Efficacy and safety of pharmacological and non-pharmacological interventions in juvenile idiopathic arthritis: A series of systematic reviews and network meta-analyses

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ABSTRACT

There is little head-to-head evidence comparing interventions available for juvenile idiopathic arthritis (JIA). This review involved a series of systematic reviews and network meta-analyses (NMAs) to evaluate the comparative efficacy and safety of pharmacological and non-pharmacological interventions among patients with JIA. Outcomes were the American College of Rheumatology Pediatric 30 (ACR Pedi 30) (disease response), its six composite outcomes, pain relief, health-related quality of life, and physical and emotional functioning. There was some evidence that etanercept had greater reduction in the number of joints with active arthritis compared to abatacept for polyarticular-course JIA and that canakinumab had improved ACR Pedi 30 over rilonacept. Non-pharmacological interventions showed no significant results for efficacy but were safe overall. Most included studies were low-quality and many were excluded from analysis because of unclear reporting or no results for outcomes of interest. As more studies are conducted this will improve the estimates from the NMAs.

EXECUTIVE SUMMARY

Background: Juvenile idiopathic arthritis (JIA) is the most common rheumatic condition in children and its cause is unknown. A recent study found a lack of randomized controlled trials (RCTs) on JIA, and that clinical practice guideline recommendations often rely on observational studies, expert opinion and extrapolations from adult studies. Considering the difficulties of research in pediatrics, other methods should be considered for identifying the most effective interventions for JIA with the limited evidence available.

Objective: The objective of this review was to conduct a series of systematic reviews and network meta-analyses (MAs) to evaluate the efficacy and safety of pharmacological and non-pharmacological interventions compared to a control or other active intervention on the measure of disease response, pain relief, health-related quality of life (HRQOL), physical functioning, and emotional functioning among children and adolescents with JIA.

Methods: Included studies were RCTs with participants 18 years old or younger diagnosed with JIA. Studies investigated pharmacological interventions (*i.e.,* non-steroidal anti-inflammatory drugs [NSAIDs], non-biologic disease-modifying anti-rheumatic drugs [DMARDs], intra-articular corticosteroid joint injections, systemic glucocorticoids, biologics) and non-pharmacological interventions (*i.e.,* physical activity, nutritional interventions, massage interventions, and psychosocial or behavioural interventions) compared to placebo, a waiting list, standard care or another active intervention. Surgical or invasive interventions were excluded. For pharmacological interventions the primary outcome of interest was disease response as measured by the American College of Rheumatology Pediatric 30 (ACR Pedi 30) and secondary outcomes were pain relief, HRQOL, and the six ACR Pedi core set of outcomes. For non-pharmacological interventions the primary outcome was pain relief and secondary outcomes were HRQOL, physical and emotional functioning, and the six ACR Pedi core set of outcomes. Safety outcomes for all intervention types were the number of withdrawals due to adverse events (AEs) and the number of participants with a serious AE. A systematic literature search was conducted and two pairs of independent reviewers screened and selected included studies, then extracted data for the outcomes of interest. The Cochrane Risk of Bias tool was used to identify high and low quality studies. Where

possible, data analysis with network MAs using a random effects Bayesian statistical model was conducted to utilize both direct and indirect evidence from the included studies. This was done to determine the comparative efficacy of interventions with respect to a common comparator. Results are presented as the median relative risk with 95% credible interval (CrI) for binary outcomes and the median mean difference or standardized mean difference (95% CrI) for continuous outcomes. MAs for pairwise comparisons were planned when not enough studies were available for a network MA. A descriptive analysis was used for an outcome when a MA could not be performed.

Results: 537 records were found in the literature search. After duplicate removal, the titles and abstracts of 361 records were screened and 151 full-text articles were reviewed. A total of 100 full-text articles and abstracts were included that make up 67 unique RCTs. The number of RCTs reported in at least one full-text article by intervention category were as follows: 14 for biologics, 10 for DMARDs, nine for NSAIDs, seven for corticosteroids (intra-articular joint injections and systemic glucocorticoids), seven for physical activity interventions, four for nutritional interventions, four for foot orthotics/foot care and splints, one for massage, and three for psychosocial or behavioural interventions. Based on the risk of bias assessments, nearly all RCTs were of low methodological quality across all intervention categories. The network MAs for withdrawal design RCTs of biologics for patients with polyarticular-course JIA had no significant results of indirect head-to-head comparisons for the ACR Pedi 30, but both doses of etanercept (0.2 mg/kg and 0.4 mg/kg twice weekly) had greater reductions in the number of active joints compared to abatacept (MD = 8.17, 95% credible interval (CrI): 0.95, 15.48 and MD = 7.92, 95% CrI: 3.51,12.36 respectively). Network MA results for the ACR Pedi 30 among parallel studies of biologics for patients with active systemic JIA showed greater reduction in disease activity for canakinumab (4 mg/kg) compared to rilonacept (2.2 mg/kg maintenance dose) (RR = 1.68, 95% CrI: 1.16, 3.10). Higher-dose MTX (30-40 mg/m^2) had worse inflammation results measured by the ESR compared to moderate-dose MTX (10-20 mg/m^2) (RR = 15.44, 95% CrI: 6.02, 24.87 mm/h). There were no significant results for indirect head-to-head comparisons in the network MAs comparing NSAIDs. For non-pharmacological interventions, there was insufficient evidence to demonstrate that one intervention had greater pain relief or improvement in HRQOL compared to another in the indirect head-to-head comparisons or to the control group of the network MAs. Based on descriptive analyses, methotrexate at a dose of 10-20 mg/m^2/week was safe for

short-term use among patients with oligoarticular and polyarticular JIA. Meloxicam (0.25 mg/kg/day) had a better safety profile than naproxen (10 mg/kg/day). Non-pharmacological interventions were safe to use overall, but the network MAs did not reveal any statistically significant differences in the comparative efficacy outcomes among interventions.

Conclusions: Canakinumab has good efficacy based on the disease response among patients with active systemic JIA. MTX at a dose of 10-20 mg/m^2 per week had a good safety profile compared to other DMARDs and was favoured over MTX at a dose of 30-40 mg/m^2 for inflammation (ESR). Among NSAIDs, naproxen (15 mg/kg/day) was safe to use and meloxicam (0.25 mg/kg) had improved overall well-being as assessed by the patient or parent compared to naproxen. Non-pharmacological interventions were safe to use overall, but there were no statistically significant differences in pain relief or HRQOL based on indirect head-to-head comparisons of interventions or an active intervention versus a control group. The challenges in identifying interventions with greater efficacy from indirect head-to-head comparisons may be in part due to the limited number of RCTs and small sample sizes contributing to the network MAs and potential bias in the estimates that are based primarily on low quality RCTs. Safety results of the interventions should be considered within the context of prospective follow-up studies of long-term use. The findings of this review should be considered in clinical practice guidelines for JIA, which previously could not base recommendations off of head-to-head comparisons. However, results should be interpreted with caution given the low-quality evidence. As more RCTs are developed that are of high methodological quality, this will improve the overall evidence and the precision of results for systematic reviews and MAs.

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LIST OF ABBREVIATIONS

ACR Pedi 30	American College of Rheumatology Pediatric 30
ACR	American College of Rheumatology
AE	Adverse event
CARRA	Childhood Arthritis and Rheumatology Research Alliance
CHAQ	Childhood Health Assessment Questionnaire
CI	Confidence interval
CPG	Clinical practice guideline
CrI	Credible interval
CRP	C-reactive protein
DIC	Deviance information criterion
DMARD	Disease-modifying antirheumatic drug
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FDA	Federal Drug Administration
HRQOL	Health-related quality of life
ILAR	International League of Associations for Rheumatology
IU	International Units
JIA	Juvenile idiopathic arthritis
MA	Meta-analysis
MD	Mean difference
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
PA	Physical activity
PEDro	Physiotherapy Evidence Database
PedsQL	Pediatric Quality of Life Inventory
PICOS	Population, intervention, comparator, outcome, study design
PPV	Positive predictive value
PRCSG	Pediatric Rheumatology Collaborative Study Group
PRINTO	Pediatric Rheumatology International Trials Organization
RCT	Randomized controlled trial
RR	Relative risk
SMD	Standardized mean difference
SR	Systematic review
VAS	Visual Analogue Scale

CHAPTER 1: INTRODUCTION

1.1 RATIONALE

Patients with juvenile idiopathic arthritis (JIA) may be treated with a combination of pharmacological and/or non-pharmacological interventions (*e.g.,* to manage signs and symptoms of disease, slow down the progression of disease, and achieve clinical remission or inactive disease (Beresford & Baildam, 2009; Gartlehner, Hansen, Jonas, Thieda, & Lohr, 2008; Ostring & Singh-Grewal, 2013). JIA is a complex disease that requires interventions that vary depending on the subtype of disease, the current disease activity, and prognosis (Kemper, Van Mater, Coeytaux, Williams, & Sanders, 2012; Ravelli & Martini, 2007). The current internationally agreed upon onset types for JIA are: oligoarticular, polyarticular (rheumatoid factor positive or negative), systemic, psoriatic, enthesitis-related, and undifferentiated (Petty, Laxer, & Wedderburn, 2016; Petty et al., 2004).

Clinical practice guidelines (CPGs) have been developed to provide recommendations for treating the subtypes of JIA (Beukelman et al., 2011; Dueckers et al., 2012; Munro et al., 2009; Ringold et al., 2013). A recent systematic critical appraisal of the CPGs for JIA found that the CPGs were based on systematic reviews (SRs) and that the overall methodological quality of these CPGs were moderate to high based on the Appraisal of Guidelines in Research and Evaluation II (AGREE II) instrument (Smith et al., 2015).

There remain, however, several gaps in the literature as demonstrated in the systematic critical appraisal of CPGs. First, many of the CPGs' recommendations were based on evidence of low quality such as extrapolations of results from adult rheumatology studies, observational studies and expert opinion. This is problematic in that there are specific considerations for the JIA population that differ from an adult rheumatology population such as growth and long-term exposure to interventions (Hayward & Wallace, 2009), and expert opinion in these CPGs is likely not based on evidence if extrapolations from adult rheumatology studies are required. Observational studies can be useful, but they are at risk of biases that randomized controlled trials (RCTs) do not face such as selection and measurement bias (Aschengrau & Seage, 2014). Secondly, when evidence was based on results from RCTs, the recommendations relied solely on results from a single RCT rather than a meta-analysis (MA) of two or more RCTs for a particular

intervention. Indirect comparisons would be useful since there are not many RCTs available (Smith et al., 2015). Lastly, while it was not possible to distinguish the quality of a CPG in presenting recommendations for pharmacological versus non-pharmacological interventions using the AGREE II instrument, those CPGs that did provide recommendations for non-pharmacological interventions lacked details on these interventions as they grouped entire disciplines together as an intervention (*e.g.,* physiotherapy and occupational therapy), which limits the application of these recommendations by healthcare professionals (Smith et al., 2015).

1.2 NEED FOR A REVIEW

Given these limitations of CPGs, it is important to conduct a systematic review with a meta-analysis of the efficacy and safety of interventions to provide stronger evidence for CPG developers to consider when making recommendations on interventions for patients with JIA. However, as mentioned there are few RCTs cited in the current recommendations in the CPGs for JIA, thus it may not be possible to conduct a MA that compares two or more RCTs of the same intervention. Other statistical methods such as a network MA may be used as a means of comparing interventions by taking into consideration both direct evidence for comparisons available from the RCTs themselves and indirect evidence of other comparisons that were not directly studied within a RCT (Jansen et al., 2011).

1.3 OBJECTIVES

The objective of this study was to conduct a series of SRs and network MAs to evaluate the efficacy and safety of pharmacological and non-pharmacological interventions compared to any type of control group or another active intervention among children and adolescents with JIA.

1.4 RESEARCH QUESTION

1. What is the evidence on the efficacy and safety of pharmacological and non-pharmacological interventions in JIA?

1.5 OUTLINE

The thesis is divided into chapters each covering a specific section. A summary of each chapter is provided below.

Chapter 1: This is an introductory chapter that introduces juvenile idiopathic arthritis (JIA), describes existing gaps in the literature and uses this information to present the study rationale and objectives. An overview of each chapter is provided as well.

Chapter 2: This chapter describes JIA, its signs and symptoms, how it is diagnosed, and why it is an important disease to study. There is also a section detailing the epidemiology of JIA, including the incidence and prevalence and why it differs by geographical location and gender. Next, there is a description of available pharmacological and non-pharmacological interventions to be used in treating JIA. Lastly, the chapter provides a summary of existing evidence in the literature by describing published systematic reviews and meta-analyses, as well as clinical practice guidelines; the gaps in the literature in terms of efficacy and safety for JIA interventions are highlighted and the rationale for conducting a network meta-analysis is presented.

Chapter 3: This chapter goes into detail on the methods of this review. Firstly, it outlines the selection criteria used to determine the included studies. Secondly, the method of handling study records is described, including how data were managed and the process of selecting and extracting the included studies. The methods of risk of bias assessment are also described. Next, details on the synthesis of the data provide a clear idea of what a network meta-analysis is and how it was conducted in this review; methods for meta-analyses and descriptive analyses were also described. Finally, identifying important subgroups and sensitivity analyses and how they would be handled was described in this chapter.

Chapter 4: This chapter provides the efficacy and safety results for all included studies. It is separated into two major sections for all results: pharmacological interventions and non-pharmacological interventions. Within pharmacological interventions, the different medication categories are further divided as follows: biologics, disease-modifying anti-rheumatic drugs, non-steroidal anti-inflammatory drugs, and corticosteroids (intra-articular corticosteroid joint injections and systemic glucocorticoids). Within non-

pharmacological interventions, the different intervention categories are further divided as follows: physical activity interventions, nutritional interventions, foot orthotics or foot care and splints, massage interventions, and psychosocial or behavioural interventions. Regardless of the intervention category, the results were presented so that first the characteristics of included studies were described, then the efficacy results were reported (with network meta-analysis results reported first, followed by meta-analysis results, and the descriptive analysis results), then any sensitivity analyses for the efficacy results were reported, and finally the safety results were reported. All tables and figures for chapter 4 are presented at the end of the chapter in numerical order.

Chapter 5: This chapter discusses the important results reported in chapter 4. It starts with a summary of the key findings across all intervention categories. Next, each intervention category has its efficacy and then safety results explained within the context of the existing literature. The order of the intervention categories is the same as in chapter 4. Next, the strengths of this review are described, followed by the limitations of the included studies and of this review, respectively. Future directions for research are then presented to guide the focus of research in the area of JIA. Lastly, there is a conclusion to summarize the important findings based on the objectives of this review and reiterates important information on the generalizability and importance of the results.

CHAPTER 2: BACKGROUND

2.1 DIAGNOSIS AND SYMPTOMS OF JUVENILE IDIOPATHIC ARTHRITIS

JIA is the most common childhood rheumatic condition and its cause is still unknown (Bloom et al., 2002; Stanley & Ward-Smith, 2011). The International League of Associations for Rheumatology (ILAR) separated JIA into seven distinct categories, which are oligoarticular, polyarticular (rheumatoid factor positive or negative), systemic, psoriatic, enthesitis-related and undifferentiated arthritis (Petty et al., 2016; Petty et al., 2004). These are distinguished based on clinical manifestations of disease such as number of active joints being fewer than five (oligoarticular) versus five or more (polyarticular) and the presence of serological markers (rheumatoid factor positive or negative polyarticular JIA), systemic symptoms, psoriasis, or enthesitis. Undifferentiated arthritis is a category for patients who either do not meet the criteria for any of the above six categories or meet criteria for more than one of the categories. A patient is diagnosed with one of these JIA onset types if they experience persistent symptoms for at least six weeks before they turn 16 years old and after ruling out other diseases (Petty et al., 2016; Petty et al., 2004).

The etiology of JIA is still not well understood in terms of the presence of genetic and environmental factors and how they interact with each other (Cobb, Hinks, & Thomson, 2014). Some progress has been made in identifying genetic factors such as HLA class I and II alleles, PTPN22 single nucleotide polymorphism rs2476601 and PTPN2 that put a person at more risk of developing certain subtypes of JIA (Cobb et al., 2014; Stanford & Bottini, 2014). Future findings may demonstrate JIA is comprised of separate diseases rather than subtypes (Cobb et al., 2014), which may impact the way interventions are studied and applied in treating patients.

Common signs and symptoms of the disease include inflammation, pain, and stiffness of the joints (Bloom et al., 2002; Bromberg, Connelly, Anthony, Gil, & Schanberg, 2014; Stanley & Ward-Smith, 2011). Patients with systemic JIA may also experience fever and rash (Bloom et al., 2002; Bromberg et al., 2014; Stanley & Ward-Smith, 2011). Complications of the disease can include uveitis, deficiencies in vitamin D, disruptions to proper bone and joint development, lower bone density that may place an

individual at higher risk of bone fractures later in life, joint erosion, macrophage activation syndrome (in about 5-8% of patients with systemic JIA), low bone mineral density, and osteopenia (Beresford & Baildam, 2009; Duffy, 2005; Ostring & Singh-Grewal, 2013; Ravelli & Martini, 2007). Proper treatment of patients with JIA is imperative as both fine and gross motor skills are limited due to the presence of joint inflammation and pain (Packham & Hall, 2002), which impacts daily activities and health-related quality of life (HRQOL). A Dutch study found HRQOL to be statistically significantly lower among children and adolescents with JIA aged 6-18 years than healthy peers of the same age (Haverman et al., 2012).

JIA continues into adulthood in about 40-70% of cases (Hashkes & Laxer, 2005). A long-term follow-up study from 2002 found that after five years, JIA resulted in permanent joint damage for two-thirds of cases, even if they had been taking non-steroidal anti-inflammatory drugs (NSAIDs) and non-biologic disease modifying antirheumatic drugs (DMARDs) (Packham & Hall, 2002). Damage to joints and soft tissues can be prevented using the biologic DMARDs (biologics) that are now available, and pharmacological interventions can be coupled with non-pharmacological interventions for improved outcomes of pain relief and HRQOL (Dueckers et al., 2012; Hashkes & Laxer, 2005; Munro et al., 2009). Other goals of non-pharmacological interventions may include improving physical function, joint range of motion, and muscle strength (Kuchta & Davidson, 2011)

2.2 EPIDEMIOLOGY OF JUVENILE IDIOPATHIC ARTHRITIS

It is challenging to report on the incidence and prevalence of JIA as it varies by region and some of this variability is due to differences in factors including: 1) identifying cases (***e.g.,*** community vs. clinic setting, age cut-offs at 12 years versus 18 years of age); 2) method of diagnosis; 3) awareness of the disease over time; 4) living conditions; and 5) definitions of disease (***i.e.,*** American College of Rheumatology (ACR) vs. European League Against Rheumatism (EULAR) vs. ILAR definition) (Harrold et al., 2013; Manners & Bower, 2002; Thierry, Fautrel, Lemelle, & Guillemin, 2014). A recent SR included studies estimating the incidence and/or prevalence of JIA and pooled the estimates in subgroups by classification criteria used (***e.g.,*** ACR, EULAR, and ILAR criteria). The pooled incidence estimate of JIA following the new ILAR classification criteria was 8.9 (95% Poisson confidence interval (CI): 8.3 to 9.6) per 100,000 children among eight European studies with time periods between 1989 and 2006 (Thierry et al., 2014).

The same review estimated the pooled prevalence of JIA following the ILAR classification criteria to be 30.0 (95% CI: 28.0 to 32.0) per 100,000 children among seven of the same European studies between the years 1999 and 2006 (Thierry et al., 2014).

A study of patients in a managed care population from Northern California used a case-finding algorithm with a sensitivity of 95% and positive predictive value (PPV) of 82% to standardize the incidence rate and point prevalence estimates. This was accomplished by multiplying the result by the PPV and dividing by the sensitivity (Harrold et al., 2013). The adjusted incidence rate was 11.9 (95% CI: 10.9 to 12.9) per 100,000 person-years; girls had a higher incidence rate (16.4 [95% CI: 14.6 to 18.1]) compared to boys (7.7 [95% CI: 6.5 to 8.9]) per 100,000 person-years. The adjusted point prevalence in the study population at the end of 2009 was 44.7 (95% CI: 39.1 to 50.2) per 100,000 children (Harrold et al., 2013). In contrast, a Canadian population-based study using health administrative data estimated the disease prevalence to be 0.8 per 100,000 in Quebec, 0.98 per 100,000 in Saskatchewan and 1.7 per 100,000 in Manitoba among those under the age of 19 years (Shiff et al., 2015). While the differences in prevalence may be due to demographics, it is also likely that the Canadian study underestimated the prevalence of JIA since case definitions relied on hospitalizations for patients with JIA and not all patients require hospitalization or have easy access to hospitals (Shiff et al., 2015).

Overall more girls than boys have JIA in the more common subtypes of oligoarticular and polyarticular JIA (Ravelli & Martini, 2007). In the SR of European epidemiological studies in JIA mentioned above, the pooled incidence and prevalence among girls were estimated at 10.0 (95% Poisson CI: 9.4 to 10.7) per 100,000 and 19.4 (95% Poisson CI: 18.3 to 20.6) per 100,000, respectively. For boys, the incidence and prevalence were estimated to be 5.7 (95% Poisson CI: 5.3 to 6.2) per 100,000 and 11.0 (95% Poisson CI: 10.2 to 11.9) per 100,000, respectively (Thierry et al., 2014). The exceptions are systemic JIA affecting a comparable proportion of girls and boys and enthesitis-related arthritis, which occurs mainly in boys (Ravelli & Martini, 2007). Overall, oligoarticular JIA was estimated to be the most common subtype (prevalence = 16.4 [95% Poisson CI: 15.0 to 17.9] per 100,000 children) (Thierry et al., 2014). However, a Canadian multiethnic cohort study found that ethnicity is an important factor for the risk of developing JIA, with individuals of European origin having the greatest risk of developing any JIA subtype with the

exception of polyarticular and systemic JIA compared to non-Europeans, whereas individuals of Black origin or from the Indian subcontinent have a greater risk of developing rheumatoid-factor positive polyarticular JIA (Saurenmann et al., 2007). While no mechanism has been described for these ethnic differences, they may likely be explained by genetic factors.

2.3 INTERVENTIONS AVAILABLE FOR JUVENILE IDIOPATHIC ARTHRITIS

2.3.1 PHARMACOLOGICAL INTERVENTIONS

The main categories of pharmacological interventions used to treat patients with JIA are NSAIDs, corticosteroids (intra-articular (IA) corticosteroid joint injections and systemic glucocorticoids), DMARDs, and biologics. More recently, systemic glucocorticoids were found to have toxic effects such as slowing down or stopping growth and are not used as often, except in systemic JIA patients with uncontrolled disease (Ravelli & Martini, 2007). The type of intervention required for a patient will vary depending on the onset type of JIA, severity, and progression of disease (Beukelman et al., 2011; Dueckers et al., 2012; Ringold et al., 2013). NSAIDs and intra-articular corticosteroid joint injections may be provided as initial interventions for pain management among patients with non-systemic onset types of JIA (Beukelman et al., 2011; Dueckers et al., 2012; Ringold et al., 2013). For individuals with symptoms that persist or those with more severe JIA onset types, DMARDs are prescribed as the next pharmacological intervention option (Beukelman et al., 2011; Dueckers et al., 2012; Ringold et al., 2013). DMARDs have been shown to be effective in delaying the progression of the disease by slowing down the process of inflammation in the body (Ostring & Singh-Grewal, 2013). Of the available DMARDs, methotrexate (MTX) is most commonly recommended due to its high efficacy and low risk profile, but it also has side effects such as nausea and dyspepsia (Beukelman et al., 2011; Dueckers et al., 2012; Ringold et al., 2013).

Biologics are the newest category of medications which also modify the disease. They are monoclonal antibodies or fusion proteins that activate or control the immune system and reduce disease activity by targeting specific signaling pathway molecules (*e.g.,* cytokines) or cell to cell interactions (Gartlehner et al., 2008; Hashkes & Laxer, 2005; Sen & Ramanan, 2014). Generally, biologics are prescribed as a second- or third-line intervention when a patient has failed to respond to other interventions such as MTX

(Beresford & Baildam, 2009; Beukelman et al., 2011; Dueckers et al., 2012; Munro et al., 2009; Ringold et al., 2013; Smith et al., 2015).

There is concern about the use of biologics as their mechanism of action may increase the risk of infection and malignancy and they may also interfere with response to vaccinations (Hayward & Wallace, 2009). As such, current Federal Drug Administration (FDA) guidelines do not recommend more than one biologic to be used concurrently (Hayward & Wallace, 2009). Direct comparisons of the safety profiles of biologics are not available, thus there is some uncertainty as to which biologics may pose a greater risk for patients than others (Hashkes, Uziel, & Laxer, 2010). Interestingly, a review considering infection rates among observational studies of patients with JIA treated using biologics found only a modest increase in the absolute risk of infections when patients were treated with biologics as compared with the baseline risk of infection among patients with JIA who were not treated with biologics. In fact, the study suggests that regardless of the pharmacological interventions used, there may be an increased risk of infections due to JIA itself (Hurd & Beukelman, 2013). A cohort study investigating the risk of malignancy among biologically-naïve patients with JIA indicate these patients had almost three times the risk of developing cancer compared to healthy controls (Nordstrom et al., 2012). While these results were not statistically significant, a subgroup of biologically naïve patients with JIA who had received methotrexate had an increased risk of cancer compared to healthy controls. The authors suggest these findings could indicate that increased risk of malignancy is related to more severe cases of JIA or possibly the use of MTX (Nordstrom et al., 2012). The control group was comparable in characteristics to the exposed group (*i.e.,* biologically naïve JIA patients), so selection bias is not likely to explain these results and while there is potential for misclassification bias, the authors had a pediatric oncologist to determine those who developed a malignancy or not so that the risk of bias was reduced (Nordstrom et al., 2012). Biologics are a promising new intervention for many patients with JIA who have not responded to other interventions or who have severe disease, and their safety profile needs to be investigated further.

2.3.2 NON-PHARMACOLOGICAL INTERVENTIONS

Multidisciplinary care is being recognized as increasingly important for treating children and adolescents with JIA in order to improve their HRQOL (Ostring & Singh-Grewal, 2013). There are many intervention

types that may be of benefit for patients such as physical modalities (*i.e.,* physical activity (PA), massage), splints and foot orthotics, nutrition, and psychosocial interventions, while they are also receiving one or more pharmacological interventions. For example, when a patient participates in PA or uses massage, they can maintain range of motion in their joints and overall functional status, and improve bone development (Boros & Whitehead, 2010; Cavallo, April, Grandpierre, Majnemer, & Feldman, 2014; Houghton, 2012).

2.4 CURRENT KNOWLEDGE BASE

In an overview of the literature, there were ten SRs retrieved on interventions in JIA, with eight of them conducted on pharmacological interventions (Gartlehner et al., 2008; Kemper et al., 2012; Otten, Anink, Spronk, & van Suijlekom-Smit, 2013; Takken, van der Net, & Helders, 2001; Tarp et al., 2016; Thornton et al., 2006; Ungar, Costa, Burnett, Feldman, & Laxer, 2013; Wallen & Gillies, 2006). The interventions investigated were: IA joint injections with corticosteroids, bisphosphonates, DMARDs, and biologics. Two non-pharmacological intervention SRs investigated exercise therapy and foot orthotics (Hawke, Burns, Radford, & Du Toit, 2008; Takken et al., 2008).

The study populations were individuals with JIA, except for three SRs: one SR on IA joint injections that included individuals with JIA and adults with rheumatoid arthritis (Wallen & Gillies, 2006), another SR on foot orthoses and foot orthotics that involved individuals of any age with any form of foot pain (Hawke et al., 2008), and the third on bisphosphonates for patients with JIA or other connective tissue diseases (Thornton et al., 2006). Four of the ten SRs mentioned above conducted a MA (with direct pairwise comparisons of two interventions) (Hawke et al., 2008; Takken et al., 2008; Takken et al., 2001; Wallen & Gillies, 2006) and two SRs used a MA with indirect comparisons to assess the efficacy of biologics for treating JIA (Otten et al., 2013; Tarp et al., 2016). The interventions analyzed with a pairwise MA were foot orthotics, exercise therapy, intra-articular corticosteroids and splints/rest, biologics, and MTX (Hawke et al., 2008; Takken et al., 2008; Takken et al., 2001; Ungar et al., 2013; Wallen & Gillies, 2006). The characteristics of existing SRs and MAs with results on efficacy and/or safety of pharmacological and non-pharmacological interventions for JIA are summarized in Table 2.1 and 2.2, respectively.

2.4.1 PHARMACOLOGICAL INTERVENTIONS

Of the pharmacological SRs, one presented the use of bisphosphonates in patients with JIA or other connective tissue diseases and found that these medications may prevent low bone mineral density and fragility fractures and were safe to use. There were 16 included studies, one of which was a RCT and the rest were observational studies (*i.e.,* cohort, case control, and case series). However, the results are not specific to JIA, the definition of JIA was not standardized, and studies were heterogeneous (Thornton et al., 2006). In addition, bisphosphonates are not an intervention of interest for this review as they have not been investigated for recommendation by current CPGs of pharmacological interventions for JIA (Beukelman et al., 2011; Dueckers et al., 2012; Munro et al., 2009; Ringold et al., 2013).

A Cochrane SR and MA investigated IA joint injections using corticosteroids, but the five included RCTs were all of adults with rheumatoid arthritis receiving IA joint injections predominantly in the knee (Wallen & Gillies, 2006). Intra-articular corticosteroid joint injections were favoured over the control in outcomes of pain relief, knee flexion and extension lag, knee circumference, morning stiffness, and duration of efficacy (Wallen & Gillies, 2006). Resting or using splints may be implemented after intra-articular corticosteroid joint injection of the knee, but not for the wrist as this did not add any benefit and may have its own complications (Wallen & Gillies, 2006). No adverse events at injection sites were reported in the RCTs. Since there were no studies of this intervention from the JIA population, extrapolations of these results to JIA must be interpreted with caution (Wallen & Gillies, 2006). It is possible that there may be new RCTs available for review since the time of publication of this SR eleven years ago because the authors called for RCTs of IA joint injections for JIA.

Another SR and MA focused on MTX included two RCTs and a single arm from one of the two RCTs was included in the analysis (Takken et al., 2001). Pooled estimates from the SR and MA indicate MTX was statistically significant over placebo in all outcomes except parent's global assessment of overall well-being. No difference was detected in the number of withdrawals between the MTX and placebo groups, suggesting that MTX may be safe to use for JIA (Takken et al., 2001). Results on functional ability and HRQOL were also not available in the included RCTs.

Once biologics started to be used among patients with JIA, a portion of the Drug Effectiveness Review Project included a SR focused on the efficacy and safety of biologics for treating patients with JIA (Gartlehner et al., 2008). There were 11 non-randomized prospective studies and one RCT for efficacy outcomes and another three observational studies with safety results. Most included studies were of etanercept, and together they indicated the efficacy of etanercept in the short-term and a good safety profile when compared to placebo (Gartlehner et al., 2008). The authors mentioned the exclusion of several RCTs that were either published only as abstracts or did not have any data available at the time of the review. As a result, they found limited evidence available for biologics other than etanercept (Gartlehner et al., 2008).

Four years later, a SR was published on six RCTs of DMARDs, seven RCTs of biologics, and three RCTs of intravenous immunoglobulin therapy for treating patients with JIA (Kemper et al., 2012). While good quality RCTs supported the efficacy of MTX, the direct evidence available for comparing the efficacy of DMARDs (*i.e.,* MTX, sulfasalazine, hydroxychloroquine, leflunomide) was lacking (Kemper et al., 2012). As for results from the biologics studies in the SR, there were only one or two RCTs at most available for each biologic (abatacept, adalimumab, anakinra, etanercept, and infliximab) versus placebo. Thus, no MA of the results could be performed (Kemper et al., 2012). Another SR of RCTs, non-randomized and observational cohort studies and patient registries was published in 2013 and focused on biologics for patients with polyarticular JIA (Ungar et al., 2013). Most of the included studies were on etanercept, which was found to have good long-term efficacy and safety based on patient registry data.

Otten et al. conducted a SR of biologics using indirect treatment comparisons for the MA. There were 11 included RCTs. The results did not indicate any biologics to be superior over another for either polyarticular-course JIA for disease flare prevention or systemic JIA for achievement of disease response (Otten et al., 2013). A second SR with indirect treatment comparisons that was recently published in 2016 focused on biologics for patients with systemic JIA and included six RCTs (Tarp et al., 2016). They found no differences in the biologics in terms of safety, but weak evidence that rilonacept had worse disease response than canakinumab and tocilizumab (Tarp et al., 2016).

Three CPGs for JIA included recommendations on pharmacological interventions (Beukelman et al., 2011; Dueckers et al., 2012; Munro et al., 2009). NSAIDs were moderately to strongly recommended as initial therapy for patients with oligoarticular JIA based on evidence from RCTs and well-designed non-randomized controlled trials (Beukelman et al., 2011; Dueckers et al., 2012; Munro et al., 2009). However, two CPGs recommended NSAIDs as a drug category overall rather than highlighting specific NSAIDs (Beukelman et al., 2011; Munro et al., 2009). The other CPG did recommend specific NSAIDs, including a high recommendation for the use of the NSAIDs diclofenac and naproxen and also indomethacin based on a non-controlled trial (Dueckers et al., 2012). However, this CPG did not conduct a MA directly comparing any of the NSAIDs it recommended against each other to determine which had better efficacy and safety (Dueckers et al., 2012). MTX received a strong recommendation as the DMARD of choice based on evidence from RCTs, particularly for polyarticular and systemic JIA subtypes (Beukelman et al., 2011; Dueckers et al., 2012). Different strengths of recommendations based on level of evidence and results of individual studies were provided by two CPGs (Beukelman et al., 2011; Dueckers et al., 2012), but the decision to give one biologic a higher recommendation than another appears to be based on expert opinion because there were no MAs that could be conducted to directly compare the biologics interventions using a head-to-head comparison.

2.4.2 NON-PHARMACOLOGICAL INTERVENTIONS

Non-pharmacological interventions have not been widely studied in the JIA population. A SR and MA of foot orthotics for treating foot pain was a broad review that included patients of all ages with any type of foot pain (Hawke et al., 2008). They found one RCT on custom foot orthotics for JIA reported a statistically significant decrease in foot pain, improvement in function, and decrease in disability compared to standard intervention. No statistically significant differences were observed when custom foot orthotics were compared to neoprene shoe inserts in the same outcomes (Hawke et al., 2008). The review found no other included RCTs of foot orthotics for JIA. A new SR on foot orthotics may reveal new RCTs that have since been published.

For the purposes of this review, the conceptual framework describing PA developed by Pettee Gabriel et al. will henceforth be used to refer to the specific domain of leisure physical activities, which include all

forms of exercise (*e.g.,* stretching, strengthening, aerobic, aquatics) (Pettee Gabriel, Morrow, & Woolsey, 2012). In one SR and MA on PA, pooled estimates for functional ability, HRQOL and aerobic capacity showed no difference between PA interventions compared to the control group. No adverse effects were found and symptoms of arthritis were not worsened during exercise (Takken et al., 2008). Since only a small number of RCTs were available and there was heterogeneity in their outcome measures, it is important to conduct an updated SR as newer RCTs on PA interventions have likely been developed for JIA to fill the gaps in the literature. In addition, the PA interventions themselves differed and the heterogeneity may have made it unsuitable to pool study results together to conduct a MA.

One CPG for JIA lacked detail for non-pharmacological interventions as it described entire disciplines (*e.g.,* physiotherapy and occupational therapy) as interventions (Dueckers et al., 2012; Smith et al., 2015). Two CPGs had conflicting recommendations for the use of PA, with one providing a high recommendation and the other providing a moderate recommendation for land-based and aquatic PA interventions (Dueckers et al., 2012; Munro et al., 2009; Smith et al., 2015). Another CPG specifically focusing on PA interventions for JIA was recently published (Cavallo et al., 2016). Recommendations were made for several PA interventions, including: Pilates, home exercises, aquatic aerobics, and a land-based aerobics program called cardio-karate (Cavallo et al., 2016). However, pairwise MAs comparing these interventions could not be conducted because of the differences in the program types.

Another CPG has recently been published that provides recommendations on foot care for patients with JIA (Brosseau 2016). This Ottawa Panel evidence-based CPG recommended use of custom-made semi-rigid orthotics over both prefabricated off-the-shelf shoe inserts and new supportive athletic shoes for at least three months for pain relief in general and for the foot specifically, and reduced limitation of activity and disability. They recommended custom-fitted preformed foot orthotics over non-customized foot orthotics for at least six months (Brosseau et al. 2016). Thus, there were two types of foot orthotics recommended.

2.5 NEED FOR A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF INTERVENTIONS FOR JIA

The benefit of synthesizing evidence from multiple studies in a SR and MA is providing a clearer picture of the efficacy and safety of being exposed to a certain intervention and whether the benefits outweigh the risks (Gopalakrishnan & Ganeshkumar, 2013). For patients with JIA, receiving pharmacological interventions is important to manage disease symptoms, slow down progression of the disease, or even achieve clinical remission (Beresford & Baildam, 2009; Gartlehner et al., 2008; Ostring & Singh-Grewal, 2013). However, there are costs associated with these interventions, as well as discomfort for the patient (*e.g.,* intra-articular corticosteroid joint injections administered with a needle or biologics such as abatacept and infliximab administered intravenously). Non-pharmacological interventions may also help to improve HRQOL and relieve pain for patients (Dueckers et al., 2012; Hashkes & Laxer, 2005; Munro et al., 2009), but they may take time for the patient and their parents (*e.g.,* time away from school and work to travel to and from a facility for PA interventions). These interventions also cost money that families of patients with JIA would want to know is worth spending due to a known benefit from the non-pharmacological intervention. For both pharmacological and non-pharmacological interventions, it is important to know the best option for a patient with JIA and that requires comparisons of interventions against each other (*e.g.,* comparing other DMARDs to MTX if there is concern a patient may not tolerate MTX or comparing foot orthotics to know which one may provide better efficacy and be worth the family spending money to purchase).

As mentioned above, there is a lack of direct evidence comparing the efficacy of DMARDs (Kemper et al., 2012). NSAIDs have also been recommended in CPGs, but without any head-to-head comparisons supporting which NSAID is a better option over another (Dueckers et al., 2012). In addition, there are several biologics available for treating patients, but not enough of each type to conduct MAs using pairwise comparisons. The majority of existing biologics RCTs also use placebo as the comparator (Gartlehner et al., 2008; Kemper et al., 2012). CPGs on the management of JIA do not clearly describe the various non-pharmacological interventions available for JIA and they rely mainly on evidence from observational studies, the opinions of experts and studies of adults due to a minimal number of existing RCTs of the JIA population (Smith et al., 2015). A clear gap exists in the literature for non-

pharmacological interventions, as evidenced by the lack of SRs, and the limited number of RCTs included in existing reviews and CPGs (Hawke et al., 2008; Smith et al., 2015; Takken, Hemel, & Helders, 2002; Takken et al., 2008). For PA interventions, one of the SRs described above found there have been some RCTs published, but they cannot be pooled in a MA because their intervention programs are quite different (Takken et al., 2008). The Ottawa Panel evidence-based CPG on foot care for JIA recommended two different types of foot orthotics and no comparison has been made between them, which makes it challenging to determine the best type of foot orthotic to give to a patient with JIA. The CPG could not determine this through a MA as there were no RCTs that they found with a direct comparison of these two foot orthotics (Brosseau et al., 2016).

A paucity of higher quality evidence (*i.e.,* RCTs) also exists for pharmacological interventions (Gartlehner et al., 2008; Kemper et al., 2012; Takken et al., 2001; Wallen & Gillies, 2006). As many of the SRs have mentioned, there is a need for the development of more RCTs of good methodological quality to strengthen current evidence on the efficacy and safety of both pharmacological and non-pharmacological interventions used in JIA. However, there are challenges with conducting RCTs in this population such as: 1) difficulty obtaining ethical approval for pediatric trials; 2) a lower prevalence requiring international studies to recruit enough patients to power the study, which would be even more challenging for a RCT of a head-to-head comparison of two active interventions; 3) individuals participating in more than one study that precludes them from being eligible for another study; and 4) a proportion of participants being exposed to placebo when existing interventions are readily available (Ruperto, Giannini, et al., 2010). With this in mind, other methods should be considered for identifying how interventions compare to each other in terms of efficacy and safety.

A network MA differs from a MA in that multiple comparisons can be made simultaneously, rather than being limited to pairwise comparisons (*e.g.,* an active intervention versus placebo or a head-to-head comparison between two active interventions). There are several drugs available as pharmacological interventions for JIA in the different medication categories, thus it would be beneficial to compare multiple interventions at once as is done in rheumatoid arthritis with network MAs (Buckley, Finckh, Huizinga, Dejonckheere, & Jansen, 2015; Graudal, Hubeck-Graudal, Tarp, Christensen, & Jurgens, 2014; Guyot et

al., 2011; Jansen, Buckley, Dejonckheere, & Ogale, 2014; Orme, Macgilchrist, Mitchell, Spurden, & Bird, 2012; Singh et al., 2009; van Walsem et al., 2015). In addition, a network MA would be valuable in JIA as it incorporates both direct and indirect evidence to compare the efficacy of several interventions. This is possible even when there are no studies conducted on a particular comparison or not enough studies of the same intervention and comparator to conduct a pairwise MA, as is the case for JIA. For example, if there was a study comparing interventions A and B and interventions B and C, then the comparison of interventions A and C can be made indirectly (Jansen et al., 2011).

Considering not all patients can tolerate MTX, it would be useful to conduct an updated SR with a network MA to allow for indirect head-to-head comparisons of efficacy and safety for DMARDs where no studies have investigated those comparisons directly in order to facilitate selection of DMARDs when patients cannot tolerate MTX. With biologics, a network MA would not only allow for pooling of results from two (or more) studies of the same biologic, but also for obtaining indirect estimates of the head-to-head comparisons of efficacy between biologics to provide further insight into intervention options for patients with JIA beyond reiterating the results of the primary studies. Non-pharmacological interventions would also benefit from indirect estimates of head-to-head comparisons because there are a limited number of RCTs and the interventions are unique, which precludes pooling them in a MA. Altogether, a network MA would be a beneficial method for assessing the efficacy and safety of pharmacological and non-pharmacological interventions for JIA and also for determining which interventions are better in comparison to others.

As mentioned, there has been one MA with indirect comparisons of biologics conducted in 2013 (Otten et al., 2013). Some of its limitations were the use of an outdated risk of bias assessment tool (*i.e.,* Jadad scale), an incomplete description of the SR (*e.g.,* the search strategy was not provided), and the use of the Bucher method with a fixed-effects frequentist approach (Otten et al., 2013). Another MA with indirect treatment comparisons was just published in 2016; however, it used a Frequentist generalized linear mixed model for analysis rather than the standard Bayesian network MA with mixed effect methods for conducting the analysis (Tarp et al., 2016). A new network MA is required because: 1) there are no current network MAs of pharmacological interventions other than biologics or any network MAs of non-

pharmacological interventions for JIA and this method would be useful for providing further evidence through direct and indirect comparisons on these interventions to assist in clinical decision-making; and 2) there are other RCTs of biologics for polyarticular-course JIA published since 2013, with the possibility of more being available. Therefore, a high quality quantitative and exhaustive SR and network MA is needed to identify the comparative efficacy of pharmacological and non-pharmacological interventions among children and adolescents with JIA.

