study design:** RCT, double-blind, multicenter, withdrawal design **Intervention(s):** - DMARD name: Tocilizumab - Dose: 8 mg/kg IV every 2 weeks - Titration: None - N: 20 **Comparator(s):** Placebo - N: 23 **Were additional arthritis**	**Number of patients:** N = 56 - Screened for inclusion: NR - Eligible for inclusion: NR - Began lead-in phase: 56 - Completed lead-in phase: 50 - Randomized: 44 - Began RCT phase: 43 (23 placebo; 20 tocilizumab) - Completed RCT: 41 - Began extension phase: 50 (44 randomized, plus 6 not randomized) - Withdrawals: - Lead-in phase: 6/56 (3 antibodies; 2 AEs; 1 lack of efficacy) - RCT placebo: 19 (1 AE; 18 early escape) - RCT tocilizumab: 4 (1 AE; 3 early escape) - Extension phase: 2 withdrawn because of AE - Loss to followup: 0 **Age:** - Mean (SD): 8.3 (4.4) - Range: 2-19 years **Sex:** - Female: 35 (62.5%) - Male: 21 (37.5%)	**1) Active joint count, median (range):** - Lead-in phase: - Baseline: 4 (0-39) - 6 weeks: 0 (0-34) - Improvement: 73% - RCT, placebo (N = 23): - Baseline: 4 (0-21) - Last observation: 0 (0-34) - RCT, tocilizumab (N = 20): - Baseline: 3.5 (0-18) - Last observation: 0 (0-4) - Extension phase: - 48 weeks: 0 (0-4) - Improvement: 88% **2) Quality of life/functional status:** CHAQ score, median (range): - Lead-in phase: - Baseline: 0.88 (0-3) - 6 weeks: 0.38 (0-3) - Improvement: 43% - RCT, placebo (N = 23): - Baseline: 0.63 (0-3) - Last observation: 0.38 (0-3) - RCT, tocilizumab (N = 20): - Baseline: 0.88 (0-2.38) - Last observation: 0.38 (0-1.63) - Extension phase: - 48 weeks: 0.13 (0-2.13) - Improvement: 67%	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Fair - Comments: Potential for significant conflict of interest, given that the data were analyzed by the sponsor of the study, which has a financial interest in tocilizumab; screening and randomization procedures not described *Adverse events:* - Overall rating: Fair - Comments: Same issues as above **Applicability:** No significant issues

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	medications allowed?: Some: - Not allowed: Intraarticular corticosteroids, methylprednisolone, immunosuppressive drugs, TNF agents, and other DMARDs - Doses of oral corticosteroids had to be stable for 2 weeks before the trial **Study duration:** Open-label lead-in phase: 6 weeks RCT phase: 12 weeks Open-label extension phase: 48 weeks Patients had to achieve an ACR Pedi 30 response and CRP concentrations < 5 mg/L at end of lead-in phase to be eligible for RCT phase **Primary outcome(s):** Proportion of patients who maintained an ACR Pedi 30 response and CRP concentrations < 15 mg/L **Secondary outcome(s):** - ACR Pedi responses, systemic feature score, and CRP assessed every 2 weeks - Active disease defined by an increase in CRP and an inadequate response to corticosteroids for longer than 3 months - Safety monitored by physical exam daily during hospital stay	**Race/ethnicity:** NR **JIA diagnosis:** JIA **Baseline severity:** Active joint count (median [range]): Start of lead-in phase: 4 (0-39) Start of RCT phase, placebo: 4 (0-21) Start of RCT phase, tocilizumab: 3.5 (0-18) Duration of disease, years (SD): Placebo: 4.7 (4.0) Tocilizumab: 4.6 (3.5) Past treatments (number [SD]): Placebo: 2.0 (1.0) Tocilizumab: 2.1 (1.0) **Percentage with uveitis:** NR **Inclusion criteria:** - 2-19 years of age - Onset of disease before 16th birthday - Met the ILAR classification criteria for systemic-onset JIA **Exclusion criteria:** - Important concurrent medical or surgical disorders - Leucopenia (< 3.5×10^9/L) or thrombocytopenia (< 100×10^9/L) - Cardiac disease (assessed by a pediatric cardiologist before enrollment) - Developed macrophage-	**3) Number of joints with limited range of motion, median (range):** - Lead-in phase: - Baseline: 0.5 (0-47) - 6 weeks: 0 (0-45) - Improvement: 54% - RCT, placebo (N = 23): - Baseline: 0 (0-37) - Last observation: 0 (0-42) - RCT, tocilizumab (N = 20): - Baseline: 0.5 (0-47) - Last observation: 0 (0-46) - Extension phase: - 48 weeks: 0 (0-62) - Improvement: 72% **4) Global assessment of current status:** - Physician, visual analog scale, 0 mm (best) to 100 mm (worst), median (range): - Lead-in phase: - Baseline: 52 (18-100) - 6 weeks: 8.5 (0-97) - Improvement: 75% - RCT, placebo (N = 23): - Baseline: 51 (18-95) - Last observation: 14 (0-84) - RCT, tocilizumab (N = 20): - Baseline: 51.0 (21-96) - Last observation: 5.5 (0-47) - Extension phase: - 48 weeks: 3.5 (0-22) - Improvement: 89% - Patient or parent's, visual analog scale, 0 mm (best) to 100 mm (worst), median (range): - Lead-in phase: - Baseline: 53 (0-90) - 6 weeks: 13.5 (0-69) - Improvement: 63%	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		activation syndrome during the prestudy hospital admission	- RCT, placebo (N = 23): - Baseline: 55 (18-85) - Last observation: 39 (2-94) - RCT, tocilizumab (N = 20): - Baseline: 51.5 (0-76) - Last observation: 4.5 (0-34) - Extension phase: - 48 weeks: 8.5 (0-70) - Improvement: 75% **5) Laboratory measures of inflammation:** - ESR, mm/h (range): - Lead-in phase: - Baseline: 44.5 (8-125) - 6 weeks: 4.0 (0-64) - Improvement: 82% - RCT, placebo (N = 23): - Baseline: 35 (8-68) - Last observation: 11 (1-41) - RCT, tocilizumab (N = 20): - Baseline: 39.5 (8-103) - Last observation: 4.0 (0-7) - Extension phase: - 48 weeks: 3.0 (0-12) - Improvement: 91% - CRP, mg/L (range): - Lead-in phase: - Baseline: 43.5 (16-190) - 6 weeks: 0.5 (0-99) - Improvement: 90% - RCT, placebo (N = 23): - Baseline: 38 (17-131) - Last observation: 15 (0-101) - RCT, tocilizumab (N = 20): - Baseline: 35 (16-190) - Last observation: 0.1 (0-22) - Extension phase: - 48 weeks: 0.1 (0-2) - Improvement: 99%	

Evidence Table 1. Studies Relevant to Key Questions 1-4 – continued

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability

			6) Radiographic evidence of progression of disease: NR
			
			7) Pain control: NR
			
			8) Clinical remission: NR
			
			9) Flare of disease: NR
			
			10) Discontinuation of DMARD due to:
			- Remission of disease: NR
			- Inefficacy: NR
			- Intolerance/AEs: Lead-in phase: 2/56 (4%); RCT placebo: 1/23 (5%); RCT tocilizumab: 1/20 (5%)
			
			Early escape (switched to another medication due to poor response):
			- Placebo: 18/23 (78%)
			- Tocilizumab: 3/20 (15%)
			
			"Median time to early escape was 4.9 weeks in the placebo group, but longer than 12 weeks in the tocilizumab group" (significance test NR)
			
			11) Mortality: None
			
			12) Adverse events reported?: Yes
			
			13) Other:
			ACR Pedi Responses:
			- Lead-in phase, N (%):
			  - ACR Pedi 30: 51 (91%)
			  - ACR Pedi 50: 38 (86%)
			  - ACR Pedi 70: 38 (68%)
			  - Both ACR Pedi 30 response and CRP < 5 mg/L: 44 (79%)	

Evidence Table 2. Studies Relevant to Key Question 5

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Bazso, Consolaro, Ruperto, et al., 2009 **#1524**	**Geographical location:** Genoa, Italy **Setting:** Specialty clinic **Study design:** Longitudinal non-RCT (1 sample, MTX) Cross-sectional (2 samples, Clinic and PRINTO) **Study objective(s):** "… to devise and test several reduced joint counts …" **Duration of followup:** MTX sample = 6 months	**Number of patients:** Clinic: 434 PRINTO: 3324 MTX: 595 Data given below are for these 3 samples **Age:** - Mean (SD): NR - Median (IQ range): 7.2 (3.9 to 11.2); 10.6 (7.2 to 14), 7.8 (4.2 to 11.3) **Sex:** NR **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** NR **Baseline severity:** Time since diagnosis, median (IQ range): 2 (0.8, 5.4); 3.8 (1.6, 6.7); 2.2 (0.4, 3.4) Active joint count: 2 (0, 4); 2 (0,5), 9 (6;16) CHAQ: 0.1 (0, 0.3); 0.4 (0, 1.1); 1.2 (0.6, 1.7) **Inclusion criteria:** - Clinic: NR - PRINTO (need ref 13) - MTX (need ref 14)	**Instrument(s) evaluated:** Childhood Health Assessment Questionnaire (CHAQ), likely an Italian version **Mode of administration:** NR	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: Spearman correlations for CHAQ compared to counts of joints with restricted movement (67 joints) Clinic sample (n = 232): 0.40 PRINTO sample (n = 2739): 0.47 MTX sample (488): 0.27 for 6-month change scores Results were virtually identical for reduced joint counts. - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	**General comments:** - The PRINTO (ref 13) and MTX (ref 14) have been reported previously - This report focused on reduced joint counts (10, 27, 35, and 45) vs. full count of 71 but for our purposes the data of interest were for the CHAQ - Report also contains correlations between physician global assessments, parent global assessments, and joint counts (Table 4) - Report also includes effects of substituting reduced joint counts in the ACR Peds score and how it affects response ratings – but not of primary interest (Table 7) **Quality assessment:** - Spectrum: 3 samples ranging from mild to moderate/severe disease - Blinding to criterion: Can't tell - Blinding to instrument: Can't tell - Validated criterion: Partial, joint counts are a relevant but incomplete clinical outcome - FU > 80%: Can't tell - 95% CI not appropriate for baseline measures (should give SD or range)

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Exclusion criteria: - Clinic: NR - PRINTO (need ref 13) - MTX (need ref 14)			
Bekkering, ten Cate, van Rossum, et al., 2007 **#1552**	**Geographical location:** Leiden, The Netherlands **Setting:** Specialty clinic **Study design:** Cross-sectional **Study objective(s):** "…to compare the measurement properties of the JFAS and the CHAQ.." **Duration of followup:** NA	**Number of patients:** 28 **Age:** - Mean (SD): NR - Median: 10 - Range: 7-13 **Sex:** - Female: 16 - Male: 12 **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 3/28 **Baseline severity:** Median (range): Time since diagnosis: 3.3 years (0.1-10.2) Active joint count: JC swollen 1.0 (0-28); JC tender 0.8 (0-8); JC limited ROM 1.0 (0-17) Other: JAFAS 0 (0-13); CHAQ 0.125 (0-2.6) NR **Inclusion criteria:**	**Instrument(s) evaluated:** JAFAS, range 0-20 CHAQ, 30 items, total score ranges from 0-3 CHAQ-9: 9 items selected to correspond to the JAFAS **Mode of administration:** Interviewer-administered	**1) Reliability:** (n = 28) - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: JAFAS 0.91; CHAQ 0.96; CHAQ-9 0.92 **2) Validity:** (n = 28) Spearman correlation coefficients; *p < 0.05, **p < 0.01 - Versus clinical outcomes: Pediatrician-rated disease activity (VAS): JAFAS 0.41*, CHAQ 0.56**, CHAQ-9 0.34 JC swollen: JAFAS 0.47*, CHAQ 0.65 **, CHAQ-9 0.48* JC tender: JAFAS 0.07, CHAQ 0.41*, CHAQ-9 0.09 JC limited ROM: JAFAS 0.44*, CHAQ 0.64**, CHAQ-9 0.59** - Versus lab results: ESR: JAFAS 0.37; CHAQ 0.62*, CHAQ-9 0.75** - Versus radiological results: NR - New instrument versus established instrument: JAFAS score correlation with CHAQ score, Spearman's r = 0.55; JAFAS correlation with CHAQ-9, Spearman's r = 0.56	**General comments:** - Sample had very little functional disability - Joint counts could range from 0-30 **Quality assessment:** - Blind criterion: Can't tell - Blinded instrument: Can't tell - Validated criterion: Partial (joint counts yes, ESR no) - F/U ≥ 80%: NA - Analyses appropriate: Yes

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		- Age 7-12 years - JIA and no other medical conditions interfering with functional ability **Exclusion criteria:** NR		**3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	
Bekkering, ten Cate, van Suijle-kom-Smit, et al, 2000 **#1784**	**Geographical location:** Leiden, Netherlands **Setting:** Specialty clinic **Study design:** Cross-sectional **Study objective(s):** To investigate the relationship between joint impairments and disabilities in children with systemic JIA. The relationship was studied at the level of (1) complete instruments, (2) upper and lower limb function separately, (3) the individual joints and items. **Duration of followup:** NA	**Number of patients:** 21 **Age:** - Mean (SD):9.3 (4.1) - Median: NR - Range: 3.6-16.4 **Sex:** - Female:10 - Male: 11 **Race/ethnicity:** NR **JIA diagnosis:** JIA-systemic **Percentage with systemic JIA:** 100% **Baseline severity:** Time since diagnosis: 4.8 (3.6), range 0.8-12.6 Other (n, mean ± SD, range): CHAQ: 18, 1.7 ± 0.7 (0.4-2.9) Pain-VAS: 17, 1.0 ± 0.8 (0-2.8) JAFAS: 15, 5.1 ± 4.6 (0-16)	**Instrument(s) evaluated:** *Joint impairment :* JCS (joint count on swollen joints) JCT (joint count on tender joints) JAM (Joint Alignment and Motion Scale) *Functional performance and ability:* JAFAS (Dutch) and CHAQ (Dutch) **Mode of administration:** Self-administered: CHAQ-c Interviewer-administered: JAFAS, JCT, JCS, JAM	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: Spearman correlation JAM, CHAQ: 0.66, $p < 0.01$ JAM, JAFAS: 0.77, $p < 0.01$ JCS, CHAQ: 0.45, $p < 0.05$ JCS, JAFAS: 0.52, $p < 0.05$ JCT, CHAQ: 0.028 JCT, JAFAS: 0.14 Other results reported include: Correlations between joint impairment and extremity-specific parts of CHAQ (CHAQ-arm, CHAQ-leg) and JAFAS (JAFAS-arm, JAFAS-leg) Correlation between a compounded measure for the range of motion of shoulder, elbow, and wrist and specific	**General comments:** - Small sample size - All patients with systemic disease **Quality assessment:**

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Inclusion criteria: - Systemic JIA - Children treated with steroids for more than a year - Children included in the study constituted a subset from an early study on effect of corticosteroids on BMD and growth **Exclusion criteria:** NR		items of CHAQ, JAFAS **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	
Brown, Wright, Lang, et al., 2005 **#337**	**Geographical location:** Ottawa, Toronto, Halifax and Winnipeg, Canada **Setting:** Specialty clinic **Study design:** Longitudinal non-RCT **Study objective(s):** "…to compare the ability of these 3 self-report functional questionnaires to measure clinically important change…" and "…to determine the extent of agreement between parent report and child report on each of the 3 questionnaires" **Duration of followup:** 6 weeks and 6 months	**Number of patients:** 74 with intra-articular steroid treatment (IAS); 18 with methotrexate, hip-tendon release or total hip replacement (MTX/Hip) **Age:** Mean (SD): 12.8 (3.0) IAS; 12.9 (3.1) MTX/Hip **Sex:** - Female: 68 - Male: 24 **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 12 (13%) **Baseline severity:** Time since diagnosis: 27 ≤ 1 yr; 17 1-3 yrs; 11 4-5 yrs; 23 6-10 yrs; 14 ≥	**Instrument(s) evaluated:** Juvenile Arthritis Functional Assessment Report (JAFAR) Childhood Health assessment Questionnaire (CHAQ) Juvenile Arthritis Functional Status Index (JASI) **Mode of administration:** "Questionnaire" - Other: joint count assessed by pediatric rheumatologist; grip strength, functional ROM and timed walk test measured by physiotherapies or occupational therapist; demographics by research assistant. JAFAR, CHAQ, JASI –	**1) Reliability:** - Test-retest: NR - Inter-rater: Mean difference for child vs. parent at baseline, 6 weeks, 6 months: JAFAR: 0.93 (p = 0.45), 0.99 (p = 0.38), 0.87 (p = 0.20) CHAQ: -0.1 (p = 0.016), -0.065 (p = 0.08), -0.089 (p = 0.027) JASI: 0.83 (p < 0.0001), 0.72 (p < 0.0001), 0.77 (p = 0.0005) - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: Standardized response mean (95% CI) at 6 weeks and 6	**General comments:** - Calculated a sample size - Few patients on DMARDs **Quality assessment:** - Spectrum: Limited; consecutive patients - Blind criterion: NA, no analyses compared instruments to a criterion - Blinded instrument: Completed blind to global assessments - Validated criterion: NA, no criterion standard - FU > 80%: Yes 84/92 - Appropriate analysis: Partial; didn't compare change scores to global status - Subgroup analyses based on very small numbers for MTX/Hip group

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		11 yrs Active joint count: Mean tender joints 6.7 (IAS), 18.0 (MTX/Hip) Mean swollen joints: 4.3 (IAS), 7.5 (MTX/Hip) **Inclusion criteria:** - Age 8 to 20 - JIA - Active inflammation of ≥ 1 joint - IAS injection, MTX treatment or orthopedic hip surgery planned - Fluent in English - Agree to 3 assessment visits **Exclusion criteria:** Comorbid medical condition that might independently affect physical function	uncertain	months - Child as respondent: JAFAR: 0.34 (0.13, 0.54), 0.41(0.19, 0.63) JASI: 0.40 (0.19, 0.61); 0.24 (0.03, 0.45) CHAQ: 0.39 (0.18, 0.60); 0.48 (0.27, 0.69) Differences not statistically significant; results similar when parent respondent , CHAQ appear higher, but not statistically significant when parent is respondent Relative efficiency (RE; ratio of paired t-test for JAFAR or JASI compared to CHAQ in the denominator): JAFAR (IAS subgroup apt 6 weeks) parent; child respondents: 0.55; 0.34 JAFAR (MTX/Hip subgroup at 6 months) parent; child respondents: 1.45; 15.11 JASI (IAS subgroup at 6 weeks) parent; child respondents: 0.53; 0.27 JASI (MTX/Hip subgroup at 6 months) parent; child respondents: 0.73; 3.94 - ROC curves: NR	

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Brunner, Johnson, Barron, et al., 2005 **#1591**	**Geographical location:** Cincinnati, OH **Setting:** Specialty clinic **Study design:** Cross-sectional **Study objective(s):** ".. to perform an initial validation of the Gastrointestinal Symptom Scale for Kids (GISSK) in children with juvenile rheumatoid arthritis…" **Duration of followup:** NA	**Number of patients:** 77 parents 52 children aged 8 or older **Age:** - Mean (SD): NR - Median: 10.3 - Range: 2-18 **Sex:** - Female: NR - Male: NR **Race/ethnicity:** NR **JIA diagnosis:** JRA **Percentage with systemic JIA:** NR **Baseline severity:** Time since diagnosis: NR Active joint count: Median 1 (range 0-46) Other: CHAQ (parent) mean 0.12 (0.66); (child) mean 0.24 (0.46) 42 (55%) were taking etanercept or infliximab, and 65 (94%) were taking methotrexate **Inclusion criteria:** Children with JRA	**Instrument(s) evaluated:** GISSK, CHAQ **Comparators:** Pain during prior week; (VAS-pain), 0-100, higher scores worse PedsQL Generic Core Sacle version 4 (PedsQL-GC), 0-100, higher scores better functional status PedsQL Rehueumatology Module (PedsQL-RM), 0-100, higher scores better functional status Parent global rating of health during prior week, (VAS-health), 0-100, higher scores better Physician global rating of disease activity, (VAS-DA), 0-100, higher scores worse Active joint count (AJC) Joints with limited range of motion (LROM) **Mode of administration:** Self-administered by parents (n = 77) or child (n = 52)	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity: (Spearman correlation coefficients, p value for association between CHAQ and outcome)** - Versus clinical outcomes: AJC: 0.39, p = 0.0010 LROM: 0.33, p = 0.0062 VAS-pain: 0.57, p < 0.0001 VAS-DA: 0.20, p < 0.0859 VAS-health: -0.59, p < 0.0001 PedsQL-GC: -0.62, p < 0.0001 PedsQL-RM: -0.63, p < 0.0001 - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	**General comments:** Data on GISSK not abstracted, as not a priority instrument **Quality assessment:** - Appears to be skewed to somewhat more severe spectrum (second-line agents) but appropriate to our study question - Parents and children completed questionnaires independently but unclear if CHAQ results available to examining clinician who completed VAS-DA - FU >80%: NA - Small sample size; no sample size calculations

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		requiring second-line agents **Exclusion criteria:** NR			
Brunner, Klein-Gateman, Miller, et al., 2004 **#1779**	**Geographical location:** Cincinnati, Ohio **Setting:** Specialty clinic **Study design:** Longitudinal non-RCT **Study objective(s):** To examine the strength of association between HRQOL and disability, pain, or well-being and whether HRQOL changes importantly as a function of the disability status **Duration of followup:** Mean 3.5 months (0.6)	**Number of patients:** 119 families **Age:** - Mean (SD): 10.5 (4.3) - Range: 3-18 **Sex:** - Female: 91 - Male: 28 **Race/ethnicity:** NR **JIA diagnosis:** JRA n = 102 Spondyloarthropathy n = 2 Psoriatic arthritis n = 8 Other (describe): Juvenile dermatomyositis (1), Castleman syndrome (1), arthritis with inflammatory bowel disease (1), sacroidosis (1), SLE (2), mixed connective tissue disease (1) **Percentage with systemic JIA:** NR **Baseline severity:** Time since diagnosis: mean 3.5 years (range, 0.3 to 14.2)	**Instrument(s) evaluated:** Physician-rated disease severity (DS), VAS 100 mm Childhood Health Assessment Questionnaire (CHAQ), includes VAS pain, 100 mm Parent and patient global rating of health (Health) and well being (Global WB), VAS 100 mm Juvenile Arthritis Quality of Life Questionnaire (JAQQ) Pediatric Quality of Life Questionnaire Inventory version 4.0 (PedsQL-c, child rating) PedsQL-rheumatology module (PedsQL-RM) Standard Gamble (SG) **Mode of administration:** Self-administered P-parent; C-child)	N varied: n = 119 for parent ratings on Health, Global, CHAQ, VAS pain; n = 87 for child ratings JAQQ n = 58; PedsQL-RM n = 94, PedsQL-GC n = 60 parents, n = 46 children **1) Reliability:** - Test-retest: NR - Inter-rater: Parent vs. Child (intraclass correlation coefficient) Health: 0.53 JAQQ: 0.69 PedsQL-GC: 0.48 PedsQL-RM: 0.57 CHAQ: 0.51 Global WB: 0.47 VAS Pain: 0.26 - Intra-rater: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: Spearman correlation coefficients for CHAQ vs: VAS Pain: 0.28 (P), 0.31 (C) Global WB: -0.45 (P), -0.23 (C)	**General comments:** None **Quality assessment:** - Sample semi-consecutive - Parents and patients completed instruments independently; instrument order varied - Analysis appropriate

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Active joint count: NR **Inclusion criteria:** - Children between 1-18 year of age - Symptoms of chronic arthritis irrespective of a specific underlying diagnosis - Arthritis present for at least 3 months continuously **Exclusion criteria:** - Diagnosis of fibromyalgia, nonspecified myalgias, or arthralgias - Symptoms were < 3 months in duration		Health: -0.52(P), -0.64 (P) JAQQ: -0.65 (P), -0.64 (C) PedsQL-GC: -0.22 (P), -0.32 (C) PedsQL-RM: -0.42 (P), -0.47 (C) Statistically significant for all Spearman correlation coefficients for JAQQ vs: VAS Pain: -0.54 (P), -0.45 (C) Global WB: 0.59 (P), 0.36 (C) Health: 0.57(P), 0.66 (P) PedsQL-GC: 0.73 (P), 0.78 (C) PedsQL-RM: 0.79 (P), 0.76(C) Statistically significant for all except PedsQL-GC parent Spearman correlation coefficients for PedsQL-GC vs: VAS Pain: 0.12 (P), -0.36 (C) Global WB: 0.64 (P), 0.44 (C) Health: 0.53(P), 0.66 (P) PedsQL-RM: 0.81 (P), 0.80 (C) Statistically significant for all except VAS pain, Global WB parent Spearman correlation coefficients for PedsQL-RM vs: VAS Pain: -0.27 (P), -0.60 (C) Global WB: 0.66 (P), 0.45 (C) Health: 0.62 (P), 0.60 (P) Statistically significant for all When disability was classified by the CHAQ as none (0), mild (0-0.25), mild to moderate (0.25-1.25), or moderate (1.26-2.0), mean HRQOL scores differed significantly on the PedsQL-RM, JAQQ, Health, Global WB, VAS	

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
				Pain, but not for the PedsQL-GC or number of involved joints **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	
Brunner, Klein-Gitelman, Miller, et al., 2005 **#1606**	**Geographical location:** Cincinnati, HO **Setting:** NR **Study design:** Longitudinal non-RCT **Study objective(s):** "…to estimate the minimum clinically important difference of the CHAQ for children who were experiencing changes in their health and well being…" **Duration of followup:** Mean 3.5 (2.3) months	**Number of patients:** 92 (67 age ≥ 8) **Age:** - Mean (SD): 8.7 years - Median: NR - Range: 1-18 **Sex:** - Female: NR - Male: NR **Race/ethnicity:** NR **JIA diagnosis:** JRA **Percentage with systemic JIA:** NR **Baseline severity:** Time since diagnosis: NR Active joint count: NR Other: 33 (36%) "no disability CHAQ parent (n = 92): Median 0.25 (IQR 0-0.91), mean 0.53 (0.61)	**Instrument(s) evaluated:** CHAQ compared to the 6 core response variables (using the Juvenile Arthritis Quality of Life Questionnaire to measure functional status) Minimum clinically important difference (MCID) analyses constrained to those with small improvement or decline (10-30 mm change on 100 mm VAS, or 1-2 points on 0-10 Likert scale, or "better" or "worse" on a 5-point Likert scale). Depending on definition used, these analyses used 25-44% of the overall sample. **Mode of administration:** Self-administered: Parents and children >7 years old Interviewer-administered: Children < 8 years old	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: CHAQ median (IQR) change for worsening in well-being for the 3 definitions ranged from 0 (0.375) to 0.25 (0.75)-child ratings; 0 (0.25) to 0.125 (0.75)-parent ratings; and worsening in disease activity as rated by physician -0.125 (0.375) CHAQ median (IQR) change for improvement in well-being for the 3 definitions ranged from -0.188 (0.5) to 0.0 (0.875)-child ratings; 0 (0.125) to 0 (1.0)-parent	**General comments:** None **Quality assessment:** - Parents and patients completed questionnaires independently; order of questionnaires randomized - Unclear if raters (e.g., AJC) blinded to CHAQ results - FU rate > 80%: Inclear, this was a convenience sample and not study flow given - Analyses: Small sample; no power calculation but otherwise appropriate - Conclusion is appropriate

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		CHAQ child (n = 67): Median 0.25 (0-0.66), mean 0.46 (0.56) **Inclusion criteria:** - Convenience sample of children age 1-18 with JRA - Symptoms of chronic arthritis for ≥ 2 months **Exclusion criteria:** NR		ratings; and worsening in disease activity as rated by physician 0 (0.375) to 0 (0.125) - ROC curves: NR Authors' conclusion: The MCID of the CHAQ for both improvement and worsening are often at or close to the level of the smallest potential difference, suggesting that the CHAQ is relatively insensitive to important short term changes in children with JRA	
Brunner, Lovell, Finck, et al., 2002 **#598** **AND** **Lovell, Giannini, Reiff, et al., 2000** **#721**	**Geographical location:** Cinncinati, OH **Setting:** Specialty clinic (confirm in ref 3) **Study design:** Randomized discontinuation trial among etanercept responders; 90 days post initiation of open-label etanercept **Study objective(s):** "…to develop preliminary criteria for defining disease flare in patients with polyarticular-course JRA by using the core response variables for JRA…"	**Number of patients:** Placebo 26; etanercept 25 **Age:** - Mean (SD): 10.6 (SD NR) - Median: NR - Range: 4-17 **Sex:** - Female: 34 (67%) - Male: 17 (33%) **Race/ethnicity:** White: 37 (73%) Black: 4 (8%) Hispanic: 8 (16%) Other: 2 (4%) **JIA diagnosis:** JRA **Percentage with systemic JIA:** 17 (33%)	**Instrument(s) evaluated:** Definitions of flare using 6 core response variables: AJC, LROM, Physician global-disease severity (0-10), Patient or Parent global overall well-being (0-10), ESR, functional status (CHAQ, 0-3) Flare definitions tested: Varied from 20% to 50% change on 2 to 4 of the core response variables. Some definitions allowed for up to 30% improvement on 1 of the remaining CRV. All 26 patients in placebo arm were assumed to flare; therefore sensitivity of flare definition = #	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: Worsening in ≥ 2 CRV by ≥ 40%, allows 1 CRV to improve: Sensitivity: 85% (95% CI 71 to 99) Specificity: 80% (64 to 94) ROC AUC: 0.677 (0.57 to 0.78) Other definitions had statistically significantly lower ROC AUC - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR	**General comments:** Variables well defined **Quality assessment:** - Appears to be skewed to somewhat more severe spectrum (failed NSAID and/or MTX) - Assessors were blind to treatment assignment (the de facto criterion) - FU >80%: Yes - Small sample size; no sample size calculations; problems with multiple testing - Criterion standard (assumptions about flare based on treatment) is suspect

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
	Duration of followup: Median to disease flare 30 days (range 6-126)	**Baseline severity:** Time since diagnosis: 5.8 years (SD NR) CHAQ: Mean 0.825 (SD NR), median 1.0 Active joint count (AJC): Mean 11 (SD NR), median 9 (range 0-29) Limited ROM joints (LROM): Mean 18, median 15 (range 0-53) **Inclusion criteria:** - Active polyarticular JRA despite treatment with NSAID or MTX - Age 4-17 - Normal or near normal platelet, WBC, ALT/AST, creatinine - Contraception if girl of child-bearing age **Exclusion criteria:** Major concurrent medical conditions	relapsed by candidate definition/total in placebo group All 25 in etanercept arm were presumed not to flare; therefore specificity of flare definition = # without relapse by candidate definition/total in etanercept group **Mode of administration:** Self-administered Interviewer-administered Other [specify]	**3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: See above	

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Cespedes-Cruz, Gutierrez-Suarez, Pistorio, et al., 2007 **#142**	**Geographical location:** 11 sites in Western Europe, USA and Australia **Setting:** Specialty clinic **Study design:** RCT **Study objective(s):** "..to compare the effect of MTX therapy on the HRQOL of patients with JIA…" **Duration of followup:** 6 months	**Number of patients:** 521 JIA 3315 healthy controls **Age:** - Mean (SD): 8.2 (4.6) JIA; 11.2 (3.8) healthy controls - Median: NR - Range: NR **Sex:** - Female: 375 (72%); 1730 (52.2%) healthy controls - Male: 146 (28%); 1585 (47.8%) healthy controls **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 75 (14%) **Baseline severity:** Time since diagnosis: Mean 2.8 (3.4) Active joint count: Mean 12.0 (9.1) Other: CHAQ: 1.2 (0.8) Parent global assessment of well-being (0-10 VAS): Mean 4.4 (2.6) **Inclusion criteria:**	**Instrument(s) evaluated:** Child Health Questionnaire (CHQ): 15 domains and physical (PhS) and psychosocial (PsS) summary scores Childhood Health Assessment Questionnaire (CHAQ) in multiple languages **Mode of administration:** Self-administered: CHAQ Completed by parent: CHQ	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: CHQ distinguished between healthy controls and subjects with JIA on all 15 domains (Fig 2) - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: Baseline CHAQ values > 1.33 were associated with poor HRQOL at 6 months as measured by the CHQ physical (OR for PhS < 30 = 5.2, 95% CI 3 to 8.9) and psychosocial (OR for PsS < 30 = 3.9, 1.5 to 10) summary scores **3) Other:** - Feasibility: NR - Responsiveness: CHQ scores improved in all 15 subscales from baseline to 6 months (Fig 2, responsiveness statistics not reported); PhS scores changed more than PsS scores - ROC curves: NR	**General comments:** Limited useful information; measure validation was not the primary purpose of the study **Quality assessment:** - Large sample, participating in RCT of MTX - Comparisons to healthy controls bias towards greater sensitivity/specificity - Analysis: No sample size calculation but large sample for most analyses - No responsiveness indices calculated

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		-PRINTO database-participants in RCT of MTX - Completed ≥ 6 months treatment - Polyarticular JIA - HRQOL assessment at baseline and 6 month followup **Exclusion criteria:** NR			
Cosolaro, Vitale, Pistaro, et al., 2007 **#1556**	**Geographical location:** Genova, Italy **Setting:** Specialty clinic and hospitalized patients **Study design:** Cross-sectional **Study objective(s):** To investigate "the discrepancy between the physicians' and parents' ratings of inactive disease in children with JIA and attempt to identify factors explaining it" **Duration of followup:** NA	**Number of patients:** 636 patients; 537 with complete data; 265 with rating of inactive disease by physician and/or parent constituted the analytic sample **Age:** - Mean (SD): NR - Median: NR - Range: NR **Sex:** - Female: NR - Male: NR **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** NR **Baseline severity:** Time since diagnosis: NR Active joint count: NR	**Instrument(s) evaluated:** Physician global assessment of overall disease activity (10 cm VAS, 0 = no activity, 10 = maximum activity) Parent global assessment of overall well being (10 cm VAS, 0 = very good, 10 = very poor) **Mode of administration:** Self-administered: Parent Physician global is presumably based on history, physical examination and laboratory data (ESR, CRP, joint counts, CHAQ completed)	**1) Reliability:** - Test-retest: NR - Inter-rater: Score of 0 by parent and physician (40%); among discordant ratings, physicians rated > 0 (35.5%) when parent rated 0, physicians rated 0 (24.5%) when parents rated > 0 - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	**General comments:** The relevance of parent ratings of overall well-being vs. physician rating of disease activity is uncertain **Quality assessment:** - Sample: Not well described, eligibility criteria not well described - Blinding: Unclear if physician global rating completed blind to parent rating - FU rate > 80%: NA - Analysis: No chance corrected agreement

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Other: NR **Inclusion criteria:** - Patients included in the clinical database from January 1992 through December 2006 - JIA by ILAR criteria **Exclusion criteria:** NR			
Dempster, Porepa, Young, et al., 2001 **#1782**	**Geographical location:** Toronto, Canada **Setting:** Specialty clinic **Study design:** Cross-sectional **Study objective(s):** To determine cutoff levels on the CHAQ for different disability levels; to determine the minimum clinically important change and whether these change scores were similar for parent-reported and child-reported assessments **Duration of followup:** NA	**Number of patients:** 131 **Age:** - Mean (SD): 9.6 (NR) - Range: 1-18 **Sex:** - Female: 90 (69%) - Male: 41 (31%) **Race/ethnicity:** NR **JIA diagnosis:** JRA, n = 101 Spondyloarthropathy, n =1 0 Psoriatic arthritis, n = 14 Other: Reactive or unclassified arthritis, n = 5 **Percentage with systemic JIA:** NR **Baseline severity:** Time since diagnosis: NR Active joint count: 4 (NR) Other: Median Steinbrocker score 1	**Instrument(s) evaluated:** CHAQ **Comparators:** Quality of My Life Questionnaire (QOMLQ), VAS 100 mm measuring overall quality of life and health-related QOL Categorical disability Scale (CDS): 6 response categories ranging from no disability ("can do everything other kids can do with no problems") to severe disability ("everything is hard for me") Categorical change scale (CCS): Rates "ability to do things" on 5-point scale ranging from "a lot worse" to "a lot better" Hypothetical situation where new medication	**1) Reliability:** - Test-retest: NR - Inter-rater: Parent vs. child (n = 56) CHAQ intraclass correlation coefficient = 0.83; CDS weighted kappa = 0.58 - Intra-rater: NR - Internal reliability: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: Median (IQR) CHAQ scores by parent described CDS: None: 0 (0) Mild: 0.13 (0.41) Mild to moderate: 0.63 (0.88) Moderate: 1.75 (0.59) No patients classified as moderate-to-severe or severe Differences statistically significant, F = 45.5, 3 df, p <	**General comments:** None **Quality assessment:** - Consecutive patients, not all had JIA, moderate to no disability so full spectrum of disease not included - Instruments completed independently - Validity of hypothetical scenario for minimal change uncertain - Categorical change score done cross-sectionally based on current status compared to remembered status

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		(range 1-4) **Inclusion criteria:** - Inflammatory arthritis - Consecutive attendees to participating rheumatology clinics **Exclusion criteria:** NR	reduces disability by "just enough to make a difference" – adjusted activities on the original CHAQ to show how scores would change; same approach but for increased disability and made adjustments on QOMLQ Active joint count Steinbrocker functional assessment scale **Mode of administration:** Self-administered by parents and independently by children age ≥ 10	0.0001 Median values for children's ratings were not statistically significantly different from parent ratings **3) Other:** - Feasibility: NR - Responsiveness: Using hypothetical situation, median CHAQ minimal change for improvement = -0.13 and for worsening = 0.75. However, threshold varied by disability class, with higher disability patients requiring larger changes for improvement and smaller changes for deterioration. Using CCS scores, median values (IQR, range): Improvement (n = NR): 0 (0.27, -1.38-1.25) Worsening (n = NR): 0.13 (0.31, -0.50-2.38) - ROC curves: NR	

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Filocamo, Sztajnbok, Cespedes-Cruz, et al., 2007 **#1555**	**Geographical location:** 1 or 2 sites in Italy **Setting:** Specialty clinic **Study design:** Longitudinal non-RCT **Study objective(s):** "to develop and validate a new short and simple measure of physical function in children with JIA" **Duration of followup:** Mean 6 (3) months	**Number of patients:** 211, 114 with longitudinal follow-up **Age:** - Mean (SD): 8.8 (4.5) - Median: 8.2 - Range: 2.2-18.0 **Sex:** - Female: 154 (73%) - Male: 57 (27%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 15 (7.1%) **Baseline severity:** Time since diagnosis: Mean 4.4 (3.4) Active joint count (0-67): Mean 3.26 (6) Other: CHAQ: Mean 0.31 (0.4) JAFS: Mean 1.9 (2.7) **Inclusion criteria:** - Consecutive patients with JIA by ILAR criteria seen at study units between April and September 2005 - Parental informed consent	**Instrument(s) evaluated:** Juvenile Arthritis Functionality Scale (JAFS), 15 items scored 0-30, three 5-question domains (lower limbs, hand/wrist, upper segment) each scored 0-10; in Italian **Measured for construct validity** Child Health Questionnaire Physical (CHQP) and Psychosocial (CHQPsy) subscales Childhood Health Assessment Questionnaire (CHAQ) – Italian Parent global assessment of well-being (PGWB), VAS 0-10 Physicians global assessment of disease activity (PGDA), VAS 0-10 **Mode of administration:** Self-administered: JAFS and CHAQ	**1) Reliability:** - Test-retest: NR - Inter-rater: (see General comments) - Intra-rater: NR - Intra-class correlation: Cronbach's alpha for JAFS total (0.82), JAFS lower limb (0.86), JAFS hand/wrist (0.81), JAFS upper segment (0.62) **2) Validity:** Spearman correlations (n varies from 158 to 204) - Versus clinical outcomes: PGDA 0.54; PGWB 0.49; CHQP -0.58; CHQPsy -0.25 - Versus lab results: ESR 0.39, CRP 0.39 - Versus radiological results: NR - New instrument versus established instrument: CHAQ correlation with JAFS, spearman 0.73. The JAFS total and 3 subscales showed statistically significant differences for patients grouped into Steinbrocker functional classes I and II Subgroup analysis for patients with CHAQ > 0.5 showed higher correlations for JAFS and all measures except physician's	**General comments:** Inter-rater reliability was assessed using Cronbach's alpha **Quality assessment:** - Consecutive patients with JIA CHAQ and JAFS were completed in random order - Sample sizes not calculated - Analysis is appropriate with possible exception of inter-rater reliability

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Exclusion criteria: - Musculoskeletal abnormalities other than JIA - Other diseases that affected functional health status		global assessment **3) Other:** - Feasibility (n = 54 parents): JAFS mean 1.4 minutes (range 1-4), CHAQ 5.3 minutes (3-10). Among 136 parents, 89 (65.4%) preferred the JAFS, 40 (29.4%) preferred the CHAQ, 7 (5.2%) judged equivalent. No missing responses for JAFS. - Responsiveness (n = 114): Standardized response mean among improved patients as rated by physician (n = 20): JAFS 0.56 (95% CI 0-1.49) CHAQ 0.60 (0.24-0.94) Results similar using parent ratings. Standardized response mean among worsened patients as rated by physician (n = 26): JAFS 0.42 (95% CI 0.17-0.68) CHAQ 0.15 (0-0.55) Results similar using parent ratings. - ROC curves: NR	

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Geerdink, Prince, Looman, et al., 2009 **#1515**	**Geographical location:** Rotterdam, The Netherlands **Setting:** Specialty clinic **Study design:** Cross-sectional **Study objective(s):** ".. to develop a reliable and user-friendly digital CHAQ…" **Duration of followup:** NA	**Number of patients:** 51 **Age:** - Mean (SD): NR - Median: 11.2 - Range: IQ 8.1-15.0 **Sex:** - Female: 36 - Male: 15 **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 7 (13.7%) **Baseline severity:** Time since diagnosis: NR Active joint count: NR **Inclusion criteria:** Consecutive patients at outpatient pediatric rheumatology clinic **Exclusion criteria:** Insufficient knowledge of written Dutch language	**Instrument(s) evaluated:** Childhood Health Assessment Questionnaire – Dutch language, digital Modifications: Some change in question order; use of help or helping devices assessed after each of the 8 domains instead of twice; parent (CHAQ-PV) and child (CHAQ-CV) versions with "minor" differences in language **Mode of administration:** Other: Physician assistant completes patient's personal data; all remaining information self-administered (patient or parent) by computer	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: Digital vs. paper correlation: 0.974 Median values: Digital 0.72 (IQ range 0.13-1.25), paper 0.66 (IQR 0.13 to 1.13); digital gives statistically significant higher values (p = 0.032) VAS-Pain (correlation 0.989) and VAS-Well-being (correlation 0.951) correlated for digital and paper version; medians did not differ significantly **3) Other:** - Feasibility: Mean administration time: Digital version 5.06 minutes (SD 1.91) vs. 3.75 minutes (SD 1.84) for paper version; 75% of patients preferred the digital version; 14% no preference; 11% paper version - Responsiveness: NR - ROC curves: NR	**General comments:** None **Quality assessment:** - Spectrum: Consecutive; severity uncertain - Blinding: NA; order of administration randomized - Validated criterion: NA - FU > 80%: NA - Analysis appropriate: Yes

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Giannini, Ruperto, Ravelli, et al., 1997 **#1734**	**Geographical location:** Multinational; patient valdiation: Cincinnati, Ohio and Pavia, Italy **Setting:** Specialty clinics Other: Subjects' data for this study were taken from a previously published study (Giannini, Brewer, Kuzmina, 1992, #1008) **Study design:** Consensus process with comparison to study data **Study objective(s):** To identify a core set of outcome variables for the assessment of children with JA **Duration of followup:** NA	**Number of patients:** 78 **Age:** NR **Sex:** NR **Race/ethnicity:** NR **JIA diagnosis:** NR **Percentage with systemic JIA:** NR **Baseline severity:** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	**Instrument(s) evaluated:** Definition of improvement based on percent improvement and worsening as defined using the core variables including: physician global assessment, parent/patient assessment of well-being, functional ability, number of joints with active arthritis, number of joints with limited range of motion, and ESR **Mode of administration:** Consensus: mailed surveys Retrospective analysis using existing data from a previous study	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** 240 definitions of improvement considered, the sensitivity and specificity calculated using the physicians' consensus rating of improvement as the reference standard. Nine of the definitions with a sensitivity and specificity greater than 80% were retained, and each of these was tested on sample of patients from previously reported placebo controlled trial of methotrexate. Selected definition was at least 30% improvement from baseline in 3 of 6 variables in core set and no more than one with worsening by > 30% selected based on highest face validity rating and performance on patient sample. In a trial of methotrexate vs. placebo, 63.3% of those in the treatment group (n = 38) and 40% of those in the placebo group (n = 39) had improvement according to this instrument **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	**General comments:** The main goal of this study was to identify the criteria. Minimal validation data. Although rates of improvement based on the instrument were presented using data from a previous study, there was no data to assess the degree to which these subjects had improvement using alternative methods of assessment. **Quality assessment:** - Poor (for validation component) - Some variables had to be derived or converted for validation in patient population - No comment on if pts in study of MTX defined as improved or worsened using previous conventions.