Table 2.1: CHARACTERISTICS OF PUBLISHED SYSTEMATIC REVIEWS ON PHARMACOLOGICAL INTERVENTIONS

Study	Design	Population	Intervention(s)	Comparator(s)	Outcomes
Wallen & Gillies 2006	SR & MA of RCTs	Rheumatoid arthritis or JIA	Intra-articular joint injections of steroids	No intervention or placebo; also rest/splints vs. no rest/splints after injection	Functional status, pain, ROM, joint circumference, no. tender joints, no. swollen joints, time to exacerbation of symptoms (joint pain, swelling, functional limitation), QOL, parent/patient/physician global assessment, acute phase reactants, safety (AEs related to splinting or injections, no. withdrawals due to lack of efficacy and side effects)
Thornton 2006	SR of RCTs, observational studies (cohort, case series, case report)	JIA; other connective tissue diseases	Bisphosphonates (alendronate, pamidronate, clodronate, etidronate)	Patients with connective tissue disease or no comparator	Bone mineral density, number of fragility fractures, safety
Takken 2001	SR & MA of RCTs and CCTs	JIA (oligoarticular, polyarticular, and systemic)	MTX	Placebo, no intervention, therapy Y, or standard care	Joint ROM, no. joints with swelling, no. joints with pain; QOL; patient/parent/physician global assessment of overall well-being, safety (no. withdrawals overall)
Kemper 2012	SR of RCTs (not explicitly stated in text) and case reports and letters for safety outcomes	JIA	Biologics or DMARDs	Placebo or conventional intervention (with or without MTX)	ACR Pedi 30, 50, 70, 90, 100, active joint count, time to flare, remission or inactive disease, physician's global assessment of disease activity, parent/patient global assessment of overall well-being, functional ability, safety
Gartlehner 2008	SR of RCTs and observational studies (and retrospective studies for safety results)	JIA	Biologics	None specified in the methods	ACR Pedi 30, radiographic progression, functional capacity, QOL, safety

Study	Design	Population	Intervention(s)	Comparator(s)	Outcomes
Ungar 2013	SR of RCTs, non-randomized & observational cohort studies and patient registries	Polyarticular JIA	Biologics	Any	ACR Pedi 30, 50, 70, disease flare (ACR criteria), rates of inactive disease, disease remission, drug withdrawal and discontinuation; severe and non-severe drug reactions (infectious and non-infectious)
Otten 2013	SR & indirect comparison MA of RCTs	JIA	Biologics	Placebo, another biologic, synthetic DMARDs	Percent with disease flare, percent achieving ACR Pedi 30
Tarp 2015	SR & network MA of RCTs	Systemic JIA	Biologics	Placebo, another biologic, conventional synthetic DMARDs	ACR Pedi 30, serious AEs, ACR Pedi 50, 70, 90, serious infections, any infections, AEs, withdrawals, withdrawal due to AEs

ACR Pedi = American College of Rheumatology Pediatric; AEs = adverse events; CCTs = controlled clinical trials; DMARDs = disease-modifying antirheumatic drugs; JIA = juvenile idiopathic arthritis; MA = meta-analysis; MTX = methotrexate; no. = number; QOL = quality of life; RCT = randomized controlled trial; ROM = range of motion; SR = systematic review

Table 2.2: CHARACTERISTICS OF PUBLISHED SYSTEMATIC REVIEWS ON NON-PHARMACOLOGICAL INTERVENTIONS

Study	Design	Population	Intervention(s)	Comparator(s)	Outcomes
Hawke 2008	SR of RCTs and CCTs	Patients of any age with any type of foot pain	Custom foot orthoses/orthotics	Any	Level of foot pain/change in foot pain, disability and/or functional ability, participant satisfaction, AEs, compliance
Takken 2008	SR & MA of RCTs	JIA	Endurance training and/or strength training, physical exercise during summer camps	Placebo (included those with assessment only), intervention Y (if very low exercise intensity), standard medical care	Functional ability, joint range of motion, number of joints with swelling, number of joints pain, HRQOL, parent/patient global assessment of overall wellbeing, pain, safety (side effects, total number of dropouts and compliance with exercise); also aerobic capacity (VO_{2peak}), muscle strength, compliance with exercise

AEs = adverse events; CCTs = controlled clinical trials; HRQOL = health-related quality of life; MA = meta-analysis; RCT = randomized controlled trial; SR = systematic review; VO_{2peak} = peak oxygen uptake

CHAPTER 3: METHODS

3.1 SELECTION CRITERIA

The PICOS method (population, intervention, comparator, outcome, and study design) was used to define selection criteria. A study had to meet the selection criteria in order to be included (Table 3.1). Studies were not excluded from the SR based on outcomes, but if they did not present results for a primary or secondary outcome reported in this review it was excluded from the analysis.

3.1.1 PARTICIPANTS

The population of interest was children and adolescents diagnosed with JIA. A diagnosis of JIA is defined as when an individual experiences six or more consecutive weeks of symptoms before 16 years of age (Petty et al., 2016; Petty et al., 2004). Participants in a study had to be 0 to 18 years old. In the event that a study defined the age of majority as 21 years old, it was not excluded so long as the majority of participants were 18 years old or younger. This was determined by looking at the available measures of statistical dispersion at baseline (*e.g.,* standard deviation, range). Patients with any subtype of JIA as defined by the ILAR were accepted. These include: systemic arthritis, oligoarthritis, polyarthritis (rheumatoid factor negative), polyarthritis (rheumatoid factor positive), psoriatic arthritis, enthesitis related arthritis, and undifferentiated arthritis (Petty et al., 2016; Petty et al., 2004). Older studies that used the EULAR or ACR criteria with subtypes classified as pauciarticular, polyarticular, or systemic juvenile chronic arthritis or juvenile rheumatoid arthritis were also included in the analysis (Brewer et al., 1977).

3.1.2 INTERVENTIONS

The following pharmacological interventions were included: biologics, DMARDs, NSAIDs, and corticosteroids (intra-articular corticosteroid joint injections and systemic glucocorticoids). Non-pharmacological interventions were also included and refer to the following types: physical interventions (*e.g.,* PA, massage, orthotics), psychosocial or behavioural interventions, and nutritional interventions.

Surgical interventions are often considered a last resort that are only suitable for patients who have finished growing and have no more options for improving joint range of motion (Iesaka, Kubiak, Bong, Su,

& Di Cesare, 2006). The more substantial surgical interventions (*i.e.,* total knee or hip arthroplasty), while effective for older adults with osteoarthritis or other forms of degenerative arthritis, can pose problems for children and adolescents with JIA due to their smaller bone structure and a longer lifespan post-surgery that would require the intervention to function for a greater number of years (De Ranieri, Wagner, Imrie, Hwang, & Goodman, 2011; Iesaka et al., 2006). This may explain the low prevalence of arthroplasty among patients with JIA in the United States (0.13 per 100,000) (Mertelsmann-Voss et al., 2014). With this in mind, surgical interventions were excluded from the analysis. Other invasive interventions were also excluded, with the exception of minimally invasive interventions such as intra-articular corticosteroid joint injections.

3.1.3 COMPARATORS

Due to the wide array of included interventions there were several acceptable comparators. These included placebo, waitlist, standard care, or another active intervention. If there was no comparison group or if the comparator consisted of healthy individuals, the study was excluded.

3.1.4 OUTCOMES

For pharmacological interventions, the primary outcome was the disease response as measured by the American College of Rheumatology Pediatric 30 (ACR Pedi 30). It is a validated binary composite outcome comprised of the following core set of outcomes: number of joints with active arthritis, number of joints with limited range of motion, physician's global assessment of disease activity, patient/parent's assessment of the child's overall well-being, functional ability, and erythrocyte sedimentation rate (ESR) (Lurati et al., 2006). To indicate disease response and an achievement of the ACR Pedi 30, a participant must improve by 30% or more for three out of the six core outcomes; a worsening of more than 30% in a maximum of one of the other core outcomes is permitted (Giannini et al., 1997; Lurati et al., 2006). Secondary outcomes were pain relief, HRQOL, physical functioning, emotional functioning (*e.g.,* anxiety, distress, depression), and the individual core outcomes from the ACR Pedi 30 (Giannini et al., 1997).

For non-pharmacological interventions, the primary outcome was pain relief. Secondary outcomes were HRQOL, physical functioning, emotional functioning (*e.g.,* anxiety, distress, depression), the ACR Pedi

30, and the ACR Pedi core set of outcomes (Giannini et al., 1997). Emotional functioning, while it was selected as an outcome of interest *a priori*, was not reported in any of the included pharmacological or non-pharmacological studies and was thus not analyzed in this review.

Safety results from all intervention types included the number of withdrawals due to an adverse event (AE) and the number of participants experiencing a serious AE.

If there were not enough studies to analyze an outcome in a network MA, a MA was conducted instead. In the event that a MA was not possible because studies did not share the same intervention and control groups for a specific pairwise comparison, a descriptive analysis was performed for that outcome.

3.1.5 STUDY DESIGN

Included studies had to be RCTs. Non-randomized studies were not considered for this review because the gap in the literature is in analyzing the available evidence from RCTs on efficacy and safety of interventions in JIA. RCTs of any overall quality level were included to ensure no RCTs were missing in the analysis. Further details on how study quality was assessed are presented in Section 3.6.

3.1.6 LANGUAGE

RCTs of any language that met the selection criteria were included in the analysis. RCTs published in articles of other languages than English or French were translated to English using translation software (*i.e.,* Google Translate) or, when possible, a colleague fluent in both English and the language of the RCT.

3.1.7 PUBLICATION STATUS

It was necessary that a RCT was published in at least one full-text article to be included in the reference case. Any abstracts, such as conference posters or oral presentations, were excluded from the reference case because of the risk for selective outcome reporting, the possibility that data were only preliminary, and a lack of detail for a full risk of bias assessment to determine the methodological study quality. RCTs reported only in abstracts were included in a sensitivity analysis to investigate the impact on the results.

3.2 SEARCH METHODS

An information specialist with experience in pediatrics (Margaret Sampson) was involved in the development of the search strategy. The following databases were searched from inception to May 18, 2015: Medline (Ovid), EMBASE (Ovid), and the Cochrane Central Register of Controlled Trials (Ovid). Medical subject headings used included juvenile rheumatoid arthritis, while key words used were psoriatic arthritis, oligoarthritis, child*, adolescent*, and infan*. No language restrictions were made during the systematic literature search and a filter for RCTs was not applied. The full search strategy for each database is presented in Appendix 1.

Clinicaltrials.gov and the Physiotherapy Evidence Database (PEDro) (www.Pedro.au) were searched for additional studies with pharmacological or non-pharmacological interventions. In addition, a hand search was performed of the reference lists of included studies, SRs in JIA, and CPGs in JIA, as well as websites of known rheumatology groups (*i.e.,* the Pediatric Rheumatology Collaborative Study Group (PRCSG), the Pediatric Rheumatology International Trials Organization (PRINTO), the Childhood Arthritis and Rheumatology Research Alliance (CARRA), and EULAR) to find any studies that may have been missed by the systematic literature search.

3.3 STUDY RECORDS

3.3.1 DATA MANAGEMENT

Records retrieved from the systematic literature search were added to a citation manager (EndNote X7), with records found in Medline added first, followed by EMBASE and finally Cochrane CENTRAL. Duplicates were removed using EndNote duplicate filters and then verified by a manual review of the records. Various combinations of the following filters were applied to identify duplicates: author, title, journal name, volume number, issue number, and page range.

A duplicate was defined as an exact copy of a RCT that was published in the same journal. If more than one record of a study was present (*i.e.,* if the same RCT was published in two separate journals and presented different results) those records were not considered as duplicates and both went on to the first

round of screening. The remaining records after duplicate removal were uploaded to an online review management software program called Covidence (www.covidence.org) for the selection process.

3.3.2 SELECTION PROCESS

The first round of screening was completed by two trained and independent reviewers (Christine Smith and Jacinthe Bisaillon). Each reviewer read the titles and abstracts of all records, referring to the selection criteria (Table 3.1) to determine which records should have their full text reviewed. If there was any uncertainty about an aspect of the record (*e.g.,* age of study participants, type of intervention, no abstract available), then the record was brought forward to the second round of screening. The first round of screening was done in Covidence to ensure the blinding of the reviewers to each other's decisions until completing the selection process. Both reviewers met to resolve conflicts in the selection of records to retrieve for full text review. When they were unable to come to a consensus, a third reviewer (Lucie Brosseau) made the final decision.

Next, the same reviewers independently read the full text of articles that were in the second round of screening. Articles were retrieved from EndNote or by searching in research databases. Each reviewer decided if a record should be included or excluded (with a reason for exclusion). As with the first round of screening, the reviewers discussed any conflicts by justifying their reason for inclusion or exclusion. A third reviewer (Lucie Brosseau) reviewed the full text to make a final decision and resolve the conflict if necessary. If no full text could be found, a hand search was made using the title and the names of other authors on the article and a request for an interlibrary loan was also made. There were seven articles that could not be found; if an abstract was available and it fit the selection criteria, it was included for sensitivity analysis. If no full text was found, the study remained as "awaiting classification". A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was used to summarize the complete study selection process.

3.3.3 DATA COLLECTION PROCESS

Relevant information from included RCTs was recorded in the data extraction form. A template of this form was created in Covidence to ensure uniformity in the method of extracting the information for RCTs

of pharmacological interventions. RCTs of non-pharmacological interventions were extracted using paper forms that had been previously developed and used for each intervention type (*e.g.,* psychosocial, PA, massage, orthotics). This difference in extraction forms was required because only one extraction template could be made in Covidence and the relevant information to extract differed between pharmacological and non-pharmacological RCTs.

Data collection was completed by independent pairs of reviewers. The primary author (Christine Smith) was the common reviewer across all intervention types. Reviewers were trained in data collection with the extraction forms to be used in this SR. In the event no consensus could be made between a pair of reviewers on the data to be extracted, a third reviewer (Lucie Brosseau) was available to review the information and resolve the conflict.

Authors were contacted by email twice to provide missing data or a clarification of unclear information that was required to include a RCT in the analysis. When data could not be retrieved on one or more outcomes or the authors did not respond, the RCT was excluded from the analysis for the outcome(s) in question.

3.4 DATA EXTRACTION

Information to be extracted from included RCTs was divided into the following categories: publication information (authors, source of funding, contact information for corresponding author); information on study design (*e.g.,* parallel group, cross-over, cluster, study arms); participants (inclusion and exclusion criteria); baseline characteristics (age, sex, disease duration, disease onset, JIA subtype, current medications); intervention characteristics (dose, frequency, route of administration, concomitant interventions); differences between groups at baseline; efficacy outcomes; safety outcomes; and a Cochrane risk of bias assessment for methodological quality.

3.5 HIERARCHY FOR EXTRACTING OUTCOMES

As mentioned above, RCTs were not excluded from this review based on outcomes. However, if a RCT did not present any of the outcomes of interest, it was excluded from the analysis. Whenever possible, a network MA of outcomes was performed. The networks were divided based on similarity of intervention

types and subtypes of JIA patients included. If there were less than three RCTs with results available, a network MA could not be performed. Instead, a MA was completed if the interventions and comparators could have their data pooled together. If that was not possible, then a descriptive analysis of that outcome was reported in the results.

The ESR is part of the core set of outcomes for the ACR Pedi 30. However, C-reactive protein (CRP) is another laboratory measure of inflammation that is commonly used because it is readily available and cheaper to use than the ESR (A. Huber, personal communication, March 5, 2016). Thus, results from RCTs reporting inflammation using CRP were included. Pain can be measured on several different scales and RCTs may report more than one pain scale. For this review, if pain using a 100 mm visual analogue scale (VAS) was available it was extracted first, followed by a 10 cm VAS. For RCTs reporting more than one type of HRQOL instrument, the Pediatric Quality of Life Inventory (PedsQL) was selected first for analysis, followed by any other scale if the PedsQL was not available.

3.6 RISK OF BIAS OF INDIVIDUAL STUDIES

An assessment for the potential risk of bias of included studies was performed using the Cochrane Risk of Bias tool (Higgins & Green, 2011). All reviewers were trained with the Cochrane online training module for risk of bias assessment. In addition, they evaluated a RCT included in a published SR in rheumatoid arthritis as a practice risk of bias assessment; the pairs of reviewers compared their answers to those provided in the SR to test their understanding of the tool. The summary table of risk of bias criteria from Cochrane was also followed by each reviewer to ensure consistency (Higgins & Green, 2011). The same pairs of reviewers that completed the data collection performed the risk of bias assessment.

The Cochrane risk of bias (ROB) tool contains the following domains: random sequence generation, allocation concealment, blinding of study patients and personnel and blinding of outcome assessors (performance bias and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias (*e.g.,* absence of washout period for cross-over study designs). For risk of attrition bias the reviewers considered the total percent of missing data, whether there was a balanced

proportion of missing data between intervention and control groups, and the reasons for missing outcomes in each group (http://training.cochrane.org/authors/intervention-reviews/olms).

A RCT was considered of low methodological quality if at least one of the following decisions was made: 1) unclear or high risk of bias for allocation concealment, 2) high risk of bias for blinding of outcome assessors, or 3) high risk of bias for incomplete outcome data (attrition bias). RCTs of any quality were included in the primary analysis. However, where possible, a sensitivity analysis was planned that included only high quality RCTs to determine the extent that including low quality RCTs influenced the findings of the pooled effect estimates (Higgins & Green, 2011).

3.7 DATA SYNTHESIS

3.7.1 NETWORK META-ANALYSIS

The primary method of analysis was a network MA using a Bayesian random effects statistical model. This allowed for a comparison of multiple interventions for the treatment of JIA that do not have any direct head-to-head results comparing interventions from RCTs. The program used in this review was WinBUGS (MRC Biostatistics Unit, Cambridge, UK) because it uses Markov chain Monte Carlo (MCMC) methods (Spiegelhalter, Thomas, Best, & Lunn, 2003). Considering the various interventions available for JIA and the variation in the types of comparisons within RCTs, this was an advantageous approach to analyzing the efficacy of pharmacological and non-pharmacological interventions compared to a MA. Tables and figures summarizing the network MA results and depicting the evidence networks were developed to facilitate interpretation of the results and the visualization of the direct and indirect comparisons.

3.7.1.1 THEORY AND METHODS OF A NETWORK META-ANALYSIS

A network MA allows for the simultaneous comparison of multiple interventions, whereas a MA can only conduct pairwise comparisons of two types of interventions or an intervention compared to a control group (Jansen et al., 2011; Mills, Thorlund, & Ioannidis, 2013). It is also possible to use a network MA to gain more insight into the efficacy or safety of an intervention by combining direct evidence available within studies and indirect evidence estimated from the model (Jansen et al., 2011). For this review in

particular, the network MA offers an advantage of investigating the comparative efficacy of interventions when there are very few known RCTs of head-to-head comparisons of interventions in the literature (Wells, Sultan, Chen, Khan, & Coyle, 2009).

The Bayesian approach to network MAs estimates the posterior probability that one intervention is superior over another (Jansen et al., 2011). Informative priors were used for binary outcomes to account for heterogeneity between RCTs (Turner, Davey, Clarke, Thompson, & Higgins, 2012), and vague priors were used in the model for continuous outcomes. A random effects model was selected because it assumes there is some level of heterogeneity between RCTs and makes adjustments for it (Mills et al., 2013).

3.7.1.2 PROCESS OF CONDUCTING THE NETWORK META-ANALYSIS

A common comparator was selected for each outcome within a category of interventions that connected the most RCTs together. Placebo was the common comparator for biologics and DMARDs, naproxen was used for NSAIDs, and a control (*i.e.,* waitlist, standard care or supportive shoes) was selected as the common comparator for outcomes of non-pharmacological interventions. For binary outcomes, the number of events and the number of participants per arm were set up in an Excel spreadsheet in a rectangular data format. For continuous outcomes, the mean change from baseline, number of participants per arm and the standard error of the mean change were likewise set up in an Excel spreadsheet in a rectangular data format (Merkle & Van Zandt, 2005). A script language was used instead of the built-in menu interface in WinBUGS. This involved preparing a folder for each separate outcome's analysis. The files included the following: 1) the number of RCTs, number of interventions and number of placebo (or common comparator) arms; 2) the data from the Excel spreadsheet; 3) separate files initializing each of the three chains; 4) the model code (for either binary or continuous outcomes); and 5) a script file to run the model (Merkle & Van Zandt, 2005).

For binary models we used a binomial likelihood function and a logit link function (Merkle & Van Zandt, 2005). For continuous models we used an identity link function and a normal likelihood function. Outcomes with more than one scale or instrument used across RCTs were analyzed using the

standardized mean difference (SMD). Data on the mean, standard deviation and number of participants in each arm were used to calculate the SMD (Appendix 2).

The best model for each outcome was selected in the following manner. First, a burn-in period with 10,000, 20,000 and 40,000 iterations were run one at a time and the Gelman-Rubin statistic for each node (*i.e.,* comparison of two interventions or an intervention to the common comparator) of these models was assessed for model convergence (Gelman & Rubin, 1992). A model was deemed to have converged when the ratio of the chains was stabilized at one for all nodes. If none of these models converged, models generating a burn-in of 20,000, 30,000 and 60,000 iterations were compared. After this, burn-in periods at increasing increments of 10,000 iterations (*i.e.,* 70,000, 80,000, etc.) were investigated for model convergence using the Gelman-Rubin Statistic. Converged models were then compared based on the width of their 95% credible intervals (CrI) and the residual deviance and total deviance information criterion (DIC) statistics (binary outcomes) or the total residual deviance and total DIC statistics (continuous outcomes). The model with narrower credible intervals of the nodes and lower values for these statistics was considered to be the best model. From this model, the median relative risk (RR) with 95% credible intervals (binary outcomes) and median mean difference (MD) or median SMD with 95% credible interval results were presented for each node in a table. The median was selected rather than the mean because it is an equal-tailed interval that ensures an equal probability of being above or below the credible interval and because WinBUGS does not provide the 95% credible interval with the mean (A. Hossain, personal communication, February 11, 2016) (Rhodes, Turner, & Higgins, 2015).

3.7.1.3 VISUAL REPRESENTATION OF THE NETWORK META-ANALYSIS

A visual representation to include as a figure for the network MA of each outcome was generated using NodeXL (Smith et al., 2010). Each vertex represents a node where two or more RCTs share a common intervention arm. Vertex size is directly proportional to the sum of the number of participants who received the intervention in one or more RCTs. The edges with a solid line indicate where a direct comparison of two interventions is possible between RCTs. The dashed lines indicate edges where no direct evidence was available and an indirect comparison of interventions was estimated. For most evidence networks visually represented in this review, the indirect comparisons were not visualized due to the complexity of

the evidence networks. A label on the solid edges indicates the number of RCTs contributing information to the direct comparison.

A staircase table was used for each evidence network to present the results of all comparisons, both direct and indirect. Table 3.2 further illustrates how to properly interpret the results for a binary outcome. If an individual was interested in results of intervention 2 compared to placebo, they would look at the row for intervention 2 and select the intersecting cell from the column for placebo to determine the relative risk and 95% CrI. Each cell that is not greyed out represents a unique node (*i.e.,* the comparison of two interventions or an intervention to a control). Those that are greyed out are either the comparison of an intervention (or control) to itself or would be the reverse of a result seen in another cell (*e.g.,* placebo compared to intervention 2 for the example above). For continuous outcomes the interpretation remains the same, only the results were presented as either the MD or SMD with a 95% CrI.

3.7.2 META-ANALYSIS

For outcomes that could not be analyzed with a network MA, the data were analyzed first in a MA using RevMan (version 5.3). For continuous outcomes, the mean, standard deviation and number of participants for each outcome measure of interest in each intervention and control group were used to calculate the MD with a 95% CI. The generic inverse variance method was used where an outcome did not have the standard deviation or standard error for each arm, but instead provided a 95% CI or p-value of the MD between study arms. Conversion of the 95% CI to a standard error was done according to the formulas presented in Appendix 2.

For binary outcomes, information on the number of events and sample size in each arm were used to calculate the relative risk (RR) with a 95% CI. A random effects model was selected in order to account for between study variation (Hochberg, Fort, Svensson, Hwang, & Sostek, 2011). An assessment of heterogeneity was conducted in two ways. Firstly, visual inspection of the forest plot was used to detect heterogeneity between RCTs. Secondly, the χ^2 and I^2 statistics were calculated and if the Cochrane Q had a $p<0.1$ it demonstrated that heterogeneity was present because the resulting I^2 value were large.

For this review, if the I^2 is ≥50% and the visual inspection also indicated elevated heterogeneity, then no pooled estimate of the effect were considered.

3.7.3 DESCRIPTIVE ANALYSIS

A descriptive analysis of the evidence was performed for the outcomes for which it was not possible to conduct a network MA or pairwise MA of the available results. This occurred when the interventions could not connect to the evidence network or the event rates were too low for a network MA and when the interventions were too different to be in a pairwise MA. The MD between intervention arms of an RCT were calculated and reported in this review when the number of participants in each arm and the event rate were available for binary outcomes and the number of participants, the mean and standard deviation or standard error were available for continuous outcomes. If no standard deviation or standard error were reported, and if there was no 95% CI or p-value of the MD between the arms, the means for each intervention arm were described qualitatively in comparison to each other.

3.7.4 SUBGROUP AND SENSITIVITY ANALYSES

Where possible, a subgroup analysis by JIA onset type was conducted to examine potential heterogeneity. Sensitivity analyses were also performed on methodological quality (*i.e.,* excluding low quality RCTs), including abstract results, and any other potential sources of heterogeneity that may impact the findings (*e.g.,* age of participants, gender, dosage, length of intervention). Funnel plots to assess the potential for publication bias and small-study effect were planned to be used for traditional and network MAs if there were at least 10 RCTs included in the MA (Begg & Mazumdar, 1994; Egger, Davey Smith, Schneider, & Minder, 1997).

3.8 CLINICAL IMPORTANCE OF FINDINGS

It is important to consider whether patients can detect a difference in an outcome (e.g., pain) after receiving an intervention. Meaningful clinically important differences (MCIDs) were used as a measure of clinical importance. Only the CHAQ had a validated MCID available in which a mean change from baseline of -0.13 represented an improvement and a mean change from baseline of 0.75 represented a

worsening in functional ability (Dempster, Porepa, Young, & Feldman, 2001). No other outcome results could be assessed for clinical importance.

TABLE 3.1. SELECTION CRITERIA

Inclusion	Exclusion
Population • Age groups 0 to ≤ 18 years old • Diagnosed with JIA[a] at least one affected joint in the extremities • Stable disease state not requiring treatment modifications	Population • Cardiac conditions • Decompensated organ failure • Metabolic disorder • Neurological conditions • Pulmonary conditions
Interventions • Physical (*e.g.,* physical activity, massage, orthotics) • Pharmacological • Psychosocial • Nutritional • Educational	Intervention • Surgical interventions • Invasive interventions • Interventions treating a complication of JIA (*e.g.,* uveitis, growth hormone)
Comparisons • Routine conventional therapies • Waiting list • Head-to-head comparison • Placebo	Comparisons • Healthy participants in comparison group • No control group
Patient outcomes • American College of Rheumatology Pediatric 30 • # joints with active arthritis • # joints with limited range of motion • Physician global assessment of disease activity • Parent/patient global assessment of overall well-being • Functional ability • Laboratory measure of inflammation (erythrocyte sedimentation rate or creatinine reactive protein) • Pain • Health-related quality of life • Physical functioning • Emotional functioning (*e.g.,* anxiety, distress, depression)	Patient outcomes • Assessment of posture • Compliance to pharmacological interventions • Non validated outcomes
Study Designs • Randomized controlled trial (RCT)	Study Designs • Non-randomized controlled trials • Cohort study • Case-control study • Case series or case report • Sample size <5 participants in intervention group

[a]All JIA onset types defined by the International League of Associations for Rheumatology or the previously defined juvenile rheumatoid arthritis onset types in older studies are considered

TABLE 3.2. EXAMPLE INTERPRETATION OF STAIRCASE TABLE FOR BINARY OUTCOMES

	Placebo	**Intervention 1**	**Intervention 2**	**Intervention 3**
Placebo				
Intervention 1	RR (95% CrI) of intervention 1 compared to placebo			
Intervention 2	RR (95% CrI) of intervention 2 compared to placebo	RR (95% CrI) of intervention 2 compared to intervention 1		
Intervention 3	RR (95% CrI) of intervention 3 compared to placebo	**RR (95% CrI)** of intervention 3 compared to intervention 1	RR (95% CrI) of intervention 3 compared to intervention 2	

RR = median relative risk; CrI = credible interval

Note: Bolded numbers indicate statistical significance ($p < 0.05$)

CHAPTER 4: EFFICACY AND SAFETY RESULTS

4.1 INCLUDED RCTS

A total of 537 records were retrieved in the literature search as follows: 133 records from Medline, 272 records Embase, and 132 records from Cochrane CENTRAL. All citations were imported into EndNote X7 and duplicates were removed, leaving 361 records. One record was found in the hand search through contact with the authors of an included RCT and was part of that RCT. After the first round of screening, 151 articles moved forward to the second screening round and of these, 100 full-text articles and conference abstracts were included in the review that accounted for 67 distinct RCTs (Appendix 3). A list of articles excluded during full-text review is presented in Appendix 4.

There were 7 articles awaiting classification in the second round of screening that were neither included nor excluded from this review because we could not retrieve the full-text, even after extensive searching of databases and requesting an interlibrary loan. Six of the articles dated back between 20 to 40 years (Alpigiani et al., 1996; Garcia-Morteo, Maldonado-Cocco, Cuttica, & Garay, 1987; Giannini et al., 1996; Maksimov, Shaikov, Speranskii, & Solov'ev, 1992; Prieur et al., 1986; Schairer, Stoeben, & Koelle, 1976), with three of these six older articles being published in another language (Alpigiani et al., 1996; Prieur et al., 1986; Schairer et al., 1976). One pending article had no author names listed in the bibliographic information ("Efficacy of etanercept in the treatment of children with polyarticular juvenile rheumatoid arthritis," 2000). A detailed diagram of the selection process following the PRISMA flow diagram is presented in Figure 4.1.

Four main categories of pharmacological interventions were included: biologics, DMARDs, NSAIDs, and corticosteroids (intra-articular corticosteroid joint injections and systemic glucocorticoids). Included non-pharmacological RCTs were divided into five main categories: PA interventions, nutritional interventions, foot orthotics/foot care or splints, massage interventions, and psychosocial or behavioural interventions. In several instances there were two or more full-text articles or conference abstracts available for a single RCT and some RCTs were only available in conference abstracts (Table 4.1).

For all included RCTs across intervention categories, it was determined *a priori* to use the end of intervention results for analysis with the assumption that the investigators selected a length of time for the RCT that was as close to when efficacy would be reached as possible. Only in the event that a RCT deviated from what was the typical length of time for interventions in the same category was an interim time point selected for analysis.

4.2 BIOLOGICS RCTS

There were 14 biologics RCTs, consisting of 16 full-text articles, included in the review. For the reference case conference abstracts were excluded. With abstracts included, there were two additional RCTs reported in four conference abstracts (Brunner et al., 2014; Burgos-Vargas et al., 2014; Burgos-Vargas et al., 2013a; Burgos-Vargas et al., 2013b), and 12 conference abstracts contributed information for the following studies: De Benedetti 2012, Ilowite 2014, Ruperto 2008, Ruperto 2012, Wallace 2012, and Yokota 2008 (Table 4.1).

The network MAs were divided into subgroups based on disease-course (polyarticular-course JIA or active systemic JIA) and study design (parallel RCT or withdrawal RCT) (Table 4.2). It was important to separate the analyses into subgroups because polyarticular-course JIA and active systemic JIA are clinically different in their disease presentation and response to biologics (Sen & Ramanan, 2014). A parallel RCT design has a basic format in which participants are randomized to one of the two or more intervention arms and are followed forward in time with no crossing over of patients between intervention arms. A withdrawal RCT differs from a parallel RCT design in that all patients received the biologic during an open-label lead-in phase. Patients who then achieved a certain level of disease response (usually based on the ACR Pedi 30 for RCTs in JIA) were randomized to either continue with the biologic or to receive placebo. Often there would be an extension phase of the RCT, which patients could enter immediately after being withdrawn from the randomization phase of the trial; non-responders from the open-label lead-in phase may also be permitted to enter the extension phase. The withdrawal study design was developed in an attempt to reduce the exposure of patients with JIA to placebo when biologics are available and are known to be useful (Ruperto, Giannini, et al., 2010). Thus, it was not possible to analyze parallel and withdrawal trials together because they were answering different

research questions, the former on disease response and the latter on maintaining disease response after it was already achieved in an open-label lead-in phase.

Another subgroup of biologics RCTs was investigating early aggressive therapy (Table 4.2). These RCTs were not the same as the polyarticular-course JIA and active systemic JIA RCTs because patients had short disease duration. The interventions were also varied and involved more than one drug, with one RCT comparing etanercept in combination with prednisolone and open-label MTX to placebo in combination with open-label MTX (Wallace et al., 2012). A second RCT with three arms had infliximab in combination with MTX versus MTX in combination with sulfasalazine and hydroxychloroquine versus MTX alone (Tynjala et al., 2011). Network MAs could not be done on the early aggressive therapy RCTs because there were not enough RCTs.

4.2.1 CHARACTERISTICS OF POLYARTICULAR-COURSE JIA RCTS

Six RCTs of polyarticular-course JIA were included in the review. Five of these used a withdrawal design (Table 4.2). Polyarticular-course JIA was defined as patients who had five or more active joints and three or more joints with limited range of motion. Placebo was the common comparator among the RCTs, though Mori (2011) conducted a head-to-head comparison of low-dose etanercept (0.2 mg/kg twice weekly) to high-dose etanercept (0.4 mg/kg twice weekly) that also connected to the network (Mori et al., 2011). Biologics studied were the TNF-α inhibitors etanercept and adalimumab in the withdrawal design RCTs; infliximab in combination with MTX was studied in a parallel design RCT for polyarticular-course JIA (Ruperto et al., 2007). The IL-1 inhibitor anakinra and abatacept, a T cell costimulatory inhibitor, were studied; no IL-6 inhibitors were administered in RCTs of polyarticular-course JIA. Study duration varied from 12 weeks to seven months. Mean age of participants across RCTs was from nine to 13.5 years old. Disease duration of participants was comparable at approximately three to four years, though Mori (2011) and Lovell (2000) had participants with mean disease durations of five or six years (Lovell et al., 2000; Mori et al., 2011). Similar medications, including NSAIDs for pain control and MTX were permitted in most RCTs so long as participants were on a stable dose before entering the study. However, Mori (2011) restricted patients from using DMARDs altogether (Mori et al., 2011). One RCT stratified participants by whether they were receiving MTX or not during the study and they analyzed strata of the intervention and

placebo groups with or without taking MTX (Lovell et al., 2008). Another permitted stable doses of folinic or folic acid and prednisone in addition to NSAIDs for pain and MTX (Ruperto et al., 2008). Table 4.3 provides further details on the characteristics of these RCTs.

Risk of bias assessments for the withdrawal design RCTs of biologics for polyarticular-course JIA revealed that three of the five RCTs had unclear risk of bias for sequence generation. Four RCTs had unclear allocation concealment while one had low risk of bias. Blinding of participants and personnel and blinding of outcome assessors were low risk for four and unclear for one due to the use of a placebo-controlled design. Two studies had high risk of attrition bias (Ilowite et al., 2009; Ruperto et al., 2008) and two had high risk of bias for selective outcome reporting (Ilowite et al., 2009; Lovell et al., 2008). Given the *a priori* criteria for determining study quality (see Section 3.6), all five of these RCTs were considered of low quality. The biologics RCT using a parallel design for polyarticular-course JIA patients was also of low quality (Table 4.4.).

4.2.2 EFFICACY RESULTS FOR POLYARTICULAR-COURSE JIA RCTS

4.2.2.1 NETWORK META-ANALYSIS RESULTS

A network MA could not be conducted for all outcomes due to either an insufficient number of study arms or an event rate that was too low, as was the case for safety data (Table 4.5). Four of the five RCTs were included in the network MA for the primary outcome of the disease response (ACR Pedi 30) (Lovell et al., 2000; Lovell et al., 2008; Mori et al., 2011; Ruperto et al., 2008). This evidence network is illustrated in Figure 4.2. Only three RCTs had sufficient data to be included in the network MAs of the core set of outcomes (Lovell et al., 2000; Mori et al., 2011; Ruperto et al., 2008). One RCT within the subgroup was excluded from all efficacy analyses because it did not report on the outcomes of interest (Ilowite et al., 2009). Table 4.6 provides a summary of the network characteristics for each outcome analyzed. The number of participants in the primary network for the disease response (ACR Pedi 30) was 318 participants and there were four studies consisting of seven interventions and three comparisons. The outcomes with three included RCTs included 131 participants contributing to the population-level data in the analysis. Figures 4.2 and 4.3 illustrate the evidence networks for the disease response (ACR Pedi 30) and its core set of outcomes.

For the primary outcome, the likelihood of patients with polyarticular-course JIA maintaining a disease response (ACR Pedi 30) is 1.91 times greater with etanercept (0.4 mg/kg dosage) compared to those receiving placebo (95% CrI: 1.28, 2.59) (Table 4.7). No other biologics had statistically significant results for the maintenance of the disease response (ACR Pedi 30) compared to placebo. Indirect estimates of the head-to-head comparisons of biologics did not demonstrate that one biologic was statistically significant compared to another (Table 4.7).

The first of the ACR Pedi 30 core set of outcomes, the number of active joints, had significant results to show abatacept (10 mg/kg every 28 days) and both low and high doses of etanercept (0.2 mg/kg twice weekly and 0.4 mg/kg twice weekly, respectively) had a greater reduction in the number of active joints compared to placebo (Table 4.8). If a patient with polyarticular-course JIA were to receive abatacept (10 mg/kg every 28 days), they would have a median of 8.17 more active joints when compared to a patient receiving 0.2 mg/kg of etanercept (95% CrI: 0.95-15.48) and have a median of 7.92 more active joints compared to someone receiving 0.4 mg/kg of etanercept (95% CrI: 3.51-12.36) (Table 4.8). This indicates that both low and high doses of etanercept have better efficacy than abatacept in reducing the number of joints with active arthritis.

Only high-dose etanercept (0.4 mg/kg) showed a reduction in the number of joints with limited range of motion compared to placebo (MD = -5.15, 95% CrI: -9.5, -0.8) (Table 4.9). In contrast, those receiving abatacept had an improvement of nearly 12 mm on the 100 mm VAS in the score for the physician's global assessment of disease activity compared to placebo (95% CrI: -17.1, -6.79) (Table 4.10). None of the biologics had greater efficacy compared to placebo or in indirect head-to-head comparisons for an improvement in functional ability (Table 4.11). Abatacept had a statistically significant improvement compared to placebo for the patient's overall well-being (MD = -6.04, 95% CrI: -11.32, -0.83), but not compared to low- or high-dose etanercept (Table 4.12). There were no significant differences when comparing the biologics to each other or to placebo for inflammation as measured by the ESR (Table 4.13).

4.2.2.2 DESCRIPTIVE ANALYSIS RESULTS

A descriptive analysis was used for pain and HRQOL because there were not at least two RCTs that could be combined in a pairwise MA due to differing biologics used (Table 4.5). Results from one RCT comparing etanercept (0.4 mg/kg twice weekly) to placebo found that after seven months, there was a two point reduction in pain (10 cm VAS) from baseline for the etanercept arm while no change in pain relief was observed for the placebo group (Lovell et al., 2000). The authors did not indicate if this difference was statistically significant and there were no measures of dispersion that were reported.

In the Ruperto (2008) RCT, those responders from the open-label phase who were randomized to continue receiving abatacept had further reductions in pain that were statistically significant compared to those randomized to receive placebo who had worsening of pain (Ruperto, Lovell, et al., 2010). HRQOL, as measured by the physical and psychosocial summary scores of the child health questionnaire (CHQ), was maintained for those continuing to receive abatacept into the randomization phase while HRQOL worsened for those in the placebo group. The difference between groups was not statistically significant ($p = 0.666$ and $p = 0.056$ for the physical and psychosocial summary scores, respectively) (Ruperto, Lovell, et al., 2010).

There was one RCT of patients with polyarticular-course JIA that used a parallel RCT design and had results for the ACR Pedi 30 and its core set outcomes (Ruperto et al., 2007). The ACR Pedi 30 disease response was similar in both groups, so there was no significant difference (RR = 1.30, 95% CI: 0.94, 1.79). Participants receiving infliximab (3 mg/kg on weeks 0, 2, 6, and 14) plus MTX (10-15 mg/m^2/week) had a greater reduction in the number of active joints after 14 weeks compared to those receiving placebo and the same dose of MTX (MD = -5.31, 95% CI: -10.35, -0.27). There was also a significant result for the physician's global assessment of disease activity among those in the intervention arm compared to the control arm (MD = -1.05, 95% CI: -2.07, -0.03). However, there were no statistically significant results for the number of joints with limited range of motion, functional ability (Childhood Health Assessment Questionnaire [CHAQ] disability index), patient/parent assessment of overall well-being (100 mm VAS), or ESR (mm/h) between the infliximab in combination with MTX arm and the placebo in combination with MTX arm (Ruperto et al., 2007).

4.2.3 SENSITIVITY ANALYSES FOR POLYARTICULAR-COURSE JIA RCTS

An abstract presenting the results of a withdrawal-design RCT of golimumab (30 mg/m^2 every 4 weeks) versus placebo among patients with polyarticular-course JIA was included in a sensitivity analysis (Brunner et al., 2014). When the results from this abstract were included in a sensitivity analysis for the disease response (ACR Pedi 30), there was no change in the statistical significance of findings. The point estimates for the relative risk were similar and the width of the 95% credible intervals remained the same in the reference case and in the sensitivity analysis including the RCT of golimumab. In the reference case network MA, there was one significant result in which the likelihood of maintaining a disease response (ACR Pedi 30) was 1.91 times better for etanercept (0.4 mg/kg twice weekly) than placebo (95% CrI: 1.28, 2.59) (Table 4.7). In the sensitivity analysis, the likelihood of maintaining disease response (ACR Pedi 30) was 1.85 times better in the etanercept group (0.4 mg/kg twice weekly) compared to the placebo group (95% CrI: 1.27, 2.37) (Appendix 5, Table 1).

It was not possible to conduct sensitivity analyses that excluded low quality RCTs, since all RCTs were of low quality according to the risk of bias assessment.

4.2.4 SAFETY RESULTS FOR POLYARTICULAR-COURSE JIA RCTS

All five RCTs provided data on the safety outcomes of interest. No serious AEs or withdrawals due to AEs occurred for any arm in the low- versus high-dose etanercept RCT (Mori et al., 2011) or in either arm of the RCT comparing anakinra (100 mg/ml/day) to placebo (Ilowite et al., 2009). There were also no withdrawals due to AEs in the adalimumab or placebo groups with or without MTX. In this RCT, one participant (2.7%) in the placebo group who was receiving MTX experienced a serious AE (gastroduodenitis) (Lovell et al., 2008). For Lovell (2000), one participant (0.04%) withdrew due to an AE (urticaria) after a single dose of etanercept (0.4 mg/kg) and two participants (8%) in the etanercept group (0.4 mg/kg twice weekly) had serious AEs leading to hospitalization (depression and personality disorder in one and gastroenteritis-flu syndrome in the other); no withdrawals due to AEs or any serious AEs occurred in the placebo group (Lovell et al., 2000). Lastly, there were no withdrawals due to AEs for the

abatacept (10 mg/kg every 28 days) and placebo arms, but two of the placebo participants (3.2%) experienced a SAE (Ruperto et al., 2008).

4.2.5 CHARACTERISTICS OF ACTIVE SYSTEMIC JIA RCTS

Five RCTs were included in the subgroup of parallel RCTs of active systemic JIA that used a biologic (Table 4.2). In general, active systemic JIA was defined by the RCTs as having at least one to two joints with active arthritis along with symptoms of systemic disease such as fever or rash. Ilowite (2014) did not require participants to have fever at the time of enrollment, but baseline characteristics indicate roughly one quarter of participants in each arm had fever in the previous seven days (Ilowite et al., 2014). The biologics studied were anakinra, rilonacept and canakinumab (IL-1 inhibitors), and tocilizumab (IL-6 inhibitor). All biologics were compared to placebo. Study duration was four weeks in four RCTs and 12 weeks in one RCT. The mean age in one RCT was 13 and 14 years in each arm, which was about three years above the comparable average in the remaining RCTs. Mean disease duration ranged from about two to four years across the RCTs. The RCTs permitted stable doses of NSAIDs, MTX, and stable oral systemic glucocorticoids (*e.g.,* prednisone), but no other biologics. Table 4.3 provides additional details on the characteristics of these RCTs.

There were two withdrawal design RCTs of biologics for active systemic JIA (Table 4.2) with the same disease definition as mentioned above (Ruperto et al., 2012; Yokota et al., 2008). The two biologics were canakinumab and tocilizumab, both compared to placebo. Disease duration among participants in the Yokota (2008) study was longer than in the second trial of Ruperto (2012). Other characteristics of the two withdrawal RCTs were comparable (Table 4.3).

A score of low or unclear risk of bias was given for all parallel design RCTs of biologics for active systemic JIA in the domains of sequence generation and allocation concealment. All RCTs had low risk of bias for blinding of participants and personnel. For blinding of outcome assessors, four RCTs had low risk of bias and one had an unclear risk (Lovell et al., 2013). Three of five RCTs had high risk of attrition bias and selective outcome reporting. Only one RCT was at high risk for the domain “other sources of bias” due to early trial termination because of an *a priori* stopping rule for achieving significant efficacy of the

primary endpoint (Ruperto et al., 2012). As for the withdrawal design RCTs, Ruperto (2012) had the same results for its parallel and withdrawal RCTs (Ruperto et al., 2012). Yokota (2008) had unclear risk of bias for the sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessors. There was high risk of attrition bias and a low risk of selective outcome reporting and other sources of bias. Detailed results of the risk of bias assessment are presented in Table 4.4.

4.2.6 EFFICACY RESULTS FOR ACTIVE SYSTEMIC JIA RCTS

4.2.6.1 NETWORK META-ANALYSIS RESULTS

All five RCTs were included for the primary outcome (*i.e.,* ACR Pedi 30), but for the core set outcomes there were only two RCTs that had usable data, so their results were summarized in a descriptive analysis (Table 4.14). For the disease response (ACR Pedi 30) network, there were five intervention nodes, five comparisons and the number of participants was 311 (Table 4.15). This evidence network is illustrated in Figure 4.4. Pain and HRQOL were reported as descriptive analyses because of a lack of RCTs reporting the outcomes (Table 4.14). Safety outcomes were also reported as descriptive analyses due to event rates that were too low to run the network MA (Table 4.14).

The primary outcome of the disease response (ACR Pedi 30) was modified for the active systemic JIA RCTs to also require that participants be free of disease-related fever. Tocilizumab, rilonacept and canakinumab were statistically significant compared to placebo in terms of achieving the modified ACR Pedi 30, but not anakinra (Table 4.16). The indirect head-to-head estimate of canakinumab versus rilonacept was statistically significant (RR = 1.68, 95% CrI: 1.16, 3.10).

4.2.6.2 DESCRIPTIVE ANALYSIS RESULTS

The RCT comparing tocilizumab to placebo was excluded from efficacy analyses for the ACR Pedi core set outcomes because it did not report its results in a way that could be compared to other RCTs; it used the “adjusted mean difference in percentage change from baseline”, which the authors did not clarify after two attempts to contact them (De Benedetti et al., 2012). There were two parallel design RCTs on systemic JIA with useable data on the ACR Pedi core set outcomes. One compared anakinra (2 mg/kg/day, subcutaneous) to placebo for four weeks (Quartier et al., 2011) and the other study

investigated rilonacept (4.4 mg/kg loading dose, then 2.2 mg/kg weekly maintenance doses) versus placebo (Ilowite et al., 2014).