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Len, Golden-berg, Ferraz, et al., 1994 **#1748**	**Geographical location:** Brazil **Setting:** Pediatric Rheumatology departments in 2 public hospitals **Study design:** Cross-sectional **Study objective(s):** To translate CHAQ into Portuguese and evaluate the reliability of the Portuguese version **Duration of followup:** NA	**Number of patients:** 53 **Age:** - Mean (SD): 11.1 - Range: 7-17 **Sex:** - Female: 28 (52.9%) - Male: 25 (47.1%) **Race/ethnicity:** NR **JIA diagnosis:** JRA **Percentage with systemic JIA (JRA):** 7.6% **Baseline severity:** Time since diagnosis: Mean 4.9 years (range 0.5-10.0) Number of involved joints: Mean 6.8 (range 1-24) Mean ESR: 29.9 mm (Westergren) **Inclusion criteria:** - Patients with JRA between 7 and 17 years old - Diagnosis of JRA according to the American Rheumatism Association 1977 criteria **Exclusion criteria:**	**Instrument(s) evaluated:** CHAQ (Portuguese version) **Mode of administration:** Interviewer-administered "First administered to children and then to parents by physiotherapist"	**1) Reliability:** - Test-retest: Pearson's correlation coefficient (n =26): Children = 0.96, parents = 0.96 - Kappa statistics: NR - Inter-rater: NR - Intra-rater:NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: Number of involved joints: CHAQ-children = 0.64 ($p < 0.01$) CHAQ-parents = 0.66 ($p < 0.01$) - Versus lab results: ESR: CHAQ-children = 0.55 ($p < 0.01$) CHAQ-parents = 0.54 ($p < 0.01$) - Versus radiological results: NR - New instrument versus established instrument: Disease Activity Index: CHAQ-children = 0.60 ($p < 0.01$) CHAQ-parents = 0.61 ($p < 0.01$) ACR Functional Class: CHAQ-children = 0.61($p < 0.01$) CHAQ-parents = 0.68 ($p < 0.01$) **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	**General comments:** None **Quality assessment:**

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Lurati, Pontikaki, Teruzzi, et. al., 2006 **#301**	**Geographical location:** Milan, Italy **Setting:** Specialty clinic **Study design:** Longitudinal non-RCT **Study objective(s):** Compare 4 sets of criteria (ACR 30, ACR 20, DAS and DAS 28) to evaluate clinical response criterion in JIA patients treated with methotrexate and/or anti-tumor necrosis factor α drugs **Duration of followup:** 6 months Patients evaluated at baseline and after 6 months of therapy with MTX or anti-TNFα drugs.	**Number of patients:** 75; patients aged > 16 years = 21; patients aged ≤ 16 years = 54 **Age:** - Mean (SD): 12.8 - Range: 2-32.9 years **Sex:** - Female: 61/75 - Male: 14/75 **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 16/75 **Baseline severity:** Stated that variables recorded were tender joint count, swollen joint count in 44 and 28 joints, limited joint count Ritchie Articular Index, ESR , pain evaluation (VAS) as reported by patient or parent/guardian, CHAQ, patients and physicians global disease activity score (VAS), but baseline values not presented in the article **Inclusion criteria:** JIA patients being treated with either MTX or anti-	**Instrument(s) evaluated:** ACR Pediatric 30 ACR 20 EULAR disease activity score (DAS) 28-joint DAS (DAS28) **Mode of administration:** Other: Investigation of indices of disease activity combining several variables with different modes of administration	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater:NR - Intra-class correlation: NR - Kohen's kappa for various comparison pairs (all patients, age < 16 years, age > 16 years): DAS/ACR Ped 30: 0.71 ± 0.1, 0.72 ± 0.1, 0.69 ± 0.2 DAS28/DAS: 0.68 ± 0.1, 0.65 ± 0.1, 0.73 ± 0.1 DAS28/ ACR Ped 30: 0.55 ± 0.1, 0.61 ± 0.1, 0.39 ± 0.2 DAS/ACR20: 0.53 ± 0.1, 0.61 ± 0.1, 0.21 ± 0.3 ACR20/ACR Ped 30: 0.53 ± 0.1, 0.56 ± 0.1, 0.33 ± 0.3 DAS28/ACR 20: 0.38 ± 0.1, 0.51 ± 0.1, invalid comparison, p > 0.05 - Fleiss Agreement Index: DAS/ACR Ped 30: Good/excellent DAS28/DAS: Good/excellent DAS28/ ACR Ped 30: Good DAS/ACR20: Good ACR20/ACR Ped 30: Good DAS28/ACR 20: Marginal/Good - Landis and Koch reproducibility index: DAS/ACR Ped 30: Substantial DAS28/DAS: Substantial DAS28/ ACR Ped 30: Moderate DAS/ACR20: Moderate	**General comments:** None **Quality assessment:**

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		TNFα drugs **Exclusion criteria:** NR		ACR20/ACR Ped 30: Moderate DAS28/ACR 20: Slight Somers' Δ for various comparison pairs (all patients, age < 16 years, age > 16 years): DAS/ACR Ped 30: 0.75 ± 0.1, 0.69 ± 0.1, 0.72 ± 0.2 DAS28/DAS: 0.73 ± 0.1, 0.61 ± 0.1, §) DAS28/ ACR Ped 30: 0.39 ± 0.1, §, §) DAS/ACR20: 0.35 ± 0.1,§ ,§ ACR20/ACR Ped 30: 0.30 ± 0.1, §, § DAS28/ACR 20: 0.33 ± 0.1, §, § § = Value not computable, because P > 0.05 **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: The concordance of different instruments using ACR Ped 30 as the gold standard: DAS (71% concordance) DAS 28- (55% concordance) ACR 20 (53% concordance) Sensitivity and specificity using ACR Ped 30 as the gold standard: DAS28: Sensitivity 0.9, Specificity 0.66 DAS: Sensitivity 0.93, Specificity 0.8	

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
				ACR20: Sensitivity 0.81, Specificity 0.84 **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: Mean area under the curve for: (a) DAS28: 0.702 (b) DAS: 0.735 (c)ACR20: 0.562	
Magni-Manzoni, Cugno, Pistorio, et al., 2005 **#1595**	**Geographical location:** Genova, Italy **Setting:** Specialty clinic **Study design:** Longitudinal non-RCT **Study objective(s):** Responsiveness of JIA clinical measures (physician and parent global assessment, the global articular severity score, and the morning stiffness to relevant increase in disease activity (disease flare) Disease flare defined as the presence of at least one of the following criteria: 1. New start, restart, or dose increase of ≥ 0.2 mg/kg/day of prednisone	**Number of patients:** 115 **Age:** - Mean (SD): NR - At onset: 4.9 (3.6) **Sex:** - Female: 91 (79%) - Male: 24 (21%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 10% **Baseline severity:** All values expressed as Mean (SD): Time since diagnosis (years): 8.9 (4.1) Active joint count: 3.2 (4.8)	**Instrument(s) evaluated:** Physician global assessment Parent global assessment Parent pain assessment CHAQ score (Italian version) **Mode of administration:** Self-administered Interviewer-administered Other	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness of clinical measures of JIA activity in the detection of disease flare in terms of Standardized Response Mean (SRM) and effect sizes (ES): Physician global assessment: Mean change: 5.4 (2.6) Effect size: 2.32	**General comments:** None **Quality assessment:**

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
	2. New start, restart, or dose increase of ≥ 5 mg/m^2/week of MTX or new start or restart of sulfasalazine 3. Association to MTX or sulfasalazine of a second-line drug including biologic agent 4. Association with increase in physician global assessment of overall disease activity ≥ 3 cm on VAS with respect to previous evaluation **Duration of followup:** Mean (range): 2.8 years (0.5 to 6.2 years)	Number of swollen joints: 1.9 (3.5) Number of joints with pain/tenderness: 1.7 (3.0) LROM score: 4.1 (7.3) Number of joints with LROM + POM/TD: 1.5 (2.5) Global articular severity score: 8.4 (12.0) ESR (mm/h): 18.9 (14.7) C-reactive protein: 1.8 (3.5) Physician global assessment: 1.8 (2.3) Parent global assessment: 1.8 (1.6) Parent pain assessment: 1.2 (2.1) CHAQ score: 0.2 (0.5) **Inclusion criteria:** - Diagnosis of JIA by ILAR criteria - Experience of disease flare - At least 6 months of follow up **Exclusion criteria:**		SRM: 2.07 95% CI: 0.67-3.17 Parent global assessment: Mean change: 1.5 (2.0) Effect size: 0.97 SRM: 0.80 95% CI: 0.19-1.28 Parent pain assessment: Mean change: 1.0 (2.5) Effect size: 0.47 SRM: 0.4 95% CI: 0-0.98 CHAQ score: Mean change: 0.2 (0.4) Effect size: 0.50 SRM: 0.60 95% CI: 0.25-0.96 - ROC curves: NR	

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Moretti, Viola, Pistorio, et al., 2005 **#401**	**Geographical location:** Genova, Italy **Setting:** Specialty clinic **Study design:** Longitudinal non-RCT **Study objective(s):** To "…compare the relative responsiveness of traditional condition specific measures with that of a generic pediatric HRQoL instrument" **Duration of followup:** 6 months	**Number of patients:** 44 **Age:** - Mean (SD): 7.2 years - Range 2.6 to 14.8 yrs **Sex:** - Female: 35 - Male: 9 **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** None **Baseline severity:** Time since diagnosis: Mean 3.4 years (range 1.2-10.4) Active joint count: Median 2.0 (range 1 to 4) Other: 24 no systemic medication; 20 NSAIDs; 8 methotrexate CHQ disability: Mean (SD) 0.36 (0.49) CHQ physical: 39.67 (13.79) CHQ psychosocial: 44.52 (9.58) **Inclusion criteria:** - JIA - ≤ 4 joints involved	**Instrument(s) evaluated:** Italian version of the Child Health Questionnaire (CHAQ, range 0-3) Italian version of the Child Health Questionnaire (CHQ) reported as physical and psychosocial subscales Physician global assessment (PGA) of overall disease activity (0-10 VAS) Parent global assessment (PGW) of overall well-being (0-10 VAS) **Mode of administration:** NR External criterion: Improved = complete remission or much improved; stable = slightly improved or unchanged; worse = slightly worse or much worse – rated by clinician and parent (results reported separately for physician and parent ratings)	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: Mean change scores (6 month – baseline) for groups classified by physician as improved (n = 23), stable (n = 14), worsened (n = 7): CHAQ disability index: -0.12, -0.13, 0.11 CHQ physical score: 4.99, 0.92, -6.00 CHQ psychosocial score: 4.69, 2.01, -10.10 PGA: -5.14, -1.37, 1.12 PGW: -1.65, 0.14, -0.16 (Note: SDs not reported) - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: Standardized responsiveness, effect size, Guyatt statistic: CHAQ disability index: 0.25, 0.17, 0.29 CHQ physical score: 0.19, 0.18, 0.33 CHQ psychosocial score: 0.28, 0.23, 0.72 PGA: 0.82, 1.46, 2.24	**General comments:** - Physician's global assessment not independent from physician's external criterion - Narrow spectrum of disease **Quality assessment:** - Spectrum: Limited - Blind criterion: Physician's "external criterion" independent and blind to CHAQ and CHQ but not physicians global assessment - Blinded instrument: Can't tell - Validated criterion: Uncertain - F/U ≥ 80%: Yes - Analyses appropriate: Yes

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		- Received an intra-articular corticosteroid injection at baseline **Exclusion criteria:** Further intra-articular corticosteroid injection during followup		PGW: 0.30, 0.33, 0.54 ROC curves: CHAQ disability index: 0.56 (95% CI 0.40 to 0.71) CHQ physical score: 0.67 (0.50 to 0.81) CHQ psychosocial score: 0.71 (0.54 to 0.85) PGA: 0.86 (0.72 to 0.95) PGW: 0.63 (0.46 to 0.78)	
Oliveira, Ravelli, Pistorio, et al., 2007 **#1777**	**Geographical location:** 32 countries in South America, Europe, Israel, Korea, Russia, Turkey and the UK **Setting:** Healthy children were siblings of JIA children or from schools; JIA participants not described **Study design:** Cross-sectional **Study objective(s):** To investigate proxy-reported HRQOL **Duration of followup:** NA	**Number of patients:** - 3324 JIA - 3315 healthy **Age:** - Mean (SD): 11.2 (3.9) healthy; 10.0 (4.4) JIA - Median: NR - Range: NR **Sex:** - Female: 1694 (51%) healthy; 2250 (68%) JIA - Male: 1621 (49%) healthy; 1074 (32%) JIA **Race/ethnicity:** NR **JIA diagnosis:** JIA: - 655 had systemic - 1130 had polyarthritis - 579 had extended oligoarthritis - 960 had persistent oligoarthritis	**Instrument(s) evaluated:** Childhood Health Assessment Questionnaire (CHAQ) – in patient's national language (includes VAS for pain) Child Health Questionnaire (CHQ), physical summary score (PhS) and psychosocial summary score (PsS) **Comparators:** Attending physician assessed: Active joint count, joints with swelling, joints with tenderness, joints with limited ROM, global assessment of overall disease activity on 10 cm VAS ESR **Mode of administration:**	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Internal validity: NR **2) Validity:** - Versus clinical outcomes: Mean score for JIA vs. healthy controls: PhS: 44.5 (10.6) vs. 54.6 (4.0) PsS: 47.6 (8.7) vs. 51.9 (7.52) Patients with "persistent oligoarthritis" had better HRQOL on all CHQ subscales and summary scores than those with extended oligoarthritis, polyarthritis, or systemic arthritis; $p < 0.001$ for all comparisons Spearman correlation coefficient for PhS: Active joints: -0.42 - Versus lab results: Spearman correlation coefficient for PhS: ESR: -0.36	**General comments:** None **Quality assessment:** - Large multinational sample - Unclear if measures completed independently from clinical assessments; unclear if order randomized - Analysis appropriate

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Percentage with systemic JIA: 19.7% of those with JIA **Baseline severity:** Time since diagnosis: 4.1 years (3.5) Active joint count: 5.8 (8.1) ESR: 30.4 (25.4) CHAQ disability index: 0.8 (0.8) **Inclusion criteria:** - Patients (JIA by ILAR criteria) and healthy children enrolled in the PRINTO study - Age ≤ 18 years **Exclusion criteria:** - Psoriatic arthritis - Enthesitis related arthritis	Self-administered Interviewer-administered Other [specify]	- Versus radiological results: NR - New instrument versus established instrument: Spearman correlation coefficient for PhS: CHAQ: -0.63 Parent VAS pain: -0.63 Parents rating of overall well-being: -0.61 Physician global: -0.52 "All Spearman's correlations between the PsS and JIA severity measures were poor (r = -0.13, 0.36)" **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: CHAQ score of > 1 determined to discriminate best between JIA and healthy controls. 838 (29%) of 2883 JIA patients had scores > 1; all healthy controls had scores < 1	

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Palmisani, Solari, Magni-Manzoni, et al., 2006 **#1569**	**Geographical location:** Genoa, Italy **Setting:** Specialty clinic **Study design:** Cross-sectional **Study objective(s):** Comparing the correlation between JIA measures of disease activity and damage in patients with early and late stage disease. Comparison is across 3 cohorts classified as: (1) early disease (ED) (disease duration ≤ 1yr); (2) advanced disease (AD) (duration 5-9.9 yrs); (3) longstanding disease (LD) (disease duration ≥ 10 yrs) **Duration of followup:** NA	**Number of patients:** Total number of patients: 223 (ED = 70, AD = 114, LD = 39) **Age:** - Median (Range) ED: 0.6 (0.1-1.5) AD: 6.5 (5.0-9.9) LD: 12.5 (10-25) **Sex:** - Female: ED: 52 (74%) AD: 90 (79%) LD: 29 (74%) - Male: ED: 18 (26%) AD: 24 (21%) LD: 10 (26%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 10% **Baseline severity:** ED = 70, AD = 114, LD = 39 Time since diagnosis: ED: 0.6 (0.1-1.5) AD: 6.5 (5.0-9.9) LD: 12.5 (10-25) Active joint count: ED: 2.5 (0-19)	**Instrument(s) evaluated:** CHAQ **Mode of administration:** Self-administered	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: ED (early stage): No. of joints with tenderness/pain on movement (0.33) No. of swollen joints (0.22) No. of joints with LROM (0.33) No. of active joints (0.14) AD (advanced disease): No. of joints with tenderness/pain on movement (0.58) No. of swollen joints (0.41) No. of joints with LROM (0.47) No. of active joints (0.53) LD (late stage): No. of joints with tenderness/pain on movement (0.73) No. of swollen joints (0.28) No. of joints with LROM (0.76) No. of active joints (0.61) - Versus lab results: ED (early stage): ESR: 0.31 CRP: 0.22 AD (advanced disease): ESR: 0.27 CRP: 0.26	**General comments:** None **Quality assessment:**

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		AD: 2 (0-30) LD: 2.0 (0-39) **Inclusion criteria:** JIA patients fulfilling the ILAR criteria for JIA **Exclusion criteria:** NR		LD (late stage): ESR: 0.23 CRP: 0.55 - Versus radiological results: ED Poznanski score (-0.31) AD Poznanski score (-0.02) LD Poznanski score (-0.62) **- New instrument versus established instrument:** Physician global: ED-0.45 AD-0.46 LD-0.38 Parent global: ED-0.62 AD-0.70 LD-0.51 **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Pouchot, Larbre, Lemelle, et al., 2002 **#1650**	**Geographical location:** France **Setting:** Outpatient clinics across 16 participating hospitals in a multi-center study in France **Study design:** Cross-sectional **Study objective(s):** Translate, cross-culturally adapt, and validate CHAQ in children with JIA **Duration of followup:** NR	**Number of patients:** 500 children including 306 patients and 194 healthy controls **Age:** - Mean (SD): Systemic: 9.4 ± 5.0 Polyarticular:11.1 ± 4.5 Extended oligoarticular: 10.0 ± 4.2 Persistent oligoarticular: 7.6 ± 3.8 Healthy children (controls): 11.4 ± 3.9 **Sex:** - Female: 77% - Male: 33% **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 23% **Baseline severity:** Time since diagnosis: Systemic: 4.0 ± 3.8 Polyarticular: 4.9 ± 4.0 Extended oligoarticular: 6.4 ± 3.9 Persistent oligoarticular: 3.7 ± 3.2 Healthy children (controls): 11.4 ± 3.9 Active joint count: NR	**Instrument(s) evaluated:** CHAQ (French version) **Mode of administration:** Self-administered	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: 0.91 (0.87-0.94) - Cronbach's alpha ≥ 0.70 for 7 of the 8 domains (0.69-0.90; 0.69 for Arising) **2) Validity, evaluated by calculating Pearson's coefficient, n = 306** - Versus clinical outcomes: Swollen joint count: 0.4 (0.0001) Painful joint count: 0.43 (0.0001) Stiff joint count: 0.57 (0.0001) - Versus lab results: ESR: 0.32 (0.0001) - Versus radiological results: NR - New instrument versus established instrument: NR -Overall physician's assessment (VAS)-0.49 (0.0001) Pain (parent's assessment, VAS)-0.49 (0.0001) Overall impact (parent's assessment, VAS): 0.54 (0.0001) **3) Other:**	**General comments:** None **Quality assessment:**

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Inclusion criteria: Children with JIA meeting Durban's 1997 criterion *and* with systemic, polyarticular, extended oligoarticular, or persistent oligoarticular disease **Exclusion criteria:** Patients with psoriatic arthritis or juvenile spondyloarthritis		- Feasibility: NR - Responsiveness: NR - ROC curves:	
Pouchot, Ecosse, Coste, et al., 2004 **#1612**	**Geographical location:** France **Setting:** Specialty clinic – outpatient pediatric clinics of 16 pediatric referral centers **Study design:** Cross-sectional **Study objective(s):** Assessment of the validity of CHAQ in two age groups of children, using Rasch model scoring to determine variation in item level difficulty by age group **Duration of followup:** NA	**Number of patients:** 306 Age 1-9: n = 156 Age ≥ 10: n = 151 **Age:** - Mean (SD): Systemic: 9.4 ± 5.0 Polyarticular: 11.1 ± 4.5 Extended oligoarticular: -10 ± 4.2 Persistent oligoarticular: 7.6 ± 3.8 **Sex:** - Female: 238 - Male: 68 **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 70/306 (23%)	**Instrument(s) evaluated:** CHAQ (French Version) **Mode of administration:** Self-administered (completed by parent)	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** Spearman correlation coefficients are reported for the two age groups (1-9 years and ≥ 10 years), P < 0.0001 for all - Versus clinical outcomes: Number of swollen joints (0.44, 0.31) Number of painful joints (0.32, 0.47) Number of joints with limited range of motion (0.47, 0.52) Number of active joints (0.45, 0.53) - Versus lab results: ESR (0.37, 0.41)	**General comments:** Assessment of the validity of CHAQ in two age groups of children, using Rasch model scoring to assess bias due to variation of item difficulty across age **Quality assessment:**

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Baseline severity: Time since diagnosis (mean ± SD, yrs): Systemic: 4.0 ± 3.8 Polyarticular: 4.9 ± 4.0 Extended oligoarticular: 6.4 ± 3.9 Persistent oligoarticular: 3.7 ± 3.2 Active joint count: Systemic: 7.3 ± 10 Polyarticular: 7.4 ± 10.2 Extended oligoarticular: 3.9 ± 4.8 Persistent oligoarticular: 1.2 ± 2.1 ESR: Systemic: 37.7 ± 26.0 Polyarticular: 16.2 ± 14.2 Extended oligoarticular: 26.1 ± 18.4 Persistent oligoarticular: 21.2 ± 17.2 Physician VAS: Systemic: 3.1 ± 2.8 Polyarticular: 2.9 ± 2.8 Extended oligoarticular: 2.7 ± 2.1 Persistent oligoarticular: 1.8 ± 1.6 **Inclusion criteria:** Children with systemic, polyarticular (5 or more joints affected), extended oligoarticular, or persistent		- Versus radiological results: NR - New instrument versus established instrument: Physician global assessment (0.45, 0.53) **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		oligoarticular JIA satisfying the Durban criteria **Exclusion criteria:** NR			
Ruperto, Ravelli, Falcini, et al., 1998 **#812**	**Geographical location:** Italy, multicenter **Setting:** Specialty clinic **Study design:** Longitudinal non-RCT **Study objective(s):** Investigate performance of core set of outcome measures and the preliminary definition of improvement in JIA population treated with MTX Variables assessed: (1) physician global assessment of disease activity; (2) parent or patient (if appropriate in age) global assessment of overall well being; (3) functional ability; (4) number of joints with active arthritis; (5) number of joints with limited range of motion; (6) erythrocyte sedimentation rate **Duration of followup:** 6 months	**Number of patients:** 111 **Age:** NR **Sex:** - Female: 74 (67%) - Male: 37 (33%) **Race/ethnicity:** NR **JIA diagnosis:** JCA (all poly) **Percentage with systemic JIA:** 40 (31%) **Baseline severity:** Time since diagnosis: 3.4 years (0.5-14.9) Active joint count: NR **Inclusion criteria:** -Diagnosis of JCA according to the criteria of the European League Against Rheumatism (EULAR) -Disease duration of at least 6 months - At least five joints with active arthritis (defined as the presence of	**Instrument(s) evaluated:** The physician global was scored on a 5-point ordered categorical scale (1 = none, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe), not the VAS* Parent/patient global was assessed by asking parents to judge their child's overall well being at 6 months as compared with baseline according to a 3-point categorical scale (better, same, worse), not VAS* Functional status: CHAQ, JAFAR, or Modified Lee Index Joint count: 64 joints **Mode of administration:** Mixed	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity, by Spearman's correlation coefficient:** - Versus clinical outcomes: Physician global versus: Parent global: 0.56 ESR: 0.47 Functional ability: 0.51 LROM: 0.40 Active joints: 0.54 Active joint count versus: Parent global: 0.36 Functional ability: 0.31 LROM: 0.7 Parent global versus: Functional ability: 0.25 LROM: 0.30 - Versus lab results: ESR versus: Physician global: 0.47 Active joint count: 0.34 Parent global: 0.27 Functional ability: 0.24 LROM: 0.29	**General comments:** - No comment on sample size or blinding - Unclear number lost to followup/dropout - Used different scales for parent and physician global assessments instead of VAS **Quality assessment:**

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		swelling or limitation of movement with either pain upon movement or tenderness) that was not adequately controlled by NSAIDs or DMARDs **Exclusion criteria:**		- Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	
Ruperto, Ravelli, Falcini, et al., 1998 **#1717**	**Geographical location:** Italy **Setting:** NR **Study design:** Longitudinal non-RCT **Study objective(s):** Examine the responsiveness of outcome variables used in clinical trials in children with oligoarticular JCA **Duration of followup:** 3 months	**Number of patients:** 26 **Age:** - Mean (SD): NR - Median: 4.7 years - Range: 1.5-14.8 years **Sex:** - Female: 22 (85%) - Male: 4 (15%) **Race/ethnicity:** NR **JIA diagnosis:** JCA-oligoarticular **Percentage with systemic JIA:** 0 **Baseline severity:** Disease duration: Median 2.5 years (range 0.2-13.2) Active joint count: NR **Inclusion criteria:** Diagnosed with oligoarticular JCA **Exclusion criteria:** NR	**Instrument(s) evaluated:** Physician global (15 cm VAS) Parent global (15 cm VAS) Parent assessment of pain (15 cm VAS) CHAQ – Italian language version Articular (64 joints): Number and score of painful joints Number and score of swollen joints Number and score of joints with LROM Number of active joints Global severity score Clinical improvement defined by PAVIA criteria: 30% improvement in 3 of 6 core variables with ≤ 1 variables worsening by > 30% **Mode of administration:** NR for patient and parent instruments All clinical assessments	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: SRM: Physician global: 0.9 Parent global: 0.5 Parent assessment of pain: 0.3 CHAQ: 0 Articular: Number and score of painful joints: 0/0.7 Number and score of swollen joints: 0.7/1.3 Number and score of joints with	**General comments:** None **Quality assessment:** - Consecutive patients but small sample - Single rater completed all physician assessments and unclear if assessments completed blind to parent/patient reported outcomes - Followup rates not explicitly reported - No sample size calculation - All assessments on individual patients made by a single rater

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
			on individual patients made by a single rater	LROM: 0.7/0.7 Number of active joints: 1.3 Global severity score: 1.3 Effect sizes: Physician global: 1.0 Parent global: 0.5 Parent assessment of pain: 0.2 CHAQ: 0 Articular: Number and score of painful joints: 0/0.4 Number and score of swollen joints: 1.3/0.9 Number and score of joints with LROM: 0.7/0.4 Number of active joints: 0.7 Global severity score: 0.9 Guyatt responsiveness statistics: Physician global: 2.5 Parent global: 1.3 Parent assessment of pain: 1.2 CHAQ: 0.5 Articular: Number and score of painful joints: -/1.3 Number and score of swollen joints: 1.3/1.3 Number and score of joints with LROM: -/1.3 Number of active joints: 2.7 Global severity score: 2.4 - ROC curves: NR 5 measures most responsive: Physician global Number swollen joints	

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
				Score swollen joints Active joint count Global articular severity score	
Ruperto, Ravelli, Falcini, et al., 1999 **#769**	**Geographical location:** Italy, multiple sites **Setting:** NR **Study design:** Longitudinal non-RCT **Study objective(s):** Examine the responsiveness of disease activity measures used in clinical trials in JCA **Duration of followup:** 6 months	**Number of patients:** 132 **Age:** NR **Sex:** - Female: 91 (67%) - Male: 41 (33%) **Race/ethnicity:** NR **JIA diagnosis:** JCA- poly **Percentage with systemic JIA:** 51 (39%) **Baseline severity:** Median disease duration (range): 1.7 years (0.5-14.9) Median active joint count: 10 **Inclusion criteria:** - Diagnosed with oligoarticular JCA - Disease duration at least 6 months - At least 5 joints with active arthritis not adequately controlled with NSAID or second-line agent	**Instrument(s) evaluated:** Physician global Parent global Parent assessment of pain Modified Lee or JAFAR or CHAQ Articular: Number and score of painful joints Number and score of swollen joints Number and score of joints with LROM Number of active joints Global severity score Morning stiffness, min Labs: ESR CRP Hgb Plts **Mode of administration:** NR	**1) Reliability:** - Test-retest: NR - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: All PedsQL scores: range 0.39 to 0.78 **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: Median change 6 months/effect size/SRM: Physician global: -2/1.33/1.33 Parent global: -0.8/1.28/1.14 Parent assessment of pain: -0.3/0.27/0.25 Modified Lee Index: -2/0.38/0.67 JAFAR: -2/0.19/0.31 CHAQ: -0.4/0.30/0.57 Articular: Number and score of painful joints Number: -4/0.53/0.76 Score: -6/0.57/0.80	**General comments:** - No discussion of how patients selected - No information on how many lost to followup - No comparison of those who participated verss not - No comment on blinding **Quality assessment:** - Fair/poor - No sample size calculation

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Exclusion criteria: NR		Number and score of swollen joints: Number: -3/0.33/0.67 Score: -6/0.47/0.80 Number and score of joints with LROM: Number: -3/0.31/0.67 Score: -5/0.33/0.67 Number of active joints: -4/0.34/0.71 Global severity score: -18/0.52/0.83 Morning stiffness, min 0: -10/0.15/0.22 Labs: ESR: -20/0.61/0.74 CRP: -1.8/0.45/0.60 Hgb: 0.6/0.41/0.49 - ROC curves: NR Measures most responsive: Painful joint number and score, global articular severity score No differences by disease subtype	

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Saad-Magal-haes, Pistorio, Ravelli, et al., 2010 **#1510**	**Geographical location:** European, U.S.A and South American sites **Setting:** NR **Study design:** Cross-sectional cohort and a longitudinal cohort **Study objective(s):** Examine whether CHAQ disability index (DI) scoring systems and its responsiveness to change differed significantly when calculated without aids/devices or help **Duration of followup:** Cross section cohort - NA Longitudinal 6 months	**Number of patients:** 2786 in cross-sectional cohort screened, 65 excluded due to age >19, 31 for missing baseline CHAQ, 27 because CHAQ incomplete Total N = 2663 (96%) 595 longitudinal cohort 54 excluded incomplete CHAQ, 9 because > 19 years, 2 for missing baseline CHAQ Total N = 530 (89%) **Age:** Cross-sectional median (range): 10.5 (7.1-13.9) Longitudinal median (range): 7.9 (4.3-11.4) **Sex:** Cross-sectional: - Female: 1779 (66.8%) - Male: 884 (33.2%) Longitudinal: - Female: 381 (71.9%) - Male: 149 (28.1%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** Cross-sectional: 557 (20.9%) Longitudinal: 73 (13.8%)	**Instrument(s) evaluated:** CHAQ and CHAQDI in participant's national language **Mode of administration:** Self-administered (parent) CHAQ scored using 4 methodologies: - Original scoring system - Omitting 14 items related to use of aids/devices - Omitting 8 items specific to the need for help from another person - Omitting both aids/devices items and need for help items	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus radiological results: NR - Versus clinical outcomes Spearman's correlation coefficient for the 4 scoring approaches Physician global: Cross: 0.43 all 4 Long: 0.31 to 0.33 Number of active joints: Cross: 0.36-0.37 Long: 0.33 Child pain VAS: Cross: 0.54 Long: 0.50-0.51 Child well-being VAS Cross: 0.56-0.58 Long: 0.52-0.54 - Versus lab results: ESR: Cross: 0.34-0.35 Long: 0.18-0.20 - New instrument versus established instrument: No differences across the 4 CHAQs	**General comments:** No comment on blinding **Quality assessment:** - Large sample - Blinding not reported - High followup in longitudinal sample - Good quality - No race/ethnicity specified, but multinational

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Baseline severity: Disease duration: Cross-sectional: 3.7(1.7-6.6) Longitudinal: 1.3 (0.7-3.6) Active joint count: Cross-sectional: 1 (0-5) Longitudinal: 9 (6-16) ESR: Cross-sectional: 20 (10-36) Longitudinal: 40 (22-62) **Inclusion criteria:** - JIA-all subtypes for cross-sectional sample; JIA-polyarticular for longitudinal sample - Age ≤ 19 years - Completion of at least 6 functional areas of the CHAQ **Exclusion criteria:**		**3) Other:** - Feasibility: NR - Responsiveness: Used longitudinal cohort: SRM large (≥ 0.8, 95% CI 0.77-0.96) for responders (ACR 30 criteria) to MTX and unchanged by 4 different measures, and poor for those who didn't respond (SRM: 0.01), no difference by 4 different measures - ROC curves: NR Mean change in score: Removing aids/help decreased score by 0.1 from cross-sectional cohort (0.64 original to 0.54 with aids/help removed; $p < 0.0001$) and by 0.15 for longitudinal cohort (1.23 to 1.07; $p < 0.0001$)	

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Sawyer, Carbone, Whitham, et al., 2005 **#1592**	**Geographical location:** South Australia **Setting:** Specialty clinic – rheumatology clinic **Study design:** Longitudinal non-RCT **Study objective(s):** - Compare ratings of children's HRQL from parents and children with JIA - Investigate extent to which these ratings change over time - Examine relationship between children's HRQL and pain and use of pain coping skills **Duration of followup:** 12 months	**Number of patients:** 81 screened 64 (79%) agreed to participate 54 completed study **Age:** - Mean (SD): 12.8 (3.3) - Median: NR - Range: NR **Sex:** - Female: 31 (57.4%) - Male: 23 (42.6%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 7% **Baseline severity:** Time since diagnosis: (phrased duration of care): Mean (SD) = 5.7 ± 2.8 Active joint count: NR **Inclusion criteria:** All children 8-18 diagnosed with JIA at least 6 months prior to study and attending the rheumatology clinic **Exclusion criteria:** Insufficient English to complete questionnaires	**Instrument(s) evaluated:** HRQL per PedsQL 4.0 Generic Core Scales and PEDS QL 3.0 Arthritis Module of the pediatric Quality of Life inventory Pain by VAS (10 cm) from the Varni-Thompson Pediatric Pain Questionnaire (PPQ) CHAQ **Mode of administration:** Self-administered – but research assistant available for questions	**2) Reliability:** - Test-retest: NR - Inter-rater: Children in 3 of 4 subscales reported higher scores (better QL) than parent reports PedsQL generic: Differences in mean scores (child vs. parent) ranged from 7.1 (social functioning) to 12.5 (emotional functioning) points higher. Correlation coefficients between parent and child for the 4 subscales ranged from 0.5 to 0.8 for the 4 subscales. Children reported higher scores than parents for 1 (daily activities) of 4 subscales Peds QL- disease specific, Daily activities: Parent: 80.9 (22.8) Child: 87.9 (17.2) Correlation coefficients ranged from 0.5 to 0.9 for 3 subscales; 0.3 for the Worry scale - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: Peds QL-generic: 3 of 4 subscales (not social functioning) were significantly associated with pain reported by parent, and all subscales were associated with child-reported pain	**General comments:** - Questionnaires completed independently - Standard measures used **Quality assessment:** - Good quality - Small sample but selected consecutively - Limited measures for construct validity (only associated with pain scores) - F/U rate good - No sample size calculation

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
				Peds QL-disease specific: 3 of 4 subscales (not daily activities) were significantly associated with pain reported by parent, and all subscales were associated with child-reported pain - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	
Selvaag, Flato, Lien, et al., 2003 **#1628**	**Geographical location:** Oslo **Setting:** Pediatric Rheumatology **Study design:** Longitudinal cohort **Study objective(s):** Identify determinants of the CHQ in JIA and assess the responsiveness of the instrument **Duration of followup:** Mean follow up 10.0 ± 3.8 months	**Number of patients:** 166 approached; 12 declined, 4 with inadequate Norwegian language skills, and 34 with incomplete data; 116 (69.9%) out of 166 children with JIA and 116 matched healthy controls **Age:** Mean (SD) JIA: 9.2 (3.4) Controls: 9.3 (3.5) **Sex:** JIA: - Female: 70 (60.3%) - Male: 46 (39.7%) Controls: - Female: 70 (60.3%) - Male: 46 (39.7%)	**Instrument(s) evaluated:** Child Health Questionnaire (CHQ) Physical (Phs) and Psychosocial (PsS) subscales – Norwegian version **Mode of administration:** Self administered: "Most of the data in this study are taken from the parents' questionnaires" Improvement defined using ACR criteria: 30% improvement from baseline to followup in at least 3 of 6 core variables and a maximum of one variable worsening by > 30%	**1) Reliability:** - Test-retest: NR - Inter-rater: Parent vs. patient: Intraclass correlation coefficient for child vs. parent ranged from 0.69 to 0.87 ($p < 0.001$) for concepts related to physical functioning Ranged from 0.38 to 0.53 for mental health, self esteem, and behavior ($p = 0.038$ to 0.003) Compared to controls, scores for JIA patients showed statistically significantly poorer physical health and parental concepts but no difference in psychosocial factors (except role emotional/behavioral) - Intra-rater: NR - Intra-class correlation: NR	**General comments:** - No comment on blinding - Multiple JIA subtypes included, but small number of subtypes other than oligoarticular and polyarticular - < 80% at followup - Discriminate validity vs. health controls is not particularly useful for our question of the validity/reliability/ responsiveness as used in trials of children with JIA **Quality assessment:** - Fair quality - Blinding not addressed - Followup rate uncertain but approximately 116/150 (77%) - No sample size calculation

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Race/ethnicity: NR **JIA diagnosis:** JRA (n = 105); Juvenile spondyloarthropathy (n = 11) **Percentage with systemic JIA:** 5 (4.3%) **Baseline severity:** Disease duration (mean [SD]): 12.1 (7.5) months Active joint count (mean [CI]): 2.2 (1.5, 2.8) Arthritis activity index (mean [CI]): 6.8 (4.8, 8.8) Physician global (mean [CI]): 2.4 (2.3, 2.6) on a scale of 1-5 **Inclusion criteria:** - JIA - Disease duration < 2.5 years **Exclusion criteria:** NR		**2) Validity:** - Versus radiological results: NR - Versus clinical outcomes: Pearson's correlation coefficients (PhS; PsS): Parent's pain VAS: -0.624*; -0.143 (p = 0.129) Parent's global: -0.661*; -0.315* Physician global: -0.556*; -0.048 (p = 0.609) No active joints: -0.360*; -0.024 (p = 0.802) - Versus lab results: ESR: -0.479*; 0.006 (p = 0.951) - New instrument versus established instrument: CHQ vs CHAQ: -0.57; -0.219 (p = 0.018) * p < 0.001 **3) Other:** - Feasibility: NR - Responsiveness: Standardized response mean (SRM) for CHQ if pts Improved (n = 45): 0.96 Worsened (n = 14): -0.60 Unchanged (n = 57): 0.16 - ROC curves: NR	

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Singh, Athreya, Fries, et al., 1994 **#1747**	**Geographical location:** Palo Alto, Philadelphia **Setting:** Subspecialty (pediatric rheumatology) **Study design:** Cross-sectional **Study objective(s):** Develop and validate a self/parent administered instrument for measuring functional status in children with JRA **Duration of followup:** Mean of 12.8 days in a subgroup (n = 13)	**Number of patients:** 72 JRA patients; 22 healthy controls (face validity only) **Age:** JRA patients: - Mean (SEM): 9.1years (0.6) - Median: NR - Range: 1-19 Controls: - Mean (SEM): 7.9 years (0.8) - Median: NR - Range: 1-17 **Sex:** JRA patients: - Female: 45 (62.5%) - Male: 27 (37.5%) Controls: - Female: 13 (59%) - Male: 9 (41%) **Race/ethnicity:** NR **JIA diagnosis:** JRA **Percentage with systemic JIA:** 16 (22%) **Baseline severity:** Disease duration: NR Active joint count: NR Other:	**Instrument(s) evaluated:** CHAQ **Mode of administration:** Self-administered	**1) 1) Reliability:** - Test-retest (N = 13): Mean time between surveys: 12.8 days Survey #1 mean (SEM): 0.96 (0.26) Survey #2 mean (SEM): 0.96 (0.23) Paired t-test no difference in means (p > 0.9) Spearmans' Correlation: 0.79 (p < 0.002) - Inter-rater (n = 29): Parent vs. patient: Mean (SEM) Parent score = 0.83 (0.26) Patient score = 0.76 (0.16) Paired t-test = no difference in means (p > 0.4) Spearman's correlation = 0.84 (p < 0.001) - Intra-rater: NR - Internal reliability: Cronbach's alpha = 0.94 **2) Validity:** - Versus radiological results: NR - Versus clinical outcomes (Kendall's tau b): Steinbrocker functional class: 0.77 Number of involved joints: 0.67 - Physician assessment of disease activity: 0.67 - Versus lab results: NR	**General comments:** - No comment on blinding - Face validity assessed by multidisciplinary group **Quality assessment:** - Small sample and eligibility criteria not specified - Blinding not addressed - No sample size calculation