For the number of active joints, there was no difference between rilonacept and placebo (MD = -12.9, 95% CI: -26.31, 0.51) (Ilowite et al., 2014). Those receiving anakinra had a median of 28 fewer active joints after four weeks compared to the placebo arm (95% CI: -53.09, -2.91) (Quartier et al., 2011). In contrast, participants in the rilonacept arm had a median of two fewer joints with limited range of motion in comparison to those in the placebo arm (95% CI: -3.94, -0.06) (Ilowite et al., 2014), whereas no significant difference was detected between those on anakinra or placebo (MD = -16.00, 95% CI: -36.97, -4.97) (Quartier et al., 2011). There was a statistically significant reduction in the physician's global assessment of disease activity (100 mm VAS), indicating improvement among participants in the anakinra arm compared to placebo (MD = -43.00, 95% CI: -67.11, -18.89) and the rilonacept arm in comparison to placebo (MD = -11.5, 95% CI: -20.27, -2.73) (Ilowite et al., 2014; Quartier et al., 2011). No significant results were found for participants receiving anakinra compared to placebo in terms of functional ability (CHAQ full scale, lower better) (MD = -28.00, 95% CI: -73.04, 17.04) (Quartier et al., 2011). Similarly, there was insufficient evidence to demonstrate that rilonacept was favoured over placebo in terms of functional ability using the CHAQ disability index (0-3, lower better) (MD = -0.20, 95% CI: -0.32, 0.12) (Ilowite et al., 2014). Results for overall well-being as assessed by the patient or parent (100 mm VAS, lower better) were also not significant between anakinra and placebo (MD = -13.00 95% CI: -54.36, 28.36), but anakinra was favoured over placebo (MD = -18.50, 95% CI: -0.32, 0.12) (Ilowite et al., 2014; Quartier et al., 2011). Inflammation was reduced by a median of -46.00 in the anakinra arm more than the placebo arm as measured by the ESR (mm/h) (95% CI: -71.68, -20.32) (Quartier et al., 2011). For rilonacept there was a median reduction in inflammation by 18.0 mm/h compared to placebo (95% CI: -30.67, -5.33) (Ilowite et al., 2014).

There was only one RCT among those for patients with active systemic JIA using a parallel study design that included pain as an outcome, but the result was not significant (MD = -8.00, 95% CI: -20.39, 4.39) (Quartier et al., 2011). None of the RCTs of active systemic JIA using a parallel study design measured the HRQOL of participants.

There were two withdrawal design RCTs included in this review (Ruperto et al., 2012; Yokota et al., 2008). One comparing tocilizumab (8 mg/kg every 2 weeks) to placebo for 12 weeks demonstrated a greater reduction in inflammation (*i.e.,* measured by CRP) in the tocilizumab than the placebo arm, but there were no other significant results for any of the five other ACR Pedi core set outcomes (Yokota et al., 2008). This RCT did not include pain or HRQOL as outcomes. In contrast, the other RCT compared canakinumab (4 mg/kg, subcutaneous) versus placebo for four weeks and had significant results in two of the six core set of outcomes (Ruperto et al., 2012). For the number of active joints, there was no difference between canakinumab and placebo (MD = 0.00, 95% CI: -0.92, 0.92) (Ruperto et al., 2012). Participants in the canakinumab arm had a median of one fewer joints with limited range of motion in comparison to those in the placebo arm (95% CI: -1.92, -0.08). There was a statistically significant reduction in the physician's global assessment of disease activity (100 mm VAS), indicating improvement among participants in the canakinumab arm in comparison to placebo (MD = -6.50, 95% CI: -12.82, -0.18). Results were not significant for functional ability (CHAQ disability index, 0-3, lower better) (MD = -0.10, 95% CI: -0.32, 0.12), overall well-being (100 mm VAS, lower better) (MD = -2.00 95% CI: -8.13, 4.13), or CRP (MD = -12.9, 95% CI: -26.31, 0.51). No HRQOL measurements were provided (Ruperto et al., 2012).

4.2.7 SENSITIVITY ANALYSES FOR ACTIVE SYSTEMIC JIA RCTS

A sensitivity analysis of the disease response (ACR Pedi 30) was completed with results from all RCTs at the end of study. In the reference case, results from the 15-day intermediate time point were analyzed for one parallel design RCT that compared canakinumab to placebo among patients with active systemic JIA. This was because 92.5% of participants in the placebo group withdrew by the end of study (29 days) (Ruperto et al., 2012). However, for this review since the decision *a priori* was to analyze the end of intervention results from all RCTs, a sensitivity analysis was conducted to determine if these results would be much different from those at the intermediate time-point. The only difference in results between both analyses was the node comparing anakinra to placebo. The result was not significant in the reference case (RR = 2.87, 95% CrI: 0.95, 4.76), whereas it was significant in the sensitivity analysis (RR = 2.93, 95% CrI: 1.01, 4.80). However, the result is still very similar between the reference case and sensitivity

analysis as both credible intervals are very close to being exactly at 1.00 (Table 4.16 and Appendix 5, Table 2). In addition, the attrition bias present by the end of the study may explain the slightly significant result because participants in the placebo group were withdrawing, which would bias the results away from the null hypothesis (*i.e.,* that there was no difference between the arms) as those who remained likely had better disease response. Therefore, the intermediate time-point of 15 days was still selected for the reference case because of the very high proportion of withdrawals by the end of study time point and the comparable values for the results.

A second sensitivity analysis for parallel design RCTs that included patients with active systemic JIA included results available from RCTs that were only available as an abstract. One abstract comparing canakinumab to placebo in a parallel design RCT was included for sensitivity analysis with the ACR Pedi core outcome of functional ability using the CHAQ disability index (Quartier et al., 2013). Unfortunately, there were not enough RCTs with usable data to do a network MA of the reference case of only full-text RCTs. The results from this sensitivity analysis are not significant for each of the direct comparisons against placebo and indirect head-to-head comparisons of the biologics (Appendix 5, Table 3). The credible intervals are also very large, which is likely due to the small number of participants included in the RCTs.

4.2.8 SAFETY RESULTS FOR ACTIVE SYSTEMIC JIA RCTS

In the parallel design trial from Ruperto 2012 (trial 1) there were no withdrawals due to AEs, but there were 2 (5%) serious AEs in both the canakinumab and placebo arms (Ruperto et al., 2012). The RCTs comparing rilonacept to placebo both had one participant (1/35 in Ilowite (2014) and 1/17 in Lovell (2013), respectively) withdraw due to an AE. For the study by Ilowite et al. (2014) there was one participant (2.8%) in the rilonacept arm and one participant (2.9%) in the placebo arm who had a serious AE (Ilowite et al., 2014). Similarly, in the study by Lovell et al. (2013) only 1 participant (5.9%) in the rilonacept arm experienced a serious AE (Lovell et al., 2013).

The RCT of anakinra versus placebo reported 2 withdrawals (16.7%) due to AEs in the placebo arm and none in the anakinra arm; there were no reported serious AEs in either study arm (Quartier et al., 2011).

For the study of tocilizumab versus placebo, 1 (1.3%) participant in the tocilizumab group withdrew due to an AE and 3 (4%) participants experienced at least one serious AE (one count of each: angiodema, urticaria, varicella, and other), whereas no one in the placebo group withdrew due to an AE or had a serious AE during the study period (De Benedetti et al., 2012).

4.2.9 CHARACTERISTICS OF EARLY AGGRESSIVE THERAPY RCTS

Two RCTs involved early aggressive therapy using a combination therapy including a biologic to treat patients recently diagnosed with JIA (Tynjala et al., 2011; Wallace et al., 2012). One RCT compared infliximab in combination with MTX, triple DMARD therapy (MTX, sulfasalazine and hydroxychloroquine) and MTX monotherapy for 54 weeks (Tynjala et al., 2011). The other RCT compared etanercept in combination with MTX and prednisone to MTX monotherapy over 24 weeks (Wallace et al., 2012). Both RCTs were parallel in design and included patients with polyarticular JIA with a mean age of between eight to 11 years. Disease duration was around half a year to two years on average, which is shorter compared to RCTs of polyarticular-course JIA and active systemic JIA described in the previous sections. Table 4.3 provides more details on the characteristics of both RCTs.

One of the early aggressive therapy RCTs was of high methodological quality because it had low risk of bias in all of the domains assessed (Wallace et al., 2012). For the other RCT, high risk of bias was assigned for blinding of participants and personnel and blinding of outcome assessors, which made it of low methodological quality (Tynjala et al., 2011). Detailed results of the Cochrane risk of bias assessment for these RCTs are found in Table 4.4.

4.2.10 DESCRIPTIVE ANALYSIS RESULTS FOR EARLY AGGRESSIVE THERAPY RCTS

As mentioned above in the characteristics of the early aggressive therapy RCTs, it was not possible to include them in the analyses because the patients were much different, particularly in terms of disease duration. Thus, a descriptive analysis of the outcomes of interest is presented below.

The RCT by Wallace et al. comparing etanercept in combination with MTX and prednisone to MTX alone did not report on any of the efficacy outcomes of interest (Wallace et al., 2012). Results for the ACR Pedi 30 and its core set of outcomes were available from the RCT of infliximab in combination with MTX versus

MTX in combination with sulfasalazine and hydroxychloroquine versus MTX alone (Tynjala et al., 2011). After 54 weeks of therapy, all 19 participants in the infliximab plus MTX arm, 17 (85%) in the DMARD triple therapy arm, and 12 (60%) in the MTX monotherapy arm achieved the ACR Pedi 30. The results were statistically significant for the infliximab plus MTX arm compared to the DMARD triple therapy arm ($p<0.05$) and the MTX monotherapy arm ($p<0.001$), but the DMARD triple therapy arm did not have a statistically significantly greater number of patients achieve the ACR Pedi 30 compared to the MTX monotherapy arm ($p = 0.06$). The infliximab plus MTX arm also had statistically significantly greater reductions in the number of active joints with arthritis ($p<0.001$), the number of joints with limited range of motion ($p<0.001$), inflammation (measured by the ESR) ($p<0.05$), and improvements in the physician's global assessment of disease activity ($p<0.001$), and the patient/parent assessment of overall well-being ($p<0.001$ versus MTX along; $p<0.05$ versus DMARD triple therapy) than the other two study arms. For the CHAQ disability index results were statistically significant compared to MTX alone ($p<0.01$), but not significant compared to DMARD triple therapy.

4.2.11 SAFETY RESULTS FOR EARLY AGGRESSIVE THERAPY RCTS

In terms of safety, there was one participant who withdrew in the DMARD triple therapy arm (5.0%) due to an AE, one from the MTX monotherapy arm (5.0%) and no participants who withdrew due to an AE in the infliximab arm. Reporting on serious AEs was not clear, as the authors only indicated that serious AEs were rare (Tynjala et al., 2011). Both intervention arms from Wallace et al. had one patient withdraw due to an AE (etanercept in combination with MTX: n = 42; MTX monotherapy: n = 43). No results on serious AEs were reported in this RCT (Wallace et al., 2012).

4.3 DMARD RCTS

4.3.1 CHARACTERISTICS OF DMARD RCTS

There were 11 DMARD RCTs included in this review (Table 4.1). A 12th study from a conference abstract was available for sensitivity analysis (Pan & Lehman, 2011) and one other included conference abstract was part of the Kvien 1985 study. All RCTs included participants with oligoarticular and polyarticular JIA (or the ACR or EULAR equivalent); six RCTs allowed for the inclusion of patients with systemic JIA. Study

duration (*i.e.,* from baseline to the end of the intervention period) varied, but the most common was six months in six RCTs, 12 months in two RCTs and 16 weeks in two RCTs. There was also one RCT that lasted six weeks and another that was 50 weeks. Methotrexate was the most common DMARD from the included RCTs, followed by penicillamine and then sulfasalazine. As many of the RCTs were published 30 to 50 years ago, there were older DMARDs that are no longer in use for JIA such as auranofin, gold sodium thiomalate, and penicillamine. However, these were included in the reference case if data for the outcomes were available and a sensitivity analysis was done to remove those RCTs where possible. Most RCTs had a mean age of participants between about eight to ten years old. Mean disease duration tended to be about three or four years, but in Laaksonen (1974) the mean disease duration was as high as 7.8 years in one stratum of the hydroxychloroquine group (Laaksonen, Koskiahde, & Juva, 1974). Lower durations of disease of less than two years were present in two RCTs (Silverman et al., 2005; van Rossum et al., 1998). Participants were permitted to take a stable dose of NSAIDs during the study period, and stable prednisone for some RCTs, but other DMARDs were not permitted. Table 4.17 provides a detailed summary of the characteristics of the DMARD RCTs included in this review.

Most of the older RCTs had unclear risk of bias for sequence generation and allocation. There were two RCTs with high risk of bias for blinding of participants and personnel and three that had high risk of bias for blinding of outcome assessors. Five of the twelve RCTs had high risk of attrition bias and selective outcome reporting was unclear in all RCTs. Only one RCT had high risk for other sources of bias because they stopped enrollment into the RCT due to an equal response rate in both arms. Overall, one RCT fit the requirements for being a high quality study based on the risk of bias assessment (Silverman et al., 2005). The full risk of bias assessment for DMARD RCTs is presented in Table 4.18.

4.3.2 EFFICACY RESULTS FOR DMARD RCTS

4.3.2.1 NETWORK META-ANALYSIS RESULTS

The ACR Pedi 30 and three of the six ACR Pedi core set of outcomes could not be analyzed in a network MA because there were only two RCTs sharing a common comparator and one RCT was disconnected from the evidence network. A descriptive analysis was conducted for outcomes not analyzed with a network MA (Table 4.19). There were four RCTs contributing data to the network MAs on pain relief and

ESR, the number of active joints had seven RCTs, and the number of joints with limited range of motion had six RCTs (Table 4.20). These evidence networks analyzed used placebo as the common comparator (Figures 4.5 to 4.8).

For the number of joints with active arthritis, sulfasalazine (50 mg/kg/day) had a median decrease of 6.43 more joints compared to penicillamine (5-10 mg/kg/day) (95% CrI: -12.1, -0.81) (Table 4.21). No statistically significant results were present in the network MA of the number of joints with limited range of motion (Table 4.22). An indirect comparison from the network MA indicated that the ESR was statistically significantly worse for those receiving high-dose MTX (30-40 mg/m^2) compared to a moderate dose of MTX (10-20 mg/m^2) (RR = 15.44, 95% CrI: 6.02, 24.87 mm/h) (Table 4.23). There were no statistically significant results when comparing any DMARD to placebo or to other DMARDs in the network MA for pain relief (Table 4.24).

4.3.2.2 DESCRIPTIVE ANALYSIS RESULTS

Three RCTs reported the disease response (ACR Pedi 30) (Ruperto et al., 2004; Silverman et al., 2005; van Rossum et al., 1998), but one of them used an incomplete ACR Pedi 30 that was missing functional ability (van Rossum et al., 1998). Results were not significant for the study of intermediate dose MTX (15-20 mg/m^2/week) versus high dose (30-40 mg/m^2/week) MTX (RR = 1.09, 95% CI: 0.76, 1.56) (Ruperto et al., 2004). Participants receiving MTX (0.5 mg/kg/week) were 1.31 times more likely to achieve a disease response (ACR Pedi 30) after 16 weeks of intervention compared to the leflunomide arm (see Table 4.17 for dose schedule) (95% CI: 1.05, 1.63) (Silverman et al., 2005). In another RCT that lasted 24 weeks, the placebo group actually had 2.14 times the likelihood of achieving a disease response (ACR Pedi 30) compared to those receiving sulfasalazine (95% CI: 1.00, 4.59), but this was not the true ACR Pedi 30 since functional ability was excluded from the composite outcome (van Rossum et al., 1998). Methotrexate at a dose of 0.5 mg/kg per week seems to provide good disease response for patients with JIA and sulfasalazine may not be a good option for patients with oligoarticular and polyarticular JIA since placebo was favoured over it in terms of disease response.

The same three RCTs reported the physician's global assessment of disease activity (Ruperto et al., 2004; Silverman et al., 2005; van Rossum et al., 1998). For Ruperto 2004, the intermediate dose of MTX

was associated with a 3.60 point reduction of the physician's global assessment on a 10 cm VAS compared to high dose MTX (95% CI: -4.14, -3.06) (Ruperto et al., 2004). On a 5-point Likert scale, patients receiving sulfasalazine saw a -0.96 point reduction in the physician's assessment of disease activity when compared to placebo (95% CI: -1.47, -0.45) (van Rossum et al., 1998). However, there was no significant difference in physician's global assessment scores (100 mm VAS) for leflunomide compared to MTX (MD = 0.60m 95% CI: -7.58, 8.78) (Silverman et al., 2005). A fourth RCT comparing penicillamine, hydroxychloroquine and placebo measured the physician's global assessment on a 5-point Likert scale and did not find any groups to be significant compared to another, though they reported a "trend toward significance" for the hydroxychloroquine group after 12 months of intervention (p = 0.16) (Brewer, Giannini, Kuzmina, & Alekseev, 1986). Lastly, in a comparison of the physician's global assessment of disease activity (dichotomized to improved or not improved), 68 participants (68%) in the auranofin arm and 52 participants (62%) in the placebo arm improved, though there was no difference between arms (p = 0.24) (Giannini, Brewer, Kuzmina, Shaikov, & Wallin, 1990).

In one RCT, the functional ability (CHAQ disability index, 0-3, lower better) of intermediate dose MTX was significant compared to high dose MTX (MD = -0.60, 95% CI: -0.81, -0.39) (Ruperto et al., 2004). In the other study that reported functional ability (CHAQ disability index, 0-3, lower better), there was no difference between leflunomide and MTX (MD = -0.05, 95% CI: -0.30, 0.20) (Silverman et al., 2005).

Intermediate MTX was again favoured over high dose MTX in terms of improvement of the patient/parent assessment of overall well-being (10 cm VAS, lower better) (-1.00, 95% CI: -1.71, -0.29) (Ruperto et al., 2004). The reported patient's score of disease activity was significantly reduced in the sulfasalazine arm than the placebo arm (MD = -0.54, 95% CI: -0.96, -0.12; scale not mentioned) (van Rossum et al., 1998). When leflunomide and MTX were compared, there was no difference in overall well-being (MD = 6.10, 95% CI: -2.08, 14.28) (Silverman et al., 2005).

Inflammation as measured by the ESR was reduced by -15.40 mm/hour (95% CI: -22.89, -7.91) for intermediate dose MTX compared to high dose MTX (Ruperto et al., 2004) and reduced by -0.70 mm/hour (95% CI: -0.91, -0.49) for those receiving sulfasalazine compared to placebo (van Rossum et al., 1998). No significant difference was found for leflunomide compared to sulfasalazine (MD = 0.70, 95%

CI: -2.77, 4.17) (Silverman et al., 2005). Another study comparing low-dose MTX (10 mg/m^2/week), very low-dose MTX (5 mg/m^2/week) and placebo found that low-dose MTX had a significant median reduction in the ESR compared to placebo (p=0.02) (Giannini et al., 1992).

None of the DMARD RCTs measured the impact of the interventions on HRQOL.

4.3.3 SENSITIVITY ANALYSES FOR DMARD RCTS

There were no sensitivity analyses that could be conducted for the DMARD RCTs as there was only one study of high quality and the included abstract had a different design than the other RCTs as it was measuring the rate of flare in patients with clinical remission continuing on MTX (Pan & Lehman, 2011). It was also not possible to remove older DMARDs no longer in use for JIA from the evidence networks because there would not be enough remaining RCTs in the reference case.

4.3.4 SAFETY RESULTS FOR DMARD RCTS

Seven of the 11 RCTs reported on safety; the included abstract did not provide details about the safety outcomes of interest (Brewer et al., 1986; Giannini, Brewer, Kuzmina, et al., 1990; Giannini et al., 1992; Kvien, Hoyeraal, & Sandstad, 1985; Silverman et al., 2005; van Rossum et al., 1998). There were a similar number of withdrawals due to AEs in a 12 month RCT of 10 mg/kg per day of penicillamine (n = 2 [3.9%]), 6 mg/kg/day of hydroxychloroquine (n = 3 [6.0%]) and placebo (n = 3 [7.1%]). Serious AEs were not clearly reported in the RCT (Brewer et al., 1986). In another study, penicillamine (starting dose of 2.5 mg/kg/day) was compared with gold sodium thiomalate (starting dose of 0.7 mg/kg once weekly) over 50 weeks. The number of withdrawals due to AEs was slightly higher in the penicillamine arm (n = 7 [18.4%]) than the gold sodium thiomalate arm (n = 5 [12.8%]). The proportion of participants with serious AEs was not clearly reported (Kvien et al., 1985).

When auranofin (*i.e.,* oral gold) at a dose of 0.15 mg/kg/day was compared to placebo for a period of six months, there were 4 participants (4.4%) in the placebo arm and only 1 participant (1%) in the auranofin arm who withdrew due to an AE. It was unclear from the study report whether any participants had a serious AE, though the authors mentioned that most AEs were mild in nature (Giannini, Brewer, Kuzmina, et al., 1990).

In a study that compared sulfasalazine (50 mg/kg/day) to placebo, 10 withdrawals (28.6%) from the sulfasalazine arm were due to AEs and none occurred in the placebo group. There was also 1 participant (2.9%) receiving sulfasalazine, but none receiving placebo that experienced a serious AE (van Rossum et al., 1998).

The oldest included RCT on MTX investigated it at a low-dose (10 mg/m^2/week) and a very low-dose (5 mg/m^2/week) compared to placebo for six months. The number of participants with withdrawals due to AEs were two (4.3%) in the low-dose MTX arm, one (2.5%) in the very low-dose MTX arm, and zero in the placebo arm. Only one serious AE occurred in the RCT and this was in the placebo arm (2.4%) (Giannini et al., 1992). A later study compared a high dose of MTX (30-40 mg/m^2/week) to an intermediate dose of MTX (15-20 mg/m^2/week). While no participants in either study arm experienced a serious AE, five participants (12.5%) in the high-dose arm and two participants (5%) in the intermediate dose arm withdrew due to AEs (Ruperto et al., 2004). Lastly, a 16-week study was conducted that compared leflunomide (see Table 4.17 for dose schedule) to MTX (0.5 mg/kg/week). There were more withdrawals due to AEs in the leflunomide arm (n = 3 [6.4%]) than the MTX arm (n = 1 [2.1%]); two of the withdrawals in the leflunomide arm were due to serious AEs. The number of participants with serious AEs was three (6.4%) in the leflunomide arm and zero in the MTX arm (Silverman et al., 2005). Overall, MTX at a moderate dose of 10-20 mg/m^2/week may be the safest for short-term use in patients with JIA, particularly those with oligoarticular or polyarticular subtypes.

4.4 NSAID RCTS

4.4.1 CHARACTERISTICS OF NSAID RCTS

A total of nine NSAID RCTs were included in the review that consisted of nine full-text articles. There were no abstracts on NSAIDs to include in a sensitivity analysis. All RCTs included participants with oligoarticular and polyarticular JIA, following the ILAR criteria or the older ACR or EULAR criteria; three RCTs also permitted patients with systemic JIA to be included. Five of the studies were 12 weeks long, one was six months and two were cross-over designs with phases lasting either three or four weeks. All included NSAID RCTs used head-to-head comparisons, with naproxen being the most common NSAID.

Other NSAIDs were celecoxib, meloxicam, rofexocib, ibuprofen, aspirin, tolmetin sodium, diclofenac, and sunlindac. The age and disease duration of participants was comparable across RCTs. However, one RCT had groups with shorter mean disease duration of about 1 year (Kvien, Hoyeraal, & Sandstad, 1984). Concurrent interventions differed between RCTs from permitting the use of stable doses of oral corticosteroids in four RCTs and a stable dose of DMARDs in three RCTs; one RCT permitted the use of a stable dose of other NSAIDs. Full details on the characteristics of included RCTs are presented in Table 4.25.

Six of the nine RCTs had unclear risk of bias for sequence generation while the remaining three were at low risk. The allocation concealment for all RCTs had an unclear risk. One RCT had high risk and three had unclear risk for blinding of participants and personnel. Two RCTs had high risk of bias for blinding of outcome assessors (one RCT for the self-assessed outcomes) and five had unclear risk. Incomplete outcome data were either high risk of bias (five RCTs) or low risk (four RCTs). Selective outcome reporting was mostly unclear risk of bias, but two RCTs were considered to have high risk of bias based on the outcomes reported in the protocol compared to the RCT. Two RCTs had high risk of other bias because they did not have a washout period between phases of the cross-over study design (Bhettay & Thomson, 1978; Leak, Richter, Clemens, Hall, & Ansell, 1988) and another RCT did not provide any baseline characteristics of included participants (Bhettay, 1986). The risk of bias assessment for all NSAID RCTs is available in Table 4.26.

4.4.2 EFFICACY RESULTS FOR NSAID RCTS

Only three of the nine RCTs were included in all network MAs and one additional RCT was included in the network MA of the ESR. This is because two RCTs did not present any of the outcomes of interest (Bhettay, 1986; Leak et al., 1988). Levinson 1977 had data for pain that could be used, but it did not have the same common comparator as the other two RCTs reporting on pain; the other outcomes the RCT reported did not have sufficient information to be included in the analysis (Levinson et al., 1977). For Giannini 1990, the number of active joints data could not be included as part of a network MA because the RCT arms did not connect with the rest of the network (Giannini, Brewer, Miller, et al., 1990). The primary outcome (ACR Pedi 30) and the six ACR Pedi 30 core set of outcomes were analyzed in a

network MA while pain and HRQOL were summarized in a descriptive analysis (Table 4.27). For the ESR, there were four RCTs with a total of 850 participants and for the other outcomes analyzed, there were three RCTs included with a total of 770 participants; naproxen was the common comparator in all network MAs (Table 4.28). The evidence network for disease response (ACR Pedi 30) and five of the six core set of outcomes is illustrated in Figure 4.9. The evidence network for the remaining core set outcome (*i.e.,* the laboratory measure of inflammation) is illustrated in Figure 4.10.

There were no significant results in the evidence network for the following outcomes: disease response (ACR Pedi 30), number of active joints, number of joints with limited range of motion, physician's global assessment of disease activity, and functional ability. This indicates that there is insufficient evidence to demonstrate whether one NSAID is better than the common comparator (naproxen) or other NSAIDs after three months of intervention (Tables 4.29 to Table 4.33). For the patient/parent assessment of overall well-being the higher dose of meloxicam (0.25 mg) had improved overall well-being compared to naproxen (-5.49, 95% CrI: -10.26, -0.74) (Table 4.34). Results were all non-significant for the laboratory measure of inflammation (Table 4.35).

4.4.3 SENSITIVITY ANALYSES FOR NSAID RCTS

Data at the three-month intermediate time point was used for Ruperto (2005) in order to have the same length of intervention as the other two RCTs that lasted three months in total. However, given the *a priori* decision to analyze the end of study results, the data at 12 months for Ruperto (2005) was used in a sensitivity analysis for the network MAs of each outcome. No changes in statistical significance were observed in the sensitivity analysis compared to the reference case for the following outcomes: disease response (ACR Pedi 30), number of active joints, number of joints with limited range of motion, physician's global assessment of disease activity and functional ability (Appendix 5, Tables 4-8). The reference case for overall well-being demonstrated a statistically significant result for meloxicam (0.25 mg) compared to naproxen (MD = -5.49, 95% CrI: -10.26, -0.74), but in the sensitivity analysis this result was no longer significant (MD = 0.32, 95% CrI: -4.52, 5.2) (Appendix 5, Table 9). The sensitivity analysis of a laboratory measure of inflammation did not have any changes in the statistical significance of the results (Appendix 5, Table 10). It is important to note that the time required for a response to NSAIDs for

patients with JIA can range from 8-12 weeks, so more time on the intervention may not have added any benefit (A. Huber, personal communication, March 5, 2016). In addition, Ruperto (2005) had high risk of attrition bias at the end of 12 months, whereas at 3 months there were fewer withdrawals, which indicates the results at 3 months were less biased.

4.4.4 SAFETY RESULTS FOR NSAID RCTS

Safety results were available from six of the included NSAID RCTs. The remaining three were cross-over designs that did not separate out the results for each study phase (Bhettay, 1986; Bhettay & Thomson, 1978; Leak et al., 1988). In one 12-week RCT comparing tolmetin sodium (starting dose of 15 mg/kg/day) and aspirin (starting dose of 50 mg/kg/day), there was only one participant (1.9%) who withdrew due to an AE in the tolmetin sodium arm compared to six participants (11.1%) who withdrew from the aspirin arm due to an AE. The number of participants with serious AEs was not clearly reported in the RCT (Levinson et al., 1977). The available results indicate that short-term use of tolmetin sodium is safer than aspirin for patients with JIA. Another 12-week study compared ibuprofen (30 mg/kg/day) to aspirin (60 mg/kg/day) and reported six withdrawals (12.8%) due to AEs in the aspirin arm, but none in the ibuprofen arm. There were also more participants who had serious AEs in the aspirin arm (n = 13 [27.7%]) compared to the ibuprofen arm (n = 4 [8.9%]) (Giannini, Brewer, Miller, et al., 1990). Thus, ibuprofen is also safer to use in the short-term than aspirin among patients with oligoarticular, polyarticular or systemic JIA. A third RCT compared naproxen (10 mg/kg bid) to aspirin (75 mg/kg bid) over a period of six months. Five participants (12.5%) in the naproxen arm and 20 participants (50%) in the aspirin arm withdrew due to an AE, which was statistically significant ($p<0.01$). Serious AEs were not clearly described in the RCT (Kvien et al., 1984). Naproxen at 10 mg/kg twice daily is safer to use in the short-term than aspirin among patients with oligoarticular and polyarticular JIA.

For one RCT with naproxen as a comparator, the number of withdrawals due to AEs was very similar to celecoxib (3 mg/kg bid), since three (3.6%) participants in the naproxen arm (7.5 mg/kg bid) and three (3.9%) participants in the lower dose celecoxib arm withdrew due to AEs. The higher dose celecoxib arm (6 mg/kg bid) had the highest number of withdrawals due to AEs (n = 7 [8.5%]). However, when looking at the number of serious AEs, none were experienced by the naproxen arm, but there were three (3.9%)

and two (2.4%) in the lower and higher dose celecoxib arms, respectively (Foeldvari et al., 2009). From this 12-week RCT, naproxen at 7.5 mg/kg twice a day is safer than both doses of celecoxib for short-term use among patients with oligoarticular or polyarticular JIA.

Similarly, in the RCT comparing rofecoxib at doses of 0.3 mg/kg/day and 0.6 mg/kg/day to naproxen at 15 mg/kg/day, the number of withdrawals due to AEs were similar in the lower dose rofecoxib arm (n = 3 [2.8%]) and naproxen arm (n = 3 [3.0%]). No withdrawals due to AEs occurred in the higher dose rofecoxib arm. The numbers of serious AEs were similar between all three groups, with one participant (0.9%) in the lower dose rofecoxib arm, two participants (2.0%) in the higher dose rofecoxib arm, and one participant (1.0%) in the naproxen arm (Reiff et al., 2006). Therefore the risk of serious AEs appears to be comparable for naproxen at 15 mg/kg/day, and rofecoxib at 0.3 mg/kg/day or 0.6 mg/kg/day for short-term use (3 months) among patients with oligoarticular and polyarticular JIA

Another RCT compared meloxicam (0.125 mg/kg/day and 0.25 mg/kg/day) to 10 mg/kg/day of naproxen. After twelve months of use, the higher dose meloxicam had the lower number of withdrawals due to AEs (n = 3 [4.1%]), followed by lower-dose meloxicam (n = 7 [9.6%]) and then naproxen (n = 10 [12.8%]). Participants receiving naproxen also had the highest proportion of serious AEs (n = 10 [12.8%]), the lower dose meloxicam arm had the fewest participants with serious AEs (n = 4 [5.5%]), and there were seven participants (9.5%) in the higher-dose meloxicam group who experienced a serious AE. However, the authors of the study report that none of these serious AEs were intervention related (Ruperto et al., 2005). From this information, it seems that the higher dose of meloxicam (0.25 mg/kg/day) had a better safety profile for patients with oligoarticular and polyarticular JIA after twelve months of intervention than the lower dose.

4.5 CORTICOSTEROIDS (INTRA-ARTICULAR CORTICOSTEROID JOINT INJECTIONS AND SYSTEMIC GLUCOCORTICOIDS) RCTS

4.5.1 CHARACTERISTICS OF INCLUDED CORTICOSTEROID RCTS

Seven RCTs on corticosteroids consisting of nine full-text articles were included in the reference case. Of these, three were of intra-articular corticosteroid injections and three investigated systemic

glucocorticoids. One of the intra-articular corticosteroid joint injection RCTs was a protocol for which no results were found; the RCT was included in the review, but was excluded from the analyses (Forster, 2000). Two additional conference abstracts of one RCT of an intra-articular corticosteroid joint injection was included for a sensitivity analysis if there were sufficient data and included RCTs in the evidence network (Bracciolini et al., 2014; Ravelli et al., 2014).

The predominant JIA subtype included in the RCTs was oligoarticular JIA, with some RCTs allowing for both extended and persistent oligoarticular JIA. Patients with systemic JIA were specifically included in two RCTs, and polyarticular JIA was included in one RCT. Two RCTs described the patient population in the RCT as “children with rheumatoid arthritis” and one of these also had patients with systemic lupus erythematosus (Popova-Kiprova, Zvetkova, Karakashoff, & Mihailova, 1974; Vignolo et al., 1991). Of the two full-text RCTs on IA joint injection interventions, study duration was mostly one or two years, but the protocol was planned for 16 weeks. Age and disease duration were similar in the RCTs that provided this information; children were young and had the disease for close to three years. The interventions were all compared head-to-head.

Study duration for the systemic glucocorticoid RCTs was six months and one RCT lasted one year. Prednisone was the common comparator among all RCTs; deflazacort, tetracosactide and methylpredisone were the other interventions. One RCT had a very low mean age of participants (5.5 and 5.6 years) compared to the other RCTs (Picco, Gattorno, Buoncompagni, Pistoia, & Borrone, 1996). Disease duration was different in the two RCTs that provided the information. Other medications such as NSAIDs were permitted. A detailed description of the characteristics of all included corticosteroid RCTs is presented in Table 4.36.

Only two of the IA joint injection RCTs could be assessed for risk of bias because they were completed studies published in at least one full-text article. The risk of bias was high for Zulian (2003), because they did not use a true randomization scheme, but rather based the sequence on the availability of the two medications used (Zulian et al., 2003). It also had high risk for blinding of participants and personnel because the allocation was not concealed. The remaining assessments were either unclear or low risk of

bias for this RCT and the other intra-articular corticosteroid joint injection RCT. All the RCTs were of low overall methodological quality (Table 4.37).

The systemic glucocorticoid RCTs all had unclear risk of bias for sequence generation, allocation concealment and selective outcome reporting. Only one RCT had high risk of bias for blinding of participants and personnel, while another RCT had a low risk of bias for blinding of outcome assessors. Risk for other sources of bias was low for three of the four RCTs; the other was high risk of bias because it was unbalanced for variables that interfere with growth, recruited only 65% of the participants estimated in the sample size calculation, and did not reach the full length of follow-up (Vignolo et al., 1991). All of the systemic glucocorticoid RCTs were of low methodological quality (Table 4.37).

4.5.2 EFFICACY RESULTS FOR CORTICOSTEROID RCTS

None of the intra-articular corticosteroid joint injection RCTs reported on the outcomes of interest for this review and were thus excluded from the efficacy analysis (Forster, 2000; Zulian et al., 2003; Zulian et al., 2004). There were not enough systemic glucocorticoid RCTs that provided results for the outcomes of interest to do either a network MA or MA, but a descriptive analysis was completed for the number of active joints and inflammation (ESR) (Table 4.38).

For the systemic glucocorticoids, one RCT reported an annual trend for a simple joint count of the number of joints with active arthritis (presence of swelling, tenderness, pain on motion or limited range of motion). The mean change from baseline in the number of active joints was -4.9 (SD = 10.4) in the deflazacort arm and the prednisone arm had no mean change from baseline in the number of active joints (SD = 10.4). However, the mean difference between arms was not significant (MD = -4.9, 95% CI: -11.89, 2.09). The RCT also measured inflammation using the ESR, but only reported a non-significant p-value of 0.6 for the difference in inflammation between deflazacort and prednisone (Loftus et al., 1993). The other three systemic glucocorticoid RCTs did not report on any outcomes of interest (Picco et al., 1996; Popova-Kiprova et al., 1974; Vignolo et al., 1991).

4.5.3 SENSITIVITY ANALYSES FOR CORTICOSTEROID RCTS

Since no network MAs or MAs were performed for the intra-articular corticosteroid joint injection and systemic glucocorticoids RCTs and they were all of low quality, it was not possible to conduct the planned sensitivity analysis of only high quality RCTs. In addition, the intra-articular corticosteroid joint injection RCT that was published in a conference abstract provided no efficacy results for the outcomes of interest (Bracciolini et al., 2014). There were no abstracts of systemic glucocorticoids.

4.5.4 SAFETY RESULTS FOR CORTICOSTEROID RCTS

Safety results were not clearly reported per study arm in any of the included intra-articular corticosteroid joint injection or systemic glucocorticoid RCTs. One RCT comparing tetracosactide and prednisone mentioned that there were more serious AEs in the prednisone (corticosteroid) arm without further details (Popova-Kiprova et al., 1974).

4.6 NON-PHARMACOLOGICAL RCTS

4.6.1 CHARACTERISTICS OF INCLUDED NON-PHARMACOLOGICAL RCTS

4.6.1.1 PHYSICAL ACTIVITY INTERVENTIONS

A total of seven non-pharmacological RCTs (eight full-text articles) on PA interventions were included. No additional RCTs were included after accounting for the two conference abstracts as they were part of the Sandstedt 2012 and Tarakci 2012 studies. The PA interventions were mostly compared to a control group that was either on a waitlist or who received standard care, but there were two RCTs with head-to-head comparisons and two that compared high versus low-intensity PA. Common types of PA interventions were strengthening and stretching exercises. Two RCTs had aquatic interventions, but the rest were on different land-based exercises. Study duration was 12 weeks in length for four of the RCTs, six months in two RCTs, and 10 weeks in one RCT. Patients with a broad range of JIA subtypes were included. Sandstedt (2012) had an older mean age of participants (13.3 in the intervention and 14.9 in the control arms) and Takken (2003) had younger participants on average than the other RCTs (about 9 years old in both groups). Disease duration was also longer for Sandstedt (2012) and Tarakci (2012) than the other

RCTs (mean duration from 4.8 to 6.5 years). In general, stable medications and leisure PA were permitted. Table 4.39 provides further details on the PA interventions among included non-pharmacological studies.

All seven RCTs of PA interventions were assessed for risk of bias (Table 4.40). The risk of bias for blinding of participants and personnel was high in all RCTs and for blinding of outcome assessors it was only low for two RCTs and one RCT for any assessor who was not the patient. Three RCTs had unclear risk of bias for sequence generation and the rest were low risk of bias. There was one RCT with high risk of allocation concealment and two with low risk of bias. Six of seven RCTs had low risk of bias for incomplete outcome data and all had low risk of other sources of bias. Selective outcome reporting had an unclear risk of bias in all but one RCT (Table 4.40). Overall, all the RCTs were considered low quality.

4.6.1.2 NUTRITIONAL INTERVENTIONS

There were four nutritional intervention RCTs reported in four full-text articles. A fifth RCT available only as an abstract was included for sensitivity analysis; its characteristics were summarized with the other nutritional intervention RCTs (Hunt, Rose, McIlvain-Simpson, & Tejani, 1997). The types of interventions were supplementation with calcium and/or vitamin D, folic acid, or omega-3 polyunsaturated fatty acids. These interventions were applied to patients of any JIA subtype in four RCTs and in just the oligoarticular or polyarticular JIA subtypes for one RCT. There was a large range in the study duration (*i.e.,* from baseline to the end of the intervention); one cross-over RCT had two six-week phases with a one-week washout period in between. The longest RCT was two years. The ages of participants were similar, but the disease duration was less than one year in the Vargova (1998) study (Vargova, Vesely, Sasinka, & Torok, 1998). One RCT did not allow for any concurrent interventions, another allowed stable doses of MTX, and in a calcium and vitamin D supplement RCT they allowed NSAIDs and MTX and gave 400 IU of vitamin D3 to all participants (Table 4.39). Two of the RCTs used a cross-over design and one of these was investigating the impact of folic acid supplements on the efficacy of MTX (Hunt et al., 1997); these RCTs were excluded from the analysis because they did not provide results of the first time point separately, thus the data were for participants as their own controls (which was an exclusion criterion for this review). The remaining three RCTs were also excluded from the efficacy analysis as they did not

provide any of the outcomes of interest (Carrasco et al., 2008; Lovell et al., 2006; Vargova et al., 1998). However, one RCT on calcium plus vitamin D supplementation versus placebo in combination with vitamin D provided safety results that are summarized in a descriptive analysis (Lovell et al., 2006).

Risk of bias assessments were performed for the four RCTs contained in full-text articles (Table 4.40). Two RCTs had unclear risk of bias for sequence generation and the same two had low risk of bias for allocation concealment. The risk of bias for blinding of participants and personnel was low for all four RCTs and for blinding of outcome assessors three RCTs had low risk of bias. There was high risk of bias for both incomplete outcome data in three RCTs. Selective outcome reporting had high risk of bias in two RCTs. There were no other sources of bias present for any of the RCTs (Table 4.40). The overall methodological quality of nutrition RCTs was low for all four RCTs.

4.6.1.3 FOOT ORTHOTICS/FOOT CARE AND SPLINTS

Foot orthotics (FOs), foot care and splint interventions were conducted in four included RCTs and results of these RCTs were reported in four full-text articles, and one book that was found through contact with the study authors. Additional abstracts were also included in the review as part of the Coda 2014 (one abstract) and Hendry (2013) (two abstracts) RCTs. One RCT differed greatly from the others in that it investigated work splints for the wrists rather than FOs or foot care; this RCT was excluded from the analysis because it did not report on any of the outcomes of interest (Eberhard, Sylvester, & Ansell, 1993). The remaining three RCTs included foot orthotics and one provided a multidisciplinary foot care program along with the FOs (Powell, Seid, & Szer, 2005). The RCTs were inclusive in that participants with most JIA subtypes were eligible for the RCTs so long as they had joint involvement of the ankle or foot for the FOs/foot care RCTs and involvement of the wrist for the splints intervention; patients with systemic JIA were only included in two RCTs (Table 4.39). Study duration was either three, six or twelve months long. The mean age of participants in Powell et al. (2005) was slightly older compared to the other RCTs. Stable medications were permitted and night splints were used by participants in the RCT by Eberhard et al. (1993) RCT. The characteristics of these RCTs are described in greater detail in Table 4.39.

All four RCTs were assessed for risk of bias (Table 4.40). Half of the RCTs had unclear risk for sequence generation and all either did not mention, or provided insufficient details to determine, the risk of bias for allocation concealment. Blinding of participants and personnel had high risk of bias for all but one RCT, and two RCTs were at high risk of bias for blinding of outcome assessors. Every RCT was graded with low risk of attrition bias and had no other sources of bias. One study had high risk of selective outcome reporting bias and the other three had unclear risk as a study protocol could not be found (Table 4.40). There was not a single RCT of the foot orthotics/foot care or splints interventions that could be considered of high methodological quality.

4.6.1.4 MASSAGE THERAPY

Only one RCT was included on massage therapy that was found in a single full-text article. It compared massage therapy to relaxation therapy, both performed by the child's parent for 15 minutes per day. The RCT was four weeks long. The mean age of both groups overall was 9.8 (range: 5.4-14.8) years and mean disease duration was 4.4 years. Standard medical care was permitted for participants. The characteristics of this included RCT are presented in Table 4.39.

In the risk of bias assessment, Field (1997) had low risk for blinding of outcome assessors (who were not the participants), incomplete outcome data and other sources of bias. There was unclear risk of bias for sequence generation, allocation concealment and selective outcome reporting (Field et al., 1997). The blinding of participants and personnel was considered high risk of bias because it was not possible to hide from the participants which group they were in (Table 4.40). Given the scoring for the domains, this RCT was considered low methodological quality.

This RCT could not be included in the evidence network for non-pharmacological RCTs because it used head-to-head comparisons and neither of the interventions was sufficiently comparable to another intervention in the evidence network to join them together. A descriptive analysis was instead completed for the outcomes of interest (see Section 4.6.2).

4.6.1.5 PSYCHOSOCIAL OR BEHAVIOURAL INTERVENTIONS

Three RCTs of psychosocial or behavioural interventions were included in this review from three full-text articles. Two more RCTs, published in three conference abstracts, were available for a sensitivity analysis (Jeppesen, Christensen, Herlin, Leegaard, & Thastum, 2012; Jeppesen, Herlin, Christensen, Leegaard, & Thastum, 2013; Stern, Blitz, Richards, & Marzan, 2012). Among all five RCTs, there was variability in the interventions' approaches and end goals. Two were Internet-based, though one had educational sessions to improve PA among patients with JIA (Lelieveld et al., 2010) and another was focused on improving patients' HRQOL and reducing physical and emotional symptoms associated with the disease through a multi-faceted self-management program (Stinson et al., 2010). A non-Internet behavioural intervention was also conducted to increase patients' calcium intake and thus their bone mass (Stark et al., 2006). Another RCT published in a conference abstract used a psychosocial intervention to improve QOL and provide pain coping strategies to patients (Jeppesen et al., 2012). Finally, there was a conference abstract describing a combined education and subsequent family pedometer walking program to improve the exercise tolerance of patients (Stern et al., 2012). Informational or educational sessions were a commonality among the RCTs and the target audience of patients with JIA included nearly all subtypes in these RCTs. However, the target age groups were different depending on the study, with two RCTs focused more on adolescents with JIA (Stern et al., 2012; Stinson et al., 2010) and one RCT on young children who were six or seven years old on average (Stark et al., 2006). The shortest RCT was six weeks long, while the longest was 17 weeks. All the RCTs compared their program to a control, which was a waitlist, standard care or "enhanced" standard care. Medications were continued in the RCTs that described concurrent interventions, but systemic corticosteroids within three months of the intervention or calcium supplementation were not permitted for Stark et al. (2006) because it was assessing bone mass. The complete description of characteristics of the included RCTs is available in Table 4.39.