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		4-point scale: Inactive: 9 (13%) Mild: 32 (44%) Moderate: 24 (33%) Severe: 7 (10%) Steinbrocker Functional Class: I: 38 (53%) II: 18 (25%) III: 14 (19%) IV: 2 (3%) **Inclusion criteria:** NR **Exclusion criteria:** NR		- New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	
Stephens, Singh-Grewal, Bar-Or, et al., 2007 **#1548**	**Geographical location:** Toronto, Ontario **Setting:** Specialty clinic **Study design:** RCT **Study objective(s):** To determine the reliability of formal exercise testing and of functional and activity questionnaires in children with JIA **Duration of followup:** 2-6 weeks	**Number of patients:** 80 enrolled 74 completed (5 dropped out after test 1, 1 patient dropped out due to change in diagnosis) **Age:** - Mean (SD): 11.4 (2.3) - Median: NR - Range: 8-16 years **Sex:** NR **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 5 (7%) **Baseline severity:**	**Instrument(s) evaluated:** CHAQ-DI **Mode of administration:** Self-administered	**1) Reliability:** - Test-retest: ICC = 0.82 - Kappa statistics: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity:** - Versus clinical outcomes: NR - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	**General comments:** None **Quality assessment:**

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		Time since diagnosis (disease duration): 3.74 (3.21) Active joint count (mean [SD]): 2.84 (5.8) **Inclusion criteria:** Children with JIA **Exclusion criteria:** - Unstable disease (defined as being likely to change medication regimen within the next 12 weeks) - Cardiac, pulmonary, or metabolic disease - Moderate or severe hip pain when walking - Active systemic features - Engaged in > 3 hours per week of structured physical activity			

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Sztajnbok, Coronel-Martinez, Diaz-Maldo-nado, et al., 2007 **#1568**	**Geographical location:** Genova, Italy **Setting:** Subspecialty **Study design:** Cross-sectional cohort **Study objective(s):** Examine the discrepancy between the physician's and parent's global assessments of disease status and the factors explaining discordance **Duration of followup:** NA	**Number of patients:** 197 **Age:** - Mean: 8.4 (4.5) - Median: 8.2 - Range: 1.2-22.3 **Sex:** - Female: 146 (74.1%) - Male: 51 (25.9%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 15 (7.6) **Baseline severity:** Disease duration (mean [SD]): 3.9 (3.7) Active joint count: Mean (SD): 3.9 (4.5) Median: 2.0 Range: 0-26.0 ESR: Mean (SD): 28.8 (24.4) Median: 20.0 Range: 1.0-130 **Inclusion criteria:** - JIA - Seen in study unit between Feb 2002 and Oct 2004 - Had to have physician	**Instrument(s) evaluated:** Physician Global disease activity (VAS, 10 cm, 10 is worst) Parent Global well-being, (VAS, 10cm, 10 is worst) Parent Pain (VAS, 10 cm, 10 is worst) **Mode of administration:** Physician global – pediatric rheumatologist exam Self-administered (parent)	**1) Reliability:** - Inter-rater: On average, global physician rating higher (worse) than parent Differences (parent-physician rating) ranged from -9.4 to 4.5 (mean -2 ± 2.8, median -1.3) Discordance defined as > 1 cm difference in physician and parent rating: 0 (no discord): 80 (40.6%) Parent < physician = negative discord: 101 (51.3%) Parent > physician = positive discord: 16 (8.1%) Predictors of discord: Duration of disease (shorter disease with positive discord) Second-line drug (greater frequency in those with 0 or positive discord) Patients with no discord or marked positive (> 3 points difference) had significantly lower extension and severity of arthritis based on joint count -Test-retest: NR - Intra-rater: NR **2) Validity:** - Versus radiological results: NR - Versus clinical outcomes Spearman's correlation	**General comments:** - Much study information obtained from chart review - No comment on if blinded - Are "global disease activity" and "well being" measuring the same constructs? **Quality assessment:** - Large sample, well described - Blinding not addressed - No sample size calculation; discordance definition arbitrary - Issue of looking at discordance of 2 measures when they are actually measuring 2 different things

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		and parent global at first visit, only mothers filled out parent global **Exclusion criteria:** - CHAQ completed by father		coefficient (no p values given): Physician Global versus: Parent pain assessment = 0.53 CHAQ = 0.38 No. of swollen joints = 0.51 No. of joints with pain on ROM/tenderness = 0.47 No. of joints with LROM = 0.4 No. of active joints = 0.47 - Versus lab results: ESR = 0.33 CRP = 0.29 Parent global versus: Physician pain assessment = 0.70 CHAQ = 0.44 No. of swollen joints = 0.42 No. of joints with pain on ROM/tenderness = 0.46 No. of joints with LROM = 0.38 No. of active joints = 0.40 - Versus lab results: ESR = 0.27 CRP = 0.31 - New instrument versus established instrument: NR **3) Other:** - Feasibility: NR - Responsiveness: NR - ROC curves: NR	

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
Takken, van den Eijkhof, Hoijtnik, et al., 2006 **#1578**	**Geographical location:** Netherlands **Setting:** Specialty clinic **Study design:** Cross sectional: 13 Longitudinal cohort: 63 **Study objective(s):** Examine the psychometric characteristics of the CHAQ-DI **Duration of followup:** NR	**Number of patients:** 76 total, 321 measures **Age:** - Mean (SD): 9.19 years (2.54) - Median: NR - Range: 4.8-15.8 years **Sex:** - Female: 56 (74%) - Male: 20 (26%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** NR **Baseline severity:** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	**Instrument(s) evaluated:** CHAQ (DI) original CHAQ (DI) 29 items CHAQ (DI) 18 itmes **Mode of administration:** Self-administered in Dutch	**1) Reliability:** Test-retest: Partial correlation with severity "average partial correlation with pain and severity within children" Parial correlation pain: CHAQ (DI) original = 0.43 CHAQ (DI) 29 items = 0.54 CHAQ (DI) 18 itmes = 0.57 Partial correlation severity: CHAQ (DI) original = 0.45 CHAQ (DI) 29 items = 0.54 CHAQ (DI) 18 itmes = 0.57 Inter-rater: NR Intra-rater: NR Internal - Cronbach's alpha: CHAQ (DI) original = 0.88 CHAQ (DI) 29 items = 0.93 CHAQ (DI) 18 itmes = 0.93 **2) Validity:** - Versus clinical outcomes: Correlation with pain (VAS): CHAQ (DI) original = 0.60 CHAQ (DI) 29 items = 0.62 CHAQ (DI) 18 itmes = 0.68 Correlation with severity: CHAQ (DI) original = 0.64 CHAQ (DI) 29 items = 0.64 CHAQ (DI) 18 itmes = 0.67 - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR	**General comments:** Check to ensure citations # 8, 9 10 , 11, 12, 18, 19, 20 are in our database **Quality assessment:** - Fair quality - Small sample - Blinding not reported; severity measure not specified - No sample size; measures not independent

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
				3) Other: - Feasibility: NR - Responsiveness: NR - ROC curves: NR	
Tennant, Kearns, Turner, et al., 2001 **#1665**	**Geographical location:** Leeds, UK **Setting:** Sub-specialty clinic **Study design:** Cross-sectional **Study objective(s):** Compare and validate four measures of disability and a locally developed functional test. **Duration of followup:** NA	**Number of patients:** 53 **Age:** - Mean (SD): 10.4 (3.1) - Median: 4.7 years - Range: 5-16 years **Sex:** - Female: 37 (70%) - Male: 16 (30%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Percentage with systemic JIA:** 7 (14%) **Baseline severity:** Disease duration: Mean (SD): 4 yrs (3.4) Active joint count: Mean (SD): 1.8 (2.6) **Inclusion criteria:** Children with JIA attending a regional JIA center with their parents **Exclusion criteria:** NR	**Instrument(s) evaluated:** CHAQ JAFAR-P JAFAR-C JAFAS TOFT(Turner Observed Functional Test) **Mode of administration:** CHAQ: Self-completed JAFAR-P: Self-completed JAFAR-C: Administered JAFAS: Observed TOFT: Observed Observations made by two experienced occupational therapists	**3) Reliability**: Test-retest: NR Inter-rater (n = 21): Kappa (range for individual items) JAFAS: 0.07-1.00 TOFT: 0.17-1.00 - Intra-rater: NR - Internal – Cronbach's α (n = 38 to 53): CHAQ: 0.90 JAFAR-P: 0.96 JAFAR-C: 0.83 JAFAS: 0.81 TOFT: 0.89 **2) Validity:** - Versus clinical outcomes (n = 37 to 51): Correlation (physician global and active joint count) CHAQ: 0.42*/0.45* JAFAR-P: 0.34^/0.30 (p = ns) JAFAR-C: 0.36^/0.29^ JAFAS: 0.38*/0.40* TOFT: 0.29*/0.20 (p = ns) *p < 0.01; ^p < 0.05 - Versus lab results: NR - Versus radiological results: NR - New instrument versus established instrument: NR	**General comments:** None **Quality assessment:** - Small sample size; eligibility criteria poorly specified - Blinding not reported - No sample size calculation - Good distribution of JIA subtypes and standard instruments (except TOFT)

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
				3) Other: - Feasibility: NR - Responsiveness (n = 24): Effect sizes: CHAQ: 0.22 JAFAR-P: 0.10 JAFAR-C: 0.06 JAFAS: 0.10 - ROC curves: NR Correlation between the JAFAR-P and JAFAR-C: 0.5	
van der Net, Prakken, Helders, et al., 1996 **#1776**	**Geographical location:** Utrecht, The Netherlands **Setting:** Specialty clinic **Study design:** Cross-sectional **Study objective(s):** "…to assess the impact of disease on the functional outcomes of patients with polyarticular juvenile chronic arthritis…" **Duration of followup:** NA	**Number of patients:** 23 **Age:** - Mean (SD): 9.8 (4.8) - Median: NR - Range: 2-16 **Sex:** - Female: 17 - Male: 6 **Race/ethnicity:** Caucasian: 20 Asian: 1 Mediterranean: 2 **JIA diagnosis:** JCA **Percentage with systemic JIA:** NR **Baseline severity:** Time since diagnosis: 4.6 years (SD 4.2; range 0.8-	**Instrument(s) evaluated:** All in Dutch Childhood Health Assessment Questionnaire (CHAQ); n = 23 parent, n = 16 child Juvenile Arthritis Functional Assessment Report (JAFAR); n = 17 parent, n = 16 child Juvenile Arthritis Functional Assessment Scale (JAFAS), n = 17 **Mode of administration:** NR	**1) Reliability:** - Test-retest: NR - Inter-rater: NR - Intra-rater: NR - Intra-class correlation: NR **2) Validity: Spearman correlation coefficients** - Versus clinical outcomes: Joint count on tenderness (scored 0-198): CHAQ-c: 0.50 CHAQ-p: 0.51* JAFAR-c: 0.49 JAFAR-p: 0.47 JAFAS: 0.10 - Versus lab results: NR - Versus radiological results: Radiographic evaluation score of both wrists (scored 0-5): CHAQ-c: 0.21 CHAQ-p: 0.48* JAFAR-c: 0.31	**General comments:** Also correlates measures with RF seropositivity, disease duration, and active inflammatory disease **Quality assessment:** - Small sample, uncertain how recruited, eligibility criteria not well specified - Blinding: Not stated - F/U: NA - Analysis: OK

Evidence Table 2. Studies Relevant to Key Question 5 – continued

Study	Study design	Patient characteristics	Instrument(s)	Results	Comments/ quality/applicability
		14.2) Active joint count: NR Joint count-tender: Median 7.0 (IQR 15.8) CHAQ parent: Median 1.8 (IQR 2.8) JAFAR parent: Median 4.0 (IQR 10.8) JAFAS: Median 1.0 (IQR 3.0) **Inclusion criteria:** Registered in Department of Pediatric Rheumatology as having polyarticular onset JCA **Exclusion criteria:** NR		JAFAR-p: 0.32 JAFAS: 0.22 - New instrument versus established instrument: NR **3) Other:** - Feasibility: 5 children were too young to complete questionnaires; 2 were unable to complete the JAFAR and CHAQ because of mental disability (Downs syndrome, lack of concentration) - Responsiveness: NR - ROC curves: NR	

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Appendix E: Adverse Events – Main Search and Horizon Scan

Note: In Parts 1-5 of the following table, the first six columns contain identical information; only the adverse events listed in columns 7-12 vary. A list of studies cited is provided at the end of Part 5 or the table.

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA – main search and horizon scan – Part 1

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
BIOLOGIC AGENTS											
Abatacept	Golmia et al., 2008[1]	Case report	1	Abatacept	1	-	-	-	-	-	-
	Ruperto et al., 2008[2]	RCT	190	Abatacept	190	66	-	-	71	30	-
				Total	**191**	**66**	**-**	**-**	**71**	**30**	**-**
Adalimumab	Burmester et al., 2009[3]	Series	171	Adalimumab	171	-	-	-	-	-	-
	Lovell et al., 2008[4]	RCT	171	Adalimumab	85	-	5	-	4	-	-
	Lovell et al., 2008[4]	RCT	171	Adalimumab + MTX	86	-	5	-	6	-	-
				Total	**342**	**-**	**10**	**-**	**10**	**-**	**-**
Anakinra	Ilowite et al., 2009[5]	RCT	86	Anakinra	86	15	86	-	-	-	-
	Kone-Paut et al., 2007[6]	Case report	1	Anakinra	1	-	1	-	-	-	-
	Lequerre et al., 2008[7]	Series	20	Anakinra	20	-	2	-	2	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	Ohlsson et al., 2008[8]	Series	7	Anakinra	7	1	1	-	1	-	-
	Zeft et al., 2009[9]	Series	32	Anakinra	32	-	-	-	-	-	-
				Total	**146**	**16**	**90**	**-**	**3**	**-**	**-**
Etanercept	Bout-Tabaku et al., 2007[10]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Elwood et al., 2003[11]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Fathalla et al., 2008[12]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Giannini et al., 2009[13]	Series	103	Etanercept	103	-	-	-	-	3	-
	Horneff et al., 2004[14]	Series	322	Etanercept	322	3	11	-	1	2	1
	Horneff et al., 2009[15]	Series	20	Etanercept	20	1	15	-	1		
	Horneff et al., 2009[16]	Series	604	Etanercept	100	-	2	-	-	-	2
	Hung et al., 2005[17]	Case reports	3	Etanercept	3	-	-	-	1	-	-
	Kimura et al., 2005[18]	Series	82	Etanercept	82	-	-	3	-	-	-
	Kunzmann et al., 2005[19]	Case report	1	Etanercept	1	-	-	-	-	1	-
	Lepore et al., 2003[20]	Case report	1	Etanercept	1	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	Livermore et al., 2002[21]	Case report	1	Etanercept	1	-	2	-	-	-	-
	Lovell et al., 2000[22]	Series	69	Etanercept	69	10	7	-	38	-	-
	Lovell et al., 2003[23]	Series	58	Etanercept	58	-	16	-	80	-	5
	Mangge et al., 2003[24]	Case report	1	Etanercept	1	-	1	-	-	-	-
	Peek et al., 2006[25]	Case report	1	Etanercept	1	1	-	-	-	-	-
	Prince et al., 2009[26]	Series	146	Etanercept	146	6	2	-	-	1	-
	Quartier et al., 2003[27]	Series	61	Etanercept	61	10	11	-	-	-	3
	Ramanan et al., 2003[28]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Skytta et al., 2000[29]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Smith et al., 2005[30]	RCT	12	Etanercept	7	-	-	-	-	-	-
	Takei et al., 2001[31]	Series	8	Etanercept	8	-	-	-	6	-	-
	Tauber et al., 2005[32]	Case reports	2	Etanercept	2	-	-	-	-	-	2
	Tauber et al., 2006[33]	Case reports	2	Etanercept	2	-	-	-	-	-	2
	Tynjala et al.,	Series	45	Etanercept	24	-	1	-	1	-	3

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	2007[34]										
	Tzaribachev et al., 2008[35]	Series	25	Etanercept	25	-	-	-	-	-	-
	Yildirim-Toruner et al., 2008[36]	Correspondence	1	Etanercept	1	-	-	-	-	-	-
	Fitch et al., 2006[37]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Giannini et al., 2009[13]	Series	294	Etanercept + MTX	294	-	-	-	1	-	-
	Holl-Wieden et al., 2008[38]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Horneff et al., 2009[16]	Series	604	Etanercept + MTX	504	2	16	3	3	15	9
	Kuemmerle-Deschner et al., 2007[39]	Series	12	Etanercept + MTX	12	-	1	-	-	-	-
				Total	**1856**	**33**	**85**	**6**	**132**	**22**	**27**
				Incidence – Etanercept		**2%**	**5%**	**0%**	**7%**	**1%**	**1%**
IVIG	de Castro et al., 2003[40]	Case reports	5	IVIG	1	-	-	-	-	-	-
	Aggarwal et al., 2004 [41]	Series	214	IVIG	1	-	-	-	-	-	-
	Silverman et al., 1994 [42]	RCT	31	IVIG	14	-	-	-	-	-	-
	Uziel et al.,	Series	27	IVIG	27	-	-	1	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	1996 [43]										
				Total	**44**	**-**	**-**	**1**	**-**	**-**	**-**
Infliximab	Becker et al., 2004[44]	Case reports	3	Infliximab	3	-	3	-	-	-	-
	Armbrust et al., 2004[45]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Billiau et al., 2002[46]	Case reports	3	Infliximab	3	-	-	-	-	-	-
	Katsicas et al., 2005 [47]	Series	6	Infliximab	6	-	1	-	-	-	-
	Lahdenne et al., 2003 [48]	Series	24	Infliximab	14	-		-	-	-	-
	Mangge et al., 2003 [49]	Case report	1	Infliximab	1	-	1	-	-	-	-
	Pipitone et al., 2005 [50]	Case report	1	Infliximab	1	-	1	-	-	-	-
	Tutar et al., 2004[51]	Case reports	2	Infliximab	2	-	-	-	-	-	1
	Tyler et al., 2007[52]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Tynjala et al., 2007[34]	Series	45	Infliximab	21	-	-	-	-	-	-
	Yildirim-Toruner et al., 2008[36]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Ruperto et al., 2007[53]	RCT	122	Infliximab + MTX	60	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
				Total	**114**	**-**	**6**	**-**	**-**	**-**	**1**
Leflunomide	Silverman et al., 2005[54]	RCT	94	Leflunomide	47	3	3	-	21	-	3
	Silverman et al., 2005[55]	Series	27	Leflunomide	27	8	5	-	9	-	
				Total	**74**	**11**	**8**		**30**		**3**
Tocilizumab	Woo et al., 2005[56]	RCT	18	Tocilizumab	18	-	-	-	-	-	-
	Yokota et al., 2008[57]	RCT	56	Tocilizumab	56	17	-	-	52	-	-
				Total	**74**	**17**	**-**	**-**	**52**	**-**	**-**
				Total – Biologics	**2840**	**143**	**199**	**7**	**298**	**52**	**31**
				Incidence – Biologics		**5%**	**7%**	**0%**	**10%**	**2%**	**1%**
NON-BIOLOGIC AGENTS											
Azathioprine	Aggarwal et al., 2004[41]	Series	214	Azathioprine	5	-	-	-	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Azathioprine	2	-	-	-	-	-	-
	Kvien et al., 1986[58]	RCT	32	Azathioprine	17	-	1	-	-	-	-
	Lin et al., 2000[59]	Series	24	Azathioprine	24	-	-	-	-	-	-
	Savolainen et al., 1997[60]	Series	129	Azathioprine	129	-	2	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	de Castro et al., 2003[40]	Case reports	5	Azathioprine + MTX	5	-	-	-	-	-	-
				Total	**182**	**-**	**3**	-	-	-	-
Clyclosporin A	Pistoia et al., 1993[61]	Series	9	Cyclosporine A	9	-	-	-	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Cyclosporine A	2	-	-	-	-	-	-
	Gattinara et al., 1994[62]	Case reports	50 35 w/ JRA	Cyclosporine A	50	3	-	16	-	-	-
	Gerloni et al., 2001[63]	Series	41	Cyclosporine A	41	2	-	16	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Cyclosporine A + MTX	1	-	-	-	-	-	-
	Krugmann et al., 2000[64]	Case report	1	Cyclosporine A + MTX	1	-	-	-	-	-	-
	Murphy et al., 1993[65]	Case report	1	Cyclosporine A	1	1	-	-	-	-	-
	Ostensen et al., 1988[66]	Series	14	Cyclosporine A	14	-	-	17	-	-	-
	Ruperto et al., 2006[67]	Series	329	Cyclosporine A	329	6	-	6	-	2	-
	Ravelli et al., 2002[68]	Series	17	Cyclosporine A + MTX	17	4	-	1	-	-	-
				Total	**465**	**16**	**-**	**56**	**-**	**2**	**-**
Pencillamine	Aggarwal et al., 2004[41]	Series	214	Penicillamine	23	-	2	1	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	Kvien et al., 1985[69]	RCT	77	Penicillamine	38	7	1	1	-	-	-
	Prieur et al., 1985[70]	RCT	74	Penicillamine	74	6	3	-	-	-	-
	Sahn et al., 1989[71]	Case report	1	Penicillamine	1	-	-	-	-	-	-
	Brewer et al., 1986[72]	RCT	162	Penicillamine	54	-	4	-	-	-	1
	Kvien et al., 1985[73]	RCT	72	Penicillamine	24	4	1	1	-	-	-
	Swartz et al., 1984[74]	Case report	1	Penicillamine	1	-	-	-	-	-	-
				Total	**215**	**17**	**11**	**3**	**-**	**-**	**1**
Methotrexate	Aggarwal et al., 2004[41]	Series	214	Methotrexate	118	5	-	-	-	-	-
	Arakawa et al., 2003[75]	report	1	Methotrexate	1	-	-	-	1	-	-
	Chedeville et al., 2005[76]	Series	27	Methotrexate	27	-	-	-	-	-	-
	Cleary et al., 2002[77]	Case report	1	Methotrexate	1	-	-	-	1	-	-
	Corona et al., 1993[78]	Series	34	Methotrexate	34	-	-	-	-	-	-
	Cron et al., 1998[79]	Case report	1	Methotrexate	1	-	-	-	1	-	-
	de Castro et al., 2003[40]	Case reports	5	Methotrexate	4	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	Falcini et al., 1997[80]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Giannini et al., 1992[81]	RCT	127	Methotrexate	86	-	1	1	-	-	-
	Giannini et al., 2009[13]	Series	197	Methotrexate	197	-	-	-	2	-	-
	Gottlieb et al., 1997[82]	Series	25	Methotrexate	25	1	-	-	-	-	-
	Graham et al., 1992[83]	Series	62	Methotrexate	62	4	-	-	-	-	-
	Halle et al., 1991[84]	Series	30	Methotrexate	30	-	-	-	-	-	-
	Huang et al., 1996[85]	Series	26	Methotrexate	26	1	-	-	-	-	-
	Hunstad et al., 2007[86]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Keim et al., 1990[87]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lee et al., 2009[88]	Case report	1	Methotrexate	1	-	-	-	1	-	-
	Lin et al., 2000[89]	Series	52	Methotrexate	52	11	-	-	-	-	-
	Londino et al., 1998[90]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Martini et al., 1991[91]	Series	27	Methotrexate	27	-	-	-	-	-	-
	Muzaffer et	Case reports	2	Methotrexate	2	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	al., 1996[92]										
	Ortiz-Alvarez et al., 2004[93]	Series	89	Methotrexate	89	-	-	-	-	-	-
	Padeh et al., 1997[94]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Ravelli et al., 1996[95]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Ravelli et al., 1998[96]	Series	256	Methotrexate	256	44	1			26	
	Ravelli et al., 2001[97]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Riddle et al., 2006[98]	Series	57	Methotrexate	20	6	-	-	1	-	-
	Rose et al., 1990[99]	Series	29	Methotrexate	29	2	-	-	-	-	-
	Ruperto et al., 2004[100]	RCT	595	Methotrexate	595	-	-	-	-	-	-
	Russo et al., 2000[101]	Series	20	Methotrexate	20	-	-	-	-	-	-
	Savolainen et al., 2001[102]	Case reports	2	Methotrexate	2	-	-	-	-	-	-
	Schmeling et al., 2005[103]	Series	58	Methotrexate	58	20	-	-	-	-	-
	Silverman et al., 2005[54]	RCT	94	Methotrexate	47	1	3	-	25	-	2
	Speckmaier et al., 1989[104]	Series	12	Methotrexate	12	1	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	Takeyama et al., 2006[105]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Truckenbrodt et al., 1986[106]	Series	19	Methotrexate	12	-	-	-	-	-	-
	van der Meer et al., 2007[107]	Series	29	Methotrexate	29	-	-	-	-	-	-
	Wallace et al., 1992[108]	Series	13	Methotrexate	13	-	-	-	-	-	-
	Yildirim et al., 200[109]	Case report	1	Methotrexate	1	-	-	-	-	-	-
				Total	**1885**	**96**	**5**	**-**	**32**	**26**	**2**
				Incidence – Methotrexate		**8%**	**0%**	**-**	**3%**	**2%**	**0%**
Sulfasalazine	Balci et al., 2009[110]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Burgos-Vargas et al., 2002[111]	RCT	33	Sulfasalazine	17	-	-	-	-	-	-
	Chen et al., 2002[112]	Series	24	Sulfasalazine	24	-	1	-	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Sulfasalazine	1	-	-	-	-	-	-
	Hertzberger-ten Cate et al., 1991[113]	Series	3	Sulfasalazine	3	-	3	-	-	-	-
	Imundo et al., 1996[114]	Series	139	Sulfasalazine	139	8	18	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
	Joos et al., 1991[115]	Series	41	Sulfasalazine	41	2	1	-	-	-	-
	van Rossum et al., 1998[116]	RCT	69	Sulfasalazine	35	-	9	-	-	-	-
	van Rossum et al., 2007[117]	Series	61	Sulfasalazine	32	-	1	-	-	-	-
	Aggarwal et al., 2004[41]	Series	214	Sulfasalazine	28	-	3	-	-	-	-
	Ansell et al., 1991[118]	Series	51	Sulfasalazine	51	-	6	-	-	-	-
	Gedalia et al., 1993[119]	Series	10	Sulfasalazine	10	-	1	-	-	-	-
	Gunnarson et al., 1997[120]	Series	8	Sulfasalazine	8	-	-	-	-	-	-
	Huang et al., 1998[121]	Series	15	Sulfasalazine	15	-	-	-	-	-	-
	Huang et al., 1998[122]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Kummerle-Deschner et al., 1995[123]	Case report	1	Sulfasalazine	1	-	1	-	-	-	-
	Ozdogan et al., 1986[124]	Series	18	Sulfasalazine	18	-	1	-	-	-	-
	Settas et al., 1991[125]	Series	18	Sulfasalazine	18	4	2	-	-	-	-
	Varbanova et al., 1999[126]	Series	32	Sulfasalazine	32	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Gastrointestinal	Dermatologic	Renal/Urologic	Respiratory	Neurologic	Ophthalmologic
				Total	**475**	**14**	**47**	**-**	**-**	**-**	**-**
				Incidence – Sulfasalazine		**3%**	**10%**	-	-	-	-
OTHER											
	Flato et al., 1998[127]	Series	117	DMARDs	28	-	3	1	-	-	2
	Lomater et al., 1994[128]	Series	7	Plaquenil + MTX + gold salts	7	-	-	-	-	-	-
	Barash et al., 199[129]	Case reports	2	Penicillamine + gold	2	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA – main search and horizon scan – Part 2