The risk of bias assessment was completed for the three RCTs that were published in at least one full-text article (Lelieveld et al., 2010; Stark et al., 2006; Stinson et al., 2010). All RCTs had high risk of bias for blinding of participants and personnel because of the nature of the interventions. One of the RCTs had

low risk of bias for blinding of outcome assessors instead of high risk on outcomes that were measured by a blinded dietician (Table 4.40).

4.6.2 EFFICACY RESULTS FOR NON-PHARMACOLOGICAL RCTS

4.6.2.1 NETWORK META-ANALYSIS RESULTS

The primary outcome for non-pharmacological RCTs (*i.e.,* pain relief), as well as HRQOL had enough RCTs included to perform a network MA. The common comparator was a control group that represented a waitlist, standard care, or supportive shoes (which was considered to be like standard care). Due to the differing types of interventions, even within the non-pharmacological categories, it was not possible to conduct pairwise comparisons in a MA. Instead, the ACR Pedi 30 and its core set of outcomes were reported in a descriptive analysis (Table 4.41). Six RCTs contributed data to the evidence network of pain with 312 participants. HRQOL had eight RCTs included with a total of 412 participants (Table 4.42). The evidence networks for pain and HRQOL from non-pharmacological RCTs are illustrated in Figures 4.11 and 4.12, respectively.

For pain relief, the evidence network compared PA interventions, FOs, a multidisciplinary foot care program and a behavioural intervention. However, none of these interventions was found to be significant over the control group or other interventions in pain relief (Table 4.43). Four RCTs that measured pain relief were excluded from the evidence network because they were RCTs with head-to-head comparisons that could not connect to the network through the common comparator or any other intervention (Baydogan, Tarakci, & Kasapcopur, 2015; Epps et al., 2005; Field et al., 1997; Singh-Grewal et al., 2007). The individual RCTs' results are reported in the descriptive analysis (section 4.6.2.2).

Results from the evidence network for HRQOL included the same interventions as the pain network in addition to two more PA interventions. One of these interventions involved muscle strengthening exercises and jump rope, and the other intervention had two aquatic conditioning phases (one of these was aerobic). None of the interventions had a significantly increased likelihood of improved HRQOL compared to the control group or any of the other interventions (Table 4.44). Two RCTs were excluded from the evidence network for HRQOL because these RCTs used head-to-head comparisons with

interventions that could not be connected by either the common comparator or another intervention (Epps et al., 2005; Singh-Grewal et al., 2007). The individual RCTs' results are reported in the descriptive analysis (section 4.6.2.2).

4.6.2.2 DESCRIPTIVE ANALYSIS RESULTS

Of the four RCTs measuring pain that were excluded from the network MA, there was no significant result in the study of combined hydrotherapy and land physiotherapy versus land therapy alone (MD = 0.22, 95% CI: -0.22, 0.67; 100 mm VAS scale) or in the RCT comparing aerobics to qigong (MD = 0.00, 95% CI: -0.47, 0.47; 100 cm [sic] scale) (Epps et al., 2005; Singh-Grewal et al., 2007). However, in the RCT with a head-to-head comparison of strengthening versus proprioceptive exercises, the proprioceptive group was favoured in terms of pain improvement (numerical rating scale, lower better) (MD = 1.32, 95% CI: 0.52, 2.13). There was also a greater reduction in pain (10 cm VAS) experienced by patients in the massage therapy group compared to those in the relaxation therapy group of a four week RCT (MD = -2.50, 95% CI: -3.68, -1.32) (Field et al., 1997).

HRQOL results were not significant in each of the two RCTs that were excluded from the network MA. For the study of combined hydrotherapy and land physiotherapy versus land physiotherapy alone measuring HRQOL (EQ-5D), the mean difference was -0.53 (95% CI: -1.10, 0.03) (Epps et al., 2005). The comparison of pain relief (10 cm VAS) after 12 weeks between aerobics to qigong had a mean difference of -0.09 (95% CI: -0.56, 0.39) (Singh-Grewal et al., 2007).

Functional ability was measured in four PA intervention RCTs and two foot orthotics or foot care RCTs. Pilates was favoured over the control arm (conventional exercise) for functional ability as measured by the full CHAQ scale (lower better) (MD = -2.01, 95% CI: -2.70, -1.32) (Mendonca et al., 2013). A home stretching and strengthening exercise program had a statistically significant improvement in functional ability (CHAQ, 0-3, lower better) compared to the control (waitlist) arm (-0.93, 95% CI: -1.39, -0.47) (Tarakci, Yeldan, Baydogan, Olgar, & Kasapcopur, 2012). There was no significant difference between aerobics and qigong in improving functional ability (CHAQ physical functioning scale, 0-4, lower better) (MD = -0.01, 95% CI: -0.14, 0.12) (Singh-Grewal et al., 2007). The RCT comparing aquatics to a waitlist group also measured functional ability using the CHAQ disability index (scale 0-3, lower better), but there

was no difference between the groups (MD = -0.32, 95% CI: -0.86, 0.22) (Takken, Van Der Net, Kuis, & Helders, 2003). No significant difference in functional ability (Child Health Questionnaire, physical functioning domain, higher better) was found for the RCT that compared a combination of rope jump and strengthening exercises to no intervention (p>0.017) (Sandstedt, Fasth, Eek, & Beckung, 2013). One RCT comparing a multidisciplinary foot care program to standard care also did not have a statistically significant result for functional ability (CHAQ disability index, 0-3, lower better) (MD = 0.00, 95% CI: -0.39, 0.39) (Hendry et al., 2013). Overall, there was insufficient evidence to demonstrate that non-pharmacological interventions improved physical functioning compared to a control group, except for Pilates.

The ACR Pedi core set outcomes were all reported in a RCT of a head-to-head comparison of a combined hydrotherapy and land physiotherapy program versus a land physiotherapy program alone over 10 weeks. In this RCT, there was no significant difference between the combined and land PA interventions for: the number of joints with active arthritis (MD = -1.00, 95% CI: -3.26, 1.26), the number of joints with limited range of motion (MD = -1.00, 95% CI: -3.22, 1.22), the physician's global assessment of disease activity (MD = -1.00, 95% CI: -9.88, 7.98), functional ability measured using the CHAQ disability index (MD = 0.19, 95% CI: -0.08, 0.46), the patient/parent assessment of overall well-being (MD = 1.00, 95% CI: -10.32, 12.32), and the ESR (MD = -0.60, 95% CI: -7.32, 6.12). However, the RCT reports that for all six of the core set of outcomes there was improvement for both groups, though not statistically significant (Epps et al., 2005).

The RCT of multidisciplinary foot care versus standard care measured four of the six ACR Pedi core set outcomes. Of these four, the number of joints with limited range of motion was favoured in the multidisciplinary foot care arm after 12 months (MD = -2.00, 95% CI: -3.60, -0.40). As mentioned in the beginning of this section, there was no statistically significant difference between arms in terms of functional ability as measured by the CHAQ (Hendry et al., 2013). Both the number of active joints (MD = -1.50, 95% CI: -3.04, 0.04) and the patient/parent assessment of overall well-being (MD = 0.00, 95% CI: -9.06, 9.06) were not significant (Hendry et al., 2013).

A 12 week PA intervention RCT reported the number of active joints in the aerobics versus qigong arms, but neither study arm was favoured (MD = -1.70, 95% CI: -3.47, 0.07) (Singh-Grewal et al., 2007). The massage therapy versus relaxation therapy RCT showed no statistically significant difference in the number of active joints between groups after four weeks (MD = -0.40, 95% CI: -1.21, 0.41) (Field et al., 1997).

4.6.3 SENSITIVITY ANALYSES FOR NON-PHARMACOLOGICAL RCTS

No sensitivity analysis was performed to remove low quality RCTs, as all RCTs were low quality. Abstracts presenting unique RCTs were not included in a sensitivity analysis of the pain and HRQOL evidence networks because one was a cross-over design without separate results for each study phase (Hunt et al., 1997), another did not report on pain or HRQOL (Stern et al., 2012), and two abstracts of the same study only reported p-values in the results (Jeppesen et al., 2012; Jeppesen et al., 2013).

4.6.4 SAFETY RESULTS FOR NON-PHARMACOLOGICAL RCTS

4.6.4.1 PHYSICAL ACTIVITY INTERVENTIONS

Six of the seven RCTs provided results on the number of participants who withdrew due to AEs (Baydogan et al., 2015; Epps et al., 2005; Mendonca et al., 2013; Singh-Grewal et al., 2007; Takken et al., 2003; Tarakci et al., 2012). Each of these RCTs reported no withdrawals due to AEs for any of the study arms. A RCT on aquatic exercises versus a control group (*i.e.,* no intervention) reported one withdrawal in the RCT without a reason given for the withdrawal and they still included the participant in the analysis because the individual had attended 75% of the sessions (Takken et al., 2003). Two RCTs provided details on the number of participants experiencing serious AEs (Mendonca et al., 2013; Singh-Grewal et al., 2007). In both of these RCTs there were no serious AEs that occurred for any participant in any study arm. Overall, these safety results indicate that PA interventions involving strengthening, stretching, Pilates, aquatic aerobic exercises, proprioceptive exercises, and aerobics are as safe for patients with JIA on stable medication to perform over the short-term as if they did not participate in PA interventions.

4.6.4.2 NUTRITIONAL INTERVENTIONS

Only one of the included RCTs reported on the safety outcomes of interest (Lovell et al., 2006). For this RCT comparing oral calcium (1000 mg) in combination with vitamin D (400 International Units [IU] per day) to placebo in combination with vitamin D (400 IU per day), there were no serious AEs reported in either arm. However, three participants (2.9%) in the calcium arm withdrew due to an AE (nausea) (Lovell et al., 2006).

4.6.4.3 FOOT ORTHOTICS OR FOOT CARE AND SPLINTS

The number of withdrawals due to AEs was presented in three of the four RCTs (Eberhard et al., 1993; Hendry et al., 2013; Powell et al., 2005). In each of these, there were no withdrawals due to AEs in any of the study arms. Two RCTs reported on the number of participants who had a serious AE. In one of these RCTs comparing a multidisciplinary foot care program to a control (standard care), there were no serious AEs experienced for the entire 12 months (Hendry et al., 2013). The RCT comparing custom orthoplast (low-temperature thermoplastic) cock-up splints to ready-made Droitwich work-splints over a six month period reported one participant had a serious AE (*i.e.,* allergic reaction with rash and broken skin) for the wrist that received an orthoplast splint (Eberhard et al., 1993). Overall, foot orthotics and foot care appear to be safe for patients with JIA for short-term use. Splints may also be safe for patients with JIA, though care should be taken to determine whether a patient has skin sensitivities to orthoplast.

4.6.4.4 MASSAGE THERAPY

In the one included RCT there were no withdrawals due to AEs in either the massage therapy or relaxation therapy arms. Information on whether participants experienced a serious AE were not reported (Field et al., 1997).

4.6.4.5 PSYCHOSOCIAL AND BEHAVIOURAL INTERVENTIONS

Two of the RCTs provided information on the number of withdrawals due to AEs (Lelieveld et al., 2010; Stinson et al., 2010); both were Internet-based interventions with educational sessions. None of the participants in the study arms of either intervention withdrew due to an AE. One of these RCTs also

clearly reported in their results that no participants in either the Internet program educating participants on PA or the control group (*i.e.,* waitlist) experienced a serious AE (Lelieveld et al., 2010). Therefore, Internet-based psychosocial or behavioural interventions aimed at educating and equipping patients with JIA to have better self-management or increased PA are safe for short-term use.

TABLE 4.1: STUDIES AND ARTICLES INCLUDED BY CATEGORY

Intervention Category	No. of studies included (reported in at least 1 full-text article)	No. of studies included (reported in at least one abstract or full-text article)	Number of full-text articles included	Number of abstracts included
Biologics	14	17	16	18
DMARDs	10	11	11	2
NSAIDs	9	9	9	0
Steroids (intra-articular joint injections and systemic glucocorticoids)	7	8	9	2
Physical activity	7	7	8	2
Nutrition	4	5	4	1
Foot orthotics or foot care	4	4	5	3
Massage	1	1	1	0
Psychosocial/behavioural	3	5	4	2

DMARDs = disease-modifying antirheumatic drugs; NSAIDs = non-steroidal anti-inflammatory drugs

TABLE 4.2: SUBGROUPS OF FULL-TEXT BIOLOGICS RCTS

	Withdrawal design	Parallel design
Polyarticular-course JIA	**5 RCTs:** **Ilowite 2009** (ANK vs PL) **Lovell 2000** (ETN vs PL) **Lovell 2008** (ADA vs PL with or without methotrexate) **Mori 2011** (low-dose ETN vs high-dose ETN) **Ruperto 2008** (ABT vs PL)	**1 RCT:** **Ruperto 2007** (IFX + MTX vs PL + MTX)
Systemic JIA	**1 RCT:** **Yokota 2008** (TOC vs PL) **Ruperto 2012, trial 2** (CAN vs PL)	**5 RCTs:** **De Benedetti 2012** (TOC vs PL) **Ilowite 2014** (RILO vs PL) **Lovell 2013** (RILO vs PL) **Quartier 2011** (ANK vs PL) **Ruperto 2012, trial 1** (CAN vs PL)
Early-aggressive therapy	**2 RCTs:** **Tynjala 2011** (IFX + MTX vs MTX + SSZ + HCQ vs MTX) **Wallace 2011** (open-label MTX + ETN + PRED vs PL + open-label MTX	**0 RCTs**

ABT = abatacept; ADA = adalimumab; ANK = anakinra; CAN = canakinumab; ETN = etanercept; HCQ = hydroxychloroquine; IFX = inflimixab; MTX = methotrexate; PL = placebo; RCT = randomized controlled trial; RILO = rilonacept; SSZ = sulfasalazine; TOC = tocilizumab

TABLE 4.3: CHARACTERISTICS OF INCLUDED BIOLOGICS RCTS

Author, year	Population	Duration	Groups	Dose, frequency, route	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
Ilowite 2009	Polyarticular-course JIA	16 wks	Placebo ANK	100 mg/mL/d, SQ 100 mg/mL/d, SQ	12 (range 4-17) 10 (range 3-17)	4.2 (range 1-16) 3.9 (range 1-11)	Stable dose of MTX for 6 wks before study entry; NSAIDs and oral corticosteroids stable for 4 wks before first dose of ANK	**Withdrawal design**; pts who experienced disease flare during blinded phase removed from primary study but had option to switch study arms and continue blinded tx
Lovell 2000	Polyarticular-course JIA with ≥ 5 active joints and ≥ 3 joints with LOM	28 wks (7 months) or until disease flare	Placebo ETN	0.4 mg/kg twice wkly (max 25 mg), SQ	12.2 8.9	6.4 5.3	NSAIDs, corticosteroids	**Withdrawal design**
Lovell 2008	Polyarticular-course JIA with ≥ 5 active joints and ≥ 3 joints with LOM	32 wks	Placebo ADA ADA + MTX Placebo + MTX	 24 mg/m^2 q other wk (max 40 mg) Same dose ADA Same dose placebo	11.3 (3.8) 11.1 (4.1) ADA+MTX = 11.7 (3.3) Placebo+MTX = 10.8 (3.4)	2.9 (3.3) 3.6 (4.0) ADA+MTX = 4.3 (4.1) Placebo + MTX = 4.0 (3.5)	Subset of pts received MTX (10 mg/m^2/wk) along with ADA or placebo	**Withdrawal design**; pts stratified by taking MTX or not; included pts did not respond to NSAIDs
Mori 2011	Polyarticular-course JIA	12 wks	Low-dose ETN High-dose ETN	0.2 mg/kg (twice wkly), SQ 0.4 mg/kg (twice wkly), SQ	13.0 13.5	6.87 6.68	Could not take DMARDs within 28 days from baseline	**Withdrawal design**; had to complete ≥ 48 wks open-label phase to enter double-blind extension study

Author, year	Population	Duration	Groups	Dose, frequency, route	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
Ruperto 2008	Active polyarticular-course JIA, ≥5 active joints (swelling or LOM and pain or tenderness) and active disease (≥ 2 active joints and 2 joints with LOM)	24 wks (6 months)	Placebo ABT	10 mg/kg (q 28 d), IV 10 mg/kg (q 28 d), IV	12.0 (3) 12.6 (3)	3.9 (3.5) 3.8 (3.7)	Stable MTX + folinic acid or folic acid, prednisone, NSAIDs (pain control)	**Withdrawal design**; Pts had to have inadequate response or intolerance to ≥1 DMARD or biological *e.g.,* ETN, IFX, ADA
Ruperto 2007	Polyarticular-course JIA, ≥5 active joints, and no active systemic symptoms	14 wks	Placebo + MTX IFX + MTX	Same dose as IFX + MTX:10-15 mg/m^2/wk, p.o. or parenteral 3 mg/kg (wks 0, 2, 6, 14), infusion + MTX: 10-15 mg/m^2/wk p.o. or parenteral	11.1 (4.0) 11.3 (4.0)	3.6 (3.4) 4.2 (3.6)	MTX; IA joint injections w/in 4 wks prior to study entry and in the trial	**Parallel design**; included pts had suboptimal response to MTX after ≥3 months tx; no prior tx with TNF-α inhibitors
Brunner 2014	Polyarticular-course JIA w/ ≥ 5 active joints and disease duration ≥ 6 months	32 wks	Placebo GLB	Same as GLB (q4 wks) 30 mg/m^2 (q4 wks – max 50 mg), SQ	NR for randomization phase; overall before open-label: median = 12 (range 2-17)	NR	MTX (10-30 mg/m^2/wk)	**Withdrawal design**; pts had been taking MTX for ≥3 months and still had active arthritis

Author, year	Population	Duration	Groups	Dose, frequency, route	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
De Benedetti 2012	Systemic JIA (ILAR criteria), ≥5 active joints or ≥2 active joints + fever (>38ºC for ≥5 d during screening period)	12 wks	Placebo TOC	NR ≤ 30 kg = 12 mg/kg q 2 wks, IV; ≥ 30 kg = 8 mg/kg q 2 wks by IV	10.0 (4.6) 9.1 (4.4)	5.2 (4.0) 5.1 (4.4)	Stable NSAIDs, oral GCs for ≥2 wks before baseline; MTX for ≥8 weeks before baseline	**Parallel design**; dose varied by weight; TOC group had higher proportion of individuals previously using an IL-1 inhibitor (55%) compared to placebo group (35%); Dosage of TOC by weight: <30 kg = 12 mg/kg q 2 weeks IV; ≥30 kg = 8 mg/kg q 2 weeks IV
Ilowite 2014	Systemic JIA (ILAR criteria), ≥2 active joints	4 wks	Placebo RILO	Same as intervention arm 4.4 mg/kg (max 320 mg) on day 0, then wkly main-tenance dose of 2.2 mg/kg (max 160 mg)	10.5 (4.4), median (IQR) = 11.0 (6.0, 14.0) 9.5 (4.6), median (IQR) = 9.5 (6.0, 13.0)	2.6 (3.1), median (IQR) = 1.4 (0.4, 3.6) 2.6 (3.6), median (IQR) = 0.7 (0.2, 4.0)	Increased/started corticosteroids if ≥ 1 of: MAS, incomplete MAS, symptomatic anemia, myocarditis, symptomatic pneumonitis, or serositis unresponsive to NSAIDs; stable dose of MTX ≥4 wks, stable dose of corticosteroids for ≥2 wks, ≤2 mg/kg (60 mg) prednisone	**Parallel design**

Author, year	Population	Duration	Groups	Dose, frequency, route	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
Lovell 2013	Systemic JIA (≥1 active joint (for at least 3 months) and ≥1 d spiking disease activity + intermittent fever (≥38.3ºC) or rash)	4 wks	Placebo RILO	2.2 mg/kg (days 0, 3, 7, 14, 21), SQ	Overall: 12.6 (4.3), median 14.0 (range 5-20) years	Overall: 3.1 years	Stable NSAIDs, MTX for ≥ 4 wks before screening; oral prednisone (or equivalent) permitted if dosage stable from ≥ 1 wk before screening	**Parallel design**; pts in 2nd tx cohort received 4.4 mg/kg RILO or placebo SQ on the same dosing schedule
Quartier 2011	Active systemic JIA (fever and/or CRP >20 mg/L and/or 1st hr ESR >20 + significant disease activity using ACR Pedi core set: ≥2 active joints, ≥2 joints LOM)	4 wks	Placebo ANK	2 mg/kg/d, SQ 2 mg/kg/d, SQ	7.5 (3.73) 9.5 (5.19)	3.2 (1.95) 4.2 (3.33)	Corticosteroids (PRED); had to stop IV intra-articular steroids, immuno-suppressive drugs and DMARDs ≥ 1 month before study or longer (depending on half-life)	**Parallel design**; included pts had to have disease duration >6 months and significant overall disease activity at day 1; no previous tx w/ IL-1 inhibitor
Ruperto 2012	Active systemic JIA (≥2 active joints, intermittent spiking fever >38ºC, CRP >30 mg/L)	4 wks (29 days); inter-mediate analysis at 15 days	Placebo CAN	4 mg/kg, SQ	median 9.0 (IQR 6.0-14.0) median 8.0 (IQR 4.0-13.0)	median 2.0 (IQR 1.2-5.2) median 2.3 (IQR 1.0-4.7)	Background therapy with a PRED equivalent; stable doses of NSAIDs and MTX; other biologics or DMARDs had to have a washout period of ≥5 half-lives	**Parallel design**; a 2nd trial used a randomized withdrawal phase
Yokota 2008	Systemic JIA (active systemic symptoms)	12 wks	Placebo TOC	8 mg/kg q 2 wks, IV 8 mg/kg q 2 wks, IV	9.3 (4.5) 8.0 (4.3)	4.7 (4.0) 4.6 (3.5)	Stable oral corticosteroids from 2 wks before trial; no tx with IA corticosteroid injections, methyl-PRED pulse tx, immuno-suppressive drugs, and DMARDs for 2 wks before 1st admin; no tx with TNF-	**Withdrawal design**; all pts had previously received oral corticosteroids and most pts had previously received ≥ 2 DMARDs or immuno-suppressive

Author, year	Population	Duration	Groups	Dose, frequency, route	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
							α agents for 12 wks before start	drugs, or both (*e.g.,* MTX and ciclosporin)
Silverman 1994	Active, refractory systemic JIA (ACR criteria)	6 months	Placebo Immuno-glubolin	1.5 g/kg of 0.1% albumin, IV 1.5 g/kg (every 2 wks for 2 months then monthly for 4 mo – total 9 infusions in 6 months), IV	NR	NR	NR	**Abstract**
Tynjala 2011	Polyarticular-course JIA (≥5 active joints and ≥3 joints with pain or tenderness and LOM)	54 wks	MTX IFX + MTX MTX + SSZ + HCQ	15 mg/m^2/wk (MTX) 3-5 mg/kg (IFX at wks 0, 2, 6 then q 6 wks), infusion + 15 mg/m^2/wk (MTX) 15 mg/m^2/wk (MTX) + 40 mg/kg/d (SSZ) + 5 mg/kg/d (HCQ)	10.1 (3.5) median = 9.6 (range 4.0-14.4) 10.5 (3.1) median = 11.6 (range 4.5-14.9) 8.3 (2.7) median = 7.7 (range 4.8-13.3)	1.8 (1.1) 1.5 (0.3) 2.3 (1.8)	IA corticosteroid injections and NSAIDs for symptomatic tx	**Parallel design**; max doses were 25 mg/wk (MTX), 2000 mg/d (SSZ), 300 mg/d (HCQ); pts had DMARD-naïve early JIA and had not received systemic corticosteroid tx

Author, year	Population	Duration	Groups	Dose, frequency, route	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
Wallace 2012	Active polyJIA (RF positive or negative) for < 12 mo	24 wks (6 months)	Placebo + MTX	Same doses as ETN + PRED (placebos) + 0.5 mg/kg/wk, SQ (MTX)	11.1 (4.1)	5.2 (0.6) months	folic acid; 1 NSAID during study; ≤ 2 IA corticosteroid injections w/in 2 wks after baseline; oral PRED taken up to 4 wks (had to stop ≥ 1 wk before enrollment; could start MTX (<0.5 mg/kg/wk) ≤ 6 wks before enrollment	Oral prednisolone would be tapered over the first 4 months of therapy; no previous biologics tx
			ETN + PRED + MTX	0.8 mg/kg/wk, SQ (ETN) + 0.5 mg/kg/d (PRED) + 0.5 mg/kg/wk, SQ (MTX)	9.9 (4.6)	4.9 (0.5) months		
Burgos-Vargas 2013	Enthesitis-related JIA (ILAR criteria), ≥3 joints (swelling or LOM and pain or tenderness) + ≥1 location enthesitis	12 wks (3 months)	Placebo	same as ADA	Overall: 12.9 (2.9)	Overall: 2.6 (2.3)	NR	**Conference abstract**; had an open-label extension phase up to 144 wks following randomization phase; pts had to be unresponsive to ≥1 NSAID and ≥1 DMARD
			ADA	24 mg/m^2 (max 40 mg eow)				

ABT = abatacept; ACR = American College of Rheumatology; ADA = adalimumab; ANK = anakinra; CAN = canakinumab; CRP = C-reactive protein; d = day; DMARDs = disease-modifying antirheumatic drugs; eow = every other week; ETN = etanercept; GCs = glucocorticoids; GLB = golimumab; HCQ = hydroxychloroquine; hr = hour; IA = intra-articular; IFX = infliximab; IL-1 = interleukin-1; ILAR = International League of Associations for Rheumatology; IQR = interquartile range; IV = intravenous; JIA = juvenile idiopathic arthritis; kg = kilogram; L = litre; LOM = limitation of motion; m^2 = meters squared; MAS = macrophage activation syndrome; max = maximum; mg = milligram; mL = millilitre; MTX = methotrexate; NR = not reported; NSAIDs = non-steroidal anti-inflammatory drugs; p.o. = oral; PRED = prednisone; pt = patient; q = every; RILO = rilonacept; SQ = subcutaneous; SSZ = sulfasalazine; TNF-α = tumour necrosis factor alpha; TOC = tocilizumab; tx = treatment; wk = week; wkly = weekly; w/ = with; yr = year

TABLE 4.4: RISK OF BIAS ASSESSMENT OF BIOLOGICS RCTS

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
POLYARTICULAR-COURSE JIA (WITHDRAWAL DESIGN)							
Ilowite 2009	Unclear	Unclear	Low	Low	High	High	Low
Lovell 2000	Low	Unclear	Low	Low	Low	Unclear	Low
Lovell 2008	Unclear	Unclear	Low	Low	Low	High	High
Mori 2011	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Ruperto 2008	Low	Low	Low	Low	High	Unclear	Low
POLYARTICULAR-COURSE JIA (PARALLEL DESIGN)							
Ruperto 2007	Unclear	Unclear	Low	Low	Low	High	Low
ACTIVE SYSTEMIC JIA (PARALLEL DESIGN)							
De Benedetti 2012	Unclear	Unclear	Low	Low	Low	Low	Low
Ilowite 2014	Low	Low	Low	Low	High	High	Low
Lovell 2013	Unclear	Low	Low	Unclear	Low	High	Low
Quartier 2011	Low	Unclear	Low	Low	High	Low	Low
Ruperto 2012	Low	Low	Low	Low	High	High	High
ACTIVE SYSTEMIC JIA (PARALLEL DESIGN)							
Yokota 2008	Unclear	Unclear	Unclear	Unclear	High	Low	Low
EARLY AGGRESSIVE THERAPY							
Tynjala 2011	Unclear	Low	High	High	Low	Low	Low
Wallace 2012	Low	Low	Low	Low	Low	Low	Low

TABLE 4.5: SUMMARY OF OUTCOMES BY ANALYSIS METHOD FOR BIOLOGICS WITHDRAWAL RCTS OF POLYARTICULAR-COURSE JIA

Network meta-analysis (no. studies contributing data)	Meta-analysis	Descriptive analysis
Disease response (ACR Pedi 30)		Pain relief
Number of active joints		Health-related quality of life
Number of joints with limitation of motion		Number of withdrawals due to AEs
Physician's global assessment of disease activity		Number of participants with a severe AE
Functional ability (CHAQ disability index)		
Patient/parent assessment of overall well-being		

ACR Pedi 30 = American College of Rheumatology Pediatric 30; CHAQ = Childhood Health Assessment Questionnaire; AE = adverse event

TABLE 4.6: SUMMARY OF NETWORK CHARACTERISTICS FOR BIOLOGICS RCTS OF POLYARTICULAR-COURSE JIA

Characteristic	ACR Pedi 30	No. active joints	No. joints with LOM	MD global	Functional ability (CHAQ DI)	Pt/parent well-being	ESR
No. of trials	4	3	3	3	3	3	3
No. of intervention nodes	7	4	4	4	4	4	4
No. of participants	318	131	131	131	131	131	131
No. of comparisons	3	2	2	2	2	2	2
No. of 2-arm trials	3	3	3	3	3	3	3
No. of multi-arm trials	1	0	0	0	0	0	0

Note: ACR Pedi 30 = American College of Rheumatology Pediatric 30; LOM = limitation of motion; MD global = physician's global assessment of disease activity; CHAQ DI = Childhood Health Assessment Questionnaire Disability Index; Pt/parent overall well-being = patient/parent assessment of overall wellbeing; ESR = erythrocyte sedimentation rate

TABLE 4.7: BIOLOGICS WITHDRAWAL RCTS FOR POLYARTICULAR-COURSE JIA (OUTCOME: DISEASE RESPONSE – ACR PEDI 30)*

	Placebo	ETN (0.2mg/kg)	ETN (0.4mg/kg)	Placebo + MTX	ABT	ADA	ADA + MTX
Placebo							
ETN (0.2mg/kg)	2.06 (0.9, 2.76)						
ETN (0.4mg/kg)	**1.91 (1.28, 2.59)**	0.93 (0.71, 1.87)					
Placebo + MTX	1.14 (0.48, 1.94)	0.57 (0.24, 1.37)	0.6 (0.26, 1.06)				
ABT	1.37 (0.73, 2.01)	0.68 (0.35, 1.56)	0.72 (0.37, 1.15)	1.2 (0.54, 2.92)			
ADA	1.55 (0.82, 2.28)	0.76 (0.42, 1.74)	0.81 (0.44, 1.27)	1.33 (0.81, 2.64)	1.12 (0.57, 2.27)		
ADA + MTX	1.66 (0.98, 2.37)	0.81 (0.5, 1.86)	0.87 (0.53, 1.32)	1.44 (0.93, 2.85)	1.21 (0.67, 2.39)	1.07 (0.73, 1.72)	

*Results are the median relative risk (95% credible interval); MTX = methotrexate; ETN = etanercept; ABT = abatacept (10 mg/kg every 28 days, intravenous); ADA = adalimumab (24 mg/m^2 every other week)

TABLE 4:8: BIOLOGICS WITHDRAWAL RCTS FOR POLYARTICULAR-COURSE JIA (OUTCOME: NO. OF ACTIVE JOINTS)*

	Placebo	ETN (0.2mg/kg)	ETN (0.4mg/kg)	ABT
Placebo				
ETN (0.2mg/kg)	**-11.23 (-18.16, -4.59)**			
ETN (0.4mg/kg)	**-11.01 (-14.59, -7.52)**	0.23 (-5.52, 6.24)		
ABT	**-3.10 (-5.88, -0.35)**	**8.17 (0.95, 15.48)**	**7.92 (3.51, 12.36)**	

*Results are the median mean difference (95% credible interval); negative values indicate improvement; ETN = etanercept; ABT = abatacept (10 mg/kg every 28 days, intravenous)

TABLE 4.9: BIOLOGICS WITHDRAWAL RCTS FOR POLYARTICULAR-COURSE JIA (OUTCOME: NO. OF JOINTS WITH LIMITED RANGE OF MOTION)*

	Placebo	**ETN (0.2mg/kg)**	**ETN (0.4mg/kg)**	**ABT**
Placebo				
ETN (0.2mg/kg)	-5.32 (-14.6, 3.8)			
ETN (0.4mg/kg)	**-5.15** **(-9.5, -0.8)**	0.38 (-7.9, 8.2)		
ABT	-1.15 (-4.7, 2.4)	4.22 (-5.7, 14)	3.91 (-1.6, 9.6)	

*Results are the median mean difference (95% credible interval); negative values indicate an improvement; ETN = etanercept; ABT = abatacept (10 mg/kg every 28 days, intravenous)

TABLE 4.10: BIOLOGICS WITHDRAWAL RCTS FOR POLYARTICULAR-COURSE JIA (OUTCOME: PHYSICIAN'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY, 100 MM VAS)*

	Placebo	**ETN (0.2mg/kg)**	**ETN (0.4mg/kg)**	**ABT**
Placebo				
ETN (0.2mg/kg)	-3.86 (-19.84, 12.34)			
ETN (0.4mg/kg)	-4.1 (-11.56, 3.23)	-0.07 (-14.59, 14.27)		
ABT	**-11.94 (-17.1, -6.79)**	-8.01 (-24.83, 8.85)	-7.78 (-16.78, 1.31)	

*Results are the median mean difference (95% credible interval); negative values indicate less disease activity; ETN = etanercept; ABT = abatacept (10 mg/kg every 28 days, intravenous)

TABLE 4.11: BIOLOGICS WITHDRAWAL RCTS FOR POLYARTICULAR-COURSE JIA (OUTCOME: FUNCTIONAL ABILITY – CHAQ DISABILITY INDEX, 0-3)*

	Placebo	**ETN (0.2mg/kg)**	**ETN (0.4mg/kg)**	**ABT**
Placebo				
ETN (0.2mg/kg)	-1.18 (-4.72, 2.4)			
ETN (0.4mg/kg)	-0.69 (-3.17, 1.8)	0.48 (-2.05, 3)		
ABT	-0.11 (-2.63, 2.35)	1.07 (-3.3, 5.38)	0.59 (-2.94, 4.07)	

*Results are the median mean difference (95% credible interval); negative values indicate better functional ability; ETN = etanercept; ABT = abatacept (10 mg/kg every 28 days, intravenous)

TABLE 4.12: BIOLOGICS WITHDRAWAL RCTS FOR POLYARTICULAR-COURSE JIA (OUTCOME: PATIENT/PARENT ASSESSMENT OF OVERALL WELL-BEING, 100 MM VAS)*

	Placebo	**ETN (0.2mg/kg)**	**ETN (0.4mg/kg)**	**ABT**
Placebo				
ETN (0.2mg/kg)	-4.74 (-22.2, 11.99)			
ETN (0.4mg/kg)	-2.08 (-9.9, 5.63)	2.78 (-12.1, 18.07)		
ABT	**-6.04 (-11.32, -0.83)**	-1.32 (-18.91, 16.92)	-3.93 (-13.27, 5.38)	

*Results are the median mean difference (95% credible interval); negative values indicate an improvement; ETN = etanercept; ABT = abatacept (10 mg/kg every 28 days, intravenous)

TABLE 4.13: BIOLOGICS WITHDRAWAL RCTS FOR POLYARTICULAR-COURSE JIA (OUTCOME: LABORATORY MEASURE OF INFLAMMATION – ESR, MM/H)*

	Placebo	**ETN (0.2mg/kg)**	**ETN (0.4mg/kg)**	**ABT**
Placebo				
ETN (0.2mg/kg)	-1.18 (-10.13, 7.7)			
ETN (0.4mg/kg)	-1.18 (-7.52, 5.04)	0.02 (-6.34, 6.41)		
ABT	-0.28 (-6.46, 6.08)	0.9 (-9.86, 11.73)	0.91 (-7.99, 9.83)	

*Results are the median mean difference (95% credible interval); negative values indicate an improvement; ETN = etanercept; ABT = abatacept (10 mg/kg every 28 days, intravenous)

TABLE 4.14: SUMMARY OF OUTCOMES BY ANALYSIS METHOD FOR BIOLOGICS PARALLEL RCTS OF ACTIVE SYSTEMIC JIA

Network meta-analysis	Meta-analysis	Descriptive analysis
Disease response (ACR Pedi 30)		**Number of active joints**
		Number of joints with limitation of motion
		Physician's global assessment of disease activity
		Functional ability (CHAQ disability index)
		Patient/parent assessment of overall well-being
		Pain relief
		Health-related quality of life
		Number of withdrawals due to AEs
		Number of participants with a severe AE

Note: ACR Pedi 30 = American College of Rheumatology Pediatric 30; CHAQ = Childhood Health Assessment Questionnaire; AE = adverse event

TABLE 4.15: SUMMARY OF NETWORK CHARACTERISTICS FOR PARALLEL BIOLOGICS RCTS OF ACTIVE SYSTEMIC JIA

Characteristic	ACR Pedi 30
No. of trials	5
No. of intervention nodes	5
No. of participants	311
No. of comparisons	5
No. of 2-arm trials	5
No. of multi-arm trials	0

Note: ACR Pedi 30 = American College of Rheumatology Pediatric 30

TABLE 4.16: BIOLOGICS PARALLEL RCTS FOR SYSTEMIC JIA (OUTCOME: DISEASE RESPONSE – ACR PEDI 30)*

	Placebo	TOC	RILO	ANK	CAN
Placebo					
TOC	**3.22 (2.22, 4.73)**				
RILO	**2.08 (1.05, 3.53)**	0.65 (0.35, 1)			
ANK	2.87 (0.95, 4.76)	0.91 (0.31, 1.32)	1.39 (0.44, 2.75)		
CAN	**3.52 (2.49, 5.24)**	1.08 (0.91, 1.44)	**1.68 (1.16, 3.1)**	1.2 (0.9, 3.54)	

*Results are the median relative risk (95% credible interval); canakinumab results are from an intermediate time point (15 days); the ACR Pedi 30 was modified in the studies to include an absence of disease-related fever; TOC = tocilizumab (12 mg/kg every 2 weeks, intravenous); RILO = rilonacept (maintenance dose of 2.2 mg/kg once weekly and either a loading dose of 4.4 mg/kg or 2.2 mg/kg with a second dose two days later); ANK = anakinra (2 mg/kg/day, subcutaneous)

TABLE 4.17: CHARACTERISTICS OF INCLUDED DMARD RCTS

Author, year	Population	Duration	Groups	Dose, frequency, route	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
Brewer 1986	All subtypes (ARA or EULAR criteria)	12 month (52 wks)	Placebo PEN HCQ	 10 mg/kg/d 6 mg/kg/d	Overall: 9.7	Overall 3.2	Stable NSAID; antibiotics for infection, APAP (for brief periods) for fever; codeine-containing compounds (for brief period for severe pain)	no SAEs b/w 1st and 2nd pt visits, dose incr. at 2 month: 10 mg/kg (PEN) or 6 mg/kg (HCQ)
Giannini 1988	Oligo, poly, systemic JIA (ACR criteria)	12 month (52 wks)	Placebo PEN HCQ	 10 mg/kg/d 6 mg/kg/d	Overall: 9.7	Overall: 3.2	No steroids, cytotoxic agents, or other SAARDs	
Giannini 1990	Oligo, poly, systemic JIA (ACR criteria)	6 months (24 wks)	Placebo Auranofin	NR 0.15 mg/kg/d (oral)	9.9 9.3	3.2 3.1	Stable NSAIDs (2 max) 1 month before randomization; prednisone; stable steroids by 1 month before randomization; medication for infection, APAP for fever; codeine-containing compounds (brief period for pain)	Initial dose of auranofin could incr. to 0.2 mg/kg/d; max of 9 tablets/d

Author, year	Population	Duration	Groups	Dose, frequency, route	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
Giannini 1992	Oligo, poly, systemic JIA (ACR criteria)	6 months (24 wks)	Placebo Low-dose MTX Very low-dose MTX	 10 mg/m^2/wk, tablets 5 mg/m^2/wk, tablets	10.6 (range 3.2-17.8) 10.1 (range 2.5-17.5) 9.6 (range 3.3-17.4)	5.8 (range 0.5-14.4) 4.8 (range 0.6-13.5) 4.8 (range 0.5-11.8)	Stable NSAIDs (2 max) and prednisone for 1 month before randomization; antibiotics for infection and APAP (brief period) for fever	Had to have ≥ 3 active joints controlled by NSAIDs or second-line agents; had to be MTX-naive
Hoza 1991	Oligo, poly JIA (EULAR criteria)	6 months (24 wks)	Delagil SSZ	3-4 mg/kg/d 20-30 mg/kg/d	NR	Overall: 33 months	NR	All patients were hospitalized at start of study and stayed there for 3 wks, but intervention was ambulatory
Kvien 1985	Oligo, poly JIA (ACR criteria)	50 wk	PEN	2.5 mg/kg/d (wks 0-4), 5 mg/kg/d (wks 5-8), 7.5 mg/kg/d (wks 9-12), 10 mg/kg/d (>12 wks)	median 128.5 (range 43-191) months	median 47 (4-142) months	Stable NSAIDs stable from 1 week before study; APAP	Pts. with active disease, poor response to NSAIDs; all patients hospitalized for first 1-2 wks then monitored at home
			GSTM	0.7 mg/kg once wkly (wks 0-20), 0.7 mg/kg once monthly (>20 wks)	median 126 (range 65-192) months	median 29 (range 4-176) months		

Author, year	Population	Duration	Groups	Dose, frequency, route	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
Laaksonen 1974	Oligo, poly JIA	6 wks	CQ	4 mg/kg/d	1-3 yrs: n = 16); 4-7 yrs: n = 17; 8-12 yrs: n = 6; 11-15 yrs: n = 17	CCs: 4.3 (3.1) No CCs: 7.2 (4.2)	NR	≥2 joints had to have swelling or LOM and continuous duration of joint symptoms for ≥ 3 months
			HCQ	5-7 mg/kg/d	1-3 yrs: n = 18; 4-7 yrs: n = 14; 8-12 yrs: n = 14; 11-15 yrs: n = 17	CCs: 7.8 (8.5) No CCs: 7.0 (4.1)		
Pan 2011	Any JIA subtype	6 months or 12 months	Pts discontinue MTX + NSAIDs 6 months after remission Pts discontinue MTX + NSAIDs 12 months after remission	MTX: max 15 mg/m^2	Overall: median = 11	NR	Could only use one NSAID and MTX at inclusion; no steroids <1 month before inclusion; no IA corticosteroids, biologics or other DMARDs up ≤3 months before inclusion	**Conference abstract**; pts had to be in clinical remission for 3 months while on medication; poly JIA not equally distributed b/w groups

Author, year	Population	Duration	Groups	Dose, frequency, route	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
Ruperto 2004	Poly JIA (RF negative) (ILAR criteria)	6 months (24 wks)	Standard-dose MTX	15 mg/m^2/wk (parenteral)	8.8 (4.8)	3.2 (3.7)	Folic acid, folinic acid and prednisone	Nonresponders from 6 months screening phase entered randomization phase; could not recruit calculated no. patients due to higher-than-expected response rate to standard-dose MTX and a high rate of noneligible pts among nonresponders
			High MTX	30 mg/m^2/wk (parenteral)	8.3 (4.3)	2.6 (2.1)		
Silverman 2005	Oligo, poly, systemic JIA (ACR criteria)	16 wks	MTX	0.5 mg/kg/wk (max 25 mg/wk)	10.2 (3.8, range 3-17)	mean (SD), median [range] 1.37 (1.97), 0.33 [0-9.00]	Stable NSAIDs, prednisone from 2 wks before enrollment; other DMARDs had to be discontinued w/in 14 d study entry	Excluded if had ACR functional class IV disease, active systemic symptoms w/in 4 wks before entry, persistent/severe infection w/in 3 months before entry, or current inflammatory disease other than JIA or history of such disease; average no. active joints = 14.0 (9.9) for MTX and 14.4 (7.9) for LEF
			LEF	**<20 kg:** 100 mg 1st d then 10 mg eod **20-40 kg**: 100 mg for 2 d then 10 mg/d **>40 kg**: 100 mg for 3 d then 20 mg/d	10.1 (4.0, range 3-17)	mean (SD), median [range] 1.69 (3.21), 0.33 [0-15.33]		

Author, year	Population	Duration	Groups	Dose, frequency, route	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
van Rossum 1998	Oligo, poly JIA (EULAR criteria)	6 months (24 wks)	Placebo	NR	9.7 (3.6) (range 2.5-15.1)	median 16.7 (IQR: 7-37; range 5.5-142.1) months	Stable NSAIDs	Pts had insufficient response to NSAIDs at optimal dosage for 3 months and IA joint injections; ≥ 1 active joint (presence of swelling or LOM w/ pain on mov't or tenderness)
			SSZ	50 mg/kg/d in 2 doses (2000 mg/d max)	8.4 (4.4) (range 2.5-17.6)	median 26.8 (IQR: 14-56; range 4.7-176.1) months		
Woo 2000	Extended oligo, systemic JIA (ILAR criteria)	4 months (16 wks) – 2-month washout – 4 months – 2-month washout	Placebo Low-dose MTX	15 mg/m^2 once wkly 15 mg/m^2 once wkly	Extended oligo JIA: 7.4 (3.0) (range 5.0-11.7) systemic JIA: 8.5 (3.3) (range 3.7-14.1)	Extended oligo JIA: 53.8 (range 4-132) months systemic JIA: 33.7 (range 4-116) months	Oral prednisone plus NSAIDs; DMARDs stopped at least 3 months before entry (Note: 1 pt took CQ until 1 month before entry)	**Cross-over design**; systemic JIA pts with active arthritis ≥ 3 months prior – many had systemic features; those with extended oligo JIA had had active polyarthritis not responding to NSAID or local steroid tx for ≥ 1 yr

ACR = American College of Rheumatology; APAP = acetaminophen; ARA = American Rheumatism Association; b/w = between; CCs = complications; CQ = chloroquine; d = day; DMARDs = disease-modifying anti-rheumatic drugs; eod = every other day; EULAR = European League Against Rheumatism; GSTM = gold sodium thiomalate; HCQ = hydroxychloroquine; IA = intra-articular; incr. = increase; IV = intravenous; IQR = interquartile range; JIA = juvenile idiopathic arthritis; kg = kilogram; LEF = leflunomide; LOM = limitation of motion; m^2 = meters squared; max = maximum; mg = milligram; mov't = movement; MTX = methotrexate; no. = number; NR = not reported; NSAID = non-steroidal anti-inflammatory drug; oligo = oligoarticular JIA; PEN = penicillamine; poly = polyarticular JIA; pt = patient; RF = rheumatoid factor; SAARDs = slow-acting anti-rheumatic drugs; SAE = serious adverse event; SD = standard deviation; SSZ = sulfasalazine; tx = treatment; wk = week; w/ = with; w/in = within; yr = year

TABLE 4.18: RISK OF BIAS ASSESSMENT OF DMARD RCTS

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Brewer 1986	Low	Unclear	Low	Low	High	Unclear	Low
Giannini 1988	Unclear	Unclear	Low	Unclear	Low	Unclear	Low
Giannini 1990	Low	High	Low	Unclear	Low	Unclear	Low
Giannini 1992	Unclear	Unclear	Low	Unclear	High	Unclear	Low
Hoza 1991	Unclear	Unclear	Unclear	High	Low	Unclear	Low
Kvien 1985	Unclear	Unclear	High	High	High	Unclear	Low
Laaksonen 1974	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Ruperto 2004	Low	Low	High	High	High	Unclear	High
Silverman 2005	Unclear	Low	Low	Unclear	Low	Unclear	Low
van Rossum 1998	Low	Low	Unclear	Unclear	High	Unclear	Low
Woo 2000	Unclear	Unclear	Low	Low	Low	Unclear	Low

TABLE 4.19: SUMMARY OF OUTCOMES BY ANALYSIS METHOD FOR DMARD RCTS

Network meta-analysis	Meta-analysis	Descriptive analysis
Pain relief		Disease response (ACR Pedi 30)
Number of active joints		Physician's global assessment of disease activity
Number of joints with limitation of motion		Functional ability (CHAQ disability index)
Laboratory measure of inflammation (ESR)		Patient/parent assessment of overall well-being
		Health-related quality of life
		Number of withdrawals due to AEs
		Number of participants with a severe AE

Note: ACR Pedi 30 = American College of Rheumatology Pediatric 30; CHAQ = Childhood Health Assessment Questionnaire; AE = adverse event

TABLE 4.20: SUMMARY OF NETWORK CHARACTERISTICS FOR DMARD RCTS

Characteristic	No. active joints	No. joints with LOM	ESR	Pain relief
No. of trials	7	6	4	4
No. of intervention nodes	10	9	6	7
No. of participants	741	694	357	454
No. of comparisons	4	4	2	3
No. of 2-arm trials	5	4	3	2
No. of multi-arm trials	2	2	1	2

Note: ACR Pedi 30 = American College of Rheumatology Pediatric 30; LOM = limited range of motion

TABLE 4.21: DMARD RCTS (OUTCOME: NO. OF ACTIVE JOINTS)*

	Placebo	PEN 5-10 mg/kg/d	MTX 10-20 mg/m^2	AUR	MTX 5 mg/m^2	GSTM	MTX 30-40 mg/m^2	LEF	SSZ	HCQ
Placebo										
PEN 5-10 mg/kg/d	1.67 (-2.24, 5.61)									
MTX 10-20 mg/m^2	-2.38 (-8.56, 3.94)	-4.04 (-11.31, 3.32)								
AUR	-1.3 (-4.29, 1.7)	-2.95 (-7.91, 1.94)	1.06 (-5.87, 7.93)							
MTX 5 mg/m^2	-0.04 (-5.41, 5.35)	-1.71 (-8.35, 4.95)	2.34 (-4.5, 9.07)	1.27 (-4.87, 7.38)						
GSTM	-1.82 (-8.53, 4.91)	-3.48 (-8.94, 1.94)	0.56 (-8.65, 9.67)	-0.54 (-7.85, 6.84)	-1.77 (-10.48, 6.81)					
MTX 30-40 mg/m^2	-2.1 (-9.23, 5.17)	-3.76 (-11.88, 4.45)	0.28 (-3.3, 3.85)	-0.78 (-8.51, 7.01)	-2.05 (-9.71, 5.64)	-0.27 (-10.1, 9.58)				
LEF	-1.58 (-8.74, 5.78)	-3.25 (-11.35, 5.04)	0.79 (-2.83, 4.43)	-0.28 (-8, 7.59)	-1.55 (-9.12, 6.22)	0.25 (-9.55, 10.16)	0.51 (-4.55, 5.63)			
SSZ	-4.77 (-8.79, -0.73)	**-6.43 (-12.1, -0.81)**	-2.38 (-9.91, 5.04)	-3.47 (-8.46, 1.53)	-4.71 (-11.5, 1.96)	-2.96 (-10.81, 4.86)	-2.68 (-10.95, 5.55)	-3.18 (-11.56, 5.04)		
HCQ	-1.33 (-5.71, 3.11)	-2.99 (-7.03, 1.02)	1.03 (-6.64, 8.63)	-0.03 (-5.31, 5.29)	-1.29 (-8.22, 5.66)	0.5 (-6.27, 7.27)	0.77 (-7.68, 9.14)	0.25 (-8.27, 8.64)	3.43 (-2.54, 9.46)	

*Results are the median mean difference (95% credible interval); negative values indicate improvement; PEN = penicillamine; MTX = methotrexate; AUR = auranofin (0.15 mg/kg/day, oral); GSTM = gold sodium thiomalate (0.7 mg/kg once weekly and then once monthly after 20 weeks); LEF = leflunomide (varies by body mass, details in Table 4.17); SSZ = sulfasalazine (50 mg/kg/day); HCQ = hydroxychloroquine (6 mg/kg/day)

TABLE 4.22: DMARD RCTS (OUTCOME: NO. OF JOINTS WITH LIMITED RANGE OF MOTION)*

	Placebo	PEN 5-10 mg/kg/d	MTX 10-20 mg/m^2	AUR	MTX 5 mg/m^2	MTX 30-40 mg/m^2	LEF	SSZ	HCQ
Placebo									
PEN 5-10 mg/kg/d	2 (-4.78, 8.72)								
MTX 10-20 mg/m^2	-4.68 (-11.95, 2.63)	-6.68 (-16.54, 3.3)							
AUR	-0.45 (-6.86, 5.99)	-2.44 (-11.75, 6.9)	4.24 (-5.51, 13.92)						
MTX 5 mg/m^2	0.19 (-7.03, 7.47)	-1.8 (-11.65, 8.13)	4.88 (-2.66, 12.42)	0.63 (-9.04, 10.35)					
MTX 30-40 mg/m^2	-7.79 (-17.76, 2.26)	-9.77 (-21.8, 2.35)	-3.1 (-9.96, 3.77)	-7.34 (-19.15, 4.61)	-7.97 (-18.11, 2.2)				
LEF	-4.59 (-14.36, 5.24)	-6.58 (-18.44, 5.35)	0.1 (-6.49, 6.67)	-4.14 (-15.83, 7.58)	-4.78 (-14.73, 5.2)	3.18 (-6.3, 12.68)			
SSZ	-0.51 (-7.23, 6.19)	-2.51 (-12, 7.03)	4.16 (-5.75, 14.06)	-0.07 (-9.38, 9.24)	-0.71 (-10.61, 9.13)	7.27 (-4.81, 19.26)	4.07 (-7.8, 15.93)		
HCQ	1.5 (-5.5, 8.44)	-0.51 (-7.27, 6.25)	6.17 (-3.96, 16.21)	1.94 (-7.56, 11.39)	1.29 (-8.81, 11.34)	9.27 (-2.97, 21.42)	6.07 (-5.99, 18.06)	2 (-7.68, 11.67)	

*Results are the median mean difference (95% credible interval); negative values indicate improvement; PEN = penicillamine; MTX = methotrexate; AUR = auranofin (0.15 mg/kg/day, oral); GSTM = gold sodium thiomalate (0.7 mg/kg once weekly and then once monthly after 20 weeks); LEF = leflunomide (varies by body mass, details in Table 4.17); SSZ = sulfasalazine (50 mg/kg/day); HCQ = hydroxychloroquine (6 mg/kg/day)

TABLE 4.23: DMARD RCTS (OUTCOME: LABORATORY MEASURE OF INFLAMMATION – ESR, MM/H)*

	Placebo	**MTX (10-20mg/ m^2)**	**MTX (5mg/ m^2)**	**MTX (30-40 mg/ m^2)**	**LEF**	**SSZ**
Placebo						
MTX (10-20mg/m^2)	-13.32 (-32.22, 5.05)					
MTX (5mg/ m^2)	-0.32 (-18.51, 18.35)	13.05 (-5.24, 31.64)				
MTX (30-40 mg/m^2)	1.99 (-19.04, 23)	**15.44 (6.02, 24.87)**	2.55 (-18.99, 22.73)			
LEF	-12.62 (-32.75, 7.11)	0.72 (-6.4, 7.82)	-12.32 (-32.19, 7.19)	-14.8 (-26.32, -2.88)		
SSZ	-0.7 (-7.01, 5.57)	12.62 (-6.9, 32.53)	-0.42 (-20.07, 18.66)	-2.69 (-24.56, 18.98)	11.85 (-8.63, 32.86)	

*Results are the median mean difference (95% credible interval); negative values indicate improvement; MTX = methotrexate; LEF = leflunomide (varies by body mass, details in Table 4.17); SSZ = sulfasalazine (50 mg/kg/day)

TABLE 4.24: DMARD RCTS (OUTCOME: PAIN RELIEF)*

	Placebo	PEN (5-10 mg/kg)	MTX (10-20mg/ m^2)	AUR	MTX (5mg/ m^2)	MTX (30-40 mg/ m^2)	HCQ
Placebo							
PEN (5-10 mg/kg)	-0.27 (-6.53, 5.95)						
MTX (10-20mg/m^2)	-0.29 (-6.58, 5.98)	-0.03 (-8.9, 8.83)					
AUR	-0.35 (-6.61, 5.88)	-0.09 (-8.9, 8.74)	-0.07 (-8.92, 8.81)				
MTX (5mg/ m^2)	0.29 (-6.06, 6.55)	0.56 (-8.29, 9.43)	0.58 (-5.67, 6.85)	0.65 (-8.24, 9.49)			
MTX (30-40 mg/m^2)	-0.61 (-9.53, 8.22)	-0.34 (-11.2, 10.57)	-0.3 (-6.62, 5.93)	-0.25 (-11.13, 10.66)	-0.89 (-9.73, 7.97)		
HCQ	-0.46 (-6.7, 5.8)	-0.19 (-6.43, 6.04)	-0.16 (-8.99, 8.69)	-0.1 (-8.95, 8.73)	-0.74 (-9.59, 8.11)	0.14 (-10.7, 11.04)	

*Results are the median standardized mean difference (95% credible interval); negative values indicate pain relief; PEN = penicillamine; MTX = methotrexate; AUR = auranofin (0.15 mg/kg/day, oral); HCQ = hydroxychloroquine (6 mg/kg/day)

TABLE 4.25: CHARACTERISTICS OF INCLUDED NSAID RCTS

Author, year	Population	Duration	Groups	Dose, frequency, route	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
Bhettay 1978	Any JIA subtype (EULAR criteria)	2 wks – 1 wk washout – 2 wks	Ketoprofen	<20 kg: 25 mg 2x/d, p.o. ≥20 kg: 50 mg 2x/d, p.o.	Ketoprofen to indomethacin: range = 3-14	NR	No corticosteroids in the past 12 months; paracetamol could be taken during the washout	**Cross-over design**; excluded pts with contra-indications to trial drugs
			Indo-methacin	<20 kg: 25 mg 2x/d, p.o. ≥20 kg: 50 mg 2x/d, p.o.	Indomethacin to ketoprofen: range = 2-16			
Bhettay 1986	Any JIA subtype (EULAR criteria)	3 wks – 1 wk washout – 3 wks	Aspirin Sunlindac	3600 mg/d 150 mg/d	**Overall**: median 11.5 (range 2-21)	NR	Stable SAARDs, gold, penicillamine	**Cross-over design**; smaller doses for <20 kg and 21-40 kg; withdrew all anti-inflammatory medication and commenced intervention 1 wk later if had a disease flare – same procedure during washout period

Author, year	Population	Duration	Groups	Dose, frequency, route	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
Foeldvari 2009	Oligo, poly JIA (ACR criteria)	12 wks	Naproxen Low-dose CEL High-dose CEL	7.5 mg/kg bid; 3 mg/kg bid; 6 mg/kg bid	10.39 (3.92) 10.44 (4.09) 10.16 (4.24)	3.41 (3.23) 2.71 (2.80) 3.77 (3.42)	Oral corticosteroid, prednisone (stable 4 wks prior), and MTX; DMARDs, biologics, or IV immunoglobulins or immune-suppresives stable for 12 wks; injectable gold salts stable for 16 wks	Post hoc exploratory evaluations for ACR Pedi 50, 70 criteria
Giannini 1990	Oligo, poly, systemic JIA (ACR criteria)	12 wks	Aspirin Ibuprofen	60 mg/kg/d 30 mg/kg/d	Overall: 7.7 (range 1.8-15.1)	NR	APAP, codeine, and antibiotics (for a short period)	After 2 wks, if satisfactory clinical control of disease had not occurred, increase to 40 mg/kg/day (ibuprofen) or 80 mg/kg/day (aspirin)

Author, year	Population	Duration	Groups	Dose, frequency, route	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
Kvien 1984	Oligo, poly (ACR criteria)	24 wks (6 months)	Aspirin Naproxen	75 mg/kg twice daily, 500 mg tablets 10 mg/kg twice daily, 100 mg tablets	median = 108 (range 38-158) months median = 137 (range 40-188) months	median = 16 (range 3-74) months median = 12 (range 3-133) months	Stable physio; codeine or APAP were permitted (except the 7 days before study start); no other NSAIDs w/in 7 days of start; no SAARDs, corticosteroids or immuno-regulatory drugs w/in 6 mo, IA injections or surgery w/in 2 months	Pts had to have mild to moderate disease activity in ≥1 joint; those w/ adverse reactions to aspirin or naproxen were excluded
Leak 1988	Sero-negative JIA (EULAR criteria)	12 wks (4 wks per arm)	Naproxen Diclofenac Tolmetin sodium	10 mg/kg/d, p.o. (in 2 divided doses) 2 mg/kg/d (in 2 divided doses) 25 mg/kg/d (in 3 divided doses)	Overall: 9.5 (range 5.5-16)	Overall: 4.75 (range 0.5-11)	NSAIDs had to be stopped at least 24 hrs before study start; any other medication was permitted if it was stable for ≥3 months before the study start; paracetamol was used as a rescue medication	**Cross-over design**; no washouts between interventions – 24 hr washout of NSAIDs taken before the trial

Author, year	Population	Duration	Groups	Dose, frequency, route	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
Levinson 1977	Any subtype (ARA criteria)	12 wks	Aspirin	50 mg/kg (max 100 mg/kg/d)	9.0 (2-16)	3.4 (0.1-10.5)	Propoxyphene for pain control; no other anti-inflammatory drugs allowed	Aspirin: incr. dose by 16.7 mg/kg/wk Tolmetin sodium: incr. dose by 5 mg/kg/wk; stop increase when efficacy achieved, AEs occurred, or reached max dose
			Tolmetin sodium	15 mg/kg (max 30 mg/kg/d)	9.4 (2-16)	3.7 (0.3-12.0)		
Reiff 2006	Oligo, poly JIA	12 wks	Naproxen	15 mg/kg/d	10.7 (4.0)	3.7 (3.3)	Stable DMARDs (6 wks) or biologics (3 wks) prior; 1 IA corticosteroid injection; oral corticosteroids if held stable starting 4 wks before randomization	Max dose rofexocib = 25 mg/d for low-dose and high-dose groups
			Low-dose rofecoxib	0.3 mg/kg/d (max 25 mg/d)	9.7 (4.3)	4.0 (3.6)		
			High-dose rofecoxib	0.6 mg/kg/d (max 25 mg/d)	9.4 (4.3)	3.4 (3.0)		
Ruperto 2005	Oligo, poly JIA	12 wks (short-term); 52 wks (long-term)	Naproxen	10 mg/kg/d	7.5 (3.7)	27.7 (24.9) months	Other NSAIDs or prednisolone (or equivalent) at stable dose	
			Low-dose MEL	0.125 mg/kg/d	8.9 (3.8)	41.6 (40.6) mo		
			High-dose MEL	0.25 mg/kg/d	9.0 (3.9)	30.0 (33.4) months		

ACR = American College of Rheumatology; ACR Pedi = American College of Rheumatology Pediatric; APAP = acetaminophen; ARA = American Rheumatism Association; bid = twice a day; CEL = celecoxib; d = day; DMARDs = disease-modifying anti-rheumatic drugs; EULAR = European League Against Rheumatism; IA = intra-articular; IV = intravenous; JIA = juvenile idiopathic arthritis; kg = kilogram; max = maximum; MEL = meloxicam; mg = milligram; MTX = methotrexate; NR = not reported; NSAIDs = non-steroidal anti-inflammatory drugs; oligo = oligoarticular JIA; p.o. = oral; poly = polyarticular JIA; pt = patient; SAARDs = slow-acting anti-rheumatic drugs; wk = week; w/ = with; w/in = within; yr = year

TABLE 4.26: RISK OF BIAS ASSESSMENT OF NSAID RCTS

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Bhettay 1978	Unclear	Unclear	High	High – self Low - other	Low	Unclear	High
Bhettay 1986	Unclear	Unclear	Low	Low	High	Unclear	High
Foeldvari 2009	Low	Unclear	Unclear	Unclear	Low	High	Low
Giannini 1990	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear
Kvien 1984	Unclear	Unclear	Low	Unclear	High	Unclear	Low
Leak 1988	Unclear	Unclear	Unclear	High	Low	Unclear	High
Levinson 1997	Unclear	Unclear	Low	Low	High	Unclear	Low
Reiff 2006	Low	Unclear	Low	Unclear	Low	Unclear	Low
Ruperto 2005	Low	Unclear	Low	Unclear	High	High	Low

TABLE 4.27: SUMMARY OF OUTCOMES BY ANALYSIS METHOD FOR NSAID RCTS

Network meta-analysis	Meta-analysis	Descriptive analysis
Disease response (ACR Pedi 30)		Pain relief
Number of active joints		Health-related quality of life
Number of joints with limitation of motion		Number of withdrawals due to AEs
Physician's global assessment of disease activity		Number of participants with a severe AE
Functional ability (CHAQ disability index)		
Patient/parent assessment of overall well-being		
Laboratory measure of inflammation (ESR)		

Note: ACR Pedi 30 = American College of Rheumatology Pediatric 30; CHAQ = Childhood Health Assessment Questionnaire; AE = adverse event

TABLE 4.28: SUMMARY OF NETWORK CHARACTERISTICS FOR NSAID RCTS

Characteristic	ACR Pedi 30	No. active joints	No. joints with LOM	MD global	Functional ability (CHAQ DI)	Pt/parent well-being	ESR
No. of trials	3	3	3	3	3	3	4
No. of intervention nodes	7	7	7	7	7	7	8
No. of participants	770	770	770	770	770	770	850
No. of comparisons	3	3	3	3	3	3	4
No. of 2-arm trials	0	0	0	0	0	0	1
No. of multi-arm trials	3	3	3	3	3	3	3

Note: ACR Pedi 30 = American College of Rheumatology Pediatric 30; LOM = limitation of motion; MD global = physician's global assessment of disease activity; CHAQ DI = Childhood Health Assessment Questionnaire Disability Index; Pt/parent overall well-being = patient/parent assessment of overall wellbeing; ESR = erythrocyte sedimentation rate

TABLE 4.29: NSAID RCTS (OUTCOME: DISEASE RESPONSE – ACR PEDI 30)*

	NAP	CEL 3mg	CEL 6mg	ROF 0.3mg	ROF 0.6mg	MEL 0.125mg	MEL 0.25mg
NAP							
CEL 3mg	1.02 (0.61, 1.37)						
CEL 6mg	1.23 (0.84, 1.5)	1.19 (0.87, 1.81)					
ROF 0.3mg	0.86 (0.47, 1.24)	0.84 (0.44, 1.56)	0.7 (0.38, 1.16)				
ROF 0.6mg	0.99 (0.59, 1.33)	0.97 (0.55, 1.73)	0.81 (0.48, 1.27)	1.15 (0.75, 1.84)			
MEL 0.125mg	0.98 (0.57, 1.34)	0.96 (0.53, 1.73)	0.8 (0.46, 1.28)	1.14 (0.6, 2.2)	0.99 (0.54, 1.78)		
MEL 0.25mg	0.9 (0.5, 1.28)	0.88 (0.46, 1.63)	0.74 (0.4, 1.21)	1.05 (0.53, 2.06)	0.91 (0.48, 1.67)	0.92 (0.57, 1.44)	

*Results are the median relative risk (95% credible interval); Ruperto 2005 data is from three months; NAP = naproxen (10-15 mg/kg/day); CEL = celecoxib (3 or 6 mg/kg twice daily); ROF = rofecoxib (0.3 or 0.6 mg/kg/day); meloxicam (0.125 or 0.25 mg/kg/day)

TABLE 4.30: NSAID RCTS (OUTCOME: NO. OF ACTIVE JOINTS)*

	NAP	CEL 3mg	CEL 6mg	ROF 0.3mg	ROF 0.6mg	MEL 0.125mg	MEL 0.25mg
NAP							
CEL 3mg	0.98 (-1.81, 3.76)						
CEL 6mg	-0.63 (-3.4, 2.15)	-1.6 (-4.4, 1.17)					
ROF 0.3mg	0.38 (-2.25, 3.02)	-0.6 (-4.42, 3.26)	1.0 (-2.82, 4.83)				
ROF 0.6mg	0.35 (-2.28, 3.01)	-0.63 (-4.47, 3.24)	0.98 (-2.83, 4.83)	-0.03 (-2.65, 2.61)			
MEL 0.125mg	0.11 (-2.84, 3.02)	-0.87 (-4.94, 3.16)	0.74 (-3.34, 4.74)	-0.27 (-4.21, 3.65)	-0.24 (-4.22, 3.65)		
MEL 0.25mg	0.01 (-2.91, 2.89)	-0.97 (-5.02, 3.05)	0.63 (-3.4, 4.63)	-0.37 (-4.32, 3.52)	-0.35 (-4.3, 3.54)	-0.1 (-3.05, 2.82)	

*Results are the median mean difference (95% credible interval); Ruperto 2005 data is from three months; negative values indicate improvement; NAP = naproxen (10-15 mg/kg/day); CEL = celecoxib (3 or 6 mg/kg twice daily); ROF = rofecoxib (0.3 or 0.6 mg/kg/day); meloxicam (0.125 or 0.25 mg/kg/day)

TABLE 4.31: NSAID RCTS (OUTCOME: NO. OF JOINTS WITH LIMITED RANGE OF MOTION)*

	NAP	CEL 3mg	CEL 6mg	ROF 0.3mg	ROF 0.6mg	MEL 0.125mg	MEL 0.25mg
NAP							
CEL 3mg	0.42 (-2.31, 3.13)						
CEL 6mg	-1.01 (-3.73, 1.68)	-1.44 (-4.14, 1.29)					
ROF 0.3mg	1.17 (-1.46, 3.81)	0.74 (-3.02, 4.53)	2.18 (-1.58, 5.97)				
ROF 0.6mg	1.02 (-1.63, 3.64)	0.6 (-3.19, 4.37)	2.03 (-1.72, 5.82)	-0.14 (-2.78, 2.47)			
MEL 0.125mg	0.3 (-2.62, 3.21)	-0.13 (-4.1, 3.88)	1.31 (-2.64, 5.29)	-0.87 (-4.76, 3.03)	-0.73 (-4.62, 3.18)		
MEL 0.25mg	1.7 (-1.23, 4.61)	1.27 (-2.7, 5.25)	2.71 (-1.26, 6.67)	0.53 (-3.39, 4.44)	0.68 (-3.24, 4.6)	1.39 (-1.54, 4.35)	

*Results are the median mean difference (95% credible interval); Ruperto 2005 data is from three months; negative values indicate improvement; NAP = naproxen (10-15 mg/kg/day); CEL = celecoxib (3 or 6 mg/kg twice daily); ROF = rofecoxib (0.3 or 0.6 mg/kg/day); meloxicam (0.125 or 0.25 mg/kg/day)

TABLE 4.32: NSAID RCTS (OUTCOME: PHYSICIAN'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY, 100 MM VAS)*

	NAP	CEL 3mg	CEL 6mg	ROF 0.3mg	ROF 0.6mg	MEL 0.125mg	MEL 0.25mg
NAP							
CEL 3mg	0.79 (-4.76, 6.38)						
CEL 6mg	-1.4 (-6.83, 4.06)	-2.18 (-7.74, 3.35)					
ROF 0.3mg	-0.35 (-4.62, 3.87)	-1.15 (-8.16, 5.79)	1.05 (-5.89, 7.92)				
ROF 0.6mg	-1.19 (-5.56, 3.15)	-1.97 (-9.03, 5.05)	0.22 (-6.78, 7.13)	-0.82 (-5.13, 3.43)			
MEL 0.125mg	1.49 (-2.99, 5.95)	0.73 (-6.48, 7.78)	2.9 (-4.16, 9.88)	1.85 (-4.29, 8.06)	2.68 (-3.55, 8.93)		
MEL 0.25mg	1.49 (-3.03, 6.02)	0.7 (-6.46, 7.83)	2.9 (-4.19, 9.94)	1.85 (-4.31, 8.05)	2.69 (-3.58, 8.98)	0.0 (-4.73, 4.77)	

*Results are the median mean difference (95% credible interval); Ruperto 2005 data is from three months; negative values indicate improvement; NAP = naproxen (10-15 mg/kg/day); CEL = celecoxib (3 or 6 mg/kg twice daily); ROF = rofecoxib (0.3 or 0.6 mg/kg/day); meloxicam (0.125 or 0.25 mg/kg/day)

TABLE 4.33: NSAID RCTS (OUTCOME: FUNCTIONAL ABILITY – CHAQ DISABILITY INDEX, 0-3)*

	NAP	CEL 3mg	CEL 6mg	ROF 0.3mg	ROF 0.6mg	MEL 0.125mg	MEL 0.25mg
NAP							
CEL 3mg	0.03 (-2.48, 2.54)						
CEL 6mg	-0.01 (-2.53, 2.51)	-0.04 (-2.55, 2.47)					
ROF 0.3mg	0.01 (-2.51, 2.54)	-0.02 (-3.57, 3.52)	0.02 (-3.54, 3.58)				
ROF 0.6mg	-0.03 (-2.54, 2.5)	-0.06 (-3.62, 3.48)	-0.02 (-3.58, 3.54)	-0.04 (-2.56, 2.47)			
MEL 0.125mg	0.2 (-2.31, 2.71)	0.17 (-3.4, 3.71)	0.21 (-3.34, 3.76)	0.19 (-3.37, 3.75)	0.23 (-3.35, 3.8)		
MEL 0.25mg	0.1 (-2.4, 2.6)	0.07 (-3.46, 3.59)	0.11 (-3.44, 3.66)	0.09 (-3.47, 3.64)	0.13 (-3.45, 3.68)	-0.1 (-2.59, 2.42)	

*Results are the median mean difference (95% credible interval); Ruperto 2005 data is from three months; negative values indicate improvement; NAP = naproxen (10-15 mg/kg/day); CEL = celecoxib (3 or 6 mg/kg twice daily); ROF = rofecoxib (0.3 or 0.6 mg/kg/day); meloxicam (0.125 or 0.25 mg/kg/day)

TABLE 4.34: NSAID RCTS (OUTCOME: PATIENT/PARENT ASSESSMENT OF OVERALL WELL-BEING, 100 MM VAS)*

	NAP	CEL 3mg	CEL 6mg	ROF 0.3mg	ROF 0.6mg	MEL 0.125mg	MEL 0.25mg
NAP							
CEL 3mg	0.26 (-6.69, 7.19)						
CEL 6mg	-2.26 (-9.11, 4.62)	-2.5 (-9.48, 4.38)					
ROF 0.3mg	-3.01 (-8.55, 2.56)	-3.25 (-12.06, 5.66)	-0.72 (-9.54, 8)				
ROF 0.6mg	-3.49 (-9.08, 2.13)	-3.72 (-12.64, 5.19)	-1.22 (-10.1, 7.59)	-0.49 (-6.08, 5.09)			
MEL 0.125mg	-3.16 (-7.89, 1.5)	-3.43 (-11.83, 5)	-0.88 (-9.23, 7.37)	-0.17 (-7.49, 7.02)	0.32 (-7, 7.57)		
MEL 0.25mg	**-5.49 (-10.26, -0.74)**	-5.77 (-14.23, 2.74)	-3.25 (-11.58, 5.14)	-2.51 (-9.79, 4.8)	-2.01 (-9.36, 5.32)	-2.33 (-7.2, 2.55)	

*Results are the median mean difference (95% credible interval); Ruperto 2005 data is from three months; scale is a 100 mm VAS, with negative values indicating an improvement in overall well-being; NAP = naproxen (10-15 mg/kg/day); CEL = celecoxib (3 or 6 mg/kg twice daily); ROF = rofecoxib (0.3 or 0.6 mg/kg/day); meloxicam (0.125 or 0.25 mg/kg/day)

TABLE 4.35: NSAID RCTS (OUTCOME: LABORATORY MEASURE OF INFLAMMATION – ESR/CRP)*

	NAP	ASA	CEL 3mg	CEL 6mg	ROF 0.3mg	ROF 0.6mg	MEL 0.125mg	MEL 0.25mg
NAP								
ASA	-0.08 (-6.38, 6.27)							
CEL 3mg	-0.14 (-6.43, 6.18)	-0.06 (-9.04, 8.86)						
CEL 6mg	-0.1 (-6.39, 6.21)	-0.03 (-9.02, 8.9)	0.03 (-6.28, 6.39)					
ROF 0.3mg	0 (-6.35, 6.3)	0.07 (-8.9, 9.04)	0.14 (-8.81, 9.11)	0.09 (-8.85, 9.03)				
ROF 0.6mg	-0.15 (-6.45, 6.19)	-0.08 (-9.07, 8.89)	-0.01 (-8.92, 8.92)	-0.05 (-8.95, 8.88)	-0.14 (-6.44, 6.15)			
MEL 0.125mg	0.16 (-6.17, 6.46)	0.22 (-8.71, 9.18)	0.29 (-8.63, 9.18)	0.26 (-8.7, 9.13)	0.17 (-8.8, 9.07)	0.3 (-8.7, 9.18)		
MEL 0.25mg	-0.22 (-6.56, 6.12)	-0.15 (-9.13, 8.81)	-0.08 (-9.03, 8.81)	-0.12 (-9.05, 8.78)	-0.22 (-9.2, 8.71)	-0.07 (-9.07, 8.81)	-0.37 (-6.66, 5.96)	

*Results are the median standardized mean difference (95% credible interval); Ruperto 2005 data is from three months; negative values indicate improvement; NAP = naproxen (10-15 mg/kg/day); ASA = aspirin (75 mg/kg twice daily); CEL = celecoxib (3 or 6 mg/kg twice daily); ROF = rofecoxib (0.3 or 0.6 mg/kg/day); meloxicam (0.125 or 0.25 mg/kg/day)

TABLE 4.36: CHARACTERISTICS OF INCLUDED CORTICOSTEROID RCTS (INTRA-ARTICULAR CORTICOSTEROID JOINT INJECTIONS OR SYSTEMIC GLUCOCORTICOIDS)

Author, year	Population	Duration	Groups	Dose, route, frequency	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
INTRA-ARTICULAR CORTICOSTEROID JOINT INJECTIONS								
Bracciolini 2014	Oligo JIA (ILAR criteria)	52 wks (12 months)	IA steroids IA steroids + MTX	 MTX: 15 mg/m^2/wk (max 20 mg/wk)	NR	NR	Not allowed to have biologics or biosimilars, or previous IA joint injection in past 3 months or newly injected in 1 knee;	**Conference abstract**; no active uveitis; median no. injected joints was 2 in both groups
Forster 2000	Oligo JIA (ACR criteria)	16 wks	NSAID + physio IA steroids + physio	NR	N/A (protocol)	N/A (protocol)	Must not have received NSAIDs in the past 6 wks before start of study	**Protocol** for a cross-over RCT design; pts diagnosed for <6 months; could not have a family history of psoriasis
Zulian 2003	Persistent oligo, extended oligo JIA (ILAR criteria)	104 wks (24 months)	TAC THA	1 mg/kg (max 40 mg), IA injection 1 mg/kg (max 40 mg), IA injection	64.7 (42.7) months 53.7 (37.9) months	32.7 (34.6) months 42.7 (44.3) months	NR	Choice of drug dependent on availability during study period
Zulian 2004	Persistent oligo, extended oligo, poly JIA (ILAR criteria)	104 wks (24 months)	TAC THA	2 mg/kg (max 80 mg), IA injection 1 mg/kg (max 40 mg), IA injection	Overall: 4.9 (range 1.1-14.8) years	Overall: 2.6 (range 0.2-9) years	Stable medication	Randomized at the joint level

Author, year	Population	Duration	Groups	Dose, route, frequency	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
				SYSTEMIC GLUCOCORTICOIDS				
Loftus 1991 & 1993	Oligo, poly, systemic JIA (EULAR criteria)	52 wks (1 yr)	Deflazacort	NR	10.25 (3.92)	4.73 (3.23), (range 1.5-13.0)	Physio, splints, ≥1 NSAID (inclu. aspirin), long-acting drugs already initiated; APAP (for fever or pain)	Dosage of corticosteroid therapy was adjusted to clinical need according to accepted practice
			Prednisone	NR	10.56 (3.68)	5.1 (2.97), (range 1.16-12.66)		
Picco 1996	Systemic JIA (EULAR criteria)	24 wks (6 months)	Prednisone	1 mg/kg/d starting dose, p.o.	5.5 (range 2.3-13.5)	NR	NSAIDs and an increase of GC dosage	
			Methyl-predisone + prednisone	5 mg/kg/d for 3 d then 2.5 mg/kg/d for 3 d; then prednisone (1 mg/kg/d) p.o.	5.6 (range 1-11.8)			
Popova-Kiprova 1974	Children with "rheumatoid arthritis" (ARA criteria)	24 wks (6 months)	Prednisone	0.5-2 mg/kg	0-3 yrs = 0; 3-7 yrs = 3; 7-14 yrs = 21	< 1 yr = 6 1-2 yrs = 6 3-7 yrs = 12	Could have normal tx (aspirin, pyramidon, vitamins) and exercise therapy	Pts all had prior unsuccessful tx w/ steroids and had side effects
			Tetraco-sactide (Cortrosyn)	0.25-1 mg (twice wkly), IM	0-3 yrs = 2; 3-7 yrs = 4; 7-14 yrs = 21	< 1 yr = 7 1-2 yrs = 8 3-7 yrs = 9		

Author, year	Population	Duration	Groups	Dose, route, frequency	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
Vignolo 1991	Rheumatoid arthritis; SLE	24 wks (at least 6 months)	Deflazacort	**mean loading dose**: 1.18 (SE = 0.241) mg/kg	Overall: (range 2.4-11.8) years	NR	NR	An interim analysis; no separation of JIA and SLE pts in results
			Prednisone	**mean loading dose:** 0.93 (SE = 0.397) mg/kg				

ACR = American College of Rheumatology; APAP = acetaminophen; ARA = American Rheumatism Association; d = day; EULAR = European League Against Rheumatism; GC = glucocorticoid; IA = intra-articular; IM = intramuscular; inclu. = including; ILAR = International League of Associations for Rheumatology; JIA = juvenile idiopathic arthritis; kg = kilogram; m = meter; max = maximum; mg = milligram; MTX = methotrexate; N/A = not applicable; no. = number; NR = not reported; NSAIDs = non-steroidal anti-inflammatory drugs; oligo = oligoarticular JIA; physio = physiotherapy; p.o. = oral; poly = polyarticular JIA; pt = patient; SE = standard error; SLE = systemic lupus erythematosus; TAC = triamcinolone acetonide; THA = triamcinolone hexacetonide; tx = treatment; wk = week; w/ = with; yr = year

TABLE 4.37: RISK OF BIAS ASSESSMENT OF CORTICOSTEROID STUDIES (INTRA-ARTICULAR CORTICOSTEROID JOINT INJECTIONS AND SYSTEMIC GLUCOCORTICOIDS)

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Intra-articular joint injections							
Forster 2000	NA	NA	NA	NA	NA	NA	NA
Zulian 2003	High	High	High	Low	Low	Unclear	Low
Zulian 2004	Unclear	Unclear	Low	Low	Low	Unclear	Low
Systemic glucocorticoids							
Loftus 1991	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Picco 1996	Unclear	Unclear	Unclear	Low	Low	Unclear	Low
Popova-Kiprova 1974	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Vignolo 1991	Unclear	Unclear	High	Unclear	Unclear	Unclear	High

NA = not applicable because it is a protocol

TABLE 4.38: SUMMARY OF OUTCOMES BY ANALYSIS METHOD FOR CORTICOSTEROID RCTS (INTRA-ARTICULAR CORTICOSTEROID JOINT INJECTIONS OR SYSTEMIC GLUCOCORTICOIDS)

Network meta-analysis	Meta-analysis	Descriptive analysis
		Number of active joints
		Laboratory measure of inflammation (ESR)
		Number of withdrawals due to AEs
		Number of participants with a severe AE

Note: AE = adverse event

TABLE 4.39: CHARACTERISTICS OF INCLUDED NON-PHARMACOLOGICAL RCTS

Author, year	Population	Duration	Groups	Dose, frequency, method	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
PHYSICAL ACTIVITY INTERVENTIONS								
Baydogan 2015	Oligo, poly (RF +ve, -ve), psoriatic JIA (no active synovitis or active arthritis)	12 wks	Balance-proprio-ceptive exercise	36 supervised sessions (3 d/wk) + home exercise other days (45-min sessions); warm-up, proprioceptive -balance exercises 8-10 up to 10-15 reps; stretching 1-3 up to 5 reps	10.00 (3.66)	3.26 (1.55)	IA corticosteroid injections not allowed for any joint	Pts all had inflammation and/or mov't restrictions in knee
			Strength exercise	36 supervised sessions (3 d/wk) + home exercise other days (45-min sessions); warm-up; strengthening leg exercises 8-10 up to 10-15 reps; stretching 1-3 up to 5 reps	9.27 (1.43)	5.56 (2.10)		
Epps 2005	Oligo, extended oligo, poly, systemic, psoriatic, enthesitis-related JIA (no severe systemic disease or	10 wks (2 wks intense + 2 months less intense as out-pt.	Land physio	16 hrly sessions, then once/wk for 2 months; also personalized home exercise program every d after 1st block 8 hrly	11 (range 4-19)	5.77 (range 0.49-16.04)	Stable medication; leisure swimming activities permitted; no hydrotherapy for pts in land physio group	Pts diagnosed w/ JIA >3 months, ≥1 active joint, problems w/ ≥2/5 JIA core set criteria; frequency + duration of exercises in both groups were pt-specific

Author, year	Population	Duration	Groups	Dose, frequency, method	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
	recent surgery)		Combined hydro-therapy + land physio	sessions hydrotherapy, 8 hrly sessions land physio (2 wks); then hydrotherapy once per 1-2 wks for 2 months; personalized home exercise program every d after 1st block	12 (range 6-19)	5.15 (range 0.32-13.73)		
Mendonça 2013	Oligo, poly, systemic JIA	24 wks (6 months)	Convl exercise	50 min twice wkly (48 sessions total); warm-up, workout (6-10 reps/exercise), and cool-down	11.0 (3.9)	3.3 (2.1)	Stable medication	No active disease that required therapy modification during study
			Pilates	50 min twice wkly (48 sessions total); 5 reps/exercise (1st 3 sessions), 8 reps (sessions 4-6) and 10 reps (remaining sessions)	11.8 (3.4)	4.5 (2.1)		
Sandstedt 2012	Oligo, poly, psoriatic enthesitis-related JIA	12 wks	Control	Nothing	14.9 (range 8.8-20.6)	onset = 4.8 (1-13.4)	MTX, TNF-blockers and/or prednisone were allowed; exercise was permitted	All pts required repeated IA corticosteroid injections in lower extremities; poly
			Exercise program	3 times/wk (100 reps jump rope,	13.3 (range 8.8-19.9)	onset = 6.1 (range 1.2-16.5)		

Author, year	Population	Duration	Groups	Dose, frequency, method	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
				muscle strength, core exercises, free-weights (0.5-2 kg for arms); 10 x 3 reps			and self-reported by level of weight-bearing	JIA was most represented subtype
Singh-Grewal 2007	Persistent oligo, extended oligo, poly, systemic, psoriatic, enthesitis-related JIA	12 wks	Qigong	18-posture program (repeat postures 8 times); no aerobic training or elevated HR; cool down w/ gentle stretching	11.5 (2.4) (range 8-16)	NR	Stable medication; no restrictions on medication use	Pts stable and unlikely to need tx changes of during study; qigong is similar to tai chi and was considered a gentle relaxation program exerting <75% maximal HR
			Cardio-karate	10-min warm-up, light stretching; 30-minute session (w/ low, moderate, high intensity progression over time); end w/ 5-10 min passive stretching	11.7 (2.5) (range 8-16)			
Takken 2003	Oligo, poly, systemic JIA	24 wks (6 months)	Control Aquatic	Nothing 1-hr sessions once/wk (20 sessions total); warm-up, then aerobic conditioning, rest, 2nd conditioning,	8.88 (1.86) 8.66 (2.29)	NR	Usual care and medical tx	Pts must remission phase w/out medication of no longer than 6 months in absence of joint pain, tenderness, and/or morning stiffness and ESR rate w/in normal

Author, year	Population	Duration	Groups	Dose, frequency, method	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
				cool-down				limits
Tarakci 2012	Oligo, poly, systemic JIA	12 wks	Control Home exercise	Waitlist 48 sessions in total; once/wk (supervised), 3 days/wk (home) for 20-45 min; 8-10 then up to 10-15 reps (strength), 3 then up to 5 reps (stretching)	10.82 (4.00) 10.02 (3.44)	6.50 (3.83) 5.31 (3.05)	Stable dose of medication; continue usual PA level throughout study; no IA corticosteroid injections or surgery in any joint	Excluded if >2 hrs/wk regular exercise
NUTRITIONAL INTERVENTIONS								
Carrasco 2008	Oligo, poly, systemic JIA (ACR criteria)	24 months	Placebo Oral Ca + vit D	Placebo tablets (same size, look, texture, taste as Ca + vit D) Ca: 500 mg (twice daily), p.o.; Vit D: 400 IU (daily), chewable tablets	11.6 (3.4) 11.8 (3.1)	5.94 (3.62) 5.21 (3.75)	None permitted; no systemic corticosteroid tx w/in 3 months before enrollment	Excluded if taking calcium supplements, calcium-containing antacids, or oral contraceptives, if a fasting random urinary calcium-to-creatinine ratio of >0.2

Author, year	Population	Duration	Groups	Dose, frequency, method	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
Hillman 2008	Oligo, poly JIA (ACR criteria)	6 months per study phase, w/ 3 months washout period b/w each	Placebo Calcium Vit D3 + Ca	Matching Ca and vit D3 tablets Ca: 500 mg Vit D3: 400 IU;	Overall: 10.0 (2.85)	NR	All pts received multivitamin w/ 400 IU vit D3; could take NSAIDs, MTX, HCQ; no systemic glucocorticoids	**Cross-over design** (4 study phases)
Hunt 1997	Any JIA subtype (ACR criteria) w/ stable disease status	6 wks – 1 wk washout – 6 wks	Placebo Folic acid	1 mg/d, liquid placebo 1 mg/d, liquid	NR	NR	Stable MTX ≥1 months before entry	**Cross-over design (abstract)**; focus was if intervention would incr. efficacy of MTX; pts had to be on MTX for ≥6 months
Vargova 1998	Any JIA subtype (EULAR criteria)	5 months	Control (no diet) Ibuprofen + omega-3 PUFAs	Nothing <10 yrs: 2 tsp fish oil twice ≥10 yrs: 2 tbsp fish oil twice	9.1 9.1	4.5 (1-12) months 9.4 (1-36) months	NR	Pts had been taking NSAIDs (esp. ibuprofen) from disease onset
Lovell 2006	Any JIA subtype (ACR criteria)	104 wks (24 months)	Placebo + vit D Oral Ca + vit D	2 placebo tablets of Ca + 400 IU/d vit D Ca: 1000 mg/d (2,500 mg tablets $CaCO_3$); vit D: 400 IU/d (multivitamin tablet)	11.6 (3.4) 11.7 (3.1)	5.8 (3.6) 5.4 (3.9)	NSAIDs and antirheumatic medications; no systemic GCs w/in 3 months; no previous use of Ca supplements	Treated outcome effect modifiers as covariates in longitudinal analysis; could not have another disease affecting bone mineralization