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
BIOLOGIC AGENTS											
Abatacept	Golmia et al., 2008[1]	Case report	1	Abatacept	1	-	-	-	-	-	-
	Ruperto et al., 2008[2]	RCT	190	Abatacept	190	12	19	-	17	35	-
				Total	**191**	**12**	**19**	**-**	**17**	**35**	**-**
Adalimumab	Burmester et al., 2009[3]	Series	171	Adalimumab	171	-	-	-	-	-	-
	Lovell et al., 2008[4]	RCT	171	Adalimumab	85	-	2	-	-	-	-
	Lovell et al., 2008[4]	RCT	171	Adalimumab + MTX	86	-	4	-	-	-	-
				Total	**342**	**-**	**6**	-	-	-	-
Anakinra	Ilowite et al., 2009[5]	RCT	86	Anakinra	86	14	13	-	7	92	26
	Kone-Paut et al., 2007[6]	Case report	1	Anakinra	1	1	-	-	-	-	1
	Lequerre et al., 2008[7]	Series	20	Anakinra	20	-	-	-	-	2	-
	Ohlsson et al., 2008[8]	Series	7	Anakinra	7	-	-	-	-	-	3
	Zeft et al., 2009[9]	Series	32	Anakinra	32	-	-	-	-	-	-
				Total	**146**	**15**	**13**	**-**	**7**	**94**	**30**

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
Etanercept	Bout-Tabaku et al., 2007[10]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Elwood et al., 2003[11]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Fathalla et al., 2008[12]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Giannini et al., 2009[13]	Series	103	Etanercept	103	-	-	-	-	1	-
	Horneff et al., 2004[14]	Series	322	Etanercept	322	5	2	-	-	12	6
	Horneff et al., 2009[15]	Series	20	Etanercept	20	2	2	-	-	3	1
	Horneff et al., 2009[16]	Series	604	Etanercept	100	-	4	-	-	2	-
	Hung et al., 2005[17]	Case reports	3	Etanercept	3	2	-	-	-	-	-
	Kimura et al., 2005[18]	Series	82	Etanercept	82	-	-	-	-	12	3
	Kunzmann et al., 2005[19]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Lepore et al., 2003[20]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Livermore et al., 2002[21]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Lovell et al., 2000[22]	Series	69	Etanercept	69	-	10	-	-	25	1
	Lovell et al.,	Series	58	Etanercept	58	6	8	-	-	63	

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	2003[23]										
	Mangge et al., 2003[24]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Peek et al., 2006[25]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Prince et al., 2009[26]	Series	146	Etanercept	146	7	9	1	-	7	-
	Quartier et al., 2003[27]	Series	61	Etanercept	61	-	-	1	1	9	-
	Ramanan et al., 2003[28]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Skytta et al., 2000[29]	Case reports	2	Etanercept	2	-	-	-	-	-	2
	Smith et al., 2005[30]	RCT	12	Etanercept	7	-	-	-	-	-	-
	Takei et al., 2001[31]	Series	8	Etanercept	8	-	-	-	-	-	-
	Tauber et al., 2005[32]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Tauber et al., 2006[33]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Tynjala et al., 2007[34]	Series	45	Etanercept	24	-	-	-	-	-	-
	Tzaribachev et al., 2008[35]	Series	25	Etanercept	25	1	-	-	-	-	-
	Yildirim-Toruner et al.,	Correspondence	1	Etanercept	1	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	2008[36]										
	Fitch et al., 2006[37]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Giannini et al., 2009[13]	Series	294	Etanercept + MTX	294	-	-	-	-	6	-
	Holl-Wieden et al., 2008[38]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Horneff et al., 2009[16]	Series	604	Etanercept + MTX	504	2	3	-	4	19	-
	Kuemmerle-Deschner et al., 2007[39]	Series	12	Etanercept + MTX	12	-	-	-	-	-	-
				Total	**1856**	**25**	**38**	**2**	**5**	**159**	**13**
				Incidence – Etanercept		**1%**	**2%**	**0%**	**0%**	**9%**	**1%**
IVIG	de Castro et al., 2003[40]	Case reports	5	IVIG	1	-	-	-	-	-	-
	Aggarwal et al., 2004 [41]	Series	214	IVIG	1	-	-	-	-	-	-
	Silverman et al., 1994 [42]	RCT	31	IVIG	14	2	-	-	-	1	-
	Uziel et al., 1996 [43]	Series	27	IVIG	27	-	-	-	-	-	-
				Total	**44**	**2**	-	-	-	**1**	**-**
Infliximab	Becker et al., 2004[44]	Case reports	3	Infliximab	3	-	-	-	-	-	-
	Armbrust et	Case report	1	Infliximab	1	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	al., 2004[45]										
	Billiau et al., 2002[46]	Case reports	3	Infliximab	3	-	-	-	-	-	-
	Katsicas et al., 2005 [47]	Series	6	Infliximab	6	-	-	-	-	-	4
	Lahdenne et al., 2003 [48]	Series	24	Infliximab	14	-	-	-	-	-	-
	Mangge et al., 2003 [49]	Case report	1	Infliximab	1	-	-	-	1	1	-
	Pipitone et al., 2005 [50]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Tutar et al., 2004[51]	Case reports	2	Infliximab	2	2	-	-	-	-	-
	Tyler et al., 2007[52]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Tynjala et al., 2007[34]	Series	45	Infliximab	21	-	-	-	-	-	-
	Yildirim-Toruner et al., 2008[36]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Ruperto et al., 2007[53]	RCT	122	Infliximab + MTX	60	-	-	-	-	-	-
				Total	**114**	**2**	**-**	**-**	**1**	**1**	**4**
Leflunomide	Silverman et al., 2005[54]	RCT	94	Leflunomide	47	4	13	-	7	32	-
	Silverman et al., 2005[55]	Series	27	Leflunomide	27	-	8	-	7	24	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
				Total	**74**	**4**	**21**		**14**	**56**	
Tocilizumab	Woo et al., 2005[56]	RCT	18	Tocilizumab	18	-	-	-	-	-	1
	Yokota et al., 2008[57]	RCT	56	Tocilizumab	56	-	-	-	-	-	-
				Total	**74**	-	-	-	-	-	**1**
				Total – Biologics	**2840**	**60**	**97**	**2**	**44**	**346**	**48**
				Incidence – Biologics		**2%**	**3%**	**0%**	**2%**	**12%**	**2%**
NON-BIOLOGIC AGENTS											
Azathioprine	Aggarwal et al., 2004[41]	Series	214	Azathioprine	5	-	-	-	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Azathioprine	2	-	-	-	-	-	-
	Kvien et al., 1986[58]	RCT	32	Azathioprine	17	1	1	-	-	1	-
	Lin et al., 2000[59]	Series	24	Azathioprine	24	-	-	-	-	-	-
	Savolainen et al., 1997[60]	Series	129	Azathioprine	129	-	1	-	-	9	1
	de Castro et al., 2003[40]	Case reports	5	Azathioprine + MTX	5	-	1	-	-	-	-
				Total	**182**	**1**	**3**			**10**	**1**
Clyclosporin A	Pistoia et al., 1993[61]	Series	9	Cyclosporine A	9	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	de Castro et al., 2003[40]	Case reports	5	Cyclosporine A	2	-	-	-	-	-	-
	Gattinara et al., 1994[62]	Case reports	50 35 w/ JRA	Cyclosporine A	50	-	-	-	-	-	-
	Gerloni et al., 2001[63]	Series	41	Cyclosporine A	41	-	-	-	-	1	-
	de Castro et al., 2003[40]	Case reports	5	Cyclosporine A + MTX	1	-	-	-	-	-	-
	Krugmann et al., 2000[64]	Case report	1	Cyclosporine A + MTX	1	-	-	-	-	-	-
	Murphy et al., 1993[65]	Case report	1	Cyclosporine A	1	-	-	-	-	-	-
	Ostensen et al., 1988[66]	Series	14	Cyclosporine A	14	-	-	-	-	-	-
	Ruperto et al., 2006[67]	Series	329	Cyclosporine A	329	-	-	-	-	-	-
	Ravelli et al., 2002[68]	Series	17	Cyclosporine A + MTX	17	-	-	-	-	-	-
				Total	**465**	-	-	-	-	**1**	**-**
Pencillamine	Aggarwal et al., 2004[41]	Series	214	Penicillamine	23	-	-	-	-	-	-
	Kvien et al., 1985[69]	RCT	77	Penicillamine	38	-	-	-	-	1	-
	Prieur et al., 1985[70]	RCT	74	Penicillamine	74	-	-	-	-	-	-
	Sahn et al.,	Case report	1	Penicillamine	1	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	1989[71]										
	Brewer et al., 1986[72]	RCT	162	Penicillamine	54	-	-	-	-	-	-
	Kvien et al., 1985[73]	RCT	72	Penicillamine	24	-	-	-	-	-	-
	Swartz et al., 1984[74]	Case report	1	Penicillamine	1	-	-	-	-	-	-
				Total	**215**	-	-	-	-	**1**	**-**
Methotrexate	Aggarwal et al., 2004[41]	Series	214	Methotrexate	118	-	-	-	-	-	-
	Arakawa et al., 2003[75]	report	1	Methotrexate	1	-	-	-	-	-	-
	Chedeville et al., 2005[76]	Series	27	Methotrexate	27	-	4	-	-	-	-
	Cleary et al., 2002[77]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Corona et al., 1993[78]	Series	34	Methotrexate	34	-	-	-	-	-	-
	Cron et al., 1998[79]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Methotrexate	4	-	-	-	-	-	-
	Falcini et al., 1997[80]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Giannini et al., 1992[81]	RCT	127	Methotrexate	86	-	-	-	-	-	-
	Giannini et	Series	197	Methotrexate	197	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	al., 2009[13]										
	Gottlieb et al., 1997[82]	Series	25	Methotrexate	25	-	-	-	-	-	-
	Graham et al., 1992[83]	Series	62	Methotrexate	62	-	14	-	-	-	-
	Halle et al., 1991[84]	Series	30	Methotrexate	30	-	6	-	-	-	-
	Huang et al., 1996[85]	Series	26	Methotrexate	26	-	-	-	-	-	-
	Hunstad et al., 2007[86]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Keim et al., 1990[87]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lee et al., 2009[88]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lin et al., 2000[89]	Series	52	Methotrexate	52	-	11	-	11	-	-
	Londino et al., 1998[90]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Martini et al., 1991[91]	Series	27	Methotrexate	27	-	-	-	-	-	-
	Muzaffer et al., 1996[92]	Case reports	2	Methotrexate	2	-	-	-	-	-	-
	Ortiz-Alvarez et al., 2004[93]	Series	89	Methotrexate	89	-	-	-	-	-	-
	Padeh et al., 1997[94]	Case report	1	Methotrexate	1	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	Ravelli et al., 1996[95]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Ravelli et al., 1998[96]	Series	256	Methotrexate	256	-	-	-	-	-	-
	Ravelli et al., 2001[97]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Riddle et al., 2006[98]	Series	57	Methotrexate	20	-	9	3	2	3	
	Rose et al., 1990[99]	Series	29	Methotrexate	29	-	-	-	-	-	-
	Ruperto et al., 2004[100]	RCT	595	Methotrexate	595	-	26	6	-	-	-
	Russo et al., 2000[101]	Series	20	Methotrexate	20	-	1	2	-	1	-
	Savolainen et al., 2001[102]	Case reports	2	Methotrexate	2	-	-	-	-	-	-
	Schmeling et al., 2005[103]	Series	58	Methotrexate	58	-	-	-	-	-	-
	Silverman et al., 2005[54]	RCT	94	Methotrexate	47	1	16	-	8	22	-
	Speckmaier et al., 1989[104]	Series	12	Methotrexate	12	-	-	-	-	-	-
	Takeyama et al., 2006[105]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Truckenbrodt et al., 1986[106]	Series	19	Methotrexate	12	-	-	-	-	-	-
	van der Meer	Series	29	Methotrexate	29	-	20	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	et al., 2007[107]										
	Wallace et al., 1992[108]	Series	13	Methotrexate	13	-	2	-	-	-	-
	Yildirim et al., 200[109]	Case report	1	Methotrexate	1	-	-	-	-	-	-
				Total	**1885**	**1**	**109**	**11**	**21**	**26**	**-**
				Incidence – Methotrexate		**0%**	**9%**	**1%**	**2%**	**2%**	**-**
Sulfasalazine	Balci et al., 2009[110]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Burgos-Vargas et al., 2002[111]	RCT	33	Sulfasalazine	17	-	-	-	-	4	-
	Chen et al., 2002[112]	Series	24	Sulfasalazine	24	-	2	-	-	2	-
	de Castro et al., 2003[40]	Case reports	5	Sulfasalazine	1	-	-	-	-	-	-
	Hertzberger-ten Cate et al., 1991[113]	Series	3	Sulfasalazine	3	3	2	-	-	-	-
	Imundo et al., 1996[114]	Series	139	Sulfasalazine	139	5	-	-	-	3	-
	Joos et al., 1991[115]	Series	41	Sulfasalazine	41	-	-	-	-	-	-
	van Rossum et al., 1998[116]	RCT	69	Sulfasalazine	35	-	10	10	5	26	1
	van Rossum	Series	61	Sulfasalazine	32	1	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	et al., 2007[117]										
	Aggarwal et al., 2004[41]	Series	214	Sulfasalazine	28	-	-	-	-	-	-
	Ansell et al., 1991[118]	Series	51	Sulfasalazine	51	1	1	-	2	1	
	Gedalia et al., 1993[119]	Series	10	Sulfasalazine	10	-	-	-	-	-	-
	Gunnarson et al., 1997[120]	Series	8	Sulfasalazine	8	-	-	-	-	-	-
	Huang et al., 1998[121]	Series	15	Sulfasalazine	15	-	1	-	2	1	-
	Huang et al., 1998[122]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Kummerle-Deschner et al., 1995[123]	Case report	1	Sulfasalazine	1	-	-	-	-	-	1
	Ozdogan et al., 1986[124]	Series	18	Sulfasalazine	18	-	1	-	2	1	-
	Settas et al., 1991[125]	Series	18	Sulfasalazine	18	-	8	4	-	6	-
	Varbanova et al., 1999[126]	Series	32	Sulfasalazine	32	-	1	-	-	1	-
				Total	**475**	**10**	**26**	**14**	**11**	**45**	**1**
				Incidence – Sulfasalazine		**2%**	**5%**	**3%**	**2%**	**9%**	**0%**
OTHER											
	Flato et al.,	Series	117	DMARDs	28	-	2	-	2	3	2

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Fever	Nausea/vomiting	Loss of appetite or weight	Diarrhea	Pain	Pruritus
	1998[127]										
	Lomater et al., 1994[128]	Series	7	Plaquenil + MTX + gold salts	7	-	1	-	-	-	-
	Barash et al., 199[129]	Case reports	2	Penicillamine + gold	2	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA – main search and horizon scan – Part 3

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
BIOLOGIC AGENTS											
Abatacept	Golmia et al., 2008[1]	Case report	1	Abatacept	1	-	-	-	-	-	-
	Ruperto et al., 2008[2]	RCT	190	Abatacept	190	-	-	-	-	17	-
				Total	**191**	-	-	-	-	**17**	-
Adalimumab	Burmester et al., 2009[3]	Series	171	Adalimumab	171	-	-	-	-	-	-
	Lovell et al., 2008[4]	RCT	171	Adalimumab	85	-	-	1	-	-	-
	Lovell et al., 2008[4]	RCT	171	Adalimumab + MTX	86	-	-	-	-	-	-
				Total	**342**	-	-	**1**	-	-	-
Anakinra	Ilowite et al., 2009[5]	RCT	86	Anakinra	86	9	-	-	-	5	-
	Kone-Paut et al., 2007[6]	Case report	1	Anakinra	1	-	-	-	-	-	-
	Lequerre et al., 2008[7]	Series	20	Anakinra	20	-	-	-	-	-	-
	Ohlsson et al., 2008[8]	Series	7	Anakinra	7	-	-	-	-	1	-
	Zeft et al., 2009[9]	Series	32	Anakinra	32	-	-	-	-	-	-
				Total	**146**	**9**	-	-	-	**6**	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
Etanercept	Bout-Tabaku et al., 2007[10]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Elwood et al., 2003[11]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Fathalla et al., 2008[12]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Giannini et al., 2009[13]	Series	103	Etanercept	103	-	-	-	-	-	-
	Horneff et al., 2004[14]	Series	322	Etanercept	322		4	2			1
	Horneff et al., 2009[15]	Series	20	Etanercept	20	-	-	-	-	-	-
	Horneff et al., 2009[16]	Series	604	Etanercept	100	-	-	-	-	-	-
	Hung et al., 2005[17]	Case reports	3	Etanercept	3	-	-	-	-	1	-
	Kimura et al., 2005[18]	Series	82	Etanercept	82	-	-	-	-	-	-
	Kunzmann et al., 2005[19]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Lepore et al., 2003[20]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Livermore et al., 2002[21]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Lovell et al., 2000[22]	Series	69	Etanercept	69	-	-	-	-	-	-
	Lovell et al.,	Series	58	Etanercept	58	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	2003[23]										
	Mangge et al., 2003[24]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Peek et al., 2006[25]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Prince et al., 2009[26]	Series	146	Etanercept	146	-	2	-	-	2	-
	Quartier et al., 2003[27]	Series	61	Etanercept	61	-	-	-	-	1	-
	Ramanan et al., 2003[28]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Skytta et al., 2000[29]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Smith et al., 2005[30]	RCT	12	Etanercept	7	-	-	-	-	-	-
	Takei et al., 2001[31]	Series	8	Etanercept	8	-	-	-	-	-	-
	Tauber et al., 2005[32]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Tauber et al., 2006[33]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Tynjala et al., 2007[34]	Series	45	Etanercept	24	-	-	-	-	-	-
	Tzaribachev et al., 2008[35]	Series	25	Etanercept	25	-	-	-	-	-	-
	Yildirim-Toruner et al.,	Correspondence	1	Etanercept	1	-	-	-	-	-	1

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	2008[36]										
	Fitch et al., 2006[37]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Giannini et al., 2009[13]	Series	294	Etanercept + MTX	294	-	-	-	-	-	-
	Holl-Wieden et al., 2008[38]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Horneff et al., 2009[16]	Series	604	Etanercept + MTX	504	-	1	-	-	-	3
	Kuemmerle-Deschner et al., 2007[39]	Series	12	Etanercept + MTX	12	-	-	-	-	-	-
				Total	**1856**	**-**	**7**	**2**	**-**	**4**	**5**
				Incidence – Etanercept		**-**	**0%**	**0%**	**-**	**0%**	**0%**
IVIG	de Castro et al., 2003[40]	Case reports	5	IVIG	1	-	-	-	-	-	-
	Aggarwal et al., 2004 [41]	Series	214	IVIG	1	-	-	-	-	-	-
	Silverman et al., 1994 [42]	RCT	31	IVIG	14	-	-	-	-	-	-
	Uziel et al., 1996 [43]	Series	27	IVIG	27	-	-	-	-	-	-
				Total	**44**	-	-	-	-	-	-
Infliximab	Becker et al., 2004[44]	Case reports	3	Infliximab	3	-	-	-	-	-	-
	Armbrust et	Case report	1	Infliximab	1	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	al., 2004[45]										
	Billiau et al., 2002[46]	Case reports	3	Infliximab	3	-	-	-	-	-	-
	Katsicas et al., 2005 [47]	Series	6	Infliximab	6	3	-	-	-	-	-
	Lahdenne et al., 2003 [48]	Series	24	Infliximab	14	-	1	-	-	-	-
	Mangge et al., 2003 [49]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Pipitone et al., 2005 [50]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Tutar et al., 2004[51]	Case reports	2	Infliximab	2	-	-	-	-	-	-
	Tyler et al., 2007[52]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Tynjala et al., 2007[34]	Series	45	Infliximab	21	-	3	-	-	-	-
	Yildirim-Toruner et al., 2008[36]	Case report	1	Infliximab	1	-	-	-	-	-	1
	Ruperto et al., 2007[53]	RCT	122	Infliximab + MTX	60	-	-	-	-	-	-
				Total	**114**	**3**	**4**	**-**	**-**	**-**	**1**
Leflunomide	Silverman et al., 2005[54]	RCT	94	Leflunomide	47	-	7	3	-	5	-
	Silverman et al., 2005[55]	Series	27	Leflunomide	27	-	8	6	-	5	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
				Total	**74**	**-**	**15**	**9**	**-**	**10**	**-**
Tocilizumab	Woo et al., 2005[56]	RCT	18	Tocilizumab	18	-	-	-	-	-	-
	Yokota et al., 2008[57]	RCT	56	Tocilizumab	56	-	-	-	-	-	-
				Total	**74**	-	-	-	-	-	-
				Total – Biologics	**2840**	**12**	**26**	**12**	**0**	**37**	**6**
				Incidence – Biologics		**0%**	**1%**	**0%**	**0%**	**1%**	**0%**
NON-BIOLOGIC AGENTS											
Azathioprine	Aggarwal et al., 2004[41]	Series	214	Azathioprine	5	-	-	-	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Azathioprine	2	-	-	-	-	-	-
	Kvien et al., 1986[58]	RCT	32	Azathioprine	17	-	1	-	-	-	-
	Lin et al., 2000[59]	Series	24	Azathioprine	24	-	-	-	-	-	-
	Savolainen et al., 1997[60]	Series	129	Azathioprine	129	-	-	-	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Azathioprine + MTX	5	-	-	-	-	-	-
				Total	**182**	**-**	**1**	**-**	**-**	**-**	**-**
Clyclosporin A	Pistoia et al., 1993[61]	Series	9	Cyclosporine A	9	1	2	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	de Castro et al., 2003[40]	Case reports	5	Cyclosporine A	2	-	-	-	-	-	-
	Gattinara et al., 1994[62]	Case reports	50 35 w/ JRA	Cyclosporine A	50	-	9	-	-	-	-
	Gerloni et al., 2001[63]	Series	41	Cyclosporine A	41	-	12	-	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Cyclosporine A + MTX	1	-	-	-	-	-	-
	Krugmann et al., 2000[64]	Case report	1	Cyclosporine A + MTX	1	-	-	-	-	-	-
	Murphy et al., 1993[65]	Case report	1	Cyclosporine A	1	-	-	-	-	-	-
	Ostensen et al., 1988[66]	Series	14	Cyclosporine A	14	-	14	-	-	-	-
	Ruperto et al., 2006[67]	Series	329	Cyclosporine A	329	-	7	-	-	-	-
	Ravelli et al., 2002[68]	Series	17	Cyclosporine A + MTX	17	-	-	-	-	-	-
				Total	**465**	-	**44**	-	-	-	-
Pencillamine	Aggarwal et al., 2004[41]	Series	214	Penicillamine	23	-	-	-	-	-	-
	Kvien et al., 1985[69]	RCT	77	Penicillamine	38	-	-	2			
	Prieur et al., 1985[70]	RCT	74	Penicillamine	74	-	-	-	-	-	-
	Sahn et al.,	Case report	1	Penicillamine	1	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	1989[71]										
	Brewer et al., 1986[72]	RCT	162	Penicillamine	54	-	-	-	-	-	-
	Kvien et al., 1985[73]	RCT	72	Penicillamine	24	-	-	-	-	-	-
	Swartz et al., 1984[74]	Case report	1	Penicillamine	1	-	-	-	-	-	-
				Total	**215**	**-**	**-**	**2**	**-**	**-**	**-**
Methotrexate	Aggarwal et al., 2004[41]	Series	214	Methotrexate	118	-	-	-	-	-	-
	Arakawa et al., 2003[75]	report	1	Methotrexate	1	-	-	-	-	-	-
	Chedeville et al., 2005[76]	Series	27	Methotrexate	27	-	-	-	-	-	-
	Cleary et al., 2002[77]	Case report	1	Methotrexate	1	-	-	-	-	-	1
	Corona et al., 1993[78]	Series	34	Methotrexate	34	-	-	-	-	-	-
	Cron et al., 1998[79]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Methotrexate	4	-	-	-	-	-	-
	Falcini et al., 1997[80]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Giannini et al., 1992[81]	RCT	127	Methotrexate	86	-	-	-	-	-	-
	Giannini et	Series	197	Methotrexate	197	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	al., 2009[13]										
	Gottlieb et al., 1997[82]	Series	25	Methotrexate	25	-	-	-	-	1	-
	Graham et al., 1992[83]	Series	62	Methotrexate	62	-	2	-	-	-	-
	Halle et al., 1991[84]	Series	30	Methotrexate	30	-	-	-	-	-	-
	Huang et al., 1996[85]	Series	26	Methotrexate	26	-	-	-	-	-	-
	Hunstad et al., 2007[86]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Keim et al., 1990[87]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lee et al., 2009[88]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lin et al., 2000[89]	Series	52	Methotrexate	52	-	-	1	-	-	-
	Londino et al., 1998[90]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Martini et al., 1991[91]	Series	27	Methotrexate	27	-	-	-	-	-	-
	Muzaffer et al., 1996[92]	Case reports	2	Methotrexate	2	-	-	-	-	-	-
	Ortiz-Alvarez et al., 2004[93]	Series	89	Methotrexate	89	-	-	-	-	-	-
	Padeh et al., 1997[94]	Case report	1	Methotrexate	1	-	-	-	-	-	1

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	Ravelli et al., 1996[95]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Ravelli et al., 1998[96]	Series	256	Methotrexate	256	-	2	-	-	-	-
	Ravelli et al., 2001[97]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Riddle et al., 2006[98]	Series	57	Methotrexate	20	-	-	-	-	-	-
	Rose et al., 1990[99]	Series	29	Methotrexate	29	-	-	-	-	-	-
	Ruperto et al., 2004[100]	RCT	595	Methotrexate	595	-	4	-	-	-	-
	Russo et al., 2000[101]	Series	20	Methotrexate	20	-	-	-	-	-	-
	Savolainen et al., 2001[102]	Case reports	2	Methotrexate	2	-	-	-	-	-	-
	Schmeling et al., 2005[103]	Series	58	Methotrexate	58	-	3	-	-	-	-
	Silverman et al., 2005[54]	RCT	94	Methotrexate	47	-	3	2	-	-	-
	Speckmaier et al., 1989[104]	Series	12	Methotrexate	12	-	-	-	-	-	-
	Takeyama et al., 2006[105]	Case report	1	Methotrexate	1	-	-	-	-	-	1
	Truckenbrodt et al., 1986[106]	Series	19	Methotrexate	12	-	-	-	-	-	-
	van der Meer	Series	29	Methotrexate	29	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	et al., 2007[107]										
	Wallace et al., 1992[108]	Series	13	Methotrexate	13	-	-	-	-	-	-
	Yildirim et al., 200[109]	Case report	1	Methotrexate	1	-	-	-	-	-	1
				Total	**1885**	**-**	**14**	**3**	**-**	**-**	**4**
				Incidence – Methotrexate		**-**	**1%**	**0%**	**-**	**-**	**0%**
Sulfasalazine	Balci et al., 2009[110]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Burgos-Vargas et al., 2002[111]	RCT	33	Sulfasalazine	17	-	-	-	-	-	-
	Chen et al., 2002[112]	Series	24	Sulfasalazine	24	-	-	-	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Sulfasalazine	1	-	-	-	-	-	-
	Hertzberger-ten Cate et al., 1991[113]	Series	3	Sulfasalazine	3	1	-	-	-	-	-
	Imundo et al., 1996[114]	Series	139	Sulfasalazine	139	-	-	-	-	-	-
	Joos et al., 1991[115]	Series	41	Sulfasalazine	41	-	-	-	-	-	-
	van Rossum et al., 1998[116]	RCT	69	Sulfasalazine	35	-	-	-	-	-	-
	van Rossum	Series	61	Sulfasalazine	32	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	et al., 2007[117]										
	Aggarwal et al., 2004[41]	Series	214	Sulfasalazine	28	-	-	-	-	-	-
	Ansell et al., 1991[118]	Series	51	Sulfasalazine	51	-	-	-	-	-	-
	Gedalia et al., 1993[119]	Series	10	Sulfasalazine	10	-	-	-	-	-	-
	Gunnarson et al., 1997[120]	Series	8	Sulfasalazine	8	-	-	-	-	-	-
	Huang et al., 1998[121]	Series	15	Sulfasalazine	15	-	-	1	-	-	-
	Huang et al., 1998[122]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Kummerle-Deschner et al., 1995[123]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Ozdogan et al., 1986[124]	Series	18	Sulfasalazine	18	-	-	-	-	-	-
	Settas et al., 1991[125]	Series	18	Sulfasalazine	18	-	-	-	-	-	-
	Varbanova et al., 1999[126]	Series	32	Sulfasalazine	32	-	-	-	-	-	-
				Total	**475**	**1**	**-**	**1**	**-**	**-**	**-**
				Incidence – Sulfasalazine		**0%**	**-**	**0%**	**-**	**-**	**-**
OTHER											
	Flato et al.,	Series	117	DMARDs	28	1	3	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Edema	Alopecia/hirsutism	Dizziness	Psychological/ emotional symptoms	Cough	Cancer
	1998[127]										
	Lomater et al., 1994[128]	Series	7	Plaquenil + MTX + gold salts	7	-	-	-	-	-	-
	Barash et al., 199[129]	Case reports	2	Penicillamine + gold	2	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA – main search and horizon scan – Part 4

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
BIOLOGIC AGENTS											
Abatacept	Golmia et al., 2008[1]	Case report	1	Abatacept	1	-	-	-	-	-	-
	Ruperto et al., 2008[2]	RCT	190	Abatacept	190	79	-	-	-	-	-
				Total	**191**	**79**	-	-	-	-	-
Adalimumab	Burmester et al., 2009[3]	Series	171	Adalimumab	171	5	-	-	-	-	-
	Lovell et al., 2008[4]	RCT	171	Adalimumab	85	11	-	-	-	-	-
	Lovell et al., 2008[4]	RCT	171	Adalimumab + MTX	86	18	-	-	-	-	-
				Total	**342**	**34**	-	-	-	-	-
Anakinra	Ilowite et al., 2009[5]	RCT	86	Anakinra	86	25	-	-	-	-	-
	Kone-Paut et al., 2007[6]	Case report	1	Anakinra	1	1	-	-	-	-	-
	Lequerre et al., 2008[7]	Series	20	Anakinra	20	5	-	-	-	-	-
	Ohlsson et al., 2008[8]	Series	7	Anakinra	7	1	-	-	-	-	-
	Zeft et al., 2009[9]	Series	32	Anakinra	32	1	-	-	-	-	-
				Total	**146**	**33**	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
Etanercept	Bout-Tabaku et al., 2007[10]	Case report	1	Etanercept	1	-	-	-	-	1	-
	Elwood et al., 2003[11]	Case report	1	Etanercept	1	1	-	-	-	-	-
	Fathalla et al., 2008[12]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Giannini et al., 2009[13]	Series	103	Etanercept	103	2	13	-	2	-	-
	Horneff et al., 2004[14]	Series	322	Etanercept	322	10	-	-	-	-	-
	Horneff et al., 2009[15]	Series	20	Etanercept	20	11	-	-	-	-	-
	Horneff et al., 2009[16]	Series	604	Etanercept	100	10	-	-	-	-	-
	Hung et al., 2005[17]	Case reports	3	Etanercept	3	-	-	-	-	-	-
	Kimura et al., 2005[18]	Series	82	Etanercept	82	9	-	-	-	-	-
	Kunzmann et al., 2005[19]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Lepore et al., 2003[20]	Case report	1	Etanercept	1	-	-	-	-	1	-
	Livermore et al., 2002[21]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Lovell et al., 2000[22]	Series	69	Etanercept	69		1	-	-	-	-
	Lovell et al.,	Series	58	Etanercept	58	9	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	2003[23]										
	Mangge et al., 2003[24]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Peek et al., 2006[25]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Prince et al., 2009[26]	Series	146	Etanercept	146	8	3	-	-	-	-
	Quartier et al., 2003[27]	Series	61	Etanercept	61	-	8	-	-	-	-
	Ramanan et al., 2003[28]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Skytta et al., 2000[29]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Smith et al., 2005[30]	RCT	12	Etanercept	7	21	-	-	-	-	-
	Takei et al., 2001[31]	Series	8	Etanercept	8	-	-	-	-	-	-
	Tauber et al., 2005[32]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Tauber et al., 2006[33]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Tynjala et al., 2007[34]	Series	45	Etanercept	24	2	-	-	-	-	-
	Tzaribachev et al., 2008[35]	Series	25	Etanercept	25	1	-	-	-	-	-
	Yildirim-Toruner et al.,	Correspondence	1	Etanercept	1	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	2008[36]										
	Fitch et al., 2006[37]	Case report	1	Etanercept + MTX	1	1	-	-	-	-	-
	Giannini et al., 2009[13]	Series	294	Etanercept + MTX	294	-	33	-	1	-	-
	Holl-Wieden et al., 2008[38]	Case report	1	Etanercept + MTX	1	1	-	-	-	-	-
	Horneff et al., 2009[16]	Series	604	Etanercept + MTX	504	63	-	-	-	-	1
	Kuemmerle-Deschner et al., 2007[39]	Series	12	Etanercept + MTX	12	1	-	-	-	-	-
				Total	**1856**	**150**	**58**	**-**	**3**	**2**	**1**
				Incidence – Etanercept		**8%**	**3%**	**-**	**0%**	**0%**	**0%**
IVIG	de Castro et al., 2003[40]	Case reports	5	IVIG	1	-	-	-	-	-	-
	Aggarwal et al., 2004 [41]	Series	214	IVIG	1	-	-	-	-	-	-
	Silverman et al., 1994 [42]	RCT	31	IVIG	14	-	-	-	-	-	-
	Uziel et al., 1996 [43]	Series	27	IVIG	27	-	-	-	-	1	-
				Total	**44**	**1**	-	-	-	**1**	-
Infliximab	Becker et al., 2004[44]	Case reports	3	Infliximab	3	-	-	-	-	-	-
	Armbrust et	Case report	1	Infliximab	1	1	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	al., 2004[45]										
	Billiau et al., 2002[46]	Case reports	3	Infliximab	3	2	-	-	-	-	-
	Katsicas et al., 2005 [47]	Series	6	Infliximab	6	-	-	-	-	-	-
	Lahdenne et al., 2003 [48]	Series	24	Infliximab	14	-	-	-	-	-	-
	Mangge et al., 2003 [49]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Pipitone et al., 2005 [50]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Tutar et al., 2004[51]	Case reports	2	Infliximab	2	1	-	-	-	-	-
	Tyler et al., 2007[52]	Case report	1	Infliximab	1	-	-	-	1	-	-
	Tynjala et al., 2007[34]	Series	45	Infliximab	21	-	-	-	-	-	-
	Yildirim-Toruner et al., 2008[36]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Ruperto et al., 2007[53]	RCT	122	Infliximab + MTX	60	46	-	-		-	-
				Total	**114**	**50**	-	-	**1**	-	-
Leflunomide	Silverman et al., 2005[54]	RCT	94	Leflunomide	47	6	-	-		-	-
	Silverman et al., 2005[55]	Series	27	Leflunomide	27	12	-	-	4	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
				Total	**74**	**18**	-	-	**4**	-	-
Tocilizumab	Woo et al., 2005[56]	RCT	18	Tocilizumab	18	2	-	-	-	-	-
	Yokota et al., 2008[57]	RCT	56	Tocilizumab	56	1	-	-	-	-	-
				Total	**74**	**3**	-	-	-	-	-
				Total – Biologics	**2840**	**367**	**58**	**0**	**8**	**3**	**1**
				Incidence – Biologics		**13%**	**2%**	**0%**	**0%**	**0%**	**0%**
NON-BIOLOGIC AGENTS											
Azathioprine	Aggarwal et al., 2004[41]	Series	214	Azathioprine	5	-	-	-	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Azathioprine	2	-	-	-	-	-	-
	Kvien et al., 1986[58]	RCT	32	Azathioprine	17	3	-	-	-	-	-
	Lin et al., 2000[59]	Series	24	Azathioprine	24	-	-	-	-	-	-
	Savolainen et al., 1997[60]	Series	129	Azathioprine	129	-	-	-	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Azathioprine + MTX	5	-	-	-	-	-	-
				Total	**182**	**3**	-	-	-	-	-
Clyclosporin A	Pistoia et al., 1993[61]	Series	9	Cyclosporine A	9	-	-	2	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	de Castro et al., 2003[40]	Case reports	5	Cyclosporine A	2	-	-	-	-	-	-
	Gattinara et al., 1994[62]	Case reports	50 35 w/ JRA	Cyclosporine A	50	8	-	-	-	-	-
	Gerloni et al., 2001[63]	Series	41	Cyclosporine A	41	3	-	6	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Cyclosporine A + MTX	1	-	-	1	-	-	-
	Krugmann et al., 2000[64]	Case report	1	Cyclosporine A + MTX	1	-	-	-	-	-	-
	Murphy et al., 1993[65]	Case report	1	Cyclosporine A	1	-	-	-	-	-	-
	Ostensen et al., 1988[66]	Series	14	Cyclosporine A	14	-	-	1	-	-	-
	Ruperto et al., 2006[67]	Series	329	Cyclosporine A	329	-	-	6	-	-	-
	Ravelli et al., 2002[68]	Series	17	Cyclosporine A + MTX	17	-	-	-	-	-	-
				Total	**465**	**11**	-	**16**	-	-	-
Pencillamine	Aggarwal et al., 2004[41]	Series	214	Penicillamine	23	-	-	-	-	-	-
	Kvien et al., 1985[69]	RCT	77	Penicillamine	38	-	-	-	-	-	-
	Prieur et al., 1985[70]	RCT	74	Penicillamine	74	2	-	-	-	-	-
	Sahn et al.,	Case report	1	Penicillamine	1	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	1989[71]										
	Brewer et al., 1986[72]	RCT	162	Penicillamine	54	-	-	-	-	-	-
	Kvien et al., 1985[73]	RCT	72	Penicillamine	24	-	-	-	-	-	-
	Swartz et al., 1984[74]	Case report	1	Penicillamine	1	-	-	-	-	-	-
				Total	**215**	**2**	-	-	-	-	-
Methotrexate	Aggarwal et al., 2004[41]	Series	214	Methotrexate	118	2	-	-	4	-	-
	Arakawa et al., 2003[75]	report	1	Methotrexate	1	-	-	-	-	-	-
	Chedeville et al., 2005[76]	Series	27	Methotrexate	27	-	-	-	-	-	-
	Cleary et al., 2002[77]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Corona et al., 1993[78]	Series	34	Methotrexate	34	-	-	-	-	-	-
	Cron et al., 1998[79]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Methotrexate	4	-	-	-	-	-	-
	Falcini et al., 1997[80]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Giannini et al., 1992[81]	RCT	127	Methotrexate	86	-	-	-	-	-	-
	Giannini et	Series	197	Methotrexate	197	-	15	-	1	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	al., 2009[13]										
	Gottlieb et al., 1997[82]	Series	25	Methotrexate	25	1	-	-	-	-	-
	Graham et al., 1992[83]	Series	62	Methotrexate	62	12	-	-	1	-	-
	Halle et al., 1991[84]	Series	30	Methotrexate	30	1	-	-	-	-	-
	Huang et al., 1996[85]	Series	26	Methotrexate	26	-	-	-	-	-	-
	Hunstad et al., 2007[86]	Case report	1	Methotrexate	1	1	-	-	-	-	-
	Keim et al., 1990[87]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lee et al., 2009[88]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lin et al., 2000[89]	Series	52	Methotrexate	52	1	-	-	-	-	-
	Londino et al., 1998[90]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Martini et al., 1991[91]	Series	27	Methotrexate	27	-	-	-	-	-	-
	Muzaffer et al., 1996[92]	Case reports	2	Methotrexate	2	-	-	-	-	-	-
	Ortiz-Alvarez et al., 2004[93]	Series	89	Methotrexate	89	-	-	-	-	-	-
	Padeh et al., 1997[94]	Case report	1	Methotrexate	1	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	Ravelli et al., 1996[95]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Ravelli et al., 1998[96]	Series	256	Methotrexate	256	-	-	-	-	-	-
	Ravelli et al., 2001[97]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Riddle et al., 2006[98]	Series	57	Methotrexate	20	-	-	-	-	-	-
	Rose et al., 1990[99]	Series	29	Methotrexate	29	-	-	-	-	-	-
	Ruperto et al., 2004[100]	RCT	595	Methotrexate	595	-	-	-	-	-	-
	Russo et al., 2000[101]	Series	20	Methotrexate	20	-	-	-	-	-	-
	Savolainen et al., 2001[102]	Case reports	2	Methotrexate	2	-	-	-	-	-	-
	Schmeling et al., 2005[103]	Series	58	Methotrexate	58	-	-	-	-	-	-
	Silverman et al., 2005[54]	RCT	94	Methotrexate	47	2	-	-	-	-	-
	Speckmaier et al., 1989[104]	Series	12	Methotrexate	12	-	1	-	-	-	-
	Takeyama et al., 2006[105]	Case report	1	Methotrexate	1	1	-	-	-	-	-
	Truckenbrodt et al., 1986[106]	Series	19	Methotrexate	12	1	-	-	-	-	-
	van der Meer	Series	29	Methotrexate	29	-	17	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	et al., 2007[107]										
	Wallace et al., 1992[108]	Series	13	Methotrexate	13	-	-	-	-	-	-
	Yildirim et al., 200[109]	Case report	1	Methotrexate	1	-	-	-	-	-	-
				Total	**1885**	**22**	**33**	-	-	-	-
				Incidence – Methotrexate		**2%**	**3%**	-	-	-	-
Sulfasalazine	Balci et al., 2009[110]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Burgos-Vargas et al., 2002[111]	RCT	33	Sulfasalazine	17	-	-	-	-	-	-
	Chen et al., 2002[112]	Series	24	Sulfasalazine	24	-	-	-	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Sulfasalazine	1	-	-	-	-	-	-
	Hertzberger-ten Cate et al., 1991[113]	Series	3	Sulfasalazine	3	-	-	-	-	-	-
	Imundo et al., 1996[114]	Series	139	Sulfasalazine	139	-	-	-	-	-	-
	Joos et al., 1991[115]	Series	41	Sulfasalazine	41	-	1	-	-	-	-
	van Rossum et al., 1998[116]	RCT	69	Sulfasalazine	35	-	-	-	-	-	-
	van Rossum	Series	61	Sulfasalazine	32	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	et al., 2007[117]										
	Aggarwal et al., 2004[41]	Series	214	Sulfasalazine	28	-	-	-	-	-	-
	Ansell et al., 1991[118]	Series	51	Sulfasalazine	51	-	-	-	-	-	-
	Gedalia et al., 1993[119]	Series	10	Sulfasalazine	10	-	-	-	-	-	-
	Gunnarson et al., 1997[120]	Series	8	Sulfasalazine	8	-	-	-	-	8	-
	Huang et al., 1998[121]	Series	15	Sulfasalazine	15	-	-	-	-	-	-
	Huang et al., 1998[122]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Kummerle-Deschner et al., 1995[123]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Ozdogan et al., 1986[124]	Series	18	Sulfasalazine	18	-	-	-	-	-	-
	Settas et al., 1991[125]	Series	18	Sulfasalazine	18	-	-	-	-	-	-
	Varbanova et al., 1999[126]	Series	32	Sulfasalazine	32	-	-	-	-	-	-
				Total	**475**	**-**	**1**	**-**	**-**	**-**	**0**
				Incidence – Sulfasalazine		**-**	**0%**	**-**	**-**	**-**	**0%**
OTHER											
	Flato et al.,	Series	117	DMARDs	28	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Infection	Psychological condition	Hypertension	Anemia	Lupus or lupus-like syndrome	Stevens-Johnson syndrome
	1998[127]										
	Lomater et al., 1994[128]	Series	7	Plaquenil + MTX + gold salts	7	-	-	-	-	-	-
	Barash et al., 199[129]	Case reports	2	Penicillamine + gold	2	-	-	-	-	-	-