Author, year	Population	Duration	Groups	Dose, frequency, method	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
FOOT ORTHOTICS/FOOT CARE OR SPLINT INTERVENTIONS								
Coda 2014	Oligo, poly (RF +ve, -ve), systemic, enthesitis-related, un-differentiated JIA	24 wks (6 months)	Control FOs	Black EVA top-cover (0.75 mm); wear gradually first few d, then always, inclu. exercise	11.17 (3.51)	NR	Medications permitted and monitored regularly; DMARDs permitted if started ≥6 months before enrollment; no previous foot surgery allowed; could already be using FOs	All pts had lower extremity joint involvement, previous failure of orthotic mng't (cannot wear foot orthoses) for ≥3 months); all could walk ≥ 15 min w/out assistive devices
			Fitted FOs	Black EVA top-cover (0.75 mm), made by primary researcher; wear gradually first few d, then always, inclu. exercise	10.64 (3.84)			
Eberhard 1993	JIA (EULAR criteria) w/ wrist involvement (wrist pain ≥1 yr before study)	6 months	Ready-made Droitwich work-splints	Smallest available type, experienced PT applied it	NR	NR	Night splints	Randomization at the level of the hand, not the pt. (each pt received both splints); Pts all had used plasterzote-vitrathene gauntlet splints before
			Orthoplast cock-up splints	Made by experienced orthotist w/ moudling and Velcro straps				

Author, year	Population	Duration	Groups	Dose, frequency, method	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
Hendry 2013	Extended oligo, persistent poly (RF +ve, -ve), psoriatic, enthesitis-related JIA	52 wks (12 months)	Usual care	Normal out-pt medical care by pediatric rheuma-tologist + referrals to podiatry care	10.0 (3.39)	4.06 (3.33)	Stable medications; (10 pts started new medications during study	Pts had ≥1 of following: 1) previously documented arthritis in foot inclu. small joints derived from medical case notes, 2) previously documented foot arthritis in ≥1 large joints (tib-talar/subtalar) derived from medical case notes, or 3) current widespread poly JIA involving large and small foot joints derived from clinical exam by consultant pediatric rheumatologist
			Multidisc. foot care	Individualized care pkgs w/ FOs, home stretching + strengthening program targeted at active joints; involved pediatric rheuma-tologist, podiatrist, sonographer and PT	10.1 (4.22)	3.75 (2.65)		

Author, year	Population	Duration	Groups	Dose, frequency, method	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
Powell 2005	Oligo, poly, systemic, enthesitis-related JIA	12 wks (3 months)	Supportive shoes	Athletic cross-training shoes (medial longitudinal arch support + shock-absorbing soles)	13.77 (4.55)	NR	Stable medications for 1 month before entry and in study (excluding joint injections); no previous use of shoe inserts or foot orthotics	Pts had active disease of ankle, subtalar hindfoot, and/or metatarsal joints (from tender and swollen joint count) and history persistent foot/ankle pain between 1 month and 2 yrs; able to walk 50 feet w/out assistive devices; baseline assessments done in pt's normal shoes, but all pts. received new athletic shoes
			Shoe inserts	Pre-made shoe inserts (1/8" flat neoprene)	12.17 (3.04)			
			Custom orthotics	Semirigid orthotics (metal particle-reinforced polyolefin w/ shock absorbing functional posts)	12.14 (3.32)			
MASSAGE THERAPY INTERVENTIONS								
Field 1997	NR	4 wks (30 d)	Relaxation therapy	15 min/night by parent; tighten + relax muscles one by one	Overall: 9.8 (range 5.4-14.8)	Overall: 4.4	Standard medical care including examinations by a pediatric rheumatologist	Pts excluded if had severe limitations
			Massage therapy	15 min/d by parent; face, stomach, legs, arms, backside				

Author, year	Population	Duration	Groups	Dose, frequency, method	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
PSYCHOSOCIAL OR BEHAVIOURAL INTERVENTIONS								
Jeppesen 2012	JIA	3 months	Control Psycho-logical tx program	Waitlist 6 sessions	NR	NR	NR	**Conference abstract**; stratified by age and address; also did follow-up measurement at 4 and 12 months
Lelieveld 2010	Any JIA subtype (ILAR criteria)	17 wks	Control "Rheumates @ Work" Internet program	Waitlist 4 group sessions; education on: JIA + benefits/self-efficacy of PA, family + school influence on PA, types of PA; also set goals	10.8 (1.4) 10.6 (1.5)	NR	Medication use was monitored – no details on which were permitted	Intervention goal was to improve PA in pts w/ JIA; pts had a computer at home w/ Internet
Stinson 2010	Oligo, extended oligo, poly (RF +ve, -ve), systemic, psoriatic, enthesitis-related, un-differentiated JIA	12 wks	Control Internet self-mng't program	Wkly phone call w/ trained personnel; discussed pt's best efforts at disease mng't Multi-component tx on restricted website w/ 12 modules self-mng't, JIA info, social support + phone calls w/ trained coach	14.8 (1.7) 14.4 (1.3)	6.7 (5.1) 6.2 (4.2)	Medical care continued through a subspecialty pediatric rheumatology clinic; medication could be taken consistently – pts set this as a study goal	Pts aged 12-18 years and able to understand and use web-based program

Author, year	Population	Duration	Groups	Dose, frequency, method	Age, yr (mean (SD)	Disease duration yr, mean (SD)	Concurrent interventions	Other relevant information
Stark 2006	Oligo, poly, systemic JIA (ACR criteria); monoarthritis	8 wks	Enhanced standard care Behavioural		6.8 (2.0) 6.1 (2.0)	NR	No systemic corticosteroids within 3 months before tx or calcium supplements	Recruited pts from outpatient rheumatology centers if aged 4-10 yrs
Stern 2012	JIA in lower extremities	6 wks	Control Family pedometer walking + education program	Nothing	Overall: 16 (range 11-19)	NR	NR	**Conference abstract**; phase 1 was open-label, phase 2 was randomized

ACR = American College of Rheumatology; b/w = between; Ca = calcium; $CaCO_3$ = calcium carbonate; convl = conventional; d = day; esp = especially; ESR = erythrocyte sedimentation rate; EVA = ethylene vinyl acetate; FOs = foot orthoses; ft = feet; GCs = glucocorticoids; HR = heart rate; hr = hour; hrly = hourly; IA = intra-articular; ILAR = International League of Associations for Rheumatology; inclu. = including; IU = international units; incr. = increase; JIA = juvenile idiopathic arthritis; kg = kilogram; LOM = limitation of motion; min = minutes; mm = millimeters; mng't = management; mov't = movement; MTX = methotrexate; NR = not reported; NSAID = non-steroidal anti-inflammatory drug; oligo = oligoarticular JIA; PA = physical activity; physio = physiotherapy; pkgs = packages; p.o. = oral route; poly = polyarticular JIA; pt = patient; PT = physiotherapist; PUFAs = poly-unsaturated fatty acids; reps = repetitions; RF = rheumatoid factor; tbsp = tablespoon; TNF-blockers = tumor necrosis factor blockers; tsp = teaspoon; tx = treatment; vit D3 = vitamin D3; wk = week; wkly = weekly; w/ = with; w/in = within; yr = year; +ve = positive; -ve = negative

TABLE 4.40: RISK OF BIAS ASSESSMENT OF NON-PHARMACOLOGICAL RCTS

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
PHYSICAL ACTIVITY INTERVENTIONS							
Baydogan 2015	Low	High	High	Low	Low	Unclear	Low
Epps 2005	Unclear	Low	High	High	Low	Unclear	Low
Mendonça 2012	Low	Low	High	Low	Low	Unclear	Low
Sandstedt 2012	Low	Unclear	High	High	Low	Unclear	Low
Singh-Grewal 2007	Unclear	Unclear	High	High – self Low- other	Low	Low	Low
Takken 2003	Unclear	Unclear	High	High	Low	Unclear	Low
Tarakci 2012	Low	Unclear	High	Low	High	Unclear	Low
NUTRITIONAL INTERVENTIONS							
Carrasco 2008	Unclear	Low	Low	Unclear	High	High	Low
Hillman 2008	Unclear	Low	Low	Low	High	High	Low
Vargova 1998	Low	Unclear	Low	Low	Unclear	Unclear	Low
Lovell 2006	Low	Low	Low	Low	High	Unclear	Low
FOOT ORTHOTICS/FOOT CARE OR SPLINT INTERVENTIONS							
Coda 2014	Low	Unclear	Low	Low	Low	Unclear	Low
Eberhard 1993	Unclear	Unclear	High	Unclear	Low	Unclear	Low
Hendry 2013	Low	Unclear	High	High	Low	High	Low
Powell 2005	Unclear	Unclear	High	High	Low	Unclear	Low
MASSAGE THERAPY INTERVENTIONS							
Field 1997	Unclear	Unclear	High	High – self Low- other	Low	Unclear	Low
PSYCHOSOCIAL OR BEHAVIOURAL INTERVENTIONS							
Lelieveld 2010	Unclear	Unclear	High	High	Low	Unclear	Low
Stinson 2010	Low	Unclear	High	High	High	Low	High
Stark 2006	Unclear	Low	High	Low	High	Unclear	Low

Self = self-reported; other = outcomes assessor-reported

TABLE 4.41: SUMMARY OF OUTCOMES BY ANALYSIS METHOD FOR NON-PHARMACOLOGICAL RCTS

Network meta-analysis	Meta-analysis	Descriptive analysis
Pain relief		Disease response (ACR Pedi 30)
Health-related quality of life		Number of active joints
		Number of joints with limitation of motion
		Physician's global assessment of disease activity
		Functional ability (CHAQ disability index)
		Patient/parent assessment of overall well-being
		Laboratory measure of inflammation (ESR)
		Number of withdrawals due to AEs
		Number of participants with a severe AE

Note: ACR Pedi 30 = American College of Rheumatology Pediatric 30; CHAQ = Childhood Health Assessment Questionnaire; AE = adverse event

TABLE 4.42: SUMMARY OF NETWORK CHARACTERISTICS FOR NON-PHARMACOLOGICAL RCTS

Characteristic	Pain relief	HRQOL
No. of trials	6	8
No. of intervention nodes	8	10
No. of participants	321	412
No. of comparisons	6	8
No. of 2-arm trials	5	7
No. of multi-arm trials	1	1

Note: HRQOL = health-related quality of life; ACR Pedi 30 = American College of Rheumatology Pediatric 30; LOM = limited range of motion; MD global = physician's global assessment of disease activity; CHAQ DI = Childhood Health Assessment Questionnaire Disability Index; Pt/parent overall well-being = patient/parent assessment of overall wellbeing; ESR = erythrocyte sedimentation rate

TABLE 4.43: NON-PHARMACOLOGICAL RCTS (OUTCOME: PAIN RELIEF)*

	Control	Home strength + stretch exercise	Fitted FOs	Multidisc foot care	Orthotics	Shoe inserts	Internet self-mngt
Control							
Home strength + stretch exercise	-0.14 (-6.45, 6.15)						
Fitted FOs	-0.77 (-7.08, 5.52)	-0.63 (-9.52, 8.19)					
Multidisc. foot care	0 (-6.33, 6.32)	0.15 (-8.75, 9.04)	0.78 (-8.14, 9.66)				
Orthotics	-1.54 (-7.9, 4.78)	-1.39 (-10.31, 7.46)	-0.76 (-9.74, 8.11)	-1.55 (-10.47, 7.36)			
Shoe inserts	0.81 (-5.53, 7.16)	0.95 (-7.97, 9.83)	1.58 (-7.37, 10.55)	0.81 (-8.1, 9.69)	2.35 (-3.96, 8.67)		
Internet self-mngt	-0.8 (-7.08, 5.45)	-0.66 (-9.5, 8.22)	-0.03 (-8.88, 8.87)	-0.79 (-9.7, 8.04)	0.75 (-8.23, 9.66)	-1.61 (-10.54, 7.33)	

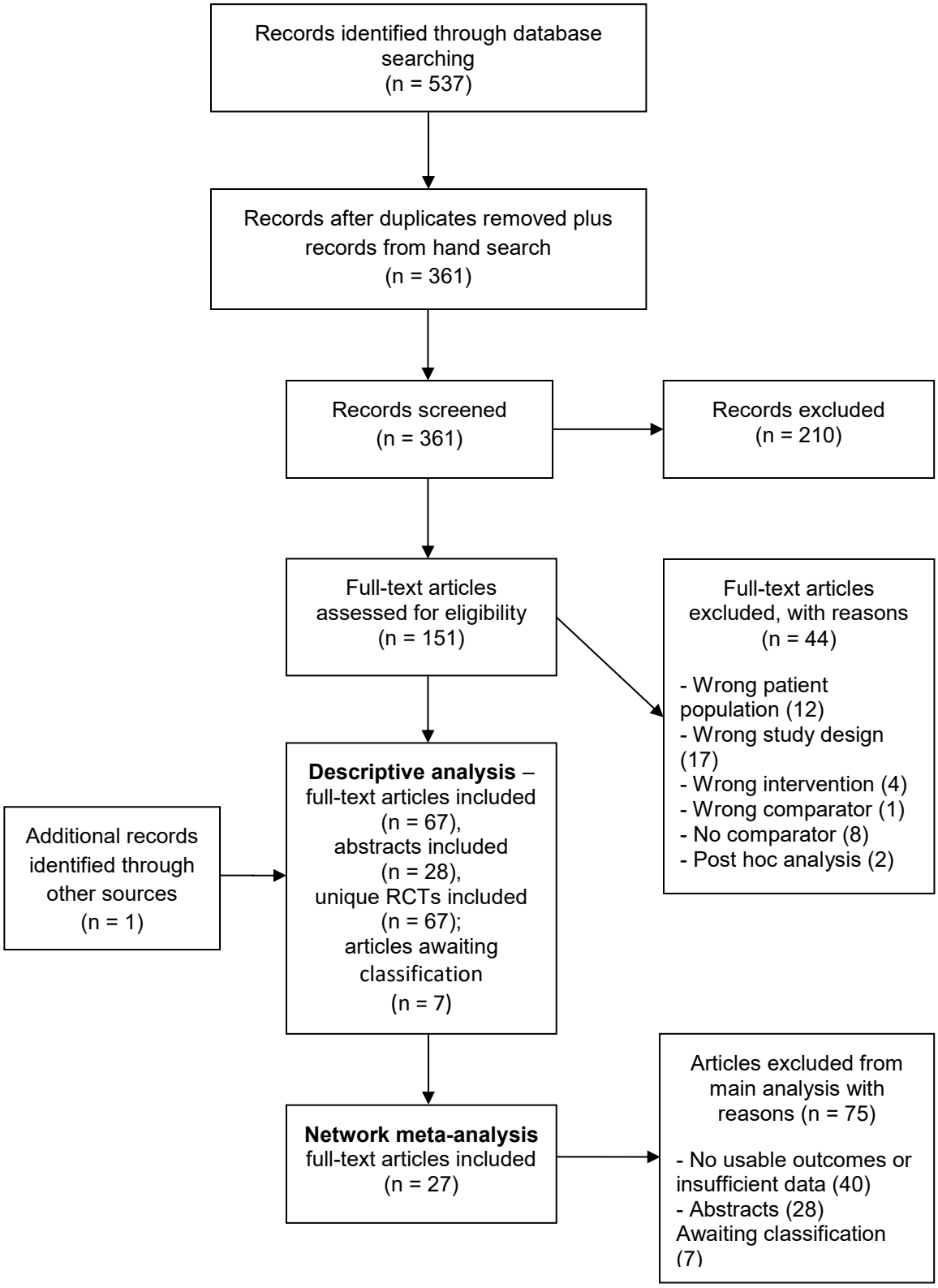
*Results are the median standardized mean difference (95% credible interval); FOs = foot orthoses; self-mngt = self-management; negative values indicate pain relief; Control = waitlist, standard care, or supportive shoes; Home strengthening and stretching exercise = 48 sessions one day supervised and 3 days at home per week for 20-45 minutes and starting with 8-10 repetitions moving up to 15 repetitions for strengthening exercises and initially 3 moving up to 5 repetitions for stretching; Fitted foot orthotics = 0.75 mm in thickness with black ethylene vinyl acetate top-cover and fit for the patient by the primary researcher; Multidisc. foot care = multidisciplinary foot care involving foot orthotics along with home stretching and strengthening program for active joints and involvement of a multidisciplinary team; Orthotics = custom semirigid orthotics made of metal particle-reinforced polyolefin with shock absorbing functional posts; Shoe inserts = pre-made shoe inserts made of 1/8 inch flat neoprene; Internet self-mngt = Internet self-management involving 12 online modules for disease self-management and information on juvenile idiopathic arthritis along with social support and phone calls with a trained coach;

TABLE 4.44: NON-PHARMACOLOGICAL RCTS (OUTCOME: HEALTH-RELATED QUALITY OF LIFE)*

	Control	Rope, strength + core exercise	Aquatics	Home strength + stretch exercise	Fitted FOs	Multidisc. Foot care	Orthotics	Shoe inserts	Internet self-mngt
Control									
Rope, strength + core exercise	-0.81 (-7.11, 5.55)								
Aquatics	-0.51 (-6.79, 5.75)	0.3 (-8.71, 9.18)							
Home strength + stretch exercise	1.27 (-5.05, 7.51)	2.09 (-6.9, 10.97)	1.79 (-7.1, 10.64)						
Fitted FOs	0.55 (-5.77, 6.84)	1.36 (-7.58, 10.32)	1.06 (-7.9, 9.96)	-0.72 (-9.63, 8.2)					
Multidisc. Foot care	-0.01 (-6.28, 6.25)	0.81 (-8.14, 9.71)	0.51 (-8.39, 9.36)	-1.28 (-10.17, 7.58)	-0.55 (-9.4, 8.27)				
Orthotics	0.58 (-5.73, 6.93)	1.4 (-7.63, 10.34)	1.09 (-7.81, 10.01)	-0.71 (-9.57, 8.18)	0.03 (-8.77, 8.91)	0.59 (-8.27, 9.52)			
Shoe inserts	-0.67 (-6.99, 5.63)	0.15 (-8.86, 9.12)	-0.15 (-9.12, 8.79)	-1.94 (-10.79, 6.96)	-1.21 (-10.15, 7.72)	-0.66 (-9.58, 8.28)	-1.24 (-7.58, 5.06)		
Internet self-mngt	-0.07 (-6.39, 6.23)	0.74 (-8.17, 9.62)	0.44 (-8.48, 9.33)	-1.35 (-10.24, 7.62)	-0.62 (-9.57, 8.3)	-0.06 (-8.98, 8.83)	-0.66 (-9.63, 8.23)	0.59 (-8.33, 9.58)	

*Results are the median standardized mean difference (95% credible interval); positive results indicate improved health-related quality of life; Control = waitlist, standard care, or supportive shoes; Rope skipping, strengthening & core exercises = 3 times per week for 12 weeks with 100 repetitions of jump rope and 10 x 3 repetitions for muscle strengthening, core exercises, free-weights (0.5-2 kg) for arms; Aquatics = 20 weekly 1-hour sessions with warm-up, aerobic conditioning, a rest, a second conditioning period, and cool-down; Home strengthening and stretching exercise = 48 sessions one day supervised and 3 days at home per week for 20-45 minutes and starting with 8-10 repetitions moving up to 15 repetitions for strengthening exercises and initially 3 moving up to 5 repetitions for stretching; Fitted foot orthotics = 0.75 mm in thickness with black ethylene vinyl acetate top-cover and fit for the patient by the primary researcher; Multidisc. foot care = multidisciplinary foot care involving foot orthotics along with home stretching and strengthening program for active joints and involvement of a multidisciplinary team; Orthotics = custom semirigid orthotics made of metal particle-reinforced polyolefin with shock absorbing functional posts; Shoe inserts = pre-made shoe inserts made of 1/8 inch flat neoprene; Internet self-mngt = Internet self-management involving12 online modules for disease self-management and information on juvenile idiopathic arthritis along with social support and phone calls with a trained coach

FIGURE 4.1: PRISMA FLOW DIAGRAM OF STUDY INCLUSION



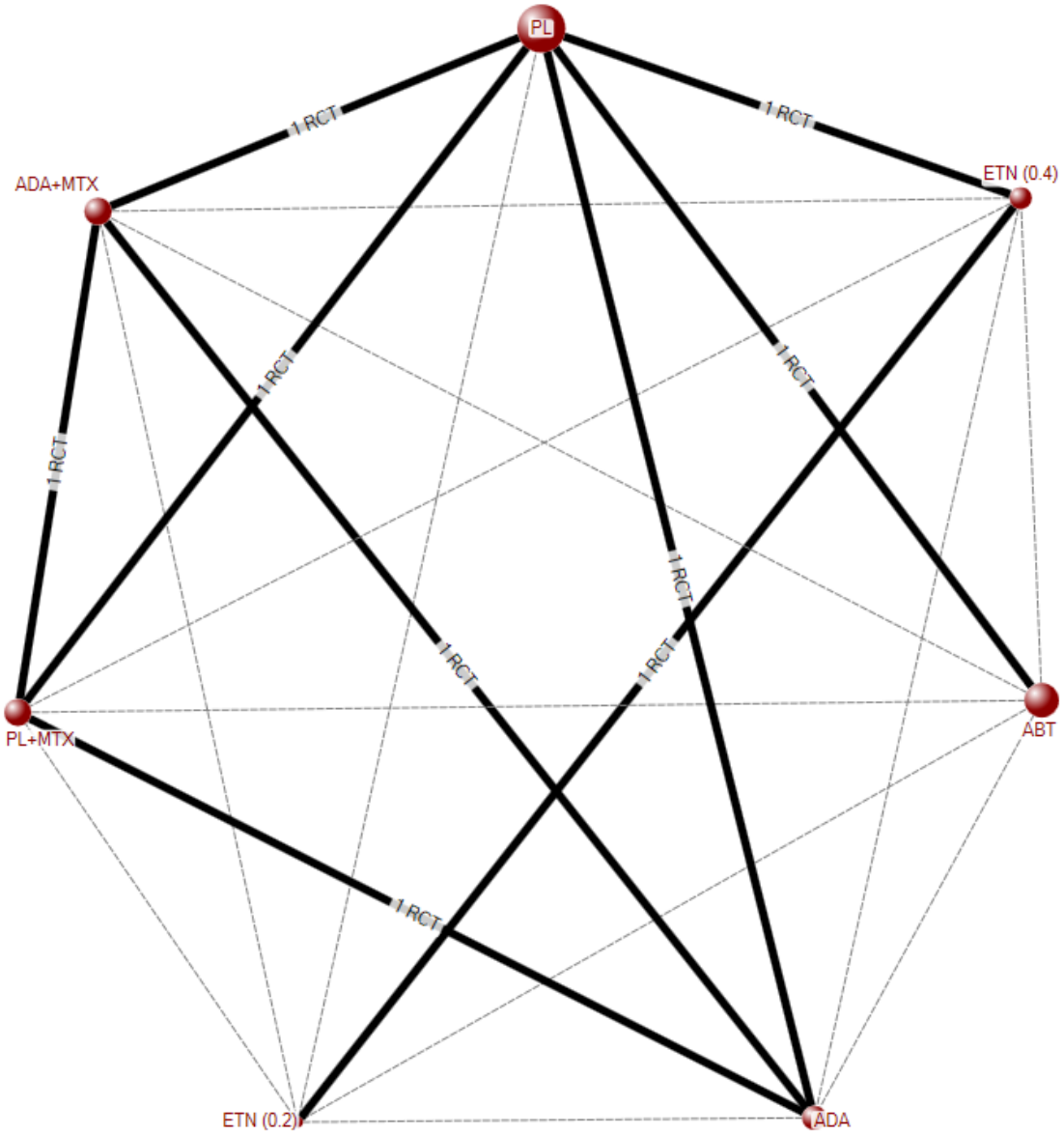


Figure 4.2. Evidence network of biologics withdrawal RCTs for polyarticular-course JIA (Outcome: Disease response – ACR Pedi 30). Black solid lines represent direct comparisons of interventions from RCTs and grey dashed lines represent indirect comparisons of interventions estimated by the model. PL = placebo; ETN (0.4) = etanercept (0.4 mg/kg twice weekly); ABT = abatacept (10 mg/kg every 28 days); ADA = adalimumab (24 mg/m^2 every other week); ETN (0.2) = etanercept (0.2 mg/kg twice weekly); PL+MTX = placebo + methotrexate (10 mg/m^2/week); ADA+MTX = adalimumab (24 mg/m^2 every other week) + methotrexate (10 mg/m^2/week). The common comparator for the network is placebo.

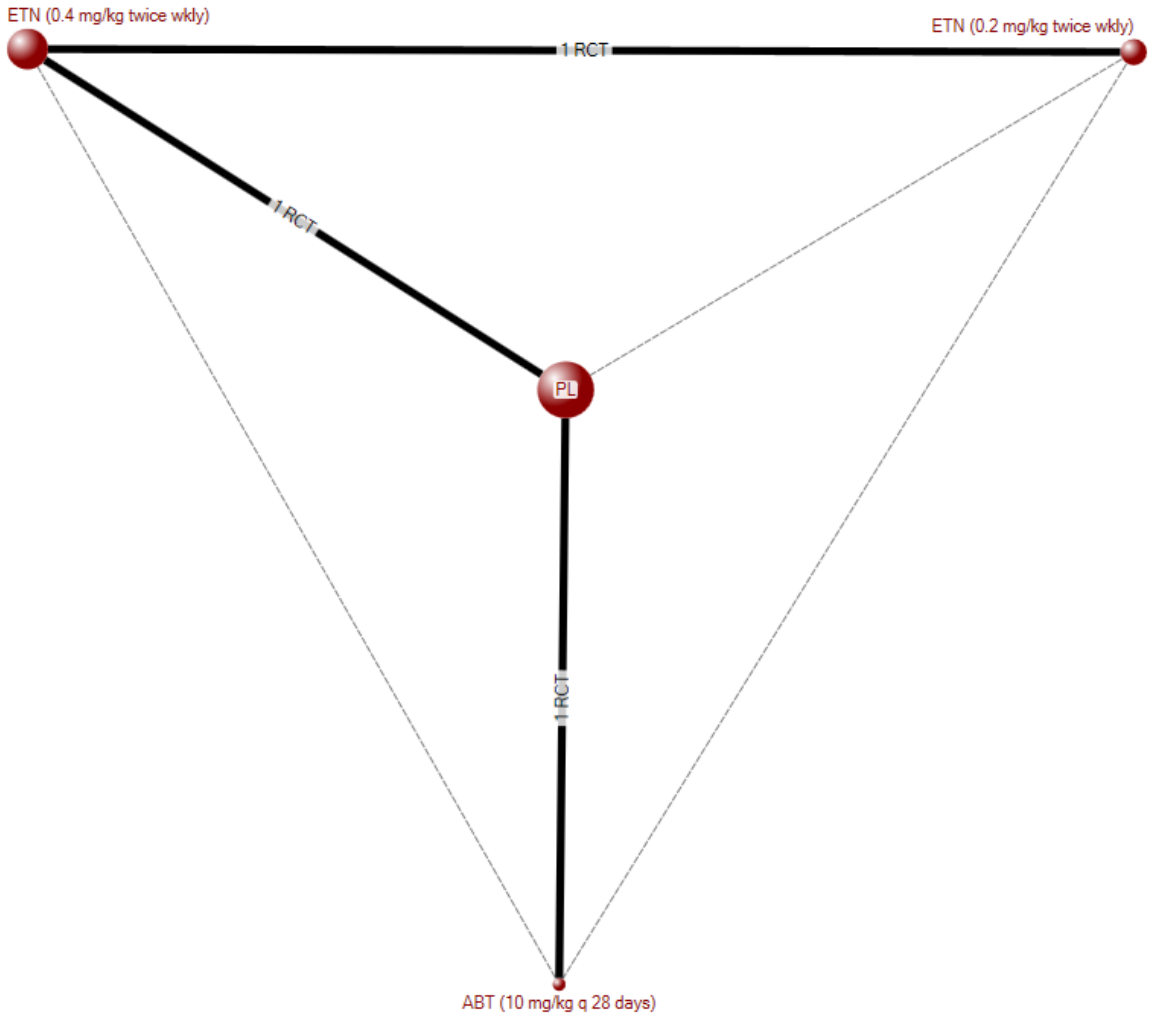


Figure 4.3. Evidence network of biologics withdrawal RCTs for polyarticular-course JIA (Outcomes: ACR Pedi core set of outcomes). Black solid lines represent direct comparisons of interventions from RCTs and grey dashed lines represent indirect comparisons of interventions estimated by the model. PL = placebo; ETN (0.4) = etanercept (0.4 mg/kg twice weekly); ABT = abatacept (10 mg/kg every 28 days); ETN (0.2) = etanercept (0.2 mg/kg twice weekly). The common comparator for the network is placebo.

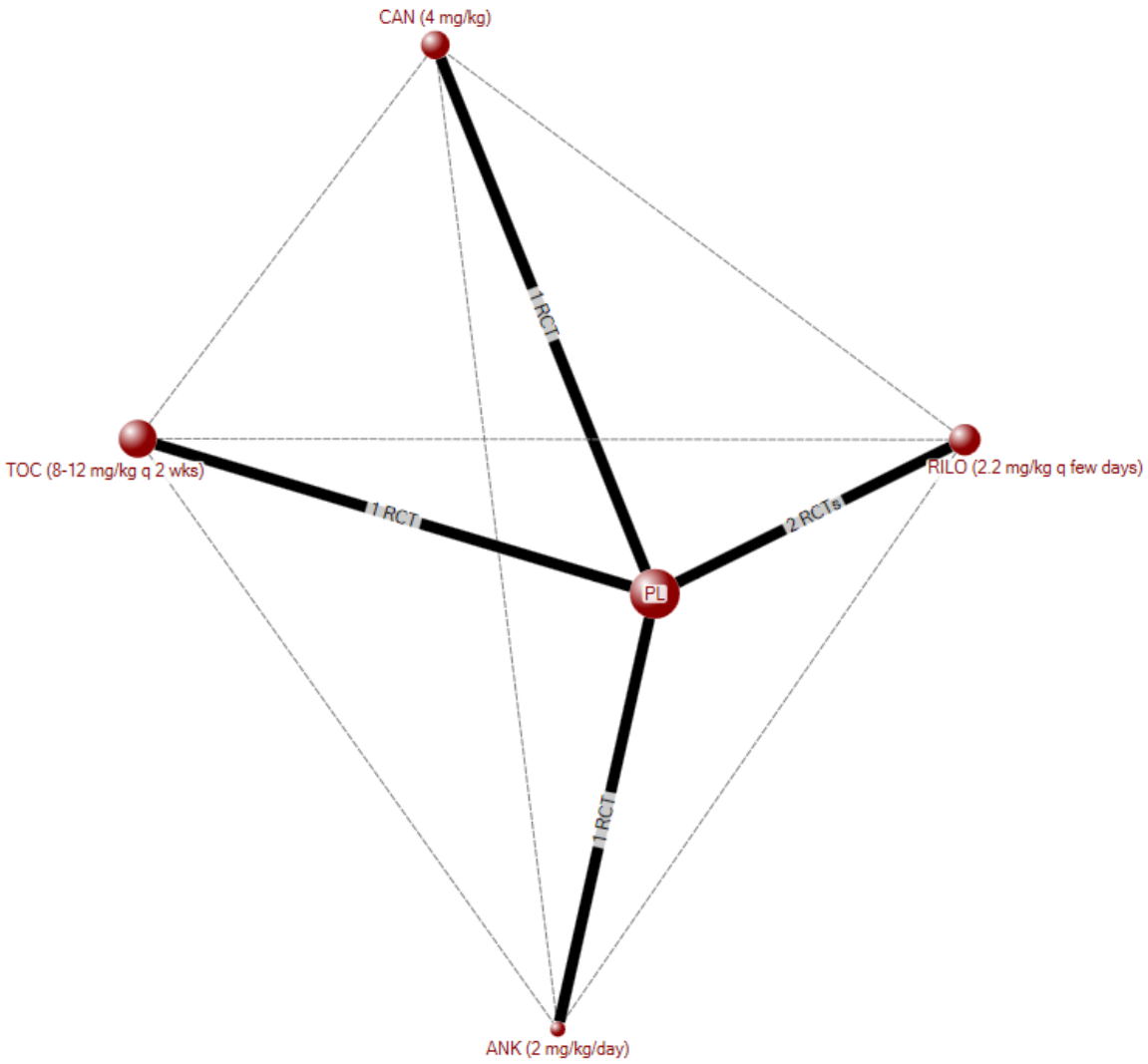


Figure 4.4. Evidence network of biologics parallel RCTs for active systemic JIA (Outcome: Disease response – ACR Pedi 30). Black solid lines represent direct comparisons of interventions from RCTs and grey dashed lines represent indirect comparisons of interventions estimated by the model. PL = placebo; CAN (4 mg/kg) = canakinumab at a dose of 4 mg/kg; RILO (2.2 mg/kg q few days) = rilonacept with a loading dose of either 4.4 mg/kg followed by weekly maintenance doses of 2.2 mg/kg or a loading dose of 2.2 mg/kg followed by a maintenance dose of 2.2 mg/kg on days 3, 7, 14, and 21; ANK (2 mg/kg/day) = anakinra at a dose of 2 mg/kg per day; TOC (8-12 mg/kg q 2 wks) = tocilizumab at a dose of 12 mg/kg every 2 weeks for patients ≤ 30 kg or 8 mg/kg every 2 weeks for patients ≥ 30 kg. The common comparator for the network is placebo.

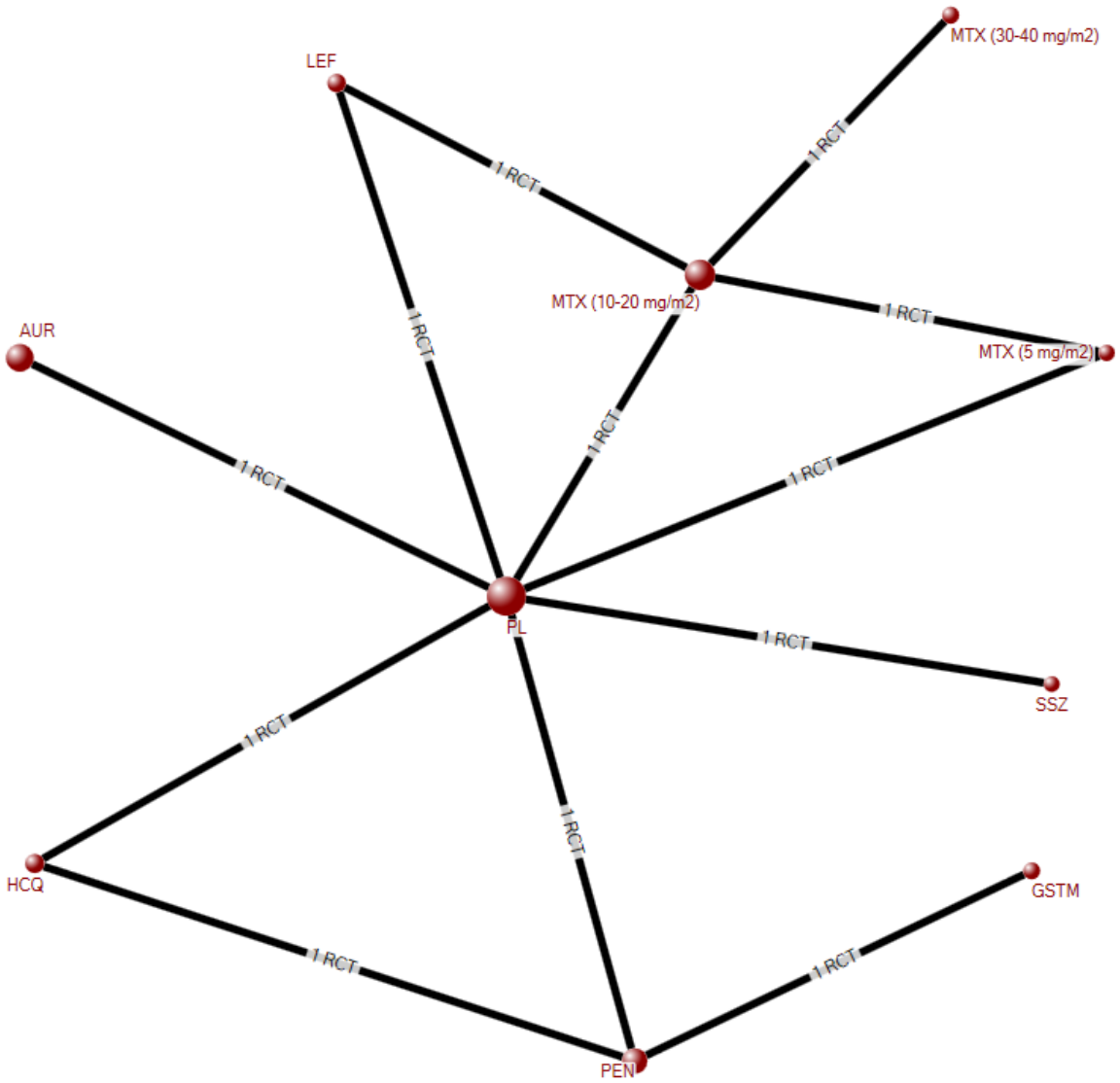


Figure 4.5. Evidence network of DMARD RCTs (Outcome: Number of active joints). Black solid lines represent direct comparisons of interventions from RCTs. The common comparator for the network is placebo. **Legend:** PL = placebo; LEF = leflunomide at a dose of 100 mg the first day followed by 10 mg every other day for patients <20 kg, 100 mg for two days followed by 10 mg per day for patients with a body mass of 20-40 kg, or 100 mg for the first 3 days then 20 mg per day for patients >40 kg; MTX (10-20 mg/m^2) = methotrexate at a dose ranging from 10 mg/m^2 per week to 20 mg/m^2 per week, depending on the RCT; MTX (30-40 mg/m^2) = methotrexate at a dose of 30 mg/m^2 per week up to a maximum dose of 40 mg/m^2 per week; MTX (5 mg/m^2) = methotrexate at a dose of 5 mg/m^2 per week; AUR = auranofin at a dose of 0.15 mg/kg per day, which could be increased 0.2 mg/kg per day; SSZ = sulfasalazine at a dose of 50 mg/kg per day in two doses up to a maximum of 2000 mg; HCQ = hydroxychloroquine at a dose of 6 mg/kg per day; PEN = penicillamine at a dose of 10 mg/kg per day; GSTM = gold sodium thiomalate at a dose of 0.7 mg/kg once weekly for the first 20 weeks then 0.7 mg/kg once monthly.

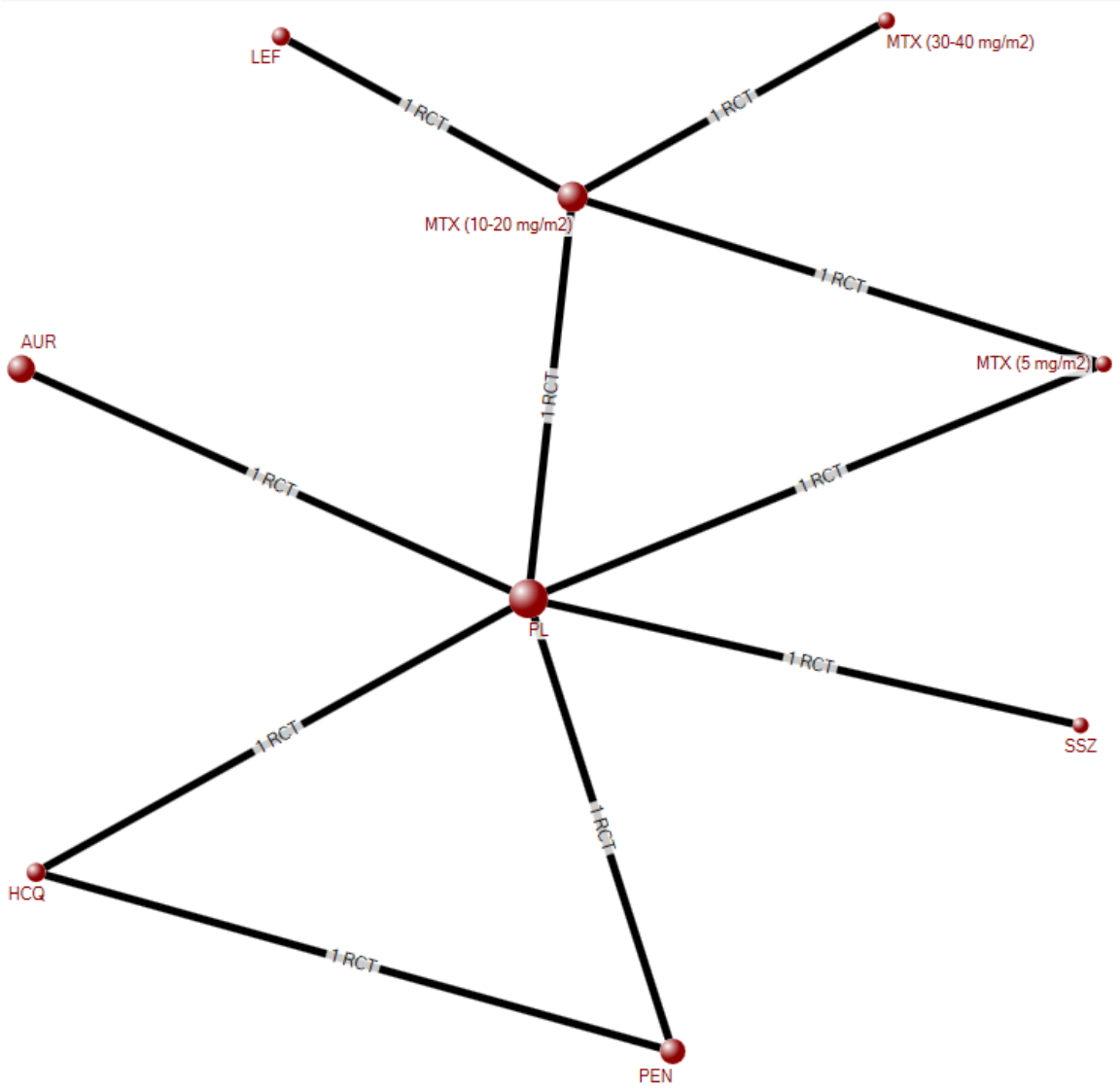


Figure 4.6. Evidence network of DMARD RCTs (Outcome: Number of joints with limited range of motion). Black solid lines represent direct comparisons of interventions from RCTs. The common comparator for the network is placebo. **Legend:** PL = placebo; LEF = leflunomide at a dose of 100 mg the first day followed by 10 mg every other day for patients <20 kg, 100 mg for two days followed by 10 mg per day for patients with a body mass of 20-40 kg, or 100 mg for the first 3 days then 20 mg per day for patients >40 kg; MTX (10-20 mg/m^2) = methotrexate at a dose ranging from 10 mg/m^2 per week to 20 mg/m^2 per week, depending on the RCT; MTX (30-40 mg/m^2) = methotrexate at a dose of 30 mg/m^2 per week up to a maximum dose of 40 mg/m^2 per week; MTX (5 mg/m^2) = methotrexate at a dose of 5 mg/m^2 per week; AUR = auranofin at a dose of 0.15 mg/kg per day, which could be increased 0.2 mg/kg per day; SSZ = sulfasalazine at a dose of 50 mg/kg per day in two doses up to a maximum of 2000 mg; HCQ = hydroxychloroquine at a dose of 6 mg/kg per day; PEN = penicillamine at a dose of 10 mg/kg per day.

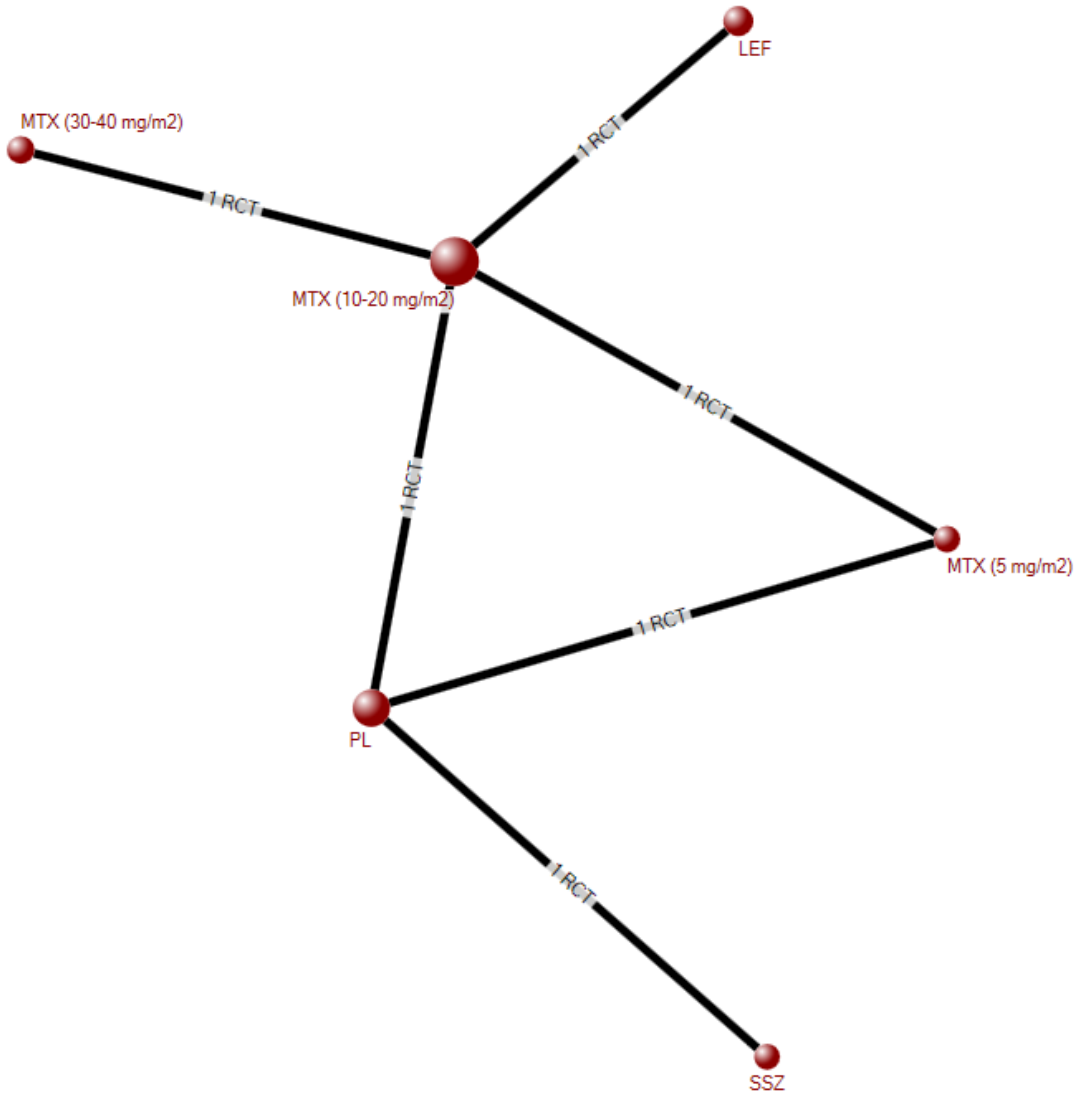


Figure 4.7. Evidence network of DMARD RCTs (Outcome: Laboratory measure of inflammation – ESR). Black solid lines represent direct comparisons of interventions from RCTs. The common comparator for the network is placebo. **Legend:** PL = placebo; LEF = leflunomide at a dose of 100 mg the first day followed by 10 mg every other day for patients <20 kg, 100 mg for two days followed by 10 mg per day for patients with a body mass of 20-40 kg, or 100 mg for the first 3 days then 20 mg per day for patients >40 kg; MTX (10-20 mg/m^2) = methotrexate at a dose ranging from 10 mg/m^2 per week to 20 mg/m^2 per week, depending on the RCT; MTX (30-40 mg/m^2) = methotrexate at a dose of 30 mg/m^2 per week up to a maximum dose of 40 mg/m^2 per week; MTX (5 mg/m^2) = methotrexate at a dose of 5 mg/m^2 per week; SSZ = sulfasalazine at a dose of 50 mg/kg per day in two doses up to a maximum of 2000 mg.

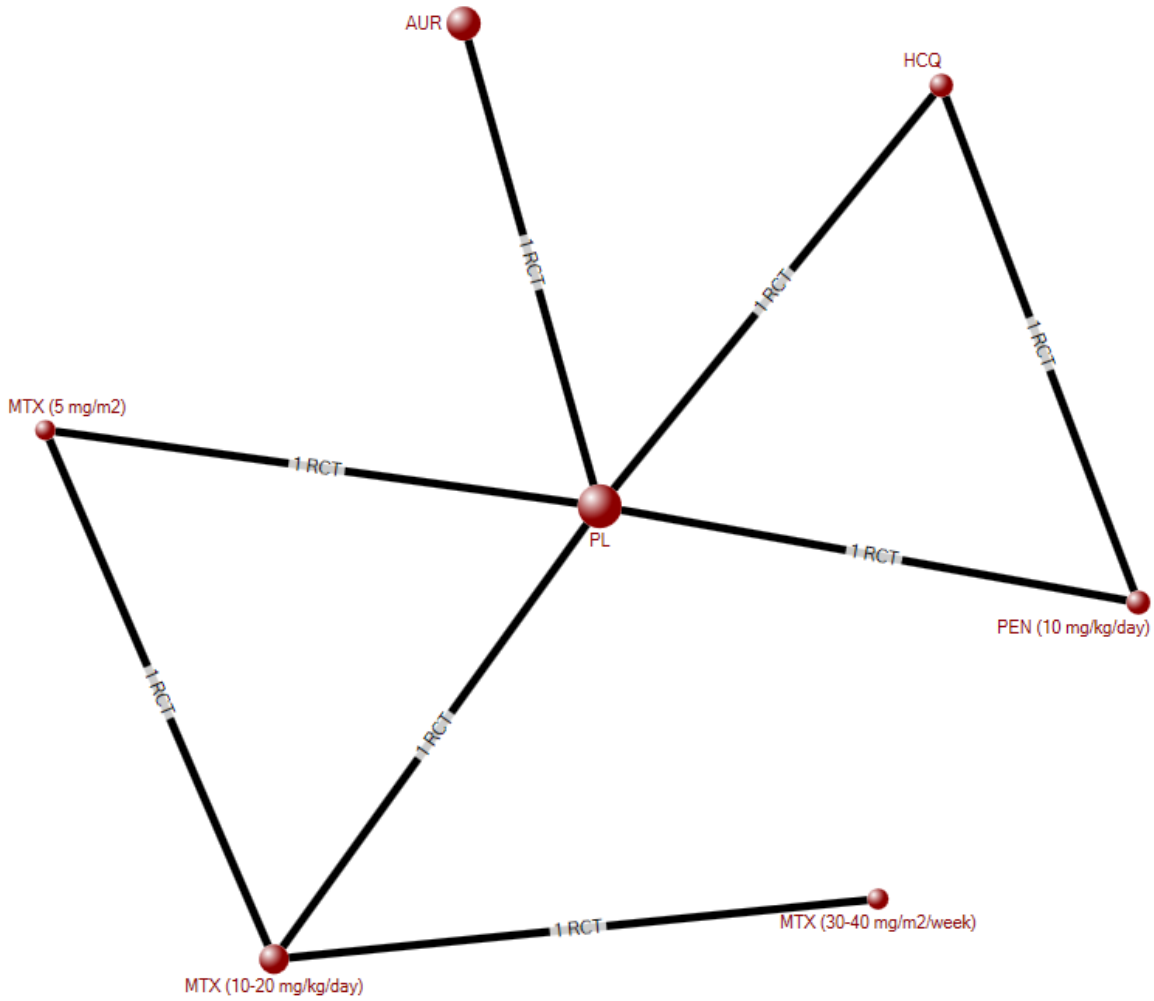


Figure 4.8. Network diagram of DMARD RCTs (Outcome: Pain relief). Black solid lines represent direct comparisons of interventions from RCTs. The common comparator for the network is placebo. **Legend:** PL = placebo; MTX (10-20 mg/m^2) = methotrexate at a dose ranging from 10 mg/m^2 per week to 20 mg/m^2 per week, depending on the RCT; MTX (30-40 mg/m^2) = methotrexate at a dose of 30 mg/m^2 per week up to a maximum dose of 40 mg/m^2 per week; MTX (5 mg/m^2) = methotrexate at a dose of 5 mg/m^2 per week; AUR = auranofin at a dose of 0.15 mg/kg per day, which could be increased 0.2 mg/kg per day; HCQ = hydroxychloroquine at a dose of 6 mg/kg per day; PEN = penicillamine at a dose of 10 mg/kg per day.

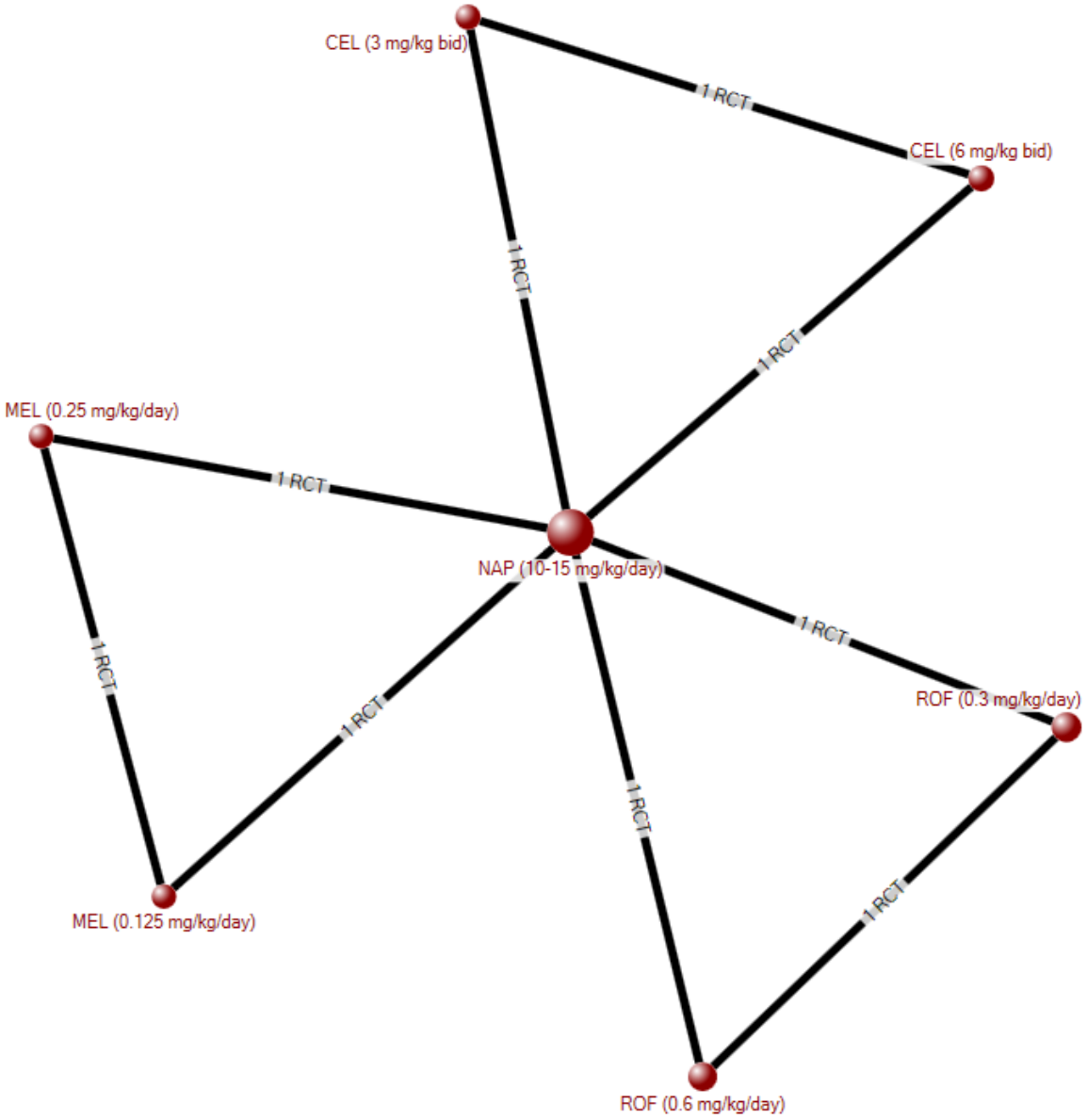


Figure 4.9. Evidence network of NSAID RCTs (Outcomes: Disease response – ACR Pedi 30 and the first five ACR Pedi core set of outcomes). Black solid lines represent direct comparisons of interventions from RCTs. The common comparator for the network is naproxen. **Legend:** NAP = naproxen at a dose ranging from 10 mg/kg per day to 15 mg/kg per day, depending on the RCT; CEL (3 mg/kg bid) = celecoxib at a lower dose of 3 mg/kg twice daily; CEL (6 mg/kg bid) = celecoxib at a higher dose of 6 mg/kg twice daily; ROF (0.3 mg/kg/day) = rofecoxib at a lower dose of 0.3 mg/kg per day with a maximum dose of 25 mg per day; ROF (0.6 mg/kg/day) = rofecoxib at a higher dose of 0.6 mg/kg per day with a maximum dose of 25 mg per day; MEL (0.125 mg/kg/day) = meloxicam at a lower dose of 0.125 mg/kg per day; MEL (0.25 mg/kg/day) = meloxicam at a higher dose of 0.25 mg/kg per day.

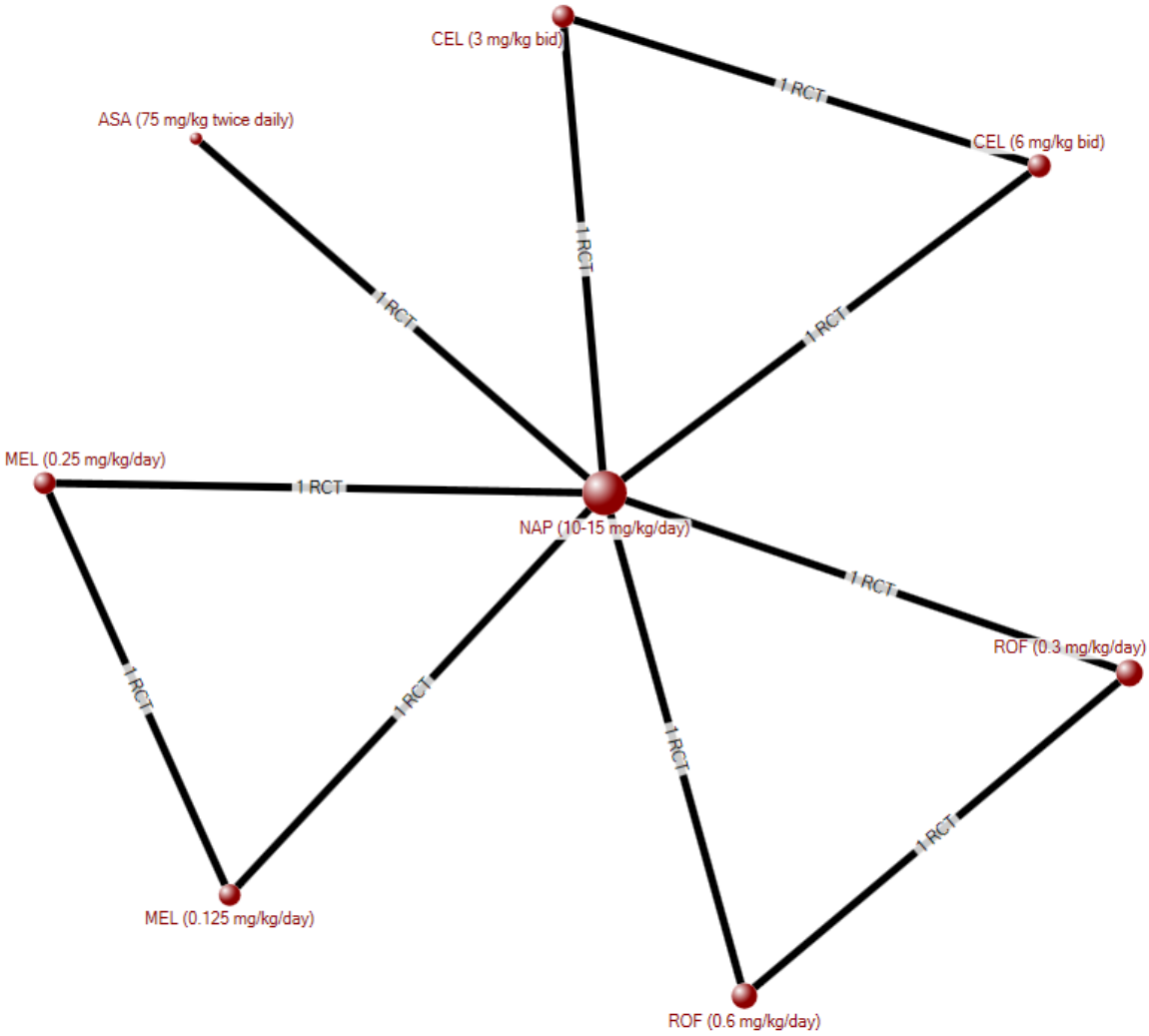


Figure 4.10. Network diagram of NSAID RCTs (Outcomes: Laboratory measure of inflammation – ESR/CRP). Black solid lines represent direct comparisons of interventions from RCTs. The common comparator for the network is naproxen. **Legend:** NAP = naproxen at a dose ranging from 10 mg/kg per day to 15 mg/kg per day, depending on the RCT; CEL (3 mg/kg bid) = celecoxib at a lower dose of 3 mg/kg twice daily; CEL (6 mg/kg bid) = celecoxib at a higher dose of 6 mg/kg twice daily; ROF (0.3 mg/kg/day) = rofecoxib at a lower dose of 0.3 mg/kg per day with a maximum dose of 25 mg per day; ROF (0.6 mg/kg/day) = rofecoxib at a higher dose of 0.6 mg/kg per day with a maximum dose of 25 mg per day; MEL (0.125 mg/kg/day) = meloxicam at a lower dose of 0.125 mg/kg per day; MEL (0.25 mg/kg/day) = meloxicam at a higher dose of 0.25 mg/kg per day; ASA = aspiring at a dose of 75 mg/kg twice daily.

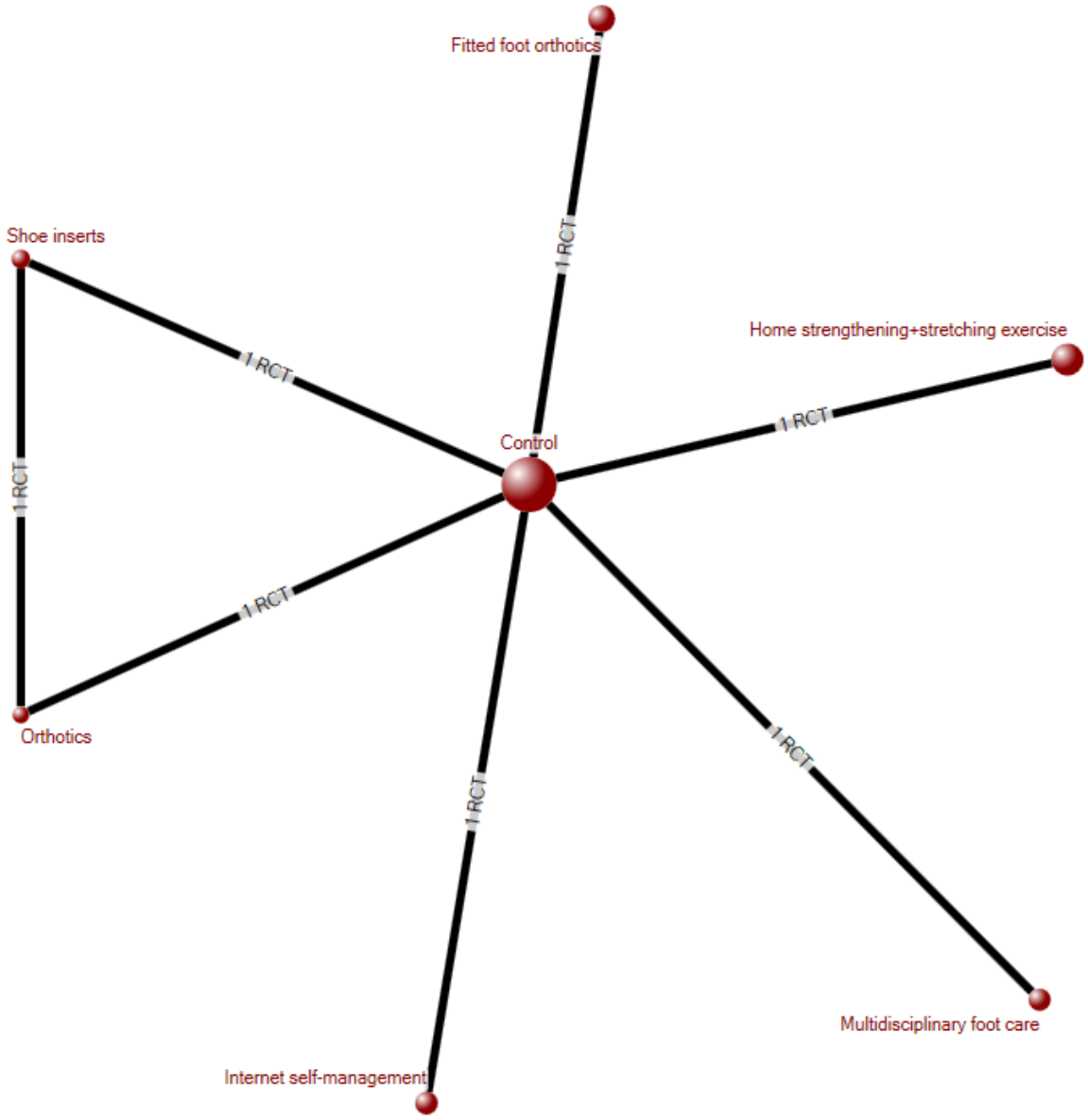


Figure 4.11. Network diagram of non-pharmacological RCTs (Outcome: Pain relief). Black solid lines represent direct comparisons of interventions from RCTs. The common comparator for the network is a control group (waitlist, standard care, or supportive shoes). **Legend:** Fitted foot orthotics = 0.75 mm in thickness with black ethylene vinyl acetate top-cover and fit for the patient by the primary researcher; Home strengthening and stretching exercise = 48 sessions one day supervised and 3 days at home per week for 20-45 minutes and starting with 8-10 repetitions moving up to 15 repetitions for strengthening exercises and initially 3 moving up to 5 repetitions for stretching; Multidisciplinary foot care = foot orthotics along with home stretching and strengthening program for active joints and involvement of a multidisciplinary team; Internet self-management = 12 online modules for disease self-management and information on juvenile idiopathic arthritis along with social support and phone calls with a trained coach; Orthotics = custom semirigid orthotics made of metal particle-reinforced polyolefin with shock absorbing functional posts; Shoe inserts = pre-made shoe inserts made of 1/8 inch flat neoprene.

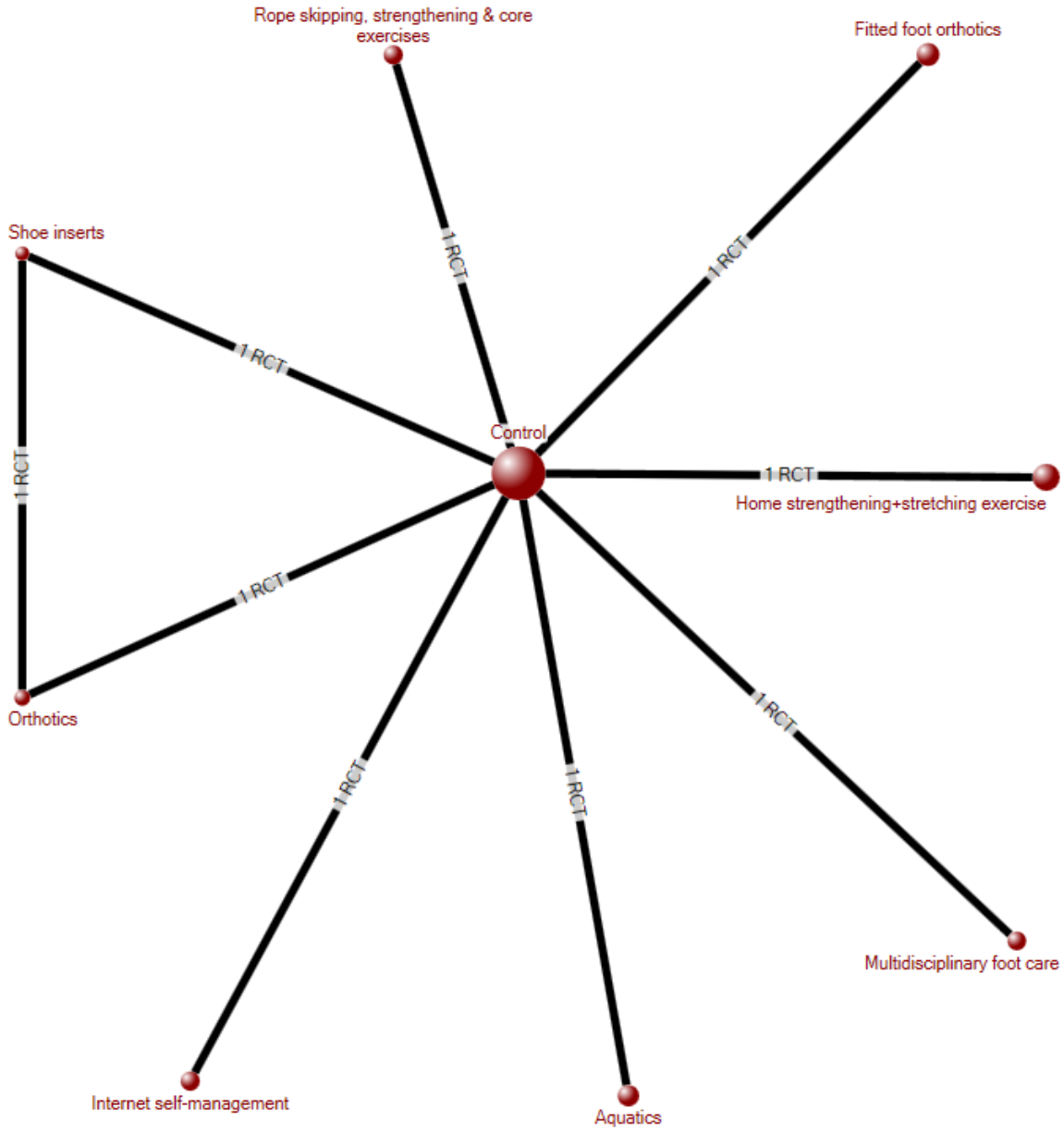


Figure 4.12. Network diagram of non-pharmacological RCTs (Outcome: HRQOL). Black solid lines represent direct comparisons of interventions from RCTs. The common comparator for the network is a control group (waitlist, standard care, or supportive shoes). **Legend:** Fitted foot orthotics = 0.75 mm in thickness with black ethylene vinyl acetate top-cover and fit for the patient by the primary researcher; Home strengthening and stretching exercise = 48 sessions one day supervised and 3 days at home per week for 20-45 minutes and starting with 8-10 repetitions moving up to 15 repetitions for strengthening exercises and initially 3 moving up to 5 repetitions for stretching; Multidisciplinary foot care = foot orthotics along with home stretching and strengthening program for active joints and involvement of a multidisciplinary team; Aquatics = 20 weekly 1-hour sessions with warm-up, aerobic conditioning, a rest, a second conditioning period, and cool-down; Internet self-management = 12 online modules for disease self-management and information on juvenile idiopathic arthritis along with social support and phone calls with a trained coach; Orthotics = custom semirigid orthotics made of metal particle-reinforced polyolefin with shock absorbing functional posts; Shoe inserts = pre-made shoe inserts made of 1/8 inch flat neoprene. Rope skipping, strengthening & core exercises = 3 times per week for 12 weeks with 100 repetitions of jump rope and 10 x 3 repetitions for muscle strengthening, core exercises, free-weights (0.5-2 kg) for arms.

CHAPTER 5: Discussion

5.1 SUMMARY

Overall, there were very few statistically significant head-to-head comparisons to demonstrate that one intervention has a greater efficacy compared to another. For biologics administered to patients with polyarticular-course JIA, both low- and high-doses of etanercept (0.2 mg/kg and 0.4 mg/kg, respectively) were statistically significantly better at reducing the median number of joints with active arthritis compared to abatacept (10 mg/kg, intravenously every 28 days). For biologics administered to patients with active systemic JIA, canakinumab (4 mg/kg) was better than rilonacept (2.2 mg/kg as a maintenance dose) for achievement of the modified ACR Pedi 30 (*i.e.,* with absence of fever as an additional component). Among DMARDs, sulfasalazine (50 mg/kg/day) was favoured over penicillamine (5-10 mg/kg/day) for the number of joints with active arthritis and MTX at a dose of 10-20 mg/m^2 had a statistically significantly better result for the ESR compared to a higher dose of MTX (30-40 mg/m^2). One outcome for NSAIDs revealed that meloxicam (0.25 mg/kg/day) was statistically significant compared to naproxen (10-15 mg/kg/day) for the patient/parent assessment of overall well-being. Non-pharmacological interventions had no statistically significant head-to-head comparisons of interventions included in the analysis for any efficacy outcomes. No network MAs were able to be conducted for intra-articular corticosteroid joint injections or systemic glucocorticoids. No MAs were performed for any of the intervention categories (when a network MA was not able to be performed) because no two RCTs had similar intervention and control groups to allow for pooling in pairwise comparisons. None of the network MA results on the CHAQ in this review met the MCID criteria for clinically important improvement (MCID = -0.13) or worsening (MCID = 0.75) in functional ability (Dempster et al., 2001).

Safety results could not be compared in a network MA for any intervention category due to the low number of events. MAs were also not conducted for the same reason as with the efficacy outcomes described above. In general, biologics were safe for short-term use among patients with polyarticular-course JIA and active systemic JIA. However, the descriptive analysis of biologics revealed that two RCTs of rilonacept for patients with active systemic JIA had conflicting results; one RCT reported a low number of serious AEs (2.2 mg/kg twice in the first week, then once per week), while one quarter of

participants receiving a 4.4 mg/kg loading dose of rilonacept (with 2.2 mg/kg weekly maintenance dose) in the other RCT experienced a serious AE and 15% of those receiving placebo also had a serious AE. Only one parallel RCT of anakinra versus placebo among patients with active systemic JIA reported a large proportion of withdrawals due to AEs in the placebo arm. Nearly one third of participants in a RCT of infliximab (3 mg/kg) in combination with MTX also experienced a serious AE. Among DMARDs, a moderate dose of 10-20 mg/m^2 per week of MTX demonstrated the best safety, while sulfasalazine (50 mg/kg/day) had over a quarter of participants withdraw due to AEs. Gold sodium thiomalate, penicillamine, and MTX (30-40 mg/ m^2) also had 12.8%, 18%, and 12.5% of participants withdraw due to AEs, respectively. Aspirin (60 mg/kg/day) had the worst safety profile among NSAIDs. Naproxen (15 mg/kg/day) is slightly safer for short-term use than celecoxib (3 and 6 mg/kg twice daily) and is comparable to rofecoxib (0.3 and 0.6 mg/kg/day). However, meloxicam (0.25 mg/kg/day) had a slightly better safety profile than naproxen (10 mg/kg/day). Safety results for intra-articular corticosteroid joint injections and systemic glucocorticoids were not reported or had insufficient detail to draw conclusions. Non-pharmacological interventions were safe overall as there were no serious AEs or withdrawals due to AEs reported in nearly all RCTs; only one nutritional intervention RCT for calcium supplementation had three participants withdraw from the calcium arm and none in the placebo arm.

Risk of bias assessments revealed that the majority of RCTs, particularly older ones, did not have a protocol available to assess selective outcome reporting. While there has been a shift in recent years to improve this with the development of the Consolidated Standards of Reporting Trials (CONSORT), there were still problems among newer RCTs in this domain of the Cochrane Risk of Bias Assessment Tool (Schulz, Altman, & Moher, 2010). Another area of weakness that was predominant across RCTs was an unclear risk of allocation concealment, resulting in low overall quality for those RCTs with that scoring. Attrition bias occurred more frequently among the active systemic JIA parallel design RCTs, possibly due to patients in the placebo arm withdrawing from a disease flare while they were not receiving a biologic. Attrition bias was also high among older RCTs of DMARDs, NSAIDs, and corticosteroids. Both of the nutritional intervention cross-over RCTs and two of the psychological or behavioural intervention RCTs had high risk of attrition bias, but not the PA intervention, and foot orthotics/foot care and splint RCTs. While there was high risk of bias for blinding among most non-pharmacological interventions, this is

because it is typically not possible to blind participants due to the nature of these types of interventions (Armijo-Olivo et al., 2016; Deyo, Walsh, Schoenfeld, & Ramamurthy, 1990). In addition, while the risk of bias is present, it does not guarantee a difference in effect sizes of the results (Armijo-Olivo et al., 2016).

5.2 BIOLOGICS RCTS

5.2.1 EFFICACY RESULTS

Our review found that patients with polyarticular-course JIA receiving etanercept (0.4 mg/kg) had a greater maintenance of disease response (ACR Pedi 30) compared to placebo, but there were no statistically significant indirect comparisons between etanercept (0.2 mg/kg), etanercept (0.4 mg/kg), abatacept (10 mg/kg every 28 days, IV) and adalimumab (24 mg/m^2 every other week). A previous SR and MA from 2013 used indirect comparisons of biologics for polyarticular-course JIA for the outcome of disease flare and also found no difference between etanercept, abatacept and adalimumab with placebo as the common comparator (Otten et al., 2013). In terms of secondary outcomes, our review found that both 0.2 and 0.4 mg/kg of etanercept were favoured over abatacept (10 mg/kg every 28 days, intravenous) for reduction in the number of joints with active arthritis. This finding could not be compared to the previous SR and indirect comparison MA because it did not analyze the ACR Pedi 30 core set of outcomes (Otten et al., 2013). Apart from our review and the previous one not reporting on the same outcomes, our review included new evidence from a RCT with a head-to-head comparison of low- and high-dose etanercept (0.2 and 0.4 mg/kg, respectively) (Mori et al., 2011), which contributed to the statistically significant finding compared with abatacept for disease response as described above.

The disease response (ACR Pedi 30, modified to include an absence of fever as one of the composite outcomes) was analyzed for parallel RCTs of biologics for patients with active systemic JIA. Tocilizumab (8-12 mg/kg every 2 weeks), rilonacept (2.2 mg/kg maintenance dose) and canakinumab (4 mg/kg) had statistically significantly improved disease response compared to placebo (De Benedetti et al., 2012; Ilowite et al., 2014; Lovell et al., 2013; Ruperto et al., 2012). While our review found that canakinumab (4 mg/kg) had better disease response than rilonacept (2.2 mg/kg maintenance dose), a previous SR and MA of indirect comparisons of RCTs for active systemic JIA did not find any statistically significant results

for head-to-head comparisons of anakinra, tocilizumab and canakinumab (Otten et al., 2013). The results of our review and the one from 2013 differ primarily because our review included rilonacept (2.2 mg/kg maintenance dose) as another biologic in the evidence network based on results from two recently published RCTs (Ilowite et al., 2014; Lovell et al., 2013; Ruperto et al., 2012). In addition, our review used a Bayesian random effects statistical model, which is more sophisticated than the frequentist fixed effects model used in the other SR and indirect comparison MA. A recently published MA with indirect treatment comparisons also found that patients receiving rilonacept had worse odds of achieving the modified ACR Pedi 30 compared to patients receiving canakinumab (OR = 10.37, 95% CI: 2.60, 41.33) (Tarp et al., 2016). In contrast to our non-significant findings comparing tocilizumab and rilonacept for the modified ACR Pedi 30 (RR = 0.65, 95% CrI: 0.35, 1.0), this study found that patients receiving tocilizumab had greater odds of achieving the modified ACR Pedi 30 compared to those receiving rilonacept (odds ratio = 0.12, 95% CI: 0.03, 0.44). The same RCTs were included as in our review and our results presented as the odds ratio are still non-significant. One explanation for this difference in findings is based on the difference in analysis method (i.e., Frequentist versus Bayesian). The 95% credible intervals are generally wider than 95% confidence intervals. Therefore, it is likely that the difference in findings is due to the wider 95% credible intervals from our Bayesian network MA because the comparison was "bordering on statistical significance".

5.2.2 SAFETY RESULTS

In general, safety for biologics used for polyarticular-course JIA patients had low numbers of withdrawals due to AEs and patients with serious AEs. There were no withdrawals due to AEs or serious AEs reported for anakinra (100 mg/ml/day) and both doses of etanercept (0.2 mg/kg and 0.4 mg/kg twice weekly). RCTs of either etanercept (0.4 mg/kg), abatacept (10 mg/kg every 28 days, IV), or adalimumab (24 mg/m^2 every other week) compared to placebo had few withdrawals due to AEs in the biologic and placebo arms (Ilowite et al., 2009; Lovell et al., 2000; Lovell et al., 2008; Mori et al., 2011; Ruperto et al., 2008). Therefore, short-term use of any of these biologics is safe for patients with polyarticular-course JIA.

Among patients with active systemic JIA, the number of withdrawals due to AEs and the number of patients with a serious AE were low in RCTs of canakinumab (4 mg/kg subcutaneous), tocilizumab (8-12 mg/kg every two weeks intravenous), rilonacept (2.2 mg/kg weekly and a total initial loading dose of 4.4 mg/kg administered on day 0 or in two doses on days 0 and 3), and anakinra (2 mg/kg/day subcutaneous), indicating good safety for short-term use (Ilowite et al., 2014; Lovell et al., 2013; Quartier et al., 2011; Ruperto et al., 2012). Similar to our review, Tarp et al. found no statistically significant difference in the number of withdrawals due to AEs or the number of patients experiencing a serious AE (Tarp et al., 2016).

5.3 DMARD RCTS

5.3.1 EFFICACY RESULTS

In the network MAs for DMARD RCTs on the number of joints with limited range of motion and pain relief (with placebo as the common comparator), there were no significant results for any of the comparisons. Results for the network MA of the number of active joints were statistically significant only for the comparison of sulfasalazine (50 mg/kg/day) to penicillamine (5-10 mg/kg/day). However, it would be more important if sulfasalazine was favoured over another DMARD since penicillamine is not commonly used for patients with JIA (Dueckers et al., 2012), but that was not the case. A moderate dose of MTX (10-20 mg/m^2) also demonstrated better results in terms of the ESR compared to a higher dose of MTX (30-40 mg/m^2). In contrast, a Cochrane SR and MA on MTX published in 2001 included two of the same MTX RCTs as in our review and found MTX was favoured over placebo for the number of joints with pain and also swelling (Giannini et al., 1992; Takken et al., 2001; Woo et al., 2000). However, it did not find the results to be clinically relevant (Takken et al., 2001). The authors of a SR on DMARDs published in 2012 commented that there is little evidence from existing RCTs to indicate that DMARDs are associated with improved health status in general (Kemper et al., 2012). Therefore, the null results for most DMARD comparisons in the network MA are in accordance with the statement of these authors. Moreover, the fact that the Cochrane SR and MA only included two RCTs and indicates results were not clinically relevant also supports that there is insufficient evidence to indicate the efficacy of DMARDs. Nevertheless, the possibility of a type II error cannot be completely ruled out because there were only a few RCTs included

in the network MA and each intervention node had a small total number of participants, so it may not have been possible to detect a difference in efficacy.

5.3.2 SAFETY RESULTS

Safety results for DMARD RCTs revealed a high number of AEs leading to withdrawals for patients receiving sulfasalazine and high-dose MTX (28.6% and 12.5%, respectively). Gold sodium thiomalate and penicillamine also had high withdrawal numbers due to AEs. Auranofin, gold sodium thiomalate, and penicillamine were not mentioned in the CPGs for JIA as they are not commonly used to treat JIA (Beukelman et al., 2011; Dueckers et al., 2012). Sulfasalazine has been recommended for use only if MTX is not tolerated by the patient or is ineffective (Dueckers et al., 2012), which fits with the results of our review that indicated its efficacy may not outweigh the safety risks. A moderate dose of MTX between 10 and 20 mg/m^2 per week was found to be safe for use in patients with JIA; these results are consistent with current CPGs that recommend a dose of MTX between 10 and 15 mg/m^2 (Beukelman et al., 2011; Dueckers et al., 2012). Furthermore, the efficacy results from the network MA on ESR favoured a moderate dose of MTX (10-20 mg/m^2) over a higher dose (30-40 mg/m^2) and provide additional support to these safety results that MTX at a dose of 10 to 20 mg/m^2 is a good option among DMARDs.

5.4 NSAID RCTS

5.4.1 EFFICACY RESULTS

Out of all outcomes assessed in network MAs for NSAID studies, only a higher dose of meloxicam (0.25 mg/kg/day) had a significant improvement in overall well-being as seen in the greater reduction of the patient/parent assessment compared to naproxen. To the author's knowledge, there were no SRs or MAs published on NSAIDs to which these results can be compared. While the results of the network MA for patient/parent assessment of overall well-being favoured meloxicam (0.25 mg/kg/day) over naproxen (10 mg/kg/day), the German CPG for JIA recommended the use of naproxen or other NSAIDs (initially as monotherapy for oligoarticular JIA or in combination with DMARDs or systemic glucocorticoids) that they deemed had higher levels of evidence in their support (Beukelman et al., 2011; Dueckers et al., 2012). Another CPG for JIA did not provide a specific preference for one NSAID over another (Munro et al.,

2009). Likewise, our review did not find any difference in efficacy between naproxen, celecoxib, rofecoxib and meloxicam through indirect comparisons for the other ACR Pedi core set of outcomes or disease response (ACR Pedi 30). However, there may still be the possibility for type II error because the evidence network only involved three RCTs and a total of 770 participants, which may not have been strong enough to detect statistically significant differences among interventions.

5.4.2 SAFETY RESULTS

Aspirin was not found to be safe for use in patients with JIA as it had high numbers of serious AEs (27.7%) and also had a greater number of withdrawals due to AEs compared to ibuprofen and tolmetin sodium. These results are not surprising since it is well known that the FDA had required warning labels on aspirin for its risk of Reye's syndrome in children (Beggs, 2008). Of the more recent RCTs, the evidence suggests that meloxicam (0.25 mg/kg/day) and naproxen (15 mg/kg/day) are safe to use over a three month period and that celecoxib (3 and 6 mg/kg every other day) also had an acceptable safety profile. It should be noted that rofecoxib, which was compared against naproxen in one of the included RCTs, was removed from the market worldwide on September 30, 2004 due to safety issues (Reiff et al., 2006). These results from our descriptive analysis are in accordance with the two CPGs that provide recommendations for specific NSAIDs. They mention the same NSAIDs and, while the potential safety risks are mentioned, recommendations for the use of naproxen, meloxicam, rofecoxib and celecoxib are still made (Dueckers et al., 2012; Munro et al., 2009).

5.5 CORTICOSTEROID RCTS

5.5.1 EFFICACY RESULTS

No network MAs or pairwise MAs could be conducted on results from intra-articular corticosteroid joint injections as the RCTs did not report on any of the outcomes of interest for our review. Based on the descriptive analysis, intra-articular joint injections with triamcinolone hexacetonide demonstrated better efficacy than triamcinolone acetonide in two included RCTs (Zulian et al., 2003; Zulian et al., 2004). One CPG's recommendations were consistent with this finding by indicating that triamcinolone hexacetonide is the preferred corticosteroid to use (Dueckers et al., 2012).

One RCT on systemic glucocorticoids reported no significant difference between deflazacort and prednisone in terms of a simple joint count for the number of joints with active arthritis and the ESR (Loftus et al., 1993). When comparing these results to CPGs, two CPGs recommend systemic glucocorticoids specifically for short-term use among patients with systemic JIA experiencing complications such as uveitis or who have features concerning for macrophage activating syndrome (Beukelman et al., 2011; Dueckers et al., 2012). The systemic glucocorticoid suggested by one of these CPGs is prednisone based on evidence such as older non-randomized prospective studies and an RCT of rheumatoid arthritis in adults (Dueckers et al., 2012), which demonstrates there is still uncertainty on the efficacy of systemic glucocorticoids and has resulted in their cautious use among specific cases of JIA.

5.5.2 SAFETY RESULTS

It was not possible to assess the safety of corticosteroids used for IA joint injections as the RCTs did not report on the outcomes of interest.

It was difficult to evaluate the safety of systemic glucocorticoids because only one RCT provided information on safety, stating there were more serious AEs in the prednisone compared to the tetracosactin arm (Popova-Kiprova et al., 1974). Nevertheless, prednisone was recommended as a systemic glucocorticoid to use among severe cases of systemic JIA by the German CPG for JIA based on older non-randomized prospective studies and an RCT of rheumatoid arthritis in adults (Dueckers et al., 2012). Due to this limited evidence, the ACR CPG did not provide detailed recommendations on doses and routes for systemic glucocorticoids (Beukelman et al., 2011). Despite the lack of evidence available from included RCTs, systemic glucocorticoids tend to be prescribed only when needed between interventions for severe cases of systemic JIA because of safety concerns due to the potential negative effects on growth and risk for Cushing's syndrome (Dueckers et al., 2012).

5.6 NON-PHARMACOLOGICAL INTERVENTION RCTS

5.6.1 EFFICACY RESULTS

5.6.1.1 PHYSICAL ACTIVITY INTERVENTION RCTS

None of the RCTs on PA included in the evidence networks for pain and HRQOL had statistically significant results compared to the control or other non-pharmacological interventions. One Cochrane SR of PA interventions in JIA found a trend toward significance for functional ability, joint range of motion, the number of joints with swelling, HRQOL and aerobic capacity, though there were no statistically significant results (Takken et al., 2008). Pain results in that SR were contradictory (Takken et al., 2008). Three newer RCTs of PA interventions published since the Cochrane SR were included in our review; these RCTs also had differing results. Two of these additional RCTs had statistically significant findings for pain relief favouring proprioceptive compared to strengthening exercises (Baydogan et al., 2015) and Pilates compared to conventional exercise (Mendonca et al., 2013), but another only had a slight trend toward significance for pain relief with land-based stretching and strengthening exercises compared to a control (waitlist) (Tarakci et al., 2012). The RCTs on strengthening compared to proprioceptive exercises and Pilates compared to conventional exercises were not included in the network MA, and the other RCT on land-based stretching and strengthening exercises compared to a control had conflicting results (Baydogan et al., 2015; Mendonca et al., 2013; Tarakci et al., 2012). Thus, it is plausible that with the limited number of RCTs included in the network MAs there was not enough precision due to wider credible intervals to see significant results for pain relief or even HRQOL.