Appendix Table AE. Adverse events associated with DMARDs in patients with JIA – main search and horizon scan – Part 5

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
BIOLOGIC AGENTS											
Abatacept	Golmia et al., 2008[1]	Case report	1	Abatacept	1	-	-	-	-	1	-
	Ruperto et al., 2008[2]	RCT	190	Abatacept	190	-	-	-	-	26	-
				Total	**191**	-	-	-	-	**27**	**-**
Adalimumab	Burmester et al., 2009[3]	Series	171	Adalimumab	171	-	-	-	-	-	-
	Lovell et al., 2008[4]	RCT	171	Adalimumab	85	-	-	-	-	8	-
	Lovell et al., 2008[4]	RCT	171	Adalimumab + MTX	86	-	-	4	2	14	-
				Total	**342**	-	-	**4**	**2**	**22**	-
Anakinra	Ilowite et al., 2009[5]	RCT	86	Anakinra	86	-	-	-	-	12	-
	Kone-Paut et al., 2007[6]	Case report	1	Anakinra	1	-	-	-	-	1	-
	Lequerre et al., 2008[7]	Series	20	Anakinra	20	-	-	-	-	-	-
	Ohlsson et al., 2008[8]	Series	7	Anakinra	7	-	-	-	-	-	-
	Zeft et al., 2009[9]	Series	32	Anakinra	32	-	-	-	-	-	-
				Total	**146**	-	-	-	-	**13**	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
Etanercept	Bout-Tabaku et al., 2007[10]	Case report	1	Etanercept	1	-	3	-	-	-	-
	Elwood et al., 2003[11]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Fathalla et al., 2008[12]	Case report	1	Etanercept	1	-	-	-	-	1	-
	Giannini et al., 2009[13]	Series	103	Etanercept	103	-	-	-	-	1	-
	Horneff et al., 2004[14]	Series	322	Etanercept	322	-	-	4	7	4	-
	Horneff et al., 2009[15]	Series	20	Etanercept	20	-	-	-	1	2	-
	Horneff et al., 2009[16]	Series	604	Etanercept	100	-	-	-	-	1	-
	Hung et al., 2005[17]	Case reports	3	Etanercept	3	-	-	-	-	-	-
	Kimura et al., 2005[18]	Series	82	Etanercept	82	-	-	-	-	6	-
	Kunzmann et al., 2005[19]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Lepore et al., 2003[20]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Livermore et al., 2002[21]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Lovell et al., 2000[22]	Series	69	Etanercept	69	-	-	-	-	-	-
	Lovell et al.,	Series	58	Etanercept	58	-	-	-	-	13	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	2003[23]										
	Mangge et al., 2003[24]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Peek et al., 2006[25]	Case report	1	Etanercept	1	-	-	-	-	-	-
	Prince et al., 2009[26]	Series	146	Etanercept	146	-	-	-	-	10	-
	Quartier et al., 2003[27]	Series	61	Etanercept	61	-	-	2	-	6	-
	Ramanan et al., 2003[28]	Case report	1	Etanercept	1	1	-	-	-	-	-
	Skytta et al., 2000[29]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Smith et al., 2005[30]	RCT	12	Etanercept	7	-	-	-	-	-	-
	Takei et al., 2001[31]	Series	8	Etanercept	8	-	-	-	-	-	-
	Tauber et al., 2005[32]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Tauber et al., 2006[33]	Case reports	2	Etanercept	2	-	-	-	-	-	-
	Tynjala et al., 2007[34]	Series	45	Etanercept	24	-	-	-	-	-	-
	Tzaribachev et al., 2008[35]	Series	25	Etanercept	25	-	-	-	-	-	-
	Yildirim-Toruner et al.,	Correspondence	1	Etanercept	1	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	2008[36]										
	Fitch et al., 2006[37]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Giannini et al., 2009[13]	Series	294	Etanercept + MTX	294	-	1	4	1	5	-
	Holl-Wieden et al., 2008[38]	Case report	1	Etanercept + MTX	1	-	-	-	-	-	-
	Horneff et al., 2009[16]	Series	604	Etanercept + MTX	504	-	-	-	-	5	-
	Kuemmerle-Deschner et al., 2007[39]	Series	12	Etanercept + MTX	12	-	-	-	1		-
				Total	**1856**	**1**	**4**	**10**	**10**	**54**	**-**
				Incidence – Etanercept		**0%**	**0%**	**1%**	**1%**	**3%**	**-**
IVIG	de Castro et al., 2003[40]	Case reports	5	IVIG	1	-	-	-	-	-	-
	Aggarwal et al., 2004 [41]	Series	214	IVIG	1	-	-	-	-	-	-
	Silverman et al., 1994 [42]	RCT	31	IVIG	14	-	-	-	-	1	-
	Uziel et al., 1996 [43]	Series	27	IVIG	27	-	-	-	-	1	-
				Total	**44**	-	-	-	-	**2**	-
Infliximab	Becker et al., 2004[44]	Case reports	3	Infliximab	3	-	-	-	-	3	-
	Armbrust et	Case report	1	Infliximab	1	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	al., 2004[45]										
	Billiau et al., 2002[46]	Case reports	3	Infliximab	3	-	-	-	-	-	-
	Katsicas et al., 2005 [47]	Series	6	Infliximab	6	-	-	-	-	-	-
	Lahdenne et al., 2003 [48]	Series	24	Infliximab	14	1	1	-	-	-	-
	Mangge et al., 2003 [49]	Case report	1	Infliximab	1	-	-	-	-	2	-
	Pipitone et al., 2005 [50]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Tutar et al., 2004[51]	Case reports	2	Infliximab	2	-	-	-	-	1	-
	Tyler et al., 2007[52]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Tynjala et al., 2007[34]	Series	45	Infliximab	21	-	-	-	3	-	-
	Yildirim-Toruner et al., 2008[36]	Case report	1	Infliximab	1	-	-	-	-	-	-
	Ruperto et al., 2007[53]	RCT	122	Infliximab + MTX	60		35	-	-	-	-
				Total	**114**	**1**	**36**	**-**	**3**	**6**	-
Leflunomide	Silverman et al., 2005[54]	RCT	94	Leflunomide	47	-	-	-	4	5	-
	Silverman et al., 2005[55]	Series	27	Leflunomide	27	-	-	-	3	14	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
				Total	**74**	-	-	-	**7**	**19**	-
Tocilizumab	Woo et al., 2005[56]	RCT	18	Tocilizumab	18	-	-	13	3	-	-
	Yokota et al., 2008[57]	RCT	56	Tocilizumab	56	-	-	1	12	1	-
				Total	**74**	-	-	**14**	**15**	**1**	-
				Total – Biologics	**2840**	**2**	**40**	**28**	**37**	**144**	**0**
				Incidence – Biologics		**0%**	**1%**	**1%**	**1%**	**5%**	**0%**
NON-BIOLOGIC AGENTS											
Azathioprine	Aggarwal et al., 2004[41]	Series	214	Azathioprine	5	-	-	-	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Azathioprine	2	-	-	-	-	-	-
	Kvien et al., 1986[58]	RCT	32	Azathioprine	17	-	-	2	-	2	-
	Lin et al., 2000[59]	Series	24	Azathioprine	24	-	-	2	-	-	-
	Savolainen et al., 1997[60]	Series	129	Azathioprine	129	-	-	3	7	-	-
	de Castro et al., 2003[40]	Case reports	5	Azathioprine + MTX	5	-	-	-	-	-	-
				Total	**182**	-	-	**7**	**7**	**2**	-
Clyclosporin A	Pistoia et al., 1993[61]	Series	9	Cyclosporine A	9	-	1	-	-	1	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	de Castro et al., 2003[40]	Case reports	5	Cyclosporine A	2	-	-	-	-	-	-
	Gattinara et al., 1994[62]	Case reports	50 35 w/ JRA	Cyclosporine A	50	-	-	1	2	5	-
	Gerloni et al., 2001[63]	Series	41	Cyclosporine A	41	-	-	1	3	6	-
	de Castro et al., 2003[40]	Case reports	5	Cyclosporine A + MTX	1	-	-	-	-	-	-
	Krugmann et al., 2000[64]	Case report	1	Cyclosporine A + MTX	1	-	-	-	-	-	1
	Murphy et al., 1993[65]	Case report	1	Cyclosporine A	1	-	-	-	-	-	-
	Ostensen et al., 1988[66]	Series	14	Cyclosporine A	14	-	-	13	-	-	-
	Ruperto et al., 2006[67]	Series	329	Cyclosporine A	329	-	-	2	-	10	-
	Ravelli et al., 2002[68]	Series	17	Cyclosporine A + MTX	17	-	-	-	1	-	-
				Total	**465**	-	-	**17**	**6**	**22**	**1**
Pencillamine	Aggarwal et al., 2004[41]	Series	214	Penicillamine	23	-	-		-	1	-
	Kvien et al., 1985[69]	RCT	77	Penicillamine	38	-	-	3	-	3	-
	Prieur et al., 1985[70]	RCT	74	Penicillamine	74	-	-	1	-	-	-
	Sahn et al.,	Case report	1	Penicillamine	1	-	-	-	-	1	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	1989[71]										
	Brewer et al., 1986[72]	RCT	162	Penicillamine	54	-	-	-	-	-	-
	Kvien et al., 1985[73]	RCT	72	Penicillamine	24	-	1	3	-	2	-
	Swartz et al., 1984[74]	Case report	1	Penicillamine	1	-	-	-	-	1	-
				Total	**215**	-	**1**	**7**	-	**8**	-
Methotrexate	Aggarwal et al., 2004[41]	Series	214	Methotrexate	118	-	-	2	-	-	-
	Arakawa et al., 2003[75]	report	1	Methotrexate	1	-	-	-	-	-	-
	Chedeville et al., 2005[76]	Series	27	Methotrexate	27	-	9	1	9	1	-
	Cleary et al., 2002[77]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Corona et al., 1993[78]	Series	34	Methotrexate	34	-	-	-	6	-	-
	Cron et al., 1998[79]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Methotrexate	4	-	-	-	1	-	-
	Falcini et al., 1997[80]	Case report	1	Methotrexate	1	-	-	-	-	1	-
	Giannini et al., 1992[81]	RCT	127	Methotrexate	86	-	-	-	1	-	-
	Giannini et	Series	197	Methotrexate	197	-	8	1	11	6	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	al., 2009[13]										
	Gottlieb et al., 1997[82]	Series	25	Methotrexate	25	-	-	-	-	-	-
	Graham et al., 1992[83]	Series	62	Methotrexate	62	-	-	-	9		-
	Halle et al., 1991[84]	Series	30	Methotrexate	30	-	-	1	3	2	-
	Huang et al., 1996[85]	Series	26	Methotrexate	26	-	-	-	4	2	-
	Hunstad et al., 2007[86]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Keim et al., 1990[87]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lee et al., 2009[88]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Lin et al., 2000[89]	Series	52	Methotrexate	52	-	-	2	6	1	-
	Londino et al., 1998[90]	Case report	1	Methotrexate	1	-	-	-	-	1	-
	Martini et al., 1991[91]	Series	27	Methotrexate	27	-	-	-	1		-
	Muzaffer et al., 1996[92]	Case reports	2	Methotrexate	2	-	-	-	-	2	-
	Ortiz-Alvarez et al., 2004[93]	Series	89	Methotrexate	89	-	-	24	13		-
	Padeh et al., 1997[94]	Case report	1	Methotrexate	1	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	Ravelli et al., 1996[95]	Case report	1	Methotrexate	1	1	-	-	-	-	-
	Ravelli et al., 1998[96]	Series	256	Methotrexate	256	-	-	-	53	4	-
	Ravelli et al., 2001[97]	Case report	1	Methotrexate	1	1	-	-	-	-	-
	Riddle et al., 2006[98]	Series	57	Methotrexate	20	-	-	-	-	5	-
	Rose et al., 1990[99]	Series	29	Methotrexate	29	-	-	-	1	1	-
	Ruperto et al., 2004[100]	RCT	595	Methotrexate	595	-	-	-		12	-
	Russo et al., 2000[101]	Series	20	Methotrexate	20	-	-	-	5	-	-
	Savolainen et al., 2001[102]	Case reports	2	Methotrexate	2	-	-	2	-	-	-
	Schmeling et al., 2005[103]	Series	58	Methotrexate	58	-	-	-	19	-	-
	Silverman et al., 2005[54]	RCT	94	Methotrexate	47	-	-	-	4	6	-
	Speckmaier et al., 1989[104]	Series	12	Methotrexate	12	-	-	-	1	1	-
	Takeyama et al., 2006[105]	Case report	1	Methotrexate	1	-	-	-	-	-	-
	Truckenbrodt et al., 1986[106]	Series	19	Methotrexate	12	-	-	-	3	-	-
	van der Meer	Series	29	Methotrexate	29	-	-	-	-	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	et al., 2007[107]										
	Wallace et al., 1992[108]	Series	13	Methotrexate	13	-	-	-	1	-	-
	Yildirim et al., 200[109]	Case report	1	Methotrexate	1	-	-	-	-	-	-
				Total	**1885**	**2**	**-**	**33**	**151**	**45**	**-**
				Incidence – Methotrexate		**0%**	**-**	**3%**	**13%**	**4%**	**-**
Sulfasalazine	Balci et al., 2009[110]	Case report	1	Sulfasalazine	1	-	-	-	-	1	-
	Burgos-Vargas et al., 2002[111]	RCT	33	Sulfasalazine	17	-	-	-	-	-	-
	Chen et al., 2002[112]	Series	24	Sulfasalazine	24	-	-	-	-	-	-
	de Castro et al., 2003[40]	Case reports	5	Sulfasalazine	1	-	-	-	-	-	-
	Hertzberger-ten Cate et al., 1991[113]	Series	3	Sulfasalazine	3	-	-	-	-	1	-
	Imundo et al., 1996[114]	Series	139	Sulfasalazine	139	-	-	7	3	-	-
	Joos et al., 1991[115]	Series	41	Sulfasalazine	41	-	-	1	-	-	-
	van Rossum et al., 1998[116]	RCT	69	Sulfasalazine	35	-	4	2	2	2	-
	van Rossum	Series	61	Sulfasalazine	32	-	1	1		1	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	et al., 2007[117]										
	Aggarwal et al., 2004[41]	Series	214	Sulfasalazine	28	-	-	-	-	-	-
	Ansell et al., 1991[118]	Series	51	Sulfasalazine	51	-	-	2	3	-	-
	Gedalia et al., 1993[119]	Series	10	Sulfasalazine	10	-	-	-	1	-	-
	Gunnarson et al., 1997[120]	Series	8	Sulfasalazine	8	-	-	-	-	-	-
	Huang et al., 1998[121]	Series	15	Sulfasalazine	15	-	-	-	-	-	-
	Huang et al., 1998[122]	Case report	1	Sulfasalazine	1	-	-	1	-	1	-
	Kummerle-Deschner et al., 1995[123]	Case report	1	Sulfasalazine	1	-	-	-	-	-	-
	Ozdogan et al., 1986[124]	Series	18	Sulfasalazine	18	-	-	1	-	-	-
	Settas et al., 1991[125]	Series	18	Sulfasalazine	18	-	-	1	-	-	-
	Varbanova et al., 1999[126]	Series	32	Sulfasalazine	32	-	-	2	-	-	-
				Total	**475**	**-**	**5**	**18**	**9**	**6**	-
				Incidence – Sulfasalazine		**-**	**1%**	**4%**	**2%**	**1%**	-
OTHER											
	Flato et al.,	Series	117	DMARDs	28	-	-	4	5	-	-

DMARD	Study	Study design	Total N	Intervention	Intervention sample size	Macrophage activation syndrome	Non-hematologic lab abnormality	Hematologic lab abnormality (excluding anemia)	Elevated liver enzymes	Other	Death
	1998[127]										
	Lomater et al., 1994[128]	Series	7	Plaquenil + MTX + gold salts	7	-	-	1	-	-	-
	Barash et al., 199[129]	Case reports	2	Penicillamine + gold	2	-	-	-	-	2	-

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Appendix F: Excluded Studies

All studies listed below were reviewed in their full-text version and excluded. Following each reference, in italics, is the reason for exclusion. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

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