5.6.1.2 FOOT ORTHOTICS OR FOOT CARE AND SPLINT INTERVENTION RCTS

Three RCTs included in this intervention category were included in the network MA for the outcomes pain and HRQOL, but the results were not statistically significant compared to the control or the other non-pharmacological interventions. A SR on foot orthotics published in 2008 only included one RCT of foot orthotics for patients with JIA; two RCTs on foot orthotics (one including a multidisciplinary foot care program) published since then were included in our review (Hawke et al., 2008). The authors of the SR indicated good evidence for the use of foot orthotics compared to shoe inserts based on the Powell 2005

RCT (Powell et al., 2005). A RCT of a multidisciplinary foot care program from 2013 revealed a significant reduction in the number of joints with limited range of motion compared to standard care (Hendry et al., 2013). The Ottawa Panel CPG on foot care for JIA did not recommend multidisciplinary foot care as no clinical benefit was found, but the use of custom fitted foot orthotics was recommended over pre-formed foot orthotics (Brosseau et al., 2016). A more recent RCT favoured custom fitted foot orthotics over control foot orthotics for pain relief and improvement in HRQOL, but these results were not significant in the network MAs. One possibility for this difference in significance between the original RCT and our review is that the RCT had a small sample size, so the mean and standard error required for the network MA were estimated from the median and interquartile range, which may have left room for error (Coda et al., 2014). The CPG on foot care also recommended use of custom fitted foot orthotics over control foot orthotics (Brosseau et al., 2016). Therefore, the non-significant results of the network MAs may be due to type II error, in which the sample size was not sufficiently large to detect a difference in efficacy between interventions because of wider credible intervals. It may also be difficult to distinguish the true effect of the foot orthotics and multidisciplinary foot care interventions since the common comparator was a control group that did not represent a true placebo (*i.e.,* participants in the control group, even if on a waitlist may still be receiving concomitant pharmacological interventions). Certain interventions may have been compared in the original RCT to something closer to a true placebo than other interventions and the combination of their comparators as a control may have made it more difficult for those interventions to demonstrate efficacy.

5.6.1.3 NUTRITIONAL INTERVENTION RCTS

Nutritional intervention RCTs could not be included in the network MAs because they did not report on the outcomes of interest. One CPG of pharmacological and non-pharmacological interventions in JIA provided a high recommendation for oral calcium and vitamin D supplementation for prevention of bone loss, especially when taking systemic glucocorticoids (Munro et al., 2009). This recommendation was based on the results of two RCTs, which were both included in our review (Lovell et al., 2006; Stark et al., 2006).

5.6.1.4 MASSAGE INTERVENTION RCTS

The one included massage intervention RCT in our review was not part of the network MAs for efficacy outcomes because it used a head-to-head design with both interventions not connecting with other interventions in the evidence network. Patients in the massage therapy arm experienced greater pain relief than those participating in relaxation therapy (Field et al., 1997). One CPG for JIA that provided recommendations on non-pharmacological interventions gave a low recommendation to thermotherapy (including use of massaging techniques), but did not reference this RCT of massage therapy versus relaxation therapy (Munro et al., 2009).

5.6.1.5 PYSCHOSOCIAL AND BEHAVIOURAL INTERVENTION RCTS

The Internet self-management program included in the evidence networks for non-pharmacological interventions did not have sufficient evidence to demonstrate it was better than a control or other interventions (Stinson et al., 2010). Psychosocial and behavioural interventions had not been described in one CPG (Dueckers et al., 2012), but another CPG gave a moderate recommendation based on one behavioural intervention RCT to increase intake of dietary calcium (Munro et al., 2009; Stark et al., 2006). Ten CPGs for rheumatoid arthritis recommended patient education or self-management interventions (Brosseau et al., 2014), hence psychosocial and behavioural interventions may likewise be important for patients with JIA despite the non-significant findings of the network MAs. Therefore the lack of RCTs investigating these types of interventions among patients with JIA may explain the insufficient evidence to demonstrate a positive effect for pain relief and improved HRQOL, as there were not many RCTs in the evidence networks (and only one was for a behavioural intervention) to improve the strength of the network MAs. In addition, there may have been type II error present in which statistically significant results failed to be detected in the network MA due to a small sample size.

5.6.2 SAFETY RESULTS FOR ALL NON-PHARMACOLOGICAL INTERVENTION RCTS

There were no significant results for any non-pharmacological intervention compared to a control (no intervention or standard care) for pain relief and HRQOL. Among the non-pharmacological interventions, there were no occurrences of serious AEs and only one RCT (1000 mg calcium in combination with 400

IU vitamin D versus placebo in combination with 400 IU vitamin D) had withdrawals due to AEs. These findings suggest that non-pharmacological interventions such as PA, massage, foot orthotics/foot care and splints, and psychosocial or behavioural interventions are safe for patients with JIA. A Cochrane SR and MA came to the same conclusion as it did not find any problems with safety over the short-term for PA interventions (Takken et al., 2008). Additionally, two CPGs recommend PA as safe to use, including strengthening exercises that involve some resistance (Dueckers et al., 2012; Munro et al., 2009). It is challenging to draw conclusions for nutritional intervention RCTs because safety outcomes were only reported in one RCT, which had a low number of withdrawals due to AEs. However, these safety results may not be generalizable to patients with more severe disease activity, such as those requiring surgery, as they were ineligible for inclusion in many of the RCTs. Though non-pharmacological interventions were safe overall, the results were not significant for the network MAs for pain relief and HRQOL comparing various interventions to a control that represented no intervention or standard care. Thus, it would also be of use to conduct a cost-benefit analysis of non-pharmacological interventions to provide more information for families of patients with JIA and their multidisciplinary healthcare team in making decisions of care.

5.7 STRENGTHS AND LIMITATIONS

To the author's knowledge, this is the first network MA that was conducted for DMARDs, NSAIDs, and non-pharmacological interventions (including PA, foot orthotics/foot care and splints, and psychological or behavioural interventions). Two previous SRs and MAs with indirect comparisons of biologics were published in 2013 and 2016 (Otten et al., 2013; Tarp et al., 2016). However, our review not only includes evidence from more recent RCTs of biologics, but it also utilizes a more sophisticated statistical approach. The former SR and MA from 2013 used the Bucher method and the review from 2016 used a Frequentist generalized linear mixed model, whereas our review used a Bayesian random effects statistical model that permits the analysis of multi-arm RCTs in the evidence network (Wells et al., 2009). The exhaustive SR and network MA of RCTs in a broad range of intervention categories will provide additional information that can be used in the development of updated CPGs that have been unable to rely on

pooled evidence from published RCTs in JIA because pairwise MAs were not possible with the different intervention and control arms used.

There were few RCTs included in each intervention category and most of them were of low methodological quality because of unclear allocation concealment, high risk of bias for blinding of patients and personnel or outcome assessors, attrition bias, or some combination of these. In addition, the RCTs had small sample sizes of less than 100 or even less than 50 per arm that also reduced the precision of the effect estimates for the network MAs. The withdrawal study design used for biologics RCTs of patients with polyarticular-course JIA may have biased results away from the null hypothesis (*i.e.,* that there was no difference between arms) if patients randomized to receive placebo were still experiencing benefits from the biologic they received during the open-label lead-in phase (Sfriso & Ravaioli, 2008). Furthermore, the type of included patients in the RCTs analyzed limit the generalizability of results from our review to mostly patients with oligoarticular, polyarticular, and systemic JIA and prevent the results from being applicable to very young children.

Several limitations for our review are also present. Firstly, there were a limited number of RCTs that could be included in each evidence network and the total number of participants was small, which reduces the precision of the estimates and increases the risk for type II error. Secondly, only descriptive analyses could be used for IA joint injections, systemic glucocorticoids, massage interventions, and nutritional interventions in terms of efficacy and safety outcomes, which made it difficult to draw conclusions about these interventions. In addition, the network geometry was mostly in a star shape because interventions were most often compared to placebo rather than to another active intervention. This precluded the testing of the consistency assumption as the closed loops that were present (*e.g.,* for DMARDs) were from single multiple-arm RCTs. The results for head-to-head comparisons are also based on indirect evidence, which is less reliable than a combination of direct and indirect evidence that would be available with a closed-loop network structure (Ades, Madan, & Welton, 2011).

Given the small sample sizes of included RCTs, some reported their results as the median and range or interquartile range (Coda et al., 2014; Hendry et al., 2013; Ilowite et al., 2014; Ruperto et al., 2012; Yokota et al., 2008). These results were converted to the mean and standard deviation in order to use the

results in the analysis. Unfortunately, this leaves room for information bias since the central limit theorem does not apply for small sample sizes and there is reason to believe the authors chose non-parametric measures because it was likely the data were not normally distributed (D'Agostino, Sullivan, & Beiser, 2006, p. 153). Values of the standard deviation and standard error that were missing in two RCTs were imputed from RCTs with similar baseline characteristics. Certain RCTs' results were also available only as figures; these were extracted using a program called WebPlotDigitizer (http://arohatgi.info/WebPlotDigitizer/). While the different conversions or extractions used for our review likely introduced errors that either biased the results toward or away from the null hypothesis, it was preferred over excluding a RCT altogether that had results for the outcomes of interest, particularly considering the limited number of included RCTs.

Grey literature was not extensively searched for this review. Including grey literature can reduce the impact of publication bias trials (*i.e.,* larger treatment effects due to published literature being based primarily on positive trials) by considering negative and neutral results from unpublished studies (Hopewell, McDonald, Clarke, & Egger, 2007). However, the extent of grey literature is vast and even with the *Grey Matters* checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters) a decision must be made about what is relevant for the review and the grey literature searched may still not be a representative sample if relevant sources are missed (Mahood, Van Eerd, & Irvin, 2014). In addition, grey literature searches in Google Scholar or Google could yield in the tens of thousands of results, yet systematic reviews involve time and resource constraints (*i.e.,* keeping the review up-to-date and involving two reviewers throughout) (Mahood et al., 2014). This review included results from conference abstracts in sensitivity analyses when possible to include a source where negative results are more likely than in published full-text articles. Results from abstracts were not included in the reference case because they cannot be assessed for risk of bias when selective outcome reporting is a possibility or the results may represent preliminary findings. Additionally, clinicaltrials.gov was searched to identify potentially eligible trials with results that had not yet been published.

Lastly, despite the small number of available RCTs in JIA the decision was made to restrict the review only to RCTs. This limits the capture of safety outcomes because they are more accurately assessed

through long-term follow-up, since events are often rare. While other study designs would be beneficial when investigating safety outcomes, the primary outcome of this review was focused on efficacy. RCTs provide more high quality estimates on efficacy than do non-randomized and observational studies because of higher interval validity (*i.e.,* no confounding due to randomization, isolation of the treatment effect to investigate causal inference) (Shrier et al., 2007), thus the decision was made to exclude other study designs. Restriction of included studies to RCTs has also been done in other systematic reviews of interventions in JIA that considered efficacy as their primary outcome (Otten et al., 2013; Takken et al., 2008; Tarp et al., 2016; Wallen & Gillies, 2006). Furthermore, it is challenging to include non-randomized and observational study designs in pairwise meta-analyses due to uncertainties as to how to weight the studies; this is further compounded when conducting network MAs as the presence of bias or confounding may compromise the validity of indirect treatment comparisons (Cameron et al., 2015). A decision to restrict these study designs to descriptive analyses alone was not made as it would not have provided new insight for addressing the gaps in the literature because CPGs, SRs, and narrative reviews for JIA have previously described the effectiveness and safety evidence from controlled trials and observational studies.

As a result of the limitations described above for the included RCTs and the review itself, the results should be interpreted with caution, particularly if interventions are used for longer periods of time than described in the RCTs.

5.8 FUTURE DIRECTIONS

The use of a network MA to compare several interventions within the same category has provided additional insight into the efficacy and safety of both pharmacological and non-pharmacological intervention options for patients with JIA. These results should be considered within the context of the existing evidence base, including observational studies that provide a longer-term investigation of the safety of interventions. Together, this information can be useful for the development and updating of CPGs so that higher recommendations can be given in favour of or against the use of interventions, depending on the specific disease characteristics and JIA subtype of a patient. In addition, it is important for policy makers to balance healthcare expenditures and decide on which programs and interventions to

fund. These policy makers can use the new information developed in our review from indirect head-to-head evidence to compare interventions and make more informed decisions.

While it is challenging to conduct RCTs in pediatric populations, those that are developed should follow rigorous methods including the publishing of a protocol, proper allocation concealment and, where possible, blinding of participants, personnel and outcome assessors. Reporting of the RCTs should also be clear to avoid receiving low quality ratings from risk of bias assessments or being excluded from MAs because of missing information. Another suggestion that has been mentioned in previous SRs is to have more well-defined outcomes to measure and report in JIA RCTs to ensure future SRs can combine the results in MAs or network MAs (Kemper et al., 2012; Takken et al., 2008). Furthermore, certain JIA subtypes may have different inflammatory molecules present, such as with systemic JIA, that affects the response to certain types of interventions (Dinarello, 2009; Ravelli & Martini, 2007; Sen & Ramanan, 2014). Therefore, future RCTs should take this into consideration and either restrict the RCT to a specific subtype or at least use subgroup analyses, as was done for biologics. With high quality RCTs there will be more reliable evidence for healthcare professionals to use in treating patients with JIA and for policy makers who must decide on which interventions to approve for use and public funding.

As mentioned in Chapter 2, however, there are several obstacles that exist for developing high quality RCTs among patients with JIA, which explains in part the low number of RCTs that are available. This also limits the ability to have robust network MAs because there are smaller sample sizes and few comparisons. One alternative for future research in JIA is to use the information available in registries, such as the Childhood Arthritis & Rheumatology Research Alliance (CARRA) registry and the Registry in Arthritis in Canadian Children (ReACCh). By using the wealth of information on patients in these registries, it would facilitate recruitment of eligible participants for multicenter RCTs that are often required for JIA because of the low prevalence (Tan, Thomas, & MacEachern, 2015). Moreover, a regression discontinuity statistical approach may be a useful alternative to RCTs. This is a quasi-experimental method that permits the study of causality among interventions by dividing patients according to existing clinical thresholds (Oldenburg, Moscoe, & Barnighausen, 2016; Venkataramani, Bor, & Jena, 2016). This method may also provide more realistic results for what patients actually experience (*e.g.,* problems with

adherence, loss to follow-up) than RCTs (Venkataramani et al., 2016). Natural experiments are another alternative to RCTs for reducing the gap in the existing evidence, particularly in cases such as these where the effect size may be small (Craig et al., 2012).

5.9 CONCLUSION

Canakinumab for active systemic JIA demonstrated greater efficacy for disease response compared to rilonacept. No significant results were found for the comparative efficacy of biologics for polyarticular-course JIA; more RCTs are needed to increase the sample sizes and improve the precision of estimates. Among DMARDs, MTX at a dose of 10-20 mg/m^2 per week showed the best safety profile and also was favoured over MTX at a dose of 30-40 mg/m^2 in the network MA for the ESR. This finding corresponds to the current evidence on DMARDs and standard doses of MTX. Among NSAIDs, naproxen at a dose of 15 mg/kg per day was shown to be safe to use, and there is some weak evidence to suggest meloxicam at a dose of 0.25 mg/kg per day improved overall well-being while also demonstrating good safety. Non-pharmacological interventions are safe to use, but more research into these interventions is needed as there was insufficient evidence to identify which interventions had greater efficacy. Due to the limitations mentioned above (*i.e.,* low methodological study quality, inconsistency in data reporting among RCTs that required data conversions and the few included RCTs that mostly had small sample sizes), the results should be interpreted with caution. Further research, involving RCTs of high methodological quality, is required to improve the precision of the findings for SRs and network MAs in JIA.

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APPENDIX 1: LITERATURE SEARCH STRATEGY

Medline (Ovid)

1. exp Arthritis, Juvenile Rheumatoid/
2. Arthritis, Psoriatic/
3. oligoarthritis.tw.
4. or/1-3
5. (child* or adolescent* or infan*).mp.
6. 4 and 5
7. limit 6 to randomized controlled trial
8. remove duplicates from 7

Embase (Ovid)

1. juvenile rheumatoid arthritis/
2. psoriatic arthritis/
3. oligoarthritis.tw.
4. or/1-3
5. limit 4 to (infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
6. 4 and (child* or adolescen* or infan*).mp.
7. 5 and 6
8. Randomized Controlled Trial/
9. random$.tw.
10. or/8-9
11. 7 and 10
12. limit 11 to embase

Cochrane CENTRAL (Ovid)

1. Juvenile arthritis or juvenile idiopathic arthritis or psoriatic arthritis or oligoarthritis:ti,ab,kw (Word variations have been searched)
2. child* or adolescent* or infan*
3. 1 and 2 - limited to trials

APPENDIX 2: EQUATIONS USED FOR DATA CONVERSIONS

Converting to change from baseline mean (SD)

$m_\Delta = m_e - m_b$ where m_Δ is the mean change from baseline, m_e is the end of study mean and m_b is the baseline mean

$$SD = \sqrt{(SD_1^2 + SD_2^2 - 2\rho SD_1 SD_2)}$$

Where SD is the pooled standard deviation of the two groups, SD_1 is the standard deviation in group 1, SD_2 is the standard deviation in group 2, and ρ is the coefficient of correlation (assumed to be 0.8) (Higgins & Green, 2011).

Converting median (IQR) to mean (SD)

Median ≈ mean

$$SD \approx \frac{IQR}{1.35}$$

Where SD is the standard deviation and IQR is the interquartile range (3rd quartile minus 1st quartile) (Higgins & Green, 2011).

Converting median (range) to mean (SD)

If n > 25, then $m \approx \bar{x}$

If n ≤ 25, then $\bar{x} = \frac{a+2m+b}{4}$

If n > 70, then $SD = \frac{range}{6}$

If 15 < n ≤ 70, then $SD = \frac{range}{4}$

If n ≤ 15, then $SD = \sqrt{\left(\frac{1}{12}\right)\left[\frac{(a-2m+b)^2}{4} + (b-a)^2\right]}$

Where SD is the standard deviation, a is the minimum value, b is the maximum value, and m is the median (Hozo, Djulbegovic, & Hozo, 2005).

Converting SD to SE

$$SE = \frac{SD}{\sqrt{n}}$$

Where SE is the standard error, SD is the standard deviation and n is the group sample size (Higgins & Green, 2011).

Converting 95% CI to SE:

$$SE = \frac{upper\ limit - lower\ limit}{3.92}$$

Where SE is the standard error between groups, and the upper and lower limits are part of the 95% CI between groups (Higgins & Green, 2011).

Converting p-values to t-values then t-values to SE

df = N_E + N_C – 2, where df are the degrees of freedom, N_E is the number in the experimental group and N_C is the number in the control group (Higgins & Green, 2011).

In Excel: *t* = *tinv(p, df)*, where the values in the brackets are the p-value presented in the study and the degrees of freedom, respectively. When a significant p-value was reported as p < 0.05, for example, the calculation was performed using the midpoint between 0.01 and 0.05 Note: A t distribution table of critical values could also be consulted to obtain the t-value (Higgins & Green, 2011).

$$SE = \frac{MD}{t}$$

Where SE is the standard error of the difference in means, MD is the mean difference, and t is the t value from the t distribution (Higgins & Green, 2011).

Note: Where a one-way analysis of variance was used in a RCT, the p-value was converted to the F statistic using these formulas: df1 = k – 1 and df2 = n – k, where k is the number of cell means and n is the total number of observations in all cells. The formula f = finv(p, df1, df2) was used to convert the p-value to an F statistic, which was then converted to a t value by taking its square root. The process was then the same as above to obtain the standard error (Higgins & Green, 2011).

Standardized Mean Difference Calculations

Pooled standard deviation

$$S = \frac{(n_1-1)(SD_1^2)+(n_2-1)(SD_2^2)}{(n_1+n_2-2)}$$

Where S is the pooled standard deviation, n_1 and $(SD_1)^2$ are the number of participants and the variance in the control arm (respectively), and n_2 and $(SD_2)^2$ are the number of participants and the variance in the intervention arm (respectively).

$$f = \frac{4((n_1+n_2-2)-4)}{(n_1+n_2-2)-1}$$

Where f is the conversion factor to go from Cohen's d to Hedge's g, n_1 is the number of participants in the control arm and n_2 is the number of participants in the intervention arm.

$$SMD = \frac{f(y2-y1)}{S}$$

Where SMD is the standardized mean difference, f is the conversion factor from Cohen's d to Hedge's g, y is the group mean, and S is the pooled standard deviation.

$$SE = \frac{f(\sqrt{(n_1+n_2)}}{(n_1 \times n_2)+(\frac{SMD^2}{2(n_1+n_2)})}$$

Where SE is the standard error of the SMD, f is the conversion factor from Cohen's d to Hedge's g, n_1 is the number of participants in the control arm, n_2 is the number of participants in the intervention arm, and SMD is the standardized mean difference.

$$V = \frac{1}{n_1}$$

Where V is the variance of the baseline intervention (used to adjust for multi-arm trials) and n_1 is the number of participants in the comparison group (L. Chen, personal communication, May 13, 2016).

APPENDIX 3: LIST OF INCLUDED STUDIES (FULL-TEXT AND CONFERENCE ABSTRACTS)

Baydogan 2015

Baydogan, S. N., Tarakci, E., & Kasapcopur, O. (2015). Effect of strengthening versus balance-proprioceptive exercises on lower extremity function in patients with juvenile idiopathic arthritis: a randomized, single-blind clinical trial. *Am J Phys Med Rehabil, 94*(6), 417-428. doi:10.1097/phm.0000000000000279

Bhettay 1978

Bhettay, E., & Thomson, A. J. (1978). Double-blind study of ketoprofen and indomethacin in juvenile chronic arthritis. *South African Medical Journal. Suid-Afrikaanse Tydskrif Vir Geneeskunde, 54*(7), 276-278.

Bhettay 1986

Bhettay, E. (1986). Double-blind study of sulindac and aspirin in juvenile chronic arthritis. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde, 70*(12), 724-726.

Braccioloni 2014 (Conference abstract)

Bracciolini, G. P., Davi, S., Pistorio, A., Consolaro, A., Verazza, S., Lattanzi, B., . . . Ravelli, A. (2014). A controlled trial of intra-articular corticosteroids with or without methotrexate in oligoarticular juvenile idiopathic arthritis. *Pediatric Rheumatology, 12*.

Ravelli, A., Bracciolini, G., Davi, S., Pistorio, A., Consolaro, A., Verazza, S., . . . Martini, A. (2014). A controlled trial of intra-articular corticosteroids with or without methotrexate in oligoarticular juvenile idiopathic arthritis. *Arthritis and Rheumatology, 66*, S127-S128. doi:http://dx.doi.org/10.1002/art.38914

Brewer 1986

Brewer, E. J., Giannini, E. H., Kuzmina, N., & Alekseev, L. (1986). Penicillamine and hydroxychloroquine in the treatment of severe juvenile rheumatoid arthritis: Results of the U.S.A.-U.S.S.R. double-blind placebo-controlled trial. *New England Journal of Medicine, 314*(20), 1269-1276. doi:10.1056/NEJM198605153142001

Giannini, E. H., Brewer, E. J., Kuzmina, N., Alekseev, L., & Shokh, B. P. (1988). Characteristics of responders and nonresponders to slow-acting antirheumatic drugs in juvenile rheumatoid arthritis. *Arthritis and Rheumatism, 31*(1), 15-20.

Brunner 2014 (Conference abstract)

Brunner, H. I., Ruperto, N., Tzaribachev, N., Horneff, G., Wouters, C., Panaviene, V. V., . . . Martini, A. (2014). A multi-center, double-blind, randomized-withdrawal trial of subcutaneous golimumab in pediatric patients with active polyarticular course juvenile idiopathic arthritis despite methotrexate therapy: Week 48 results. *Arthritis and Rheumatology, 66*, S414-S415. doi:http://dx.doi.org/10.1002/art.38914

Burgos-Vargas 2013 (Conference abstract)

Burgos-Vargas, R., Tse, S. M. L., Horneff, G., Pangan, A. L., Unnebrink, K., & Anderson, J. K. (2013). Efficacy and safety of adalimumab in pediatric patients with enthesitis related arthritis. *Arthritis and Rheumatism, 65*, S336. doi:http://dx.doi.org/10.1002/art.38216

Burgos-Vargas, R., Tse, S., Horneff, G., Pangan, A., Unnebrink, K., & Anderson, J. (2014). Efficacy and safety of adalimumab in pediatric patients with enthesitis related arthritis. *Journal of Rheumatology, 41 (7)*, 1531-1532. doi:http://dx.doi.org/10.3899/jrheum.140420

Burgos-Vargas, R., Tse, S., Horneff, G., Pangan, A. L., Unnebrink, K., & Anderson, J. K. (2013). PReS-FINAL-2179: Efficacy and safety of adalimumab in pediatric patients with enthesitis related arthritis. *Pediatric Rheumatology, 11*. doi:http://dx.doi.org/10.1186/1546-0096-11-S2-O14

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Coda 2014

Coda, A., Fowlie, P. W., Davidson, J. E., Walsh, J., Carline, T., & Santos, D. (2014). Foot orthoses in children with juvenile idiopathic arthritis: a randomised controlled trial. *Archives of disease in childhood, 99*(7), 649-651. doi:10.1136/archdischild-2013-305166

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De Benedetti 2014 (Conference abstract)

De Benedetti, F., Ruperto, N., Zuber, Z., Cuttica, R., Keltsev, V., Xavier, R., . . . Brunner, H. I. (2014). Efficacy and safety of tocilizumab in patients with polyarticular juvenile idiopathic arthritis: 2-Year data from the CHERISH study. *Rheumatology (United Kingdom), 53*, iii1-iii2. doi:http://dx.doi.org/10.1093/rheumatology/keu268.002

De Benedetti 2012

De Benedetti, F., Brunner, H. I., Ruperto, N., Kenwright, A., Wright, S., Calvo, I., . . . Martini, A. (2012). Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *New England Journal of Medicine, 367*(25), 2385-2395. doi:http://dx.doi.org/10.1056/NEJMoa1112802

De Benedetti, F., Ruperto, N., Espada, G., Gerloni, V., Flato, B., Horneff, G., . . . Lovell, D. J. (2012). Catch-up growth during tocilizumab therapy for systemic juvenile idiopathic arthritis: 2-year data from a phase 3 clinical trial. *Arthritis and Rheumatism, 64*, S327. doi:http://dx.doi.org/10.1002/art.37735

De Benedetti, F., Ruperto, N., Espada, G., Gerloni, V., Flato, B., Horneff, G., . . . Lovell, D. J. (2013). Catch-up growth during tocilizumab therapy for systemic juvenile idiopathic arthritis: Tender 2-year data. *Rheumatology (United Kingdom), 52*, i34. doi:http://dx.doi.org/10.1093/rheumatology/ket200

Heinzl, S. (2010). TENDER study: Tocilizumab is effective in systemic juvenile idiopathic arthritis. [German]. *Arzneimitteltherapie, 28*(9), 287-288.

Eberhard 1993

Eberhard, B. A., Sylvester, K. L., & Ansell, B. M. (1993). A comparative study of orthoplast cock-up splints versus ready-made Droitwich work splints in juvenile chronic arthritis. *Disability & Rehabilitation, 15*(1), 41-43.

Epps 2005

Epps, H., Ginnelly, L., Utley, M., Southwood, T., Gallivan, S., Sculpher, M., & Woo, P. (2005). Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis. *Health Technology Assessment (Winchester, England), 9*(39), iii-iv, ix. doi:96-32-08

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Field, T., Hernandez-Reif, M., Seligman, S., Krasnegor, J., Sunshine, W., Rivas-Chacon, R., . . . Kuhn, C. (1997). Juvenile rheumatoid arthritis: benefits from massage therapy. *Journal of Pediatric Psychology, 22*(5), 607-617.

Foeldvari 2009

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Forster 2000 (Protocol)

Forster, J. (2000). [Prospective study of JCR-Oligo I of the Child and Adolescence Rheumatology Working Group]. *Zeitschrift fur Rheumatologie, 59*(2), 122-123.

Giannini 1992

Giannini, E. H., Brewer, E. J., Kuzmina, N., Shaikov, A., Maximo, A., Vorontson, I., . . . Zemel, L. S. (1992). Methotrexate in resistant juvenile rheumatoid arthritis - Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. *New England Journal of Medicine, 326*(16), 1043-1049.

Giannini 1990 (ibuprofen)

Giannini, E. H., Brewer, E. J., Miller, M. L., Gibbas, D., Passo, M. H., Hoyeraal, H. M., . . . Scheinbaum, M. L. (1990). Ibuprofen suspension in the treatment of juvenile rheumatoid arthritis. *Journal of Pediatrics, 117*(4), 645-652.

Giannini 1990 (auranofin)

Giannini, E. H., Brewer Jr, E. J., Kuzmina, N., Shaikov, A., & Wallin, B. (1990). Auranofin in the treatment of juvenile rheumatoid arthritis. Results of the USA-USSR double-blind, placebo-controlled trial. *Arthritis and Rheumatism, 33*(4), 466-476. doi:http://dx.doi.org/10.1002/art.1780330402

Hendry 2013

Hendry, G. J., Watt, G. F., Brandon, M., Friel, L., Turner, D. E., Lorgelly, P. K., . . . Woodburn, J. (2013). The effectiveness of a multidisciplinary foot care program for children and adolescents with juvenile idiopathic arthritis: an exploratory trial. *Journal of Rehabilitation Medicine, 45*(5), 467-476. doi:10.2340/16501977-1130

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Hendry, G., Watt, G., Brandon, M., Friel, L., Sturrock, R., Gardner-Medwin, J., . . . Woodburn, J. (2012). A feasibility trial of multidisciplinary foot care for children and adolescents with juvenile idiopathic arthritis. *Internal Medicine Journal, 42*, 7. doi:http://dx.doi.org/10.1111/j.1445-5994.2012.02760.x

Hillman 2008

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APPENDIX 4: LIST OF ARTICLES EXCLUDED AT FULL-TEXT REVIEW

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APPENDIX 5: SENSITIVITY ANALYSES

TABLE 1: SENSITIVITY ANALYSIS INCLUDING ABSTRACTS OF BIOLOGICS WITHDRAWAL RCTS FOR POLYARTICULAR-COURSE JIA (OUTCOME: DISEASE RESPONSE – ACR PEDI 30)

	Placebo	**ETN (0.2mg/kg)**	**ETN (0.4mg/kg)**	**Placebo + MTX**	**ABT**	**ADA**	**ADA + MTX**	**GLM**
Placebo								
ETN (0.2mg/kg)	1.99 (0.89, 2.50)							
ETN (0.4mg/kg)	**1.85 (1.27, 2.37)**	0.94 (0.72, 1.84)						
Placebo + MTX	1.14 (0.49, 1.86)	0.58 (0.26, 1.37)	0.62 (0.27, 1.06)					
ABT	1.36 (0.74, 1.92)	0.69 (0.37, 1.54)	0.74 (0.40, 1.15)	1.19 (0.56, 2.84)				
ADA	1.52 (0.83, 2.12)	0.77 (0.43, 1.72)	0.83 (0.46, 1.25)	1.31 (0.82, 2.55)	1.11 (0.59, 2.18)			
ADA + MTX	1.63 (0.99, 2.20)	0.83 (0.52, 1.84)	0.88 (0.54, 1.31)	1.41 (0.93, 2.76)	1.19 (0.69, 2.29)	1.07 (0.75, 1.68)		
GLM	1.14 (0.60, 1.69)	0.58 (0.30, 1.33)	0.62 (0.32, 1.01)	1.00 (0.46, 2.45)	0.84 (0.42, 1.68)	0.75 (0.38, 1.48)	0.703 (0.36, 1.27)	

Results are the median relative risk (95% credible interval); MTX = methotrexate; GLB = golimumab

TABLE 2: Sensitivity analysis of biologics parallel RCTs for active systemic JIA with end of intervention results for Ruperto 2012 (Outcome: DISEASE RESPONSE – ACR Pedi 30)

	Placebo	Tocilizumab	Rilonacept	Anakinra	Canakinumab
Placebo					
Tocilizumab	**3.24 (2.24, 4.76)**				
Rilonacept	**2.10 (1.08, 3.54)**	0.65 (0.35, 1.00)			
Anakinra	**2.93 (1.01, 4.80)**	0.92 (0.33, 1.32)	1.40 (0.47, 2.74)		
Canakinumab	**3.50 (2.46, 5.21)**	1.07 (0.89, 1.42)	**1.66 (1.15, 3.03)**	1.17 (0.88, 3.30)	

Results are the median relative risk (95% credible interval); canakinumab results are from end of intervention (28 days); result in blue is different than the reference case

TABLE 3: Sensitivity analysis of biologics parallel RCTs for active systemic JIA with abstracts included (Outcome: functional ability, CHAQ disability index)

	Placebo	Rilonacept	Anakinra	Canakinumab
Placebo				
Rilonacept	-0.20 (-2.73, 2.32)			
Anakinra	-32.6 (-74.56, 7.59)	-32.37 (-74.46, 7.84)		
Canakinumab	-0.66 (-3.15, 1.89)	-0.47 (-3.97, 3.15)	31.92 (-8.28, 74.05)	

Results are the median mean difference (95% credible interval)

TABLE 4: SENSITIVITY ANALYSIS OF NSAID STUDIES WITH RESULTS ALL AT THE END OF INTERVENTION (OUTCOME: DISEASE RESPONSE – ACR PEDI 30)

	Naproxen	Celecoxib 3mg/kg	Celecoxib 6mg/kg	Rofecoxib 0.3mg/kg	Rofecoxib 0.6mg/kg	Meloxicam 0.125mg/kg	Meloxicam 0.25mg/kg
Naproxen							
Celecoxib 3mg/kg	1.03 (0.61, 1.33)						
Celecoxib 6mg/kg	1.21 (0.84, 1.44)	1.17 (0.87, 1.75)					
Rofecoxib 0.3mg/kg	0.88 (0.48, 1.22)	0.86 (0.46, 1.55)	0.73 (0.40, 1.17)				
Rofecoxib 0.6mg/kg	1.0 (0.60, 1.30)	0.97 (0.56, 1.69)	0.83 (0.50, 1.27)	1.13 (0.76, 1.78)			
Meloxicam 0.125mg/kg	1.04 (0.62, 1.36)	1.01 (0.59, 1.76)	0.87 (0.52, 1.32)	1.18 (0.66, 2.22)	1.05 (0.60, 1.82)		
Meloxicam 0.25mg/kg	1.02 (0.60, 1.34)	0.99 (0.57, 1.74)	0.85 (0.50, 1.30)	1.16 (0.64, 2.20)	1.03 (0.58, 1.79)	0.98 (0.65, 1.46)	

Results are the median relative risk (95% credible interval); ACR Pedi 30 = American College of Rheumatology Pediatric 30; 12 month end of intervention results presented for Ruperto 2005

TABLE 5: SENSITIVITY ANALYSIS OF NSAID STUDIES WITH RESULTS ALL AT THE END OF INTERVENTION (OUTCOME: NUMBER OF ACTIVE JOINTS)

	Naproxen	Celecoxib 3mg/kg	Celecoxib 6mg/kg	Rofecoxib 0.3mg/kg	Rofecoxib 0.6mg/kg	Meloxicam 0.125mg/kg	Meloxicam 0.25mg/kg
Naproxen							
Celecoxib 3mg/kg	1.0 (-1.79, 3.78)						
Celecoxib 6mg/kg	-0.61 (-3.39, 2.17)	-1.61 (-4.4, 1.18)					
Rofecoxib 0.3mg/kg	0.37 (-2.24, 3)	-0.63 (-4.42, 3.21)	0.99 (-2.8, 4.79)				
Rofecoxib 0.6mg/kg	0.36 (-2.25, 3)	-0.64 (-4.44, 3.2)	0.96 (-2.82, 4.81)	-0.02 (-2.64, 2.62)			
Meloxicam 0.125mg/kg	-0.31 (-3.23, 2.59)	-1.31 (-5.34, 2.71)	0.3 (-3.72, 4.32)	-0.68 (-4.6, 3.2)	-0.67 (-4.58, 3.22)		
Meloxicam 0.25mg/kg	-0.51 (-3.38, 2.37)	-1.51 (-5.52, 2.5)	0.1 (-3.9, 4.11)	-0.88 (-4.78, 2.99)	-0.86 (-4.79, 2.98)	-0.19 (-3.15, 2.72)	

Results are the median mean difference (95% credible interval); ACR Pedi 30 = American College of Rheumatology Pediatric 30; 12 month end of intervention results presented for Ruperto 2005

TABLE 6: SENSITIVITY ANALYSIS OF NSAID STUDIES WITH RESULTS ALL AT THE END OF INTERVENTION (OUTCOME: NUMBER OF JOINTS WITH LIMITED RANGE OF MOTION)

	Naproxen	Celecoxib 3mg/kg	Celecoxib 6mg/kg	Rofecoxib 0.3mg/kg	Rofecoxib 0.6mg/kg	Meloxicam 0.125mg/kg	Meloxicam 0.25mg/kg
Naproxen							
Celecoxib 3mg/kg	0.43 (-2.31, 3.14)						
Celecoxib 6mg/kg	-1.02 (-3.73, 1.7)	-1.44 (-4.16, 1.27)					
Rofecoxib 0.3mg/kg	1.17 (-1.46, 3.8)	0.74 (-3.02, 4.5)	2.19 (-1.56, 5.95)				
Rofecoxib 0.6mg/kg	1.02 (-1.61, 3.67)	0.59 (-3.19, 4.4)	2.04 (-1.73, 5.82)	-0.16 (-2.76, 2.5)			
Meloxicam 0.125mg/kg	-0.29 (-3.21, 2.63)	-0.72 (-4.7, 3.28)	0.73 (-3.28, 4.7)	-1.46 (-5.4, 2.45)	-1.31 (-5.2, 2.61)		
Meloxicam 0.25mg/kg	0.51 (-2.39, 3.38)	0.07 (-3.9, 4.04)	1.53 (-2.47, 5.48)	-0.65 (-4.55, 3.22)	-0.5 (-4.44, 3.36)	0.8 (-2.12, 3.72)	

Results are the median mean difference (95% credible interval); ACR Pedi 30 = American College of Rheumatology Pediatric 30; 12 month end of intervention results presented for Ruperto 2005

TABLE 7: SENSITIVITY ANALYSIS OF NSAID STUDIES WITH RESULTS ALL AT THE END OF INTERVENTION (OUTCOME: PHYSICIAN'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY)

	Naproxen	Celecoxib 3mg/kg	Celecoxib 6mg/kg	Rofecoxib 0.3mg/kg	Rofecoxib 0.6mg/kg	Meloxicam 0.125mg/kg	Meloxicam 0.25mg/kg
Naproxen							
Celecoxib 3mg/kg	0.94 (-4.66, 6.41)						
Celecoxib 6mg/kg	-1.32 (-6.85, 4.2)	-2.21 (-7.78, 3.35)					
Rofecoxib 0.3mg/kg	-0.39 (-4.59, 3.8)	-1.32 (-8.13, 5.64)	0.95 (-6.02, 7.78)				
Rofecoxib 0.6mg/kg	-1.21 (-5.56, 3.13)	-2.15 (-9.16, 4.94)	0.11 (-6.87, 7.07)	-0.81 (-5.1, 3.5)			
Meloxicam 0.125mg/kg	-1.26 (-5.76, 3.34)	-2.22 (-9.23, 4.95)	0.03 (-7.01, 7.22)	-0.89 (-6.98, 5.39)	-0.08 (-6.31, 6.31)		
Meloxicam 0.25mg/kg	-1.43 (-6.01, 3.25)	-2.35 (-9.42, 4.79)	-0.08 (-7.33, 7.15)	-1.01 (-7.3, 5.22)	-0.22 (-6.59, 6.16)	-0.18 (-4.99, 4.62)	

Results are the median mean difference (95% credible interval); ACR Pedi 30 = American College of Rheumatology Pediatric 30; 12 month end of intervention results presented for Ruperto 2005

TABLE 8: SENSITIVITY ANALYSIS OF NSAID STUDIES WITH RESULTS ALL AT THE END OF INTERVENTION (OUTCOME: FUNCTIONAL ABILITY)

	Naproxen	Celecoxib 3mg/kg	Celecoxib 6mg/kg	Rofecoxib 0.3mg/kg	Rofecoxib 0.6mg/kg	Meloxicam 0.125mg/kg	Meloxicam 0.25mg/kg
Naproxen							
Celecoxib 3mg/kg	0.03 (-2.51, 2.55)						
Celecoxib 6mg/kg	-0.01 (-2.54, 2.5)	-0.04 (-2.58, 2.49)					
Rofecoxib 0.3mg/kg	0.01 (-2.52, 2.52)	-0.01 (-3.57, 3.57)	0.02 (-3.53, 3.59)				
Rofecoxib 0.6mg/kg	-0.03 (-2.57, 2.49)	-0.05 (-3.64, 3.52)	-0.02 (-3.61, 3.57)	-0.04 (-2.58, 2.49)			
Meloxicam 0.125mg/kg	0.1 (-2.42, 2.62)	0.07 (-3.5, 3.64)	0.11 (-3.46, 3.7)	0.09 (-3.48, 3.64)	0.13 (-3.45, 3.71)		
Meloxicam 0.25mg/kg	0 (-2.52, 2.53)	-0.03 (-3.58, 3.56)	0.01 (-3.56, 3.6)	-0.01 (-3.58, 3.56)	0.03 (-3.53, 3.61)	-0.1 (-2.63, 2.43)	

Results are the median mean difference (95% credible interval); ACR Pedi 30 = American College of Rheumatology Pediatric 30; 12 month end of intervention results presented for Ruperto 2005

TABLE 9: SENSITIVITY ANALYSIS OF NSAID STUDIES WITH RESULTS ALL AT THE END OF INTERVENTION (OUTCOME: PATIENT/PARENT ASSESSMENT OF OVERALL WELL-BEING)

	Naproxen	Celecoxib 3mg/kg	Celecoxib 6mg/kg	Rofecoxib 0.3mg/kg	Rofecoxib 0.6mg/kg	Meloxicam 0.125mg/kg	Meloxicam 0.25mg/kg
Naproxen							
Celecoxib 3mg/kg	0.33 (-6.65, 7.22)						
Celecoxib 6mg/kg	-2.18 (-9.07, 4.64)	-2.5 (-9.47, 4.4)					
Rofecoxib 0.3mg/kg	-3.01 (-8.63, 2.57)	-3.33 (-12.31, 5.56)	-0.81 (-9.69, 7.97)				
Rofecoxib 0.6mg/kg	-3.51 (-9.16, 2.12)	-3.84 (-12.82, 5.1)	-1.34 (-10.27, 7.53)	-0.5 (-6.13, 5.04)			
Meloxicam 0.125mg/kg	-0.29 (-4.88, 4.33)	-0.6 (-8.87, 7.75)	1.86 (-6.29, 10.25)	2.74 (-4.5, 9.98)	3.24 (-4.05, 10.52)		
Meloxicam 0.25mg/kg	0.32 (-4.52, 5.2)	-0.01 (-8.37, 8.47)	2.48 (-5.86, 10.93)	3.33 (-4.07, 10.77)	3.84 (-3.62, 11.34)	0.59 (-4.27, 5.49)	

Results are the median mean difference (95% credible interval); ACR Pedi 30 = American College of Rheumatology Pediatric 30; 12 month end of intervention results presented for Ruperto 2005

TABLE 10: SENSITIVITY ANALYSIS OF NSAID STUDIES WITH RESULTS ALL AT THE END OF INTERVENTION (OUTCOME: ESR/CRP)

	Naproxen	Aspirin	Celecoxib 3mg/kg	Celecoxib 6mg/kg	Rofecoxib 0.3mg/kg	Rofecoxib 0.6mg/kg	Meloxicam 0.125mg/kg	Meloxicam 0.25mg/kg
Naproxen								
Aspirin	-0.08 (-6.35, 6.25)							
Celecoxib 3mg/kg	-0.15 (-6.42, 6.16)	-0.08 (-9, 8.83)						
Celecoxib 6mg/kg	-0.11 (-6.36, 6.2)	-0.04 (-8.95, 8.89)	0.03 (-6.25, 6.36)					
Rofecoxib 0.3mg/kg	0 (-6.27, 6.26)	0.07 (-8.83, 8.96)	0.15 (-8.74, 9.04)	0.1 (-8.76, 8.97)				
Rofecoxib 0.6mg/kg	-0.15 (-6.41, 6.19)	-0.08 (-9.02, 8.83)	0 (-8.87, 8.91)	-0.04 (-8.88, 8.87)	-0.14 (-6.4, 6.12)			
Meloxicam 0.125mg/kg	0.13 (-6.14, 6.39)	0.2 (-8.72, 9.13)	0.27 (-8.61, 9.13)	0.24 (-8.67, 9.05)	0.14 (-8.74, 9)	0.28 (-8.65, 9.1)		
Meloxicam 0.25mg/kg	-0.25 (-6.56, 6.01)	-0.19 (-9.09, 8.75)	-0.11 (-8.99, 8.74)	-0.14 (-9.04, 8.71)	-0.25 (-9.16, 8.59)	-0.1 (-9.02, 8.72)	-0.38 (-6.67, 5.92)	

Results are the median standardized mean difference (95% credible interval); ACR Pedi 30 = American College of Rheumatology Pediatric 30; 12 month end of intervention results presented for Ruperto 2